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CHEST® Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

Mitchel L. Zoler/MDedge News

Dr. Joshua B. Goldberg

Pulmonary embolism incidence nearly doubled over 2004-2015

MITCHEL L. ZOLER
MDedge News

NEW ORLEANS – The incidence of pulmonary embolism diagnosed in hospitalized U.S. patients nearly doubled during the period 2004-2015 based on data collected by the National Inpatient Sample.

During 2004-2015 the incidence of all diagnosed pulmonary embolism (PE), based on discharge diagnoses, rose from 5.4 cases/1,000 hospitalized patients in 2004 to 9.7 cases/1,000 hospitalized patients in 2015, an 80% increase, Joshua B. Goldberg, MD, said at the annual meeting of the American College of Cardiology. The incidence of major PE – defined as a patient who needed vasopressor treatment, mechanical ventilation, or had nonseptic shock – rose from 7.9% of all hospitalized PE diagnoses in 2004 to 9.7% in 2015, a 23% relative increase.

The data also documented a shifting pattern of treatment for all hospitalized patients with PE, and especially among patients with major PE. During the study period, treatment with systemic thrombolysis for all PE rose nearly threefold, and catheter-directed therapy began to show a steady rise in use from 0.2% of all patients in 2011 (and before) to 1% of all patients by 2015. Surgical intervention remained lightly used throughout, with about 0.2% of all PE patients undergoing surgery annually.

PULMONARY EMBOLISM // *continued on page 6*

PAP cut all-cause mortality in obese patients with severe OSA

BY ERIK GREB
MDedge News

The prescription of positive airway pressure is associated with reduced all-cause mortality, according to the results of a cohort study published in JAMA Otolaryngology–Head & Neck Surgery.

The association becomes evident several years after positive airway pressure (PAP) initiation, according to the researchers. Obstructive sleep apnea (OSA) is among the top 10 modifiable cardiovascular risk factors, and is associated with increased risks of coronary artery disease, stroke, and death. PAP is the most effective treatment for OSA, but this treatment's effect on all-cause and cardiovascular mortality is uncertain. Randomized trials have yielded inconclusive answers to this question, and evidence from observational studies has been weak.

To investigate the association between PAP prescription and mortality in patients with obesity and severe OSA, Quentin Lisan, MD, of the Paris Cardiovascular Research Center and his colleagues conducted a multicenter, pop-

PAP // *continued on page 7*

INSIDE HIGHLIGHT

NEWS FROM CHEST

SLEEP STRATEGIES
The role of sleep-related hypoxia

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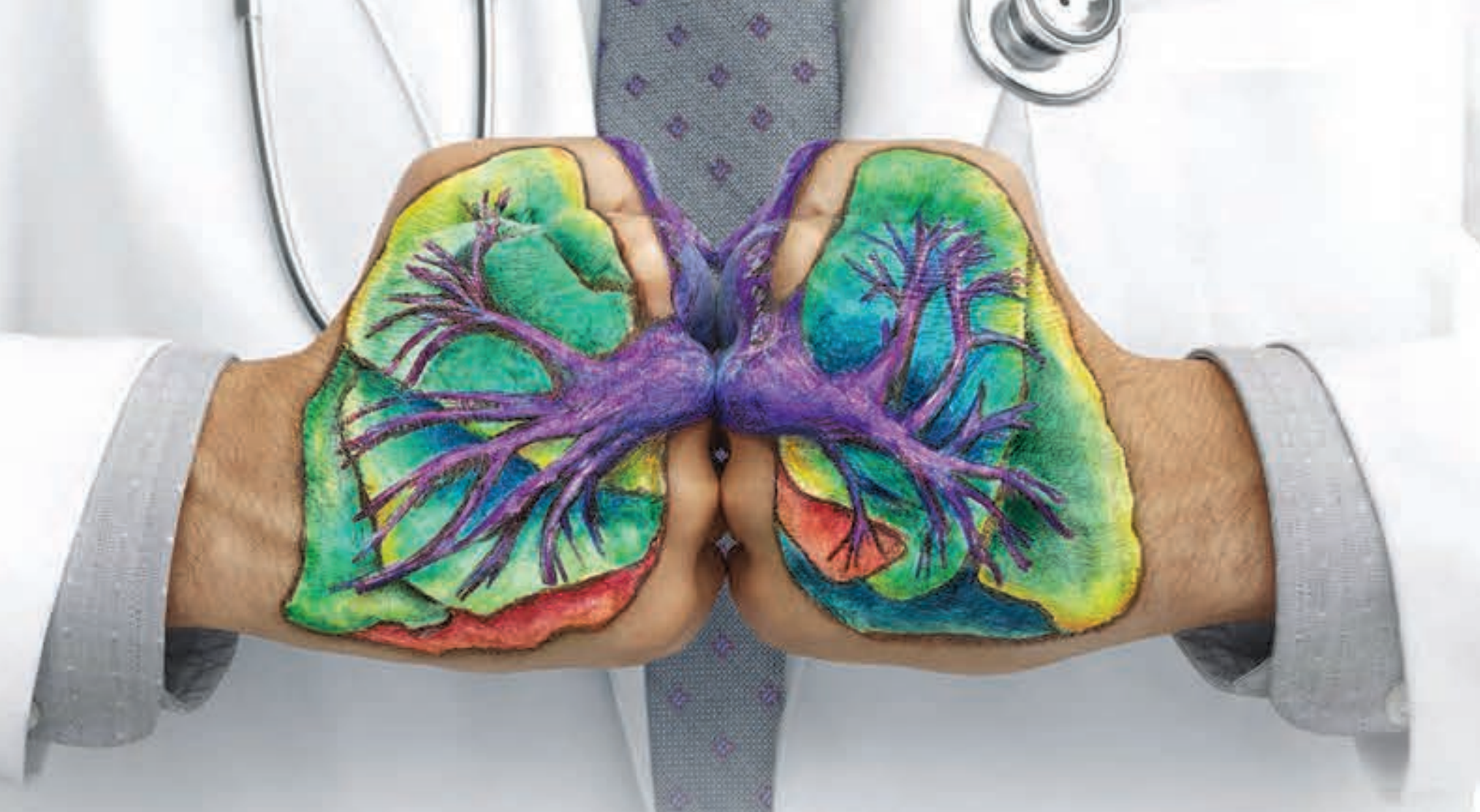

Indication

Esbriet® (pirfenidone) is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

Select Important Safety Information

Elevated liver enzymes: Patients treated with Esbriet had a higher incidence of ALT and/or AST elevations of ≥3× ULN (3.7%) compared with placebo patients (0.8%). In some cases, these have been associated with concomitant elevations in bilirubin. No Esbriet-related cases of liver transplant or death due to liver failure have been reported. However, combined elevations of transaminases and bilirubin without evidence of obstruction is considered an important predictor of severe liver injury that could lead to death or the need for a transplant.

Measure ALT, AST, and bilirubin levels prior to initiating Esbriet, then monthly for the first 6 months, and every 3 months thereafter. Dosage modifications or interruption may be necessary.

Photosensitivity reaction or rash: Patients treated with Esbriet had a higher incidence of photosensitivity reactions (9%) compared with placebo patients (1%). Patients should avoid or minimize exposure to sunlight and sunlamps, regularly use sunscreen (SPF 50 or higher), wear clothing that protects against sun exposure, and avoid concomitant medications that cause photosensitivity. Dosage reduction or discontinuation may be necessary.

Gastrointestinal (GI) disorders: Patients treated with Esbriet had a higher incidence of nausea, diarrhea, dyspepsia, vomiting, gastroesophageal reflux disease (GERD), and abdominal pain. GI events required dose reduction or interruption in 18.5% of 2403 mg/day Esbriet-treated patients, compared with 5.8% of placebo patients; 2.2% of 2403 mg/day Esbriet-treated patients discontinued treatment due to a GI event, compared with 1.0% of placebo patients. The most common (>2%) GI events leading to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. Dosage modifications may be necessary.

Adverse reactions: The most common adverse reactions (≥10%) were nausea, rash, abdominal pain, upper respiratory tract infection, diarrhea, fatigue, headache, dyspepsia, dizziness, vomiting, anorexia, GERD, sinusitis, insomnia, weight decreased, and arthralgia.

Drug Interactions:
CYP1A2 inhibitors: Concomitant use of Esbriet and strong CYP1A2 inhibitors (e.g., fluvoxamine) is not recommended, as CYP1A2 inhibitors increase systemic exposure of Esbriet. If discontinuation of the CYP1A2 inhibitor prior to starting Esbriet is not possible, dosage reductions of Esbriet are recommended. Monitor for adverse reactions and consider discontinuation of Esbriet.

Concomitant use of ciprofloxacin (a moderate CYP1A2 inhibitor) at the dosage of 750 mg BID and Esbriet are not recommended. If this dose of ciprofloxacin cannot be avoided, dosage reductions of Esbriet are recommended, and patients should be monitored.

Moderate or strong inhibitors of both CYP1A2 and other CYP isoenzymes involved in the metabolism of Esbriet should be avoided during treatment.

CYP1A2 inducers: Concomitant use of Esbriet and strong CYP1A2 inducers should be avoided, as CYP1A2 inducers may decrease the exposure and efficacy of Esbriet.

Specific Populations:
Mild to moderate hepatic impairment: Esbriet should be used with caution in patients with Child Pugh Class A and B. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed.

Severe hepatic impairment: Esbriet is not recommended for patients with Child Pugh Class C. Esbriet has not been studied in this patient population.

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Mild (CL_{cr} 50-80 mL/min), moderate (CL_{cr} 30-50 mL/min), or severe (CL_{cr} <30 mL/min) renal impairment: Esbriet should be used with caution. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed.

End-stage renal disease requiring dialysis: Esbriet is not recommended. Esbriet has not been studied in this patient population.

Smokers: Smoking causes decreased exposure to Esbriet which may affect efficacy. Instruct patients to stop smoking prior to treatment and to avoid smoking when using Esbriet.

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch or to Genentech at 1-888-835-2555.

Please see Brief Summary of Prescribing Information on adjacent pages for additional Important Safety Information.

References: 1. Esbriet Prescribing Information. Genentech, Inc. October 2017. **2.** King TE Jr, Bradford WZ, Castro-Bernardini S, et al; for the ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis [published correction appears in *N Engl J Med.* 2014;371(12):1172]. *N Engl J Med.* 2014;370(22):2083–2092. **3.** Noble PW, Albera C, Bradford WZ, et al; for the CAPACITY Study Group. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet.* 2011;377(9779):1760–1769. **4.** Data on file. Genentech, Inc. 2016.

Learn more about Esbriet and how to access medication at EsbrietHCP.com

IPF=idiopathic pulmonary fibrosis.

*The safety and efficacy of Esbriet were evaluated in three phase 3, randomized, double-blind, placebo-controlled, multicenter trials in which 1247 patients were randomized to receive Esbriet (n=623) or placebo (n=624).[1] In ASCEND, 555 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo for 52 weeks. Eligible patients had percent predicted forced vital capacity (%FVC) between 50%–90% and percent predicted diffusing capacity of lung for carbon monoxide ($\%DL_{co}$) between 30%–90%. The primary endpoint was change in %FVC from baseline at 52 weeks.[2] In CAPACITY 004, 348 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo. Eligible patients had %FVC ≥50% and $\%DL_{co}$ ≥35%. In CAPACITY 006, 344 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo. Eligible patients had %FVC ≥50% and $\%DL_{co}$ ≥35%. For both CAPACITY trials, the primary endpoint was change in %FVC from baseline at 72 weeks.[3] Esbriet had a significant impact on lung function decline and delayed progression of IPF vs placebo in ASCEND.[1,2] Esbriet demonstrated a significant effect on lung function for up to 72 weeks in CAPACITY 004, as measured by %FVC and mean change in FVC (mL).[1,3,4] **No statistically significant difference vs placebo in change in %FVC or decline in FVC volume from baseline to 72 weeks was observed in CAPACITY 006.[1,3]**

†In clinical trials, serious adverse reactions, including elevated liver enzymes, photosensitivity reactions, and gastrointestinal disorders, have been reported with Esbriet. Some adverse reactions with Esbriet occurred early and/or decreased over time (ie, photosensitivity reactions and gastrointestinal events).[1]

‡Esbriet Access Solutions offers a range of access and reimbursement support for your patients and practice. Clinical Coordinators are available to educate patients with IPF. The Esbriet® Inspiration Program™ motivates patients to stay on treatment.

§The safety of pirfenidone has been evaluated in more than 1400 subjects, with over 170 subjects exposed to pirfenidone for more than 5 years in clinical trials.[1]

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Medicare HF readmission penalty sparks concern

BY MITCHEL L. ZOLER
MDedge News

NEW ORLEANS – Mounting evidence shows that heart failure patient mortality increased as an unintended consequence of a Medicare program that penalizes hospitals with too many 30-day readmissions of heart failure patients. This has prompted discussions among cardiologists, Medicare officials, and other stakeholders in an attempt to modify the penalty program so it no longer considers just readmissions but instead bases penalties on broader and more nuanced measures of patient outcomes.

Staffers at the Centers for Medicare & Medicaid Services, the federal agency that manages Medicare, "said that they take this seriously and will look into it, and they are interested in next-generation measures that are

more patient centered" than simply the 30-day readmission rate, Gregg C. Fonarow, MD, said in an interview at the annual meeting of the American College of Cardiology. "This is a case where there is credible evidence of increased mortality that is consistent, reproducible, and strongly associated with the penalty and cannot be otherwise explained," said Dr. Fonarow, professor of medicine and cochief of cardiology at the University of California, Los Angeles.

He is among the most active researchers to document that, while CMS's Hospital Readmissions Reduction Program (HRRP) led to significantly reduced readmission rates in patients with heart failure, this came at a cost of a significant increase in mortality among the same patients. For example, an article he published in 2018 that analyzed more than 115,000 Medicare beneficiaries during 2006-2014 showed that during the penalty phase, which began in 2012, readmissions fell after adjustment by a relative 8%, but adjusted mortality rose by a relative 10%, compared with how patients had fared prior to launching the HRRP (JAMA Cardiol. 2018 Jan;3[1]:44-53). Recent reports from other research groups have had similar findings, such as a study of more than 3 million Medicare beneficiaries with heart failure during 2005-2015 that also showed significantly increased mortality after the penalty phase for readmissions began (JAMA. 2018 Dec 25;320[24]:2542-52). In a commentary that accompanied this report, Dr. Fonarow cited the multiple analyses that show consistent findings and the need for CMS to "initiate an expeditious reconsideration and revision" of their current approach to penalizing hospitals for heart failure readmissions (JAMA. 2018 Dec 25;320[24]:2539-41).

Dr. Fonarow

The groups recently in discussion with CMS about this issue include the American College of Cardiology, the American Heart Association, the Heart Failure Society of America, the American College of Physicians, the American Hospital Association, and several other medical professional groups, said Biykem Bozkurt, MD, who has worked with Dr. Fonarow and representatives from these organizations in talks with CMS.

"We are trying to find a harmonized approach with patient-centric outcomes that reflect true improvements in quality of care," she said in an interview. One possibility up for consideration is a combined measure of heart failure readmissions, mortality, and a patient-reported outcome. The measure would go to CMS directly from each patient's electronic medical record, making data collection less burdensome to clinicians, said Dr. Bozkurt, professor of medicine at Baylor College of Medicine and cardiology section chief at the VA Medical Center in Houston. She expressed hope that a change in the CMS metric might happen later this year.

"CMS can't simply stop the HRRP, so the discussion is on how to get a meaningful change. I'm increasingly optimistic, because the findings of harm [from current policies] are impossible to ignore," Dr. Fonarow said. "There will be increasing pressure on CMS to develop a pathway to make modifications. It's egregious to continue a policy that's been associated with harm" to heart failure patients.

Dr. Fonarow and Dr. Bozkurt had no relevant commercial disclosures.

mzoler@mdedge.com

Pulmonary embolism // *continued from page 1*

Most of these intervention options focused on patients with major PE. Among patients in this subgroup with more severe disease, use of one of these three types of interventions rose from 6% in 2004 to 12% in 2015, mostly driven by a rise in systemic thrombolysis, which jumped from 3% of major PE in 2004 to 9% in 2015. However, the efficacy of systemic thrombolysis in patients with major PE remains suspect. In 2004, 39% of patients with major PE treated with systemic thrombolysis died in hospital; in 2015 the number was 47%. "The data don't support using systemic thrombolysis to treat major PE; the mortality is high," noted Dr. Goldberg, a cardiothoracic surgeon at Westchester Medical Center in Valhalla, N.Y.

Although catheter-directed therapy began to be much more widely used in U.S. practice starting in about 2015, during the period studied its use for major PE held fairly steady at roughly 2%-3%, but this approach also showed substantial shortcomings for the major PE population. These sicker patients treated with catheter-directed therapy had 37% mortality in 2004 and a 31% mortality in 2015, a difference that was not statistically significant. In general, PE patients enrolled in the catheter-directed therapy trials were not as sick as the major PE patients who get treated with surgery in routine practice, Dr. Goldberg said in an interview.

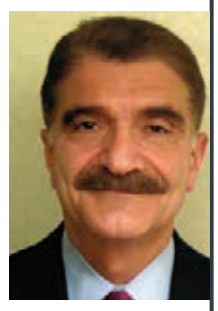
The data showed much better performance using surgery, although only 1,237 patients of the entire group of 713,083 PE patients studied in the database underwent surgical embolectomy. Overall, in-hospital mortality in these patients was 22%, but in a time trend analysis, mortality among all PE patients treated with surgery fell from 32% in 2004 to 14% in 2015; among patients with major PE treated with surgery, mortality fell from 52% in 2004 to 21% in 2015.

Dr. Goldberg attributed the success of surgery in severe PE patients to the definitive nature of embolectomy and the concurrent use of extracorporeal membrane oxygenation that helps stabilize acutely ill PE patients. He also cited refinements that surgery underwent during the 2004-2015 period based on the experience managing chronic thromboembolic pulmonary hypertension, including routine use of cardiopulmonary bypass during surgery. "Very high risk [PE] patients should go straight to surgery, unless the patient is at high risk for surgery because of conditions like prior sternotomy or very advanced age,

Continued on following page

VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments: With an aging population with higher comorbidities, there has been an increase in the incidence of pulmonary embolism (PE) in hospitalized patients and despite the advances in technology, major PE remains a highly lethal disease. Systemic anticoagulation and catheter-directed thrombolysis (CDT) have been advocated for and used by interventionalists (cardiologists, radiologists) for treatment of major PE with varying results from randomized, controlled trials and with survivors having a high chance of developing chronic thromboembolic pulmonary hypertension (CTEPH). Meta-analyses of randomized trials have also shown no major benefit of CDT in stable PE (Blood. 2015;125[14]:2191-9). The argument for the use of thrombolytic therapy as the preferred choice is based on the historical results of surgical intervention for thrombectomy in critically ill and unstable patients. The availability of mechanical circulatory support devices (MCSD) however, has changed the outlook for many patients who are in shock with a failing heart and with a low chance of survival. Already, there are encouraging results with the use of MCSD in the treatment of patients with another highly lethal condition, ie. postinfarction ventricular septal rupture. This should provide impetus for a change in the current practice pattern of considering surgery as the last resort to surgery as the preferred option for emergency surgical embolectomy and cardiac support for the failing heart in patients with major PE and right ventricular dysfunction to accomplish the dual goals of improving their chances of survival and preventing the development of CTEPH.



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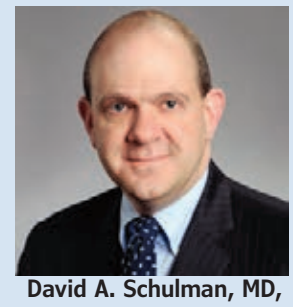

David A. Schulman, MD, FCCP, is Medical Editor in Chief of *CHEST Physician*.

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PAP studied for long-term impact

// *continued from page 1*

ulation-based cohort study. The researchers examined data for 392 participants in the Sleep Heart Health Study, in which adult men and women age 40 years or older were recruited from nine population-based studies between 1995 and 1998 and followed for a mean of 11.1 years. With each participant who had been prescribed PAP, the investigators matched as many as four participants who had not been prescribed PAP, on the basis of age, sex, and apnea-hypopnea index. Of this sample, 81 patients were prescribed PAP, and 311 were not.

All participants had a clinic visit and underwent overnight polysomnography at baseline. At 2-3 years, participants had a follow-up visit or phone call, during which they were asked whether their physicians had prescribed PAP. Participants were monitored for cardiovascular and all-cause mortality.

In all, 319 of the 392 participants were men; the population's mean age was 63 years. Patients who had received a PAP prescription had a higher body mass index and more education, compared with patients who had not received a prescription. Mean follow-up duration was 11.6 years in the PAP-prescribed group and 10.9 years in the nonprescribed group.

A total of 96 deaths occurred during follow-up: 12 in the PAP-prescribed group and 84 in the nonprescribed group. The crude incidence rate of mortality was 24.7 deaths per 1,000 person-years in the nonprescribed group and 12.8 deaths per 1,000 person-years in the PAP-prescribed group. The difference in survival between the prescribed and nonprescribed groups was evident in survival curves after 6-7 years of follow-up. After adjustments for prevalent cardiovascular disease, hypertension, diabetes, body mass index, education level, smoking status, and alcohol consumption, the hazard ratio of all-cause mortality for the prescribed group was 0.38, compared with the nonprescribed group.

Dr. Lisan and his colleagues identified 27 deaths of cardiovascular origin, one of which occurred in the prescribed group. After adjustment for prevalent cardiovascular disease, the hazard ratio of cardiovascular mortality for the prescribed group was 0.06, compared with the nonprescribed group.

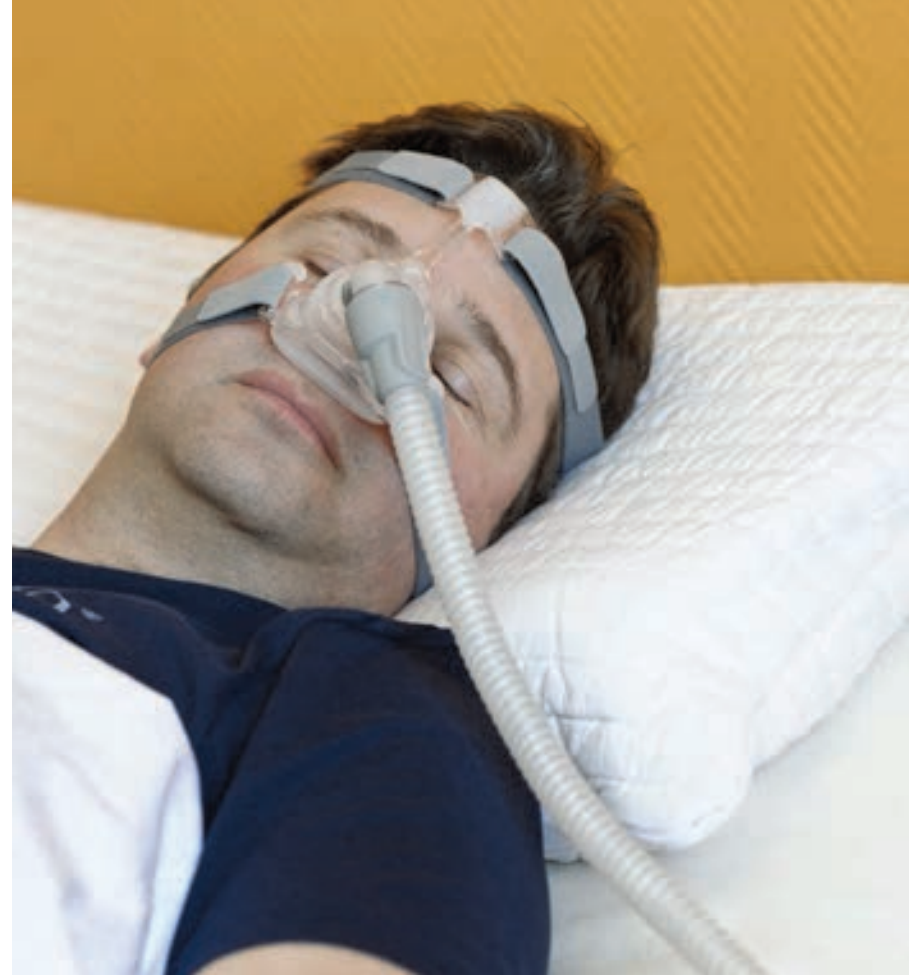
One reason that the reduction in mortality associated with PAP was not found in previous randomized, controlled trials could be that their mean length of follow-up was not long enough, the researchers wrote. For example, the mean length of follow-up in the SAVE trial was 3.7 years, but the survival benefit was not apparent in the present analysis until 6-7 years after treatment initiation.

These results are exploratory and require confirmation in future research, Dr. Lisan and his colleagues wrote. No information on adherence to PAP was available, and the researchers could not account for initiation and interruption of PAP therapy. Nevertheless, "prescribing PAP in patients with OSA should be pursued and encouraged, given its potential major public health implication," they concluded.

The Sleep Heart Health Study was supported by grants from the National Institutes of Health.

egreb@mdedge.com

SOURCE: Lisan Q et al. *JAMA Otolaryngol Head Neck Surg*. 2019 Apr 11. doi: 10.1001/jamaoto.2019.0281.



GRAUSTUFE/THINKSTOCK

VIEW ON THE NEWS

Findings may help clinicians persuade patients to use PAP

Further confirmation of the benefits of positive airway pressure (PAP) on mortality in patients with obstructive sleep apnea (OSA) may follow the results published by Lisan et al., wrote Clete A. Kushida, MD, PhD, in an accompanying editorial. Dr. Kushida is a professor of psychiatry and behavioral sciences at Stanford (Calif.) University. "Of the study limitations described by Lisan et al., a major factor is the participants' use of PAP therapy: The participants self-reported if they were prescribed PAP therapy, but their PAP adherence data (i.e., duration and frequency of PAP use) were unknown. Discrepancies exist between self-reported versus objective PAP adherence, as well as between patterns of PAP adherence over time, and the lack of adherence data would be expected to limit our understanding of the effects of PAP therapy on mortality." A further limitation is that the study's findings are restricted to patients with obesity and severe OSA.

"Even taking into consideration the technological improvement in size, comfort, and convenience of these devices since PAP was first tried on patients with OSA, every knowledgeable sleep specialist has had difficulty in convincing some patients of the need to treat their OSA with these devices, and/or the need to improve their use of the devices once they have been prescribed," Dr. Kushida continued. "Although at this point experienced sleep specialists cannot say with certainty that use of PAP improves survival, the study by Lisan et al. will undoubtedly make these clinicians' jobs a little easier by enabling them to present to their patients evidence that PAP may be associated with reduced mortality, particularly in those with severe OSA and comorbid obesity."

Dr. Kushida receives salary support from a contract between Stanford University and Philips-Respironics for the conduct of a clinical trial. These comments are from an accompanying editorial (JAMA Otolaryngol Head Neck Surg. 2019 Apr 11. doi: 10.1001/jamaoto.2019.0345).

Continued from previous page

in which case catheter-directed therapy may be a safer option, he said. He cited a recent 5% death rate after surgery at his center among patients with major PE who did not require cardiopulmonary resuscitation.

The database Dr. Goldberg and his collaborator reviewed included 12,735 patients treated by systemic thrombolysis, and 2,595 treated by catheter-directed therapy. Patients averaged 63 years old. The most common indicator of major PE was mechanical ventilation, used on 8% of all PE patients in the study. Non-septic shock occurred in 2%, and just under 1% needed vasopressor treatment.

Published guidelines on PE management from several medical groups are "vague and have numerous caveats," Dr. Goldberg said. He is participating in an update to the 2011 PE management statement from the American College of Cardiology and American Heart Association (Circulation. 2011 Apr 26;123[16]:1788-830).

The study received no commercial funding. Dr. Goldberg had no disclosures.

mzoler@mdedge.com

SOURCE: **Haider A** et al. J Amer Coll Cardiol. 2019 Mar;73:9(suppl 1). doi: 10.1016/S0735-1097(19)32507-0.

Candida auris: Dangerous and here to stay

BY KARI OAKES
MDedge News

Critical care units and long-term care facilities are on alert for cases of *Candida auris*, a novel fungal infection that is both dangerous to vulnerable patients and difficult to eradicate. The increased profile of *C. auris* is not a welcome development but is no surprise to critical care physicians.

This pathogen was first identified 10 years ago and has since been found in increasing numbers of patients all over the world. As expected, cases of *C. auris* are on the rise in the United States.

The Centers for Disease Control and Prevention stated, "*Candida auris* is an emerging fungus that presents a serious global health threat." This is an opportunistic pathogen that hits critically ill patients and those with compromised immunity.

On March 29, CDC reported that confirmed clinical cases of *C. auris* in the United States have more than doubled over the past year, from 257 cases in 2018 to 587 cases with an additional 1,056 colonized patients identified as of February 2019. "Most *C. auris* cases in the United States have been detected in the New York City area, New Jersey, and the Chicago area. Strains of *C. auris* in the United States have been linked to other parts of the world. U.S. *C. auris* cases are a result of inadvertent introduction into the United States from a patient who recently received health care in a country where *C. auris* has been reported or a result of local spread after such an introduction."

Case reports have found a mortality rate of up to 50% in patients with *C. auris* candidemia. The total number of cases is still small, but the trajectory is clear. The hunt is on in labs all over the world for optimal treatments and processes to handle outbreaks.

Expert looks at *C. auris* characteristics

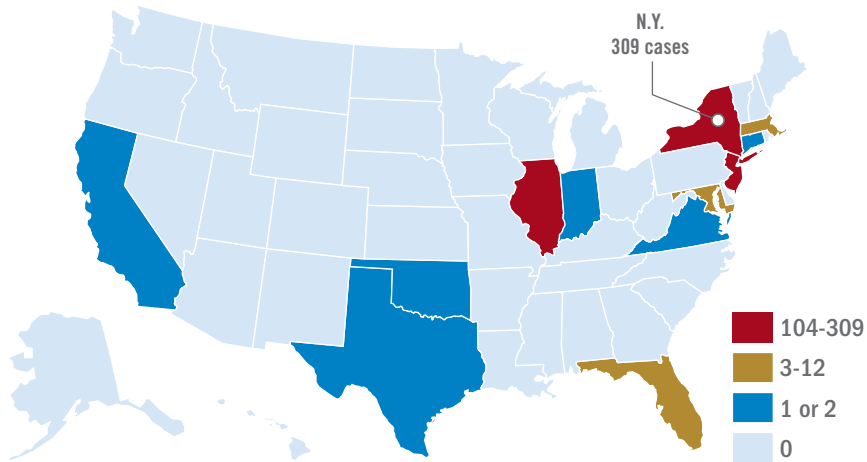
Jeniel Nett, MD, an infectious disease specialist, and a team of investigators at the University of Wisconsin, Madison, have focused their research on the characteristics of *C. auris* and its progression in patients and in medical facilities.

According to Dr. Nett, it's not clear why this emerging threat has cropped up in multiple locations globally. "*Candida auris* was first recognized in 2009, in Japan, and relatively quickly we saw emergence of this species in relatively distant locations," she said, adding that independent clades in these locations ruled out transmission as the source of the multiple outbreaks. Antifungal resistance is an epidemiologic area of concern and increased antifungal use may be a contributor, she said.

Once established, the organism is persistent: "It is found on mattresses, on bedsheets, IV poles, and a lot of reusable equipment," said Dr. Nett in an interview. "It appears to persist in the environment for weeks – maybe longer." In addition, "it seems to behave differently than a lot of the *Candida* species that we see; it readily colonizes the skin" to a much greater extent than does other *Candida* species, she said. "This allows it to be transmitted readily person to person, particularly in the hospitalized setting." However, it can also colonize both the urinary and respiratory tracts, she said.

"Many of these patients have undergone multiple procedures; they may have undergone mechanical ventilation as well as different surgical procedures," said Dr. Nett. Affected patients often have received many rounds of antibiotic and antifungal treatment as well, she said, and may have an underlying illness like diabetes or malignancy.

Confirmed clinical cases of *Candida auris* as of Feb. 28, 2019



MDedge News

Along with these 587 cases, *C. auris* colonization has been found in 1,056 other patients through targeted screening in seven states with clinical cases.

Outbreak progression studied

A prospective cohort study of a large outbreak of *C. auris* was conducted by Alba Ruiz-Gaitán, MD, and her colleagues at La Fe University and Polytechnic Hospital, Valencia, Spain (Expert Rev Anti Infect Ther. 2019 Apr;17[4]:295-305). The researchers followed 114 patients who were colonized with *C. auris* or had *C. auris* candidemia. The patients were compared with 114 case-matched controls within the hospital's adult surgical and medical intensive care units over an 11-month period during the hospital's protracted outbreak.

The investigators found a crude mortality rate of 58.5% at 30 days for patients with *C. auris* candidemia. All isolates in the study were completely resistant to fluconazole and had reduced susceptibility to voriconazole.

In critical care units at Hospital La Fe, investigators found *C. auris* on 25% of blood pressure cuffs, 10% of patient tables and keyboards, and 8% of infusion pumps.

Among the patients at Hospital La Fe, multivariable analysis revealed that those most likely to develop *C. auris* colonization or candidemia were individuals with polytrauma, cardiovascular disease, and cancer.

Patients receiving parenteral nutrition (odds ratio, 3.49) or mechanical ventilation (OR, 2.43), and especially those having indwelling central venous catheters (OR, 13.48) were more likely to be colonized or have candidemia as well, according to Dr. Ruiz-Gaitán and her coauthors.

Once identified, how should *C. auris* be treated? "The majority of strains – upward of 90% – are resistant to fluconazole," said Dr. Nett. "Moreover, 30%-50% of them are resistant to another antifungal, often amphotericin B. The isolates that we see in the United States are most often susceptible to an echinocandin, and echinocandins remain the choice for treatment of *Candida auris* pending susceptibility tests."

However, in Valencia, "The susceptibility to echinocandins presented interesting features. These antifungals were not fungicidal against *C. auris*," wrote Dr. Ruiz-Gaitán and her colleagues. They found that for caspofungin "most isolates presented a clear paradoxical growth after 24 hours of incubation." Additionally, fungal growth was inhibited at lower caspofungin concentrations, but rebounded at higher levels. Similar patterns were seen for anidulafungin and micafungin, they said.

Most large clinical laboratories, she said, can now detect *C. auris*. Matrix-assisted laser desorption/ionization–time of flight is the identification technique of choice, provided that the databases are updated.

Smaller laboratories that use phenotypic tests may misidentify *C. auris* as another *Candida* species, or even as *Saccharomyces cerevisiae* – common beer yeast. Facilities without matrix-assisted laser desorption/ionization can find guidance for interpretation of phenotypic testing on the CDC website as well, said Dr. Nett.

After experiencing what they believe to be the largest *C. auris* outbreak at a single European hospital, Dr. Ruiz-Gaitán and her colleagues offered best-practice tips for treatment of patients with *C. auris* candidemia. These include removing mechanical devices as early as is safely practical; performing ophthalmologic examinations for endophthalmitis, a known *C. auris* complication; obtaining blood cultures every other day to track antimicrobial therapy to the point of sterilization; and searching for metastatic foci if blood cultures remain positive.

Cases should be reported to CDC

All instances of *C. auris* laboratory identification should be reported to the CDC at candidaauris@cdc.gov, and to local and state health agencies. The CDC recommends strict isolation and cleaning protocols, similar to those used for the spore-forming *Clostridium difficile*.

Dr. Nett reported funding support from the National Institutes of Health, the Burroughs Wellcome Fund, and the Doris Duke Charitable Foundation. She reported no conflicts of interest. Dr. Ruiz-Gaitán and her collaborators reported funding from Instituto de Salud Carlos III, Spain, and the Spanish Ministry of Science and University. They reported no conflicts of interest.

koakes@mdedge.com

European NAVIGATE data support safety of electromagnetic navigation bronchoscopy

BY WILL PASS
MDedge News

Dr. Anne-Marie Dingemans

Dr. Kelvin Lau

PHOTOS WILL PASS/MDEDGE NEWS

GENEVA – For lung lesion biopsy, electromagnetic navigation bronchoscopy (ENB) offers high navigational success with a relatively low rate of pneumothorax, according to European data from the international NAVIGATE study.

In addition to lung lesion biopsy, ENB can facilitate concurrent lymph node sampling and fiducial placement during a single anesthetic event, reported lead author Kelvin Lau, MD, chief of thoracic surgery at Barts Thorax Centre in London, and his colleagues. According to Dr. Lau, who presented at the European Lung Cancer Conference, the findings from this European cohort add weight to previously published data from the NAVIGATE trial, which aims to demonstrate real-world use of ENB.

"The outcomes show that [ENB] is very safe in terms of pneumothorax rate, despite the fact that many of these patients were challenging and actually were turned down by the percutaneous radiologist before they came to us," Dr. Lau said at the meeting, presented by the European Society for Medical Oncology.

Out of 1,200 patients enrolled in the NAVIGATE trial in the United States and Europe, the present 1-month interim analysis showed experiences with 175 patients treated at eight European centers. Anyone undergoing navigational bronchoscopy was eligible. The primary outcome was pneumothorax rate and the secondary outcome was diagnostic yield.

Data analysis showed that lesions were most frequently in the upper lobe (62.6%) and in the peripheral third of the lung (72.7%), the latter of which is beyond the reach of a conventional bronchoscope. In two out of three patients (66.8%), a bronchus sign was present, which "means that the bronchoscope runs straight into the lesion, and theoretically means it's easier to access," Dr. Lau said. Almost all patients had ENB for lung biopsy (99.4%), while in a small minority (8.0%), ENB was used for fiducial marking. The median total procedure time was 43.5 minutes, of which 32.9 minutes were spent navigating and sampling with ENB.

The ENB-related pneumothorax rate was 7.4%, although a slightly lower percentage, 5.1%, required intervention or hospitalization. According to the ENB-related Common Terminology Criteria for Adverse Events, 2.3% of patients had grade 2 or higher bronchopulmonary hemorrhage and 0.6% of patients had grade 4 or higher respiratory failure. Although the secondary endpoint, diagnostic yield, was not met because of inadequate follow-up time, the navigational success rate, defined as access to the intended lung lesion, was 96.6%, which offers some sense of efficacy.

"The purpose of this study is to show that [ENB] is very safe," Dr. Lau said in an interview. "And the numbers are significantly better than historic CT-guided biopsy data."

Considering the choice between ENB and CT-guided biopsy, invited discussant Anne-Marie Dingemans, MD, of Maastricht (the Netherlands) University offered a different viewpoint.

"CT-guided biopsies are low cost ... and the sensitivity is very, very high," Dr. Dingemans said. "In good hands, with a good radiologist, you have a high chance that you will have a good diagnosis of the nodules." She also noted that a bronchus sign does not impact efficacy.

"I'm very into CT-guided biopsies," Dr. Dingemans continued, noting that the radiologist at her treatment center takes biopsies with a 10-gauge large-core needle. With this technique, Dr. Dingemans reported a 5.7% pneumothorax rate, which is comparable with the present NAVIGATE data.

However, Dr. Lau contested this figure.

"The pneumothorax rates [for CT-guided biopsy] in larger studies have always been about 20%-40%," Dr. Lau said. "You can't compare large overall practice in a pragmatic study capturing everyone versus one single center. The truth is, most centers will have a 20% pneumothorax rate."

Dr. Lau added that patient experiences are likely to be better with ENB than with CT-guided percutaneous biopsy.

"To me, patient comfort for biopsy is essential," Dr. Lau said. "Having a needle stuck into your chest – it's very uncomfortable. I've had patients who've come to me after they had a percutaneous biopsy and who for some reason needed a re-biopsy. ... Those patients almost always wish they had navigational bronchoscopy the first time because there would be no pain for them."

When asked about capital cost concerns surrounding ENB, Dr. Lau suggested that the benefits outweigh the costs.

"The most expensive procedure is the one you have to do again," Dr. Lau said. "So what we do is put a brush in, and a needle, and a biopsy, and hopefully, one of those three, if not all three, gets tissue, and we can do that with navigational bronchoscopy because there is one channel down. You can't repeatedly stick needles into patients. By definition, you can't throw three needle jabs, because you will get a 90% pneumothorax rate. And that's the beauty of navigational bronchoscopy as well, because in the NAVIGATE series, a number of patients, about 10%, had multiple lesions biopsied." Furthermore, Dr. Lau noted, percutaneous biopsy is "almost never" performed bilaterally, for fear of collapsing both lungs, but this is not the case with ENB. "We've done it on patients who have one lung," he said.

Dr. Lau predicted that costs of ENB will come down with time. "Because of the number of products increasing, the price will drop," he said.

Concluding the interview, Dr. Lau offered a summarizing message: "If you want to give the patient the safe option, you should do [ENB], and when it becomes more popular, the price will fall," he said.

Medtronic funded the study. The investigators reported financial relationships with Olympus, Ambu, PulmonX, Boston Scientific, and others.

chestphysicannews@chestnet.org

SOURCE: Lau et al. ELCC 2019, Abstract 680.

VIEW ON THE NEWS

Jacques Pierre Fontaine, MD, FCCP, comments: This study is an interim analysis of 175 patients out of the 1,200 patients enrolled in the NAVIGATE study. It reveals only that the complication rate of the procedure is very low. However, the results about the diagnostic yield of this procedure are not yet available. ENB is a safe procedure and certainly has an important role to play in the diagnostic workup of lung nodules but will not completely replace the need for CT-guided biopsies in certain patients.

FASENRA is indicated as an add-on maintenance treatment of patients 12 years and older with severe eosinophilic asthma.

POWER TO PREVENT EXACERBATIONS[1-3]

ACCORDING TO AN ANALYSIS OF NHANES DATA, 69% OF ADULT PATIENTS WITH ASTHMA HAD EOSINOPHILIC ASTHMA*[4]

GET STARTED AT FASENRAFACTS.COM

FASENRA is proven to reduce annual exacerbation rate in patients with severe eosinophilic asthma.[1-3]

NHANES=National Health and Nutrition Examination Survey.

*Data from the 2005 to 2006 annual survey of a nationally representative sample of a noninstitutionalized United States population in patients with asthma (aged 18-64 years) identified based on the participants' self-report. Eosinophilic asthma was defined as a blood eosinophil cutoff point of ≥150 cells/µL. Of the 310 adult patients, 69% had a blood eosinophil level ≥150 cells/µL.[4]

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

Known hypersensitivity to benralizumab or excipients.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

Hypersensitivity reactions (eg, anaphylaxis, angioedema, urticaria, rash) have occurred after administration of FASENRA. These reactions generally occur within hours of administration, but in some instances have a delayed onset (ie, days). Discontinue in the event of a hypersensitivity reaction.

Acute Asthma Symptoms or Deteriorating Disease

FASENRA should not be used to treat acute asthma symptoms, acute exacerbations, or acute bronchospasm.

Reduction of Corticosteroid Dosage

Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with FASENRA. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

FASENRA is not indicated for treatment of other eosinophilic conditions or for the relief of acute bronchospasm or status asthmaticus.

CHARACTERISTICS OF PATIENTS WITH ALLERGIC OR NONALLERGIC EOSINOPHILIC ASTHMA[5,6]:

Elevated level of blood eosinophils

AND/OR

Frequent exacerbations (≥2 exacerbations annually)

ICS at high doses are insufficient to control the disease

CHOOSE FASENRA FOR PATIENTS WITH SEVERE EOSINOPHILIC ASTHMA

IMPORTANT SAFETY INFORMATION (cont'd)

Parasitic (Helminth) Infection
It is unknown if FASENRA will influence a patient's response against helminth infections. Treat patients with pre-existing helminth infections before initiating therapy with FASENRA. If patients become infected while receiving FASENRA and do not respond to anti-helminth treatment, discontinue FASENRA until infection resolves.

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥ 5%) include headache and pharyngitis.

Injection site reactions (eg, pain, erythema, pruritus, papule) occurred at a rate of 2.2% in patients treated with FASENRA compared with 1.9% in patients treated with placebo.

Please see additional Important Safety Information on next page and accompanying Brief Summary of full Prescribing Information.

Fasenra® (benralizumab) Subcutaneous Injection 30 mg

FROM THE START

FASENRA IS THE #1 RESPIRATORY BIOLOGIC

SELECTED BY PHYSICIANS FOR NEW PATIENTS IN SEVERE EOSINOPHILIC ASTHMA*[7]

*Data are not intended to suggest comparison of safety or efficacy to any other IL-5 or IL-5Rα treatment.[7]

STUDY DESIGNS

TRIALS 1 AND 2

Trial 1 (48-week) and Trial 2 (56-week) were 2 randomized, double-blind, parallel-group, placebo-controlled, multicenter studies comparing **FASENRA** 30 mg SC Q4W for the first 3 doses, then Q8W thereafter; benralizumab 30 mg SC Q4W, and placebo SC. A total of 1204 (Trial 1) and 1306 (Trial 2) patients aged 12-75 years old with severe asthma uncontrolled on high-dose ICS (Trial 1) and medium- to high-dose ICS (Trial 2) plus LABA with or without additional controllers were included. Patients had a history of ≥2 exacerbations requiring systemic corticosteroids or temporary increase in usual dosing in the previous year. Patients were stratified by geography, age, and blood eosinophil counts (≥300 cells/μL and <300 cells/μL). The primary endpoint was annual exacerbation rate ratio vs placebo in patients with blood eosinophil counts of ≥300 cells/μL on high-dose ICS and LABA. Exacerbations were defined as a worsening of asthma that led to use of systemic corticosteroids for ≥3 days, temporary increase in a stable OCS background dose for ≥3 days, emergency/urgent care visit because of asthma that needed systemic corticosteroids, or inpatient hospital stay of ≥24 hours because of asthma. Key secondary endpoints were pre-bronchodilator FEV_1 and total asthma symptom score at Week 48 (Trial 1) and Week 56 (Trial 2) in the same population.[2,3]

References: 1. FASENRA® (benralizumab) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; November 2017. **2.** Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet*. 2016;388:2115-2127. **3.** FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2016;388:2128-2141. **4.** Tran TN, Zeiger RS, Peters SP, et al. Overlap of atopic, eosinophilic, and TH2-high asthma phenotypes in a general population with current asthma. *Ann Allergy Asthma Immunol*. 2016;116(1):37-42. **5.** de Groot JC, ten Brinke A, Bel EH. Management of the patient with eosinophilic asthma: a new era begins. *ERJ Open Res*. 2015;1:1-11. **6.** de Groot JC, Storm H, Amelink M, et al. Clinical profile of patients with adult-onset eosinophilic asthma. *ERJ Open Res*. 2016;2(2):1-8. **7.** Data on File, US-22015, AZPLP.

IMPORTANT SAFETY INFORMATION (cont'd)

USE IN SPECIFIC POPULATIONS

The data on pregnancy exposure from the clinical trials are insufficient to inform on drug-associated risk. Monoclonal antibodies such as benralizumab are transported across the placenta during the third trimester of pregnancy; therefore, potential effects on a fetus are likely to be greater during the third trimester of pregnancy.

INDICATION

FASENRA is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype.

- FASENRA is not indicated for treatment of other eosinophilic conditions
- FASENRA is not indicated for the relief of acute bronchospasm or status asthmaticus

PLEASE SEE ADJACENT BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION.

You are encouraged to report negative side effects of prescription drugs to the FDA.
*Visit **www.FDA.gov/medwatch** or call 1-800-FDA-1088.*

Fasenra® (benralizumab) Subcutaneous Injection 30 mg

FROM THE START

FASENRA™ (benralizumab) injection, for subcutaneous use

Initial U.S. Approval: 2017

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

FASENRA is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype *[see Clinical Studies (14) in the full Prescribing Information]*.

Limitations of use:

- FASENRA is not indicated for treatment of other eosinophilic conditions.
- FASENRA is not indicated for the relief of acute bronchospasm or status asthmaticus.

DOSAGE AND ADMINISTRATION

Recommended Dose

FASENRA is for subcutaneous use only.

The recommended dose of FASENRA is 30 mg administered once every 4 weeks for the first 3 doses, and then once every 8 weeks thereafter by subcutaneous injection into the upper arm, thigh, or abdomen.

Preparation and Administration

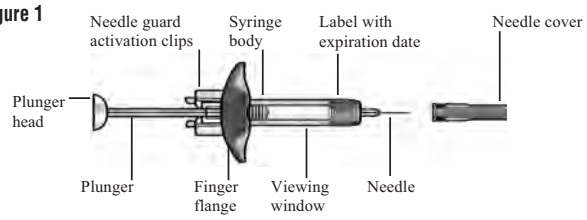
FASENRA should be administered by a healthcare professional. In line with clinical practice, monitoring of patients after administration of biologic agents is recommended *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

Prior to administration, warm FASENRA by leaving carton at room temperature for about 30 minutes. Administer FASENRA within 24 hours or discard into sharps container.

Instructions for Prefilled Syringe with Needle Safety Guard

Refer to **Figure 1** to identify the prefilled syringe components for use in the administration steps.

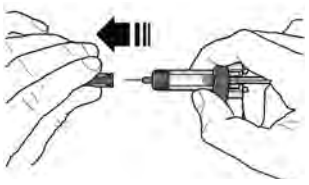
Figure 1



Do not touch the needle guard activation clips to prevent premature activation of the needle safety guard.

1 **Grasp the syringe body,** not the plunger, to remove prefilled syringe from the tray. Check the expiration date on the syringe. Visually inspect FASENRA for particulate matter and discoloration prior to administration. FASENRA is clear to opalescent, colorless to slightly yellow, and may contain a few translucent or white to off-white particles. Do not use FASENRA if the liquid is cloudy, discolored, or if it contains large particles or foreign particulate matter. The syringe may contain a small air bubble; this is normal. **Do not** expel the air bubble prior to administration.

2



Do not remove needle cover until ready to inject. Hold the syringe body and remove the needle cover by pulling straight off. Do not hold the plunger or plunger head while removing the needle cover or the plunger may move. If the prefilled syringe is damaged or contaminated (for example, dropped without needle cover in place), discard and use a new prefilled syringe.

3

Gently pinch the skin and insert the needle at the recommended injection site (i.e., upper arm, thigh, or abdomen).

4

Inject all of the medication by pushing in the plunger all the way until the plunger head is **completely between** the needle guard activation clips. **This is necessary to activate the needle guard.**

5

After injection, maintain pressure on the plunger head and remove the needle from the skin. Release pressure on the plunger head to allow the needle guard to cover the needle. **Do not re-cap the prefilled syringe.**

6 Discard the used syringe into a sharps container.

CONTRAINDICATIONS

FASENRA is contraindicated in patients who have known hypersensitivity to benralizumab or any of its excipients *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

Hypersensitivity reactions (e.g., anaphylaxis, angioedema, urticaria, rash) have occurred following administration of FASENRA. These reactions generally occur within hours of administration, but in some instances have a delayed onset (i.e., days). In the event of a hypersensitivity reaction, FASENRA should be discontinued *[see Contraindications (4) in the full Prescribing Information]*.

Acute Asthma Symptoms or Deteriorating Disease

FASENRA should not be used to treat acute asthma symptoms or acute exacerbations. Do not use FASENRA to treat acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with FASENRA.

Reduction of Corticosteroid Dosage

Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with FASENRA. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Parasitic (Helminth) Infection

Eosinophils may be involved in the immunological response to some helminth infections. Patients with known helminth infections were excluded from participation in clinical trials. It is unknown if FASENRA will influence a patient's response against helminth infections.

Treat patients with pre-existing helminth infections before initiating therapy with FASENRA. If patients become infected while receiving treatment with FASENRA and do not respond to anti-helminth treatment, discontinue treatment with FASENRA until infection resolves.

ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:

- Hypersensitivity Reactions *[see Warnings and Precautions (5.1) in the full Prescribing Information]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Across Trials 1, 2, and 3, 1,808 patients received at least 1 dose of FASENRA *[see Clinical Studies (14) in the full Prescribing Information]*. The data described below reflect exposure to FASENRA in 1,663 patients, including 1,556 exposed for at least 24 weeks and 1,387 exposed for at least 48 weeks. The safety exposure for FASENRA is derived from two phase 3 placebo-controlled studies (Trials 1 and 2) from 48 weeks duration [FASENRA every 4 weeks (n = 841), FASENRA every 4 weeks for 3 doses, then every 8 weeks (n = 822), and placebo (n = 847)]. While a dosing regimen of FASENRA every 4 weeks was included in clinical trials, FASENRA administered every 4 weeks for 3 doses, then every 8 weeks thereafter is the recommended dose *[see Dosage and Administration (2.1) in the full Prescribing Information]*. The population studied was 12 to 75 years of age, of which 64% were female and 79% were white.

Adverse reactions that occurred at greater than or equal to 3% incidence are shown in **Table 1**.

Table 1. Adverse Reactions with FASENRA with Greater than or Equal to 3% Incidence in Patients with Asthma (Trials 1 and 2)

Adverse Reactions	FASENRA (N= 822) %	Placebo (N=847) %
Headache	8	6
Pyrexia	3	2
Pharyngitis*	5	3
Hypersensitivity reactions**	3	3

* Pharyngitis was defined by the following terms: 'Pharyngitis', 'Pharyngitis bacterial', 'Viral pharyngitis', 'Pharyngitis streptococcal'.

** Hypersensitivity Reactions were defined by the following terms: 'Urticaria', 'Urticaria papular', and 'Rash' *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

28-Week Trial

Adverse reactions from Trial 3 with 28 weeks of treatment with FASENRA (n = 73) or placebo (n = 75) in which the incidence was more common in FASENRA than placebo include headache (8.2% compared to 5.3%, respectively) and pyrexia (2.7% compared to 1.3%, respectively) *[see Clinical Studies (14) in the full Prescribing Information]*. The frequencies for the remaining adverse reactions with FASENRA were similar to placebo.

Injection site reactions

In Trials 1 and 2, injection site reactions (e.g., pain, erythema, pruritus, papule) occurred at a rate of 2.2% in patients treated with FASENRA compared with 1.9% in patients treated with placebo.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to benralizumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Overall, treatment-emergent anti-drug antibody response developed in 13% of patients treated with FASENRA at the recommended dosing regimen during the 48 to 56 week treatment period. A total of 12% of patients treated with FASENRA developed neutralizing antibodies. Anti-benralizumab antibodies were associated with increased clearance of benralizumab and increased blood eosinophil levels in patients with high anti-drug antibody titers compared to antibody negative patients. No evidence of an association of anti-drug antibodies with efficacy or safety was observed.

The data reflect the percentage of patients whose test results were positive for antibodies to benralizumab in specific assays.

DRUG INTERACTIONS

No formal drug interaction studies have been conducted.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

The data on pregnancy exposure from the clinical trials are insufficient to inform on drug-associated risk. Monoclonal antibodies such as benralizumab are transported across the placenta during the third trimester of pregnancy; therefore, potential effects on a fetus are likely to be greater during the third trimester of pregnancy. In a prenatal and postnatal development study conducted in cynomolgus monkeys, there was no evidence of fetal harm with IV administration of benralizumab throughout pregnancy at doses that produced exposures up to approximately 310 times the exposure at the maximum recommended human dose (MRHD) of 30 mg SC [see Data].

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk:

In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

Data

Animal Data

In a prenatal and postnatal development study, pregnant cynomolgus monkeys received benralizumab from beginning on GD20 to GD22 (dependent on pregnancy determination), on GD35, once every 14 days thereafter throughout the gestation period and 1-month postpartum (maximum 14 doses) at doses that produced exposures up to approximately 310 times that achieved with the MRHD (on an AUC basis with maternal IV doses up to 30 mg/kg once every 2 weeks). Benralizumab did not elicit adverse effects on fetal or neonatal growth (including immune function) up to 6.5 months after birth. There was no evidence of treatment-related external, visceral, or skeletal malformations. Benralizumab was not teratogenic in cynomolgus monkeys. Benralizumab crossed the placenta in cynomolgus monkeys. Benralizumab concentrations were approximately equal in mothers and infants on postpartum day 7, but were lower in infants at later time points. Eosinophil counts were suppressed in infant monkeys with gradual recovery by 6 months postpartum; however, recovery of eosinophil counts was not observed for one infant monkey during this period.

Lactation

Risk Summary

There is no information regarding the presence of benralizumab in human or animal milk, and the effects of benralizumab on the breast fed infant and on milk production are not known. However, benralizumab is a humanized monoclonal antibody (IgG1/κ-class), and immunoglobulin G (IgG) is present in human milk in small amounts. If benralizumab is transferred into human milk, the effects of local exposure in the gastrointestinal tract and potential limited systemic exposure in the infant to benralizumab are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for benralizumab and any potential adverse effects on the breast-fed child from benralizumab or from the underlying maternal condition.

Pediatric Use

There were 108 adolescents aged 12 to 17 with asthma enrolled in the Phase 3 exacerbation trials (Trial 1: n=53, Trial 2: n=55). Of these, 46 received placebo, 40 received FASENRA every 4 weeks for 3 doses, followed by every 8 weeks thereafter, and 22 received FASENRA every 4 weeks. Patients were required to have a history of 2 or more asthma exacerbations requiring oral or systemic corticosteroid treatment in the past 12 months and reduced lung function at baseline (pre-bronchodilator FEV_1<90%) despite regular treatment with medium or high dose ICS and LABA with or without OCS or other controller therapy. The pharmacokinetics of benralizumab in adolescents 12 to 17 years of age were consistent with adults based on population pharmacokinetic analysis and the reduction in blood eosinophil counts was similar to that observed in adults following the same FASENRA treatment. The adverse event profile in adolescents was generally similar to the overall population in the Phase 3 studies *[see Adverse Reactions (6.1) in the full Prescribing Information]*. The safety and efficacy in patients younger than 12 years of age has not been established.

Geriatric Use

Of the total number of patients in clinical trials of benralizumab, 13% (n= 320) were 65 and over, while 0.4% (n=9) were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

OVERDOSAGE

Doses up to 200 mg were administered subcutaneously in clinical trials to patients with eosinophilic disease without evidence of dose-related toxicities.

There is no specific treatment for an overdose with benralizumab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions (e.g., anaphylaxis, angioedema, urticaria, rash) have occurred after administration of FASENRA. These reactions generally occurred within hours of FASENRA administration, but in some instances had a delayed onset (i.e., days). Instruct patients to contact their healthcare professional if they experience symptoms of an allergic reaction *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

Not for Acute Symptoms or Deteriorating Disease

Inform patients that FASENRA does not treat acute asthma symptoms or acute exacerbations. Inform patients to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with FASENRA *[see Warnings and Precautions (5.2) in the full Prescribing Information]*.

Reduction of Corticosteroid Dosage

Inform patients to not discontinue systemic or inhaled corticosteroids except under the direct supervision of a physician. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy *[see Warnings and Precautions (5.3) in the full Prescribing Information]*.

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Diagnostic test helps clinicians distinguish IPF from interstitial pneumonia

BY JEFF CRAVEN
MDedge News

Researchers used a machine learning algorithm to identify a molecular signature for usual interstitial pneumonia in patients with suspected idiopathic pulmonary fibrosis, according to recent research published in the Lancet Respiratory Medicine.

The results of the molecular test, called the Envisia Genomic Classifier (Veracyte; San Francisco), had a high positive predictive value of proven usual interstitial pneumonia, and could be used in place of surgical lung biopsy to confirm a diagnosis of idiopathic pulmonary fibrosis (IPF), wrote Ganesh Raghu, MD, director at the Center for Interstitial Lung Diseases and professor of medicine at the University of Washington, Seattle, and his colleagues. The Envisia Genomic Classifier recently received final Medicare local coverage determination for IPF diagnosis, according to a recent press release by Veracyte.


Dr. Raghu

"IPF is often challenging to distinguish from other [interstitial lung disease], but timely and accurate diagnosis is critical so that patients with IPF can access therapies that may slow progression of the disease, while avoiding potentially harmful treatments," Dr. Raghu stated in a press release. "Our results with molecular classification through machine learning [the Envisia classifier] are promising and, along with clinical information and radiological features in high-resolution CT imaging, physicians through multidisciplinary discussions, may be able to utilize the molecular classification as a diagnostic tool to make a more informed and confident diagnoses."

The researchers prospectively recruited 237 patients from 29 centers in the United States and Europe who were evaluated with the Bronchial Sample Collection for a Novel Genomic Test for suspected interstitial lung disease and who underwent surgical biopsy, transbronchial biopsy, or cryobiopsy for sample collection. They used histopathology and RNA sequence data from 90 patients to create a training data set of an unusual interstitial pneumonia pattern for the machine learning algorithm.

The classifier found usual interstitial pneumonia diagnoses in 49 patients; the test had a specificity of 88% (95% confidence interval, 70%-98%) and a sensitivity of 70% (95% CI, 47%-87%). Of 42 patients with inconsistent or possible usual interstitial pneumonia identified from high-resolution CT imaging, there was a positive predictive value of 81% (95% CI, 54%-96%). When multidisciplinary teams made diagnoses with the molecular classifier data, there was a clinical agreement of 86% (95% CI, 78%-92%) with diagnoses made using histopathology data. In 18 cases of IPF, there was an improvement in diagnostic confidence using the molecular classifier data, with 89% of diagnoses designated as high confidence, compared with 56% of cases based on histopathologic data (P = .0339). In 48 patients with nondiagnostic pathology or nonclassifiable fibrosis histopathology, 63% of diagnoses with the molecular classifier data were high confidence, compared with 42% using histopathologic data (P = .0412).

This study was funded by Veracyte, creator of the Envisia Genomic Classifier. Some authors reported relationships with Veracyte and other companies.

chestphysiciannews@chestnet.org

SOURCE: Raghu G et al. Lancet Respir Med. 2019 Apr 1. doi: 10.1016/S2213-8587(19)300.

VIEW ON THE NEWS

Molecular classification could help identify less clear-cut IPF

Use of a molecular classifier could be most helpful in situations where patients have atypical radiology results or in cases where multidisciplinary teams disagree on the diagnosis, Simon Hart, PhD, wrote in a related editorial.

According to the 2018 international guidelines for idiopathic pulmonary fibrosis, usual interstitial pneumonia certainty is defined as honeycombing seen on high-resolution CT (HRCT), probable if there is presence of traction bronchiectasis but not honeycombing, and indeterminate if there is no presence of usual interstitial pneumonia or another diagnosis. As radiologists "often disagree on HRCT patterns," IPF sometimes becomes a working diagnosis based on progression of disease, Dr. Hart wrote. In these cases, molecular classifier samples could help identify IPF in patients who have undergone less invasive transbronchial lung biopsy.

Among patients for whom diagnoses using identical clinical features have different results, HRCT and pathology data, particularly in cases of nonspecific interstitial pneumonia and chronic hypersensitivity pneumonitis that follow a similar disease course to idiopathic pulmonary fibrosis, molecular classifier testing could help identify patients with these diseases so treatments such as to avoid treating these patients with anti-inflammatory or immunosuppressive therapy.

"It seems conceivable that in future interstitial lung diseases could be classified by a simple dichotomy: primarily scarring diseases characterized by molecular usual interstitial pneumonia to be treated with antifibrotics versus immune-driven conditions without usual interstitial pneumonia that need an anti-inflammatory approach," he wrote.

Dr. Hart is from the respiratory research group at Castle Hill Hospital in Cottingham, England. These comments summarize his editorial in response to Raghu et al. (Lancet Respir Med. 2019 Apr 1. doi 10.1016/S2213-2600[19]30058-X). He reported receiving grants and support to attend conferences, and consultancy fees from Boehringer Ingelheim.

NIH beginning first in-human trial of universal flu vaccine

BY LUCAS FRANKI
MDedge News

The National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health, is launching the first in-human trial of a universal influenza vaccine candidate.

The experimental vaccine, H1ssF_3928, is derived from the stem of an H1N1 virus and has a surface made from hemagglutinin and ferritin. With only the stem of the virus included, which changes less than the head, the vaccine should require fewer updates. A similar vaccine made from the same materials was shown to be safe and well tolerated in humans.

The clinical trial (NCT03814720) will be conducted at the NIH Clinical Center in Bethesda, Md., and will gradually enroll at least 53 healthy adults aged 18-70 years. The first 5 participants will receive one 20-mcg intramuscular injection of the vaccine; the other 48 participants will receive two 60-mcg vaccinations 16 weeks apart. Patients will return for 9-11 follow-ups over a 12- to 15-month period, and will provide blood samples for analysis of anti-influenza antibodies.

"Seasonal influenza is a perpetual public health challenge, and we continually face the possibility of an influenza pandemic resulting from the emergence and spread of novel influenza viruses. This phase 1 clinical trial is a step forward in our efforts to develop a durable and broadly protective universal influenza vaccine," Anthony S. Fauci, MD, director of the National Institute of Allergy and Infectious Diseases, said in the press release.

lfranki@mdedge.com

Hookah smoking entails CV risk similar to cigarettes

BY HEIDI SPLETE
MDedge News

Smoking a water pipe, or hookah, can result in significant inhalation of toxins and an increased risk for short- and long-term cardiovascular health problems, according to a scientific statement issued by the American Heart Association on March 8.

In the statement, published in the journal Circulation, Aruni Bhatnagar, PhD, of the University of Louisville (Ky.) and his colleagues reviewed the potential dangers of water pipe use and offered strategies for prevention.

Data from the 2016 National Youth Tobacco Survey showed that current use (defined as use within the past 30 days) of water pipes by high school students increased in a nonlinear trend from 4.1% in 2011 to 4.8% in 2016, with a peak of 9.4% in 2014. Water pipe tobacco is sold in flavors such as cherry, chocolate, and coffee that appeal to younger consumers, and epidemiology data suggest that youth view water pipes as safer than conventional cigarettes because the water "filters out toxins" according to the statement.

Findings from the National Adult Tobacco Survey showed an increase as well, from 1.5% during 2009-2010 to 3.2% during 2013-2014. Adults cite cultural and social influences, as well as psychological benefits of reduced stress and anger and improved concentration, which may be attributable to nicotine, the researchers noted.

Water pipe smoking involves placing charcoal briquettes on top of a tobacco-filled bowl with a stem immersed in water such that the smoke is pulled through and bubbles up through the water into a mouthpiece. The harmful or potentially harmful constituents (HPHCs) involved in water pipe are similar to those in standard cigarettes and include tar, phenanthrene, carbon monoxide, heavy metals, and arsenic, as well as nicotine.

The patterns of exposure to toxins during water pipe smoking are unclear, the authors noted. But the risks for both short-term and long-term health effects are similar to those associated with cigarettes. "Overall, the short-term cardiovascular effects are consistent with the sympathomimetic effects of nicotine," according to the statement.

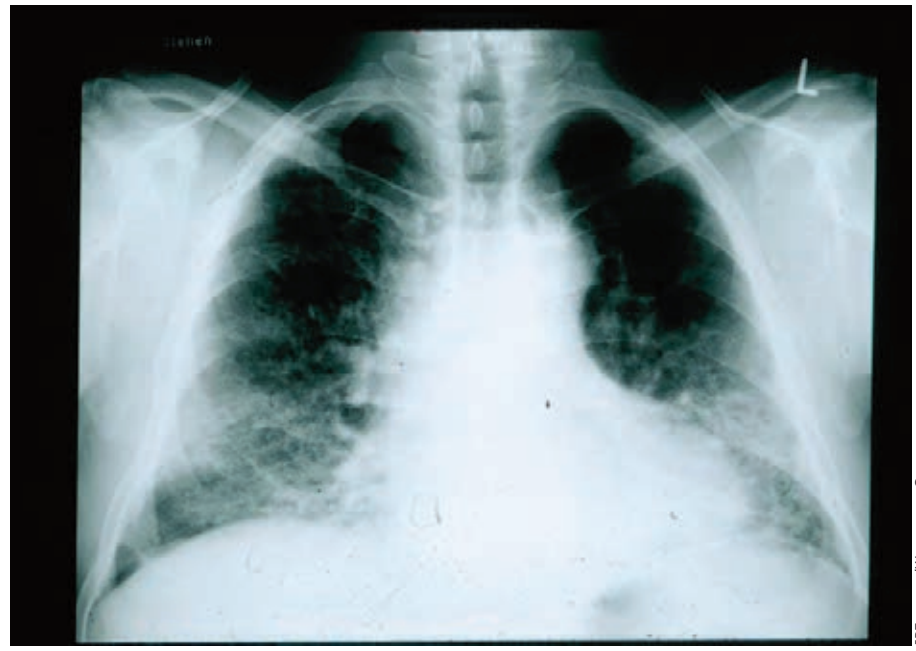
Data on the long-term effects of water pipe smoking on cardiovascular health are limited, but "lifetime exposures exceeding 40 water pipe–years (2 water pipes per day for a total of 20 years or 1 water pipe for 40 years) are associated with a threefold increase in the odds of angiographically diagnosed coronary artery stenosis. Dr. Bhatnagar received funding from the National Institutes of Health, but he had no other financial conflicts to disclose.

chestphysiciannews@chestnet.org

SOURCE: Bhatnagar A et al. Circulation. 2019 Mar 8. doi: 10.1161/CIR.0000000000000671.

Don't delay palliative care for IPF patients

BY THERESE BORDEN
MDedge News



IPFeditor/Wikimedia Commons

Rapid deterioration of life quality in patients with idiopathic pulmonary fibrosis (IPF) begins years before death and indicates that early, integrated palliative care should be a priority, according to the finding of a survey study.

"Patients with IPF suffer from exceptionally low [health-related quality of life] together with severe breathlessness and fatigue already 2 years before death. In addition, physical and emotional well-being further deteriorates near death concurrently with escalating overall symptom burden," wrote Kaisa Rajala, MD, and her colleagues at Helsinki University Hospital.

They conducted a substudy of patients in the larger FinnishIPF study to assess health-related quality of life (HRQOL) and symptom burden in the period before death. Among 300 patients invited to participate, 247 agreed. Patient disease and sociodemographic data were collected from the FinnishIPF records and the study group completed questionnaires five times at 6-month intervals. The study began in April 2015 and continued until August 2017, by which time 92 (37%) of the patients had died.

The investigators used self-reporting tools to look at HRQOL and symptom burden: RAND 36-item Health Survey (RAND-36), the Modified Medical Research and Council Dyspnea Scale (MMRC), the Modified Edmonton Symptom Assessment Scale (ESAS), and the Numeric Rating Scale (NRS).

About 35% of these patients were being treated with antifibrotic medication. Most of the patients had comorbidities, with cardiovascular disease being the most common.

The dimensions of HRQOL studied were physical function, general health, vitality, mental health, social function, and bodily pain. These patients experienced a gradual impairment in HRQOL similar to that of patients with chronic obstructive pulmonary disease (COPD), but with a pronounced, rapid deterioration beginning in the last 2 years of life.

The symptom burden also intensified in the last 2 years of life and ramped up significantly in the last 6 months before death. NRS scores are on a scale of 0-10, from no symptoms to worst symptoms. In most clinical situations, NRS scores equal to or greater than 4 trigger more comprehensive symptom assessment. The scores for symptoms for these patients during the last 6 months were dyspnea, 7.1 (standard deviation, 2.8); tiredness, 6.0 (SD, 2.5), cough, 5.0 (SD, 3.5), pain with movement, 3.9 (SD, 3.1), insomnia, 3.9 (SD, 2.9), anxiety, 3.9 (SD, 2.9), and depression, 3.6 (SD, 3.1).

Investigators noted the steep change in the proportion of patients with MMRC scores greater than or equal to 3 (needing to stop walking after approximately 100 m or a few minutes because of breathlessness) beginning in the last 2 years of life.

The study limitations are its relatively small size, the self-reported data, and the lack of lung function measurements in most patients in the last 6 months of life.

The findings point to the urgent need for early palliative care in IPF patients, the investigators concluded. They noted that the sharp decline in HRQOL is similar to that seen in lung cancer patients, in contrast to the more gradual trend seen in COPD patients.

But there are common benefits of an early palliative program for all of these patients, they stressed. "Early integrated palliative care for patients with lung cancer has shown substantial benefits, such as lower depression scores, higher HRQOL, better communication of end-of-life care preferences, less aggressive care at the end of life, and longer overall survival.

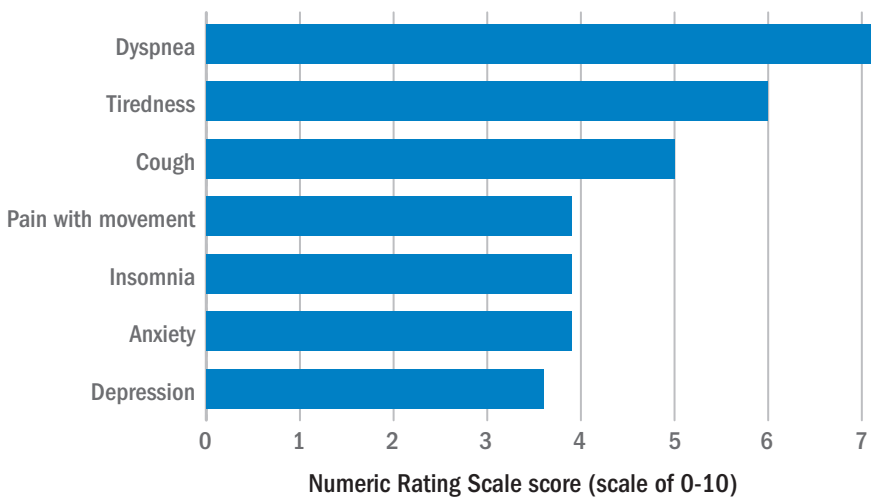
Similarly, a randomized trial demonstrated better control of dyspnea and a survival benefit with integrated palliative care in patients with COPD and interstitial lung disease. In addition to cancer patients, early integrated palliative care may reduce end-of-life acute care utilization, and allow patients with IPF to die in their preferred locations. Integrated palliative care in IPF patients seems to lower respiratory-related emergency room visits and hospitalizations and may allow more patients to die at home."

The study was funded by The Academy of Finland and various Finnish nonprofit organizations funded the study.

tborden@mdedge.com

SOURCE: Rajala K et al. BMC Pulm Med. 2018;18:172. doi: 0.1186/s12890-018-0738-x.

Symptom burden in patients with idiopathic pulmonary fibrosis



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Note: Based on data for 247 patients from the larger FinnishIPF study.
Source: BMC Pulm Med. 2018;18:172. doi: 0.1186/s12890-018-0738-x

VIEW ON THE NEWS

Eric Gartman, MD, FCCP, comments: As stated in the article, the impact of early involvement of palliative care services in patients with conditions with equal (or even better) longevity compared to IPF is well described, and we potentially could dramatically improve the overall care of our IPF patients with an early integrative approach with palliative care. Further, with early involvement, symptom management adapts as progression occurs, unnecessary and undesired care is avoided, and a more streamlined transition to hospice care is possible. There are several factors that may serve as barriers to palliative care referral – from recognition of the extent of our patients' symptoms, the focus on active treatment, and the availability of palliative care consultative services in the community. This study shines light on the fact that we as providers need to actively address this component of care, that patients should be asked about the real-life limitations resulting from their disease, and that health systems and payers need to ensure the availability of this vital and compassionate service to all types of patients who may benefit.

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CT scan honeycombing key to hypersensitivity pneumonitis prognosis

BY ANDREW D. BOWSER
MDedge News

FROM THE JOURNAL *CHEST*® ▪ In patients with hypersensitivity pneumonitis, presence of radiologic honeycombing suggests a poor prognosis in line with what might be expected with idiopathic pulmonary fibrosis, results of a recent study suggest.

When radiologic honeycombing was present, event-free survival was uniformly poor whether the patient had hypersensitivity pneumonitis (HP) or idiopathic pulmonary fibrosis (IPF). By contrast, HP patients with nonhoneycomb fibrosis had longer event-free survival than IPF patients with honeycomb features on CT, wrote researchers led by Margaret L. Salisbury, MD, of the division of pulmonary and critical care medicine at the University of Michigan, Ann Arbor.

"Given the uniformly poor outcome among subjects with radiologic honeycombing, pursuit of invasive diagnostic tests directed at differentiating IPF from HP may be of limited value," Dr. Salisbury and her coinvestigators wrote in Chest.

In the study, 117 patients with HP and 161 with IPF underwent high-resolution CT, results of which were evaluated by three thoracic radiologists. Patients with HP who had no fibrosis on CT had the best event-free median survival, or time to transplant or death, at greater than 14.73 years. For HP patients with nonhoneycomb fibrosis, that median survival was greater than 7.95 years, compared with just 5.20 years in IPF patients without honeycomb features.

Specifically for patients with honeycomb features, median event-free survival was poor for both HP and IPF patients, at 2.76 and 2.81 years, respectively.

The HP patients with no fibrosis had a significant improvement in percent predicted forced vital capacity over time, while fibrotic patients experienced significant declines, the investigators wrote. Thus, HP patients with nonhoneycomb fibrosis had forced vital capacity declines despite longer transplant-free survival.

"These results highlight the importance of making a correct diagnosis of HP versus IPF in patients with nonhoneycomb fibrosis, as well as the limited utility in differentiating HP from IPF among patients with radiologic honeycombing," Dr. Salisbury and her coinvestigators concluded.

Dr. Salisbury reported grants from the National Institutes of Health during the study. Her coauthors reported disclosures related to the NIH, Bayer, Centocor, Gilead, Promedior, Ikaria, Genentech, Nycomed/Takeda, Pfizer, and others.

chestphysiciannews@chestnet.org

SOURCE: Salisbury ML et al. Chest. 2019 Apr;155(4):699-711.

VIEW ON THE NEWS

Daniel Ouellette, MD, FCCP, comments: My patient and I finally knew what was wrong. The robust man in his mid-50s had come to see me with new and progressive dyspnea. Although his chest CT scan had some honeycombing, the pattern of abnormalities was not specific enough to diagnose a particular interstitial lung disease. Now, after a lung biopsy, positive serology for avian antigens, and photos of pigeons in rooftop air ducts taken by my patient at his workplace, we knew that he had chronic hypersensitivity pneumonitis.

Like all physicians, I had hoped to stabilize or reverse the course of my patient's disease. Five years later, my patient is off oxygen, playing golf, and taking his kids on vacation: this happening after his lung transplantation. New information from Dr. Salisbury and colleagues will help us better predict these outcomes.

Dupilumab relieves severe sinusitis with polyposis

BY MITCHEL L. ZOLER
MDedge News

SAN FRANCISCO – Dupilumab, an anti-inflammatory drug already approved for use in the United States, met its efficacy endpoints for treating chronic rhinosinusitis with nasal polyps in a pivotal trial with 276 patients.

The results make it likely that dupilumab (Dupixent) will receive a new indication from the Food and Drug Administration, pending similar results in a second pivotal trial for nasal polyps that researchers will report soon. Dupilumab, which works by blocking a receptor for both interleukin 4 and interleukin 13 and thereby shutting down type 2 inflammation, is already approved in the United States for treating atopic dermatitis and asthma.

Type 2 inflammation drives polyp formation in patients with chronic rhinosinusitis that can produce severe nasal congestion, breathing difficulty, and substantially reduced quality of life.

In the new trial, the drug showed efficacy by significantly improving both the nasal congestion score reported by patients and the nasal polyp score measured by sinus endoscopy after 24 weeks on treatment, when compared with control patients on placebo, Joseph K. Han, MD, said at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

Patients enrolled in the study had chronic, severe sinusitis and nasal polyps that remained uncontrolled despite prior surgery, for 75% of enrolled patients, or treatment with systemic corticosteroids, used on about 90% of the patients within the prior 2 years. During the 24 weeks of treatment, 23% of patients in the control arm had to restart systemic corticosteroid treatment or have surgery, compared with 7% of patients on dupilumab treatment, a statistically significant difference.

The new drug is a "game changer," for these patients, Dr. Han said in a video interview.

In some patients, treatment produced complete polyp resolution. He and his colleagues in the otolaryngology field are now trying to decide exactly which patients with polyps secondary to sinusitis will be good candidates for dupilumab after it receives an expected indication for shrinking nasal polyps.

Roughly 4% of the adult population has chronic rhinosinusitis that generates polyps. How many of these patients are affected severely enough to warrant dupilumab treatment is not clear, but will likely include several hundreds of thousands of U.S. adults, said Dr. Han, professor of otolaryngology and chief of the division of allergy at Eastern Virginia Medical School in Norfolk.

The SINUS-24 (A Controlled Clinical Study of Dupilumab in Patients With Nasal Polyps) trial enrolled patients at 76 sites in the United States and in several European countries. The study randomized 143 patients who received standard treatment plus a 300-mg dupilumab subcutaneous injection every 2 weeks, and 133 patients who received standard treatment plus placebo injections.

After 24 weeks of treatment, the endoscopically measured nasal polyp score, which averaged about 6 at baseline on a scale of 0-8, fell by an average of 2.06 points, compared with controls, which was a statistically significant and clinically meaningful change, said Dr. Han.

The second primary endpoint, patient self-assessment of nasal congestion on a scale of 0-3, showed an average 0.89 improvement, compared with controls, which was also a statistically significant and meaningful change from the average baseline score of about 2.4.

Other efficacy measures showed benefits from treatment, including a substantial improvement compared with controls in a quality-of-life measure. The safety profile was benign compared with placebo, and consistent with safety data for the drug.

SINUS-24 was funded by Regeneron and Sanofi, the companies that market dupilumab. Dr. Han has been an adviser to Regeneron and Sanofi.

mzoler@mdedge.com

SOURCE: Han JK et al. AAAAI 2019, Abstract L4.

THE SPEED THEY WANT

WITH THE CONTROL THEY NEED

SPEED

– Better breathing fast—Majority of patients' FEV_1* improvement occurred at 5 minutes in COPD and 15 minutes in asthma[1-5]

– Reduction of rescue use in asthma from Day 1[1,6†]

CONTROL

– Reduction in COPD exacerbations[1]

*1-hour postdose FEV_1 for COPD and 2-hour postdose FEV_1 for asthma.

†In Study 1, SYMBICORT 160/4.5 provided a 70% reduction in albuterol use vs baseline within 1 day of the first dose and a 57% reduction over 12 weeks.

SYMBICORT is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms

Please see study designs on following pages.

- SYMBICORT 160/4.5 for the maintenance treatment of COPD and for reducing COPD exacerbations
- SYMBICORT for asthma patients ≥12 years of age uncontrolled on an ICS

IMPORTANT SAFETY INFORMATION

- Use of long-acting $beta_2$-adrenergic agonists (LABA) as monotherapy (without inhaled corticosteroids [ICS]) for asthma is associated with an increased risk of asthma-related death. Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA. When LABA are used in fixed dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared to ICS alone
- SYMBICORT is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms
- SYMBICORT should not be initiated in patients during rapidly deteriorating episodes of asthma or COPD
- Patients who are receiving SYMBICORT should not use additional formoterol or other LABA for any reason
- Localized infections of the mouth and pharynx with *Candida albicans* has occurred in patients treated with SYMBICORT. Patients should rinse the mouth after inhalation of SYMBICORT
- Lower respiratory tract infections, including pneumonia, have been reported following the administration of ICS
- Due to possible immunosuppression, potential worsening of infections could occur. A more serious or even fatal course of chickenpox or measles can occur in susceptible patients
- It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression may occur, particularly at higher doses. Particular care is needed for patients who are transferred from systemically active corticosteroids to ICS. Deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available ICS
- Caution should be exercised when considering administration of SYMBICORT in patients on long-term ketoconazole and other known potent CYP3A4 inhibitors
- As with other inhaled medications, paradoxical bronchospasm may occur with SYMBICORT
- Immediate hypersensitivity reactions may occur, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm
- Excessive beta-adrenergic stimulation has been associated with central nervous system and cardiovascular effects. SYMBICORT should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension
- Long-term use of ICS may result in a decrease in bone mineral density (BMD). Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating SYMBICORT and periodically thereafter
- ICS may result in a reduction in growth velocity when administered to pediatric patients

Please see additional Important Safety Information and Brief Summary of Prescribing Information on adjacent pages.

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(budesonide/formoterol fumarate dihydrate) Inhalation Aerosol

THE SPEED THEY WANT...

SYMBICORT 160/4.5 for the maintenance treatment of COPD; SYMBICORT for asthma patients ≥12 years of age uncontrolled on an ICS

BETTER BREATHING—FAST[1-5]

Majority of patients' FEV_1 improvement occurred at 5 minutes in COPD and 15 minutes in asthma[1-5]

COPD: In a serial spirometry subset of patients taking SYMBICORT 160/4.5* (n=121) in the SUN Study, 67% of 1-hour postdose FEV_1 improvement occurred at **5 minutes** on day of randomization and 84% at end of treatment[1-3]

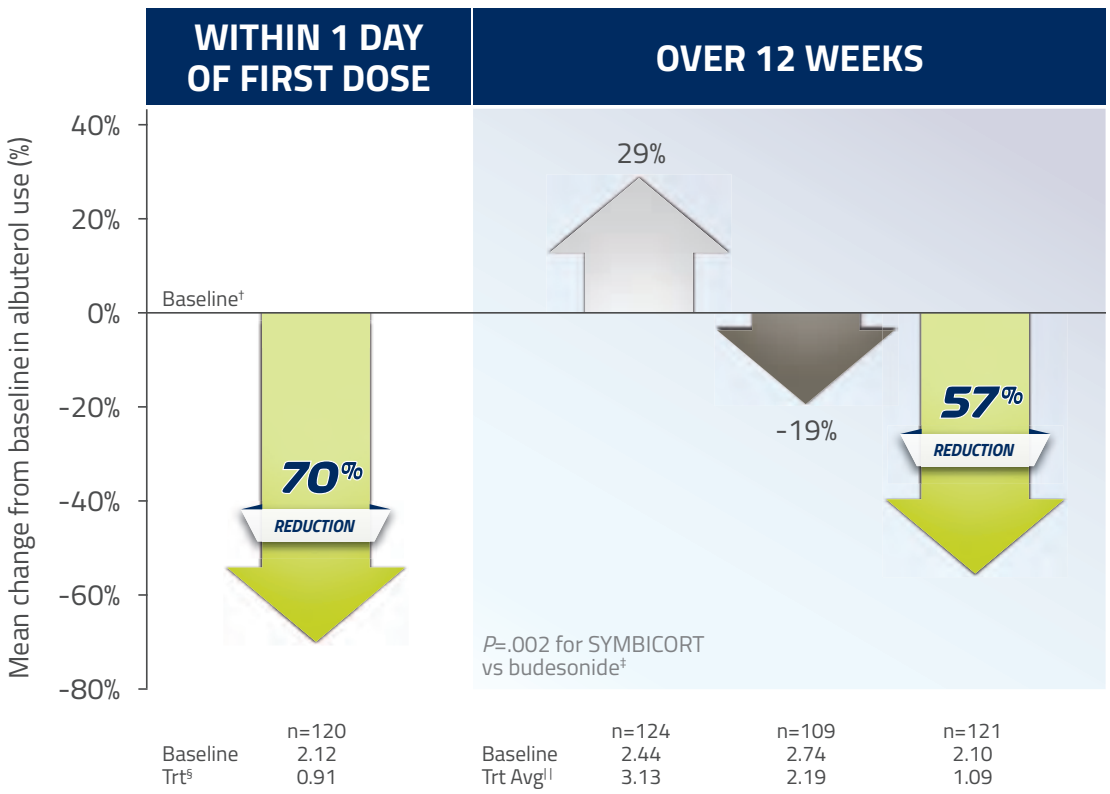
ASTHMA: In patients ≥12 years of age with asthma taking SYMBICORT 160/4.5* (n=124) in Study 1, 79% of 2-hour postdose FEV_1 improvement occurred at **15 minutes** on day of randomization and 90% at end of treatment[1,4,5]

- Sustained improvement in lung function was demonstrated in COPD in a 12-month efficacy and safety study[2,3] and in asthma patients ≥12 years of age in a 12-week efficacy and safety study[4,5]

SYMBICORT for asthma patients uncontrolled on an ICS

REDUCTION OF RESCUE USE FROM DAY 1[1,6]

In Study 1, SYMBICORT 160/4.5 provided a 70% reduction in albuterol use vs baseline within 1 day of the first dose and a 57% reduction over 12 weeks[1,6]



SYMBICORT 160/4.5 mcg*
Budesonide 160 mcg*
Placebo*

Study 1: A 12-week efficacy and safety study of patients ≥12 years of age with moderate to severe asthma[1,6]

- The primary comparison for this secondary endpoint was SYMBICORT vs placebo over 12 weeks ($P<.001$)[1,6‡]

Study 2: A 12-week efficacy and safety study of patients ≥12 years of age with mild to moderate asthma[1,6]

- SYMBICORT 80/4.5 reduced rescue medication use by 51% vs baseline within 1 day of the first dose and 67% over 12 weeks[1,6]

SYMBICORT is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms

*Administered as 2 inhalations twice daily. †Baseline is defined as the mean of all values obtained during the run-in period. During run-in, patients received budesonide 80 mcg administered as 2 inhalations twice daily and albuterol as a rescue medication. ‡*P* values based on treatment comparison of absolute mean change from baseline for SYMBICORT vs budesonide and placebo. §Treatment (Trt) is the mean value in puffs/day of albuterol used within 1 day of the first dose of SYMBICORT. ‖Treatment Average (Trt Avg) is defined as the mean of all values obtained during the double-blind treatment period in puffs/day of albuterol.

IMPORTANT SAFETY INFORMATION (cont'd)

- Glaucoma, increased intraocular pressure, and cataracts have been reported following the administration of ICS, including budesonide, a component of SYMBICORT. Close monitoring is warranted in patients with a change in vision or history of increased intraocular pressure, glaucoma, or cataracts
- In rare cases, patients on ICS may present with systemic eosinophilic conditions
- SYMBICORT should be used with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines
- Beta-adrenergic agonist medications may produce hypokalemia and hyperglycemia in some patients
- The most common adverse reactions ≥3% reported in asthma clinical trials included nasopharyngitis, headache, upper respiratory tract infection, pharyngolaryngeal pain, sinusitis, pharyngitis, rhinitis, influenza, back pain, nasal congestion, stomach discomfort, vomiting, and oral candidiasis
- The most common adverse reactions ≥3% reported in COPD clinical trials included nasopharyngitis, oral candidiasis, bronchitis, sinusitis, and upper respiratory tract infection

Please see additional Important Safety Information and Brief Summary of Prescribing Information on adjacent pages.

...THE CONTROL THEY NEED

SYMBICORT 160/4.5 for reducing COPD exacerbations

REDUCTION IN COPD EXACERBATIONS

SYMBICORT 160/4.5 significantly reduced the annual rate of moderate/severe COPD exacerbations versus formoterol alone[1,7]

Study 4: 12-month exacerbation clinical trial[1,7]

Annual rate estimate: **1.05, formoterol 4.5 mcg* (n=403)**

P<.001 vs formoterol[7]

Estimate rate ratio=0.65;
95% CI: 0.53, 0.80

Annual rate estimate: **0.68, SYMBICORT 160/4.5 mcg* (n=404)**

Study 3: 6-month exacerbation clinical trial. SYMBICORT 160/4.5 significantly reduced the annual rate of moderate/severe COPD exacerbations by 26% vs formoterol (estimate rate ratio=0.74; 95% CI: 0.61, 0.91; *P*=.004)[1,7]

- Annual rate estimate was 0.94 for SYMBICORT 160/4.5 mcg* (n=606) vs 1.27 for formoterol 4.5 mcg* (n=613)

- In **Study 3**, COPD exacerbations were defined as worsening of ≥2 major symptoms (dyspnea, sputum volume, sputum color/purulence) or worsening of any 1 major symptom together with ≥1 of the minor symptoms (sore throat, cold [nasal discharge and/or nasal congestion], fever without other cause, increased cough or increased wheeze) for ≥2 consecutive days. COPD exacerbation severity was classified as moderate if symptoms required systemic corticosteroid (≥3 days) and/or antibiotic treatment, and severe if symptoms required hospitalization
- In **Study 4**, COPD exacerbations were defined as worsening of COPD that required treatment with a course of oral steroids and/or hospitalization

*Administered as 2 inhalations twice daily.

IMPORTANT SAFETY INFORMATION (cont'd)

- SYMBICORT should be administered with caution to patients being treated with MAO inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents
- Beta-blockers may not only block the pulmonary effect of beta-agonists, such as formoterol, but may produce severe bronchospasm in patients with asthma
- ECG changes and/or hypokalemia associated with nonpotassium-sparing diuretics may worsen with concomitant beta-agonists. Use caution with the coadministration of SYMBICORT

INDICATIONS

SYMBICORT is indicated for the treatment of asthma in patients 6 years and older not adequately controlled on a long-term asthma-control medication such as an ICS or whose disease warrants initiation of treatment with both an ICS and LABA. (also see DOSAGE AND ADMINISTRATION).

SYMBICORT 160/4.5 is indicated for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, and to reduce COPD exacerbations.

SYMBICORT is NOT indicated for the relief of acute bronchospasm.

The difference is

Symbicort®

(budesonide/formoterol fumarate dihydrate) Inhalation Aerosol

COPD

Lung Function Studies

Study 1 (SHINE): A 6-month, randomized, double-blind, double-dummy, placebo-controlled, parallel-group, multicenter study of 1704 patients with COPD compared SYMBICORT pressurized metered-dose inhaler (pMDI) 160/4.5 mcg (n=277), SYMBICORT pMDI 80/4.5 mcg (n=281), budesonide 160 mcg (n=275), formoterol 4.5 mcg (n=284), the free combination of budesonide 160 mcg plus formoterol 4.5 mcg (n=287), and placebo (n=300), each administered as 2 inhalations twice daily. Subjects were current or ex-smokers with a smoking history of ≥10 pack-years, aged ≥40 years with a clinical diagnosis of COPD and symptoms for >2 years. The study included a 2-week run-in period followed by a 6-month treatment period. This study was designed to assess change from baseline to the average over the randomized treatment period in predose FEV_1 and in 1-hour postdose FEV_1. The prespecified primary comparison for predose FEV_1 was vs formoterol and for 1-hour postdose was vs budesonide.

Study 2 (SUN): A 12-month, randomized, double-blind, double-dummy, placebo-controlled, parallel-group, multicenter study of 1964 patients with COPD compared SYMBICORT pMDI 160/4.5 mcg (n=494), SYMBICORT pMDI 80/4.5 mcg (n=494), formoterol 4.5 mcg (n=495), and placebo (n=481), each administered as 2 inhalations twice daily. Subjects were current or ex-smokers with a smoking history of ≥10 pack-years, aged ≥40 years with a clinical diagnosis of COPD and symptoms for >2 years. The study included a 2-week run-in period followed by a 12-month treatment period. This study was designed to assess change from baseline to the average over the randomized treatment period in predose FEV_1 and in 1-hour postdose FEV_1 (coprimary endpoints). The prespecified primary comparisons for predose FEV_1 were vs placebo and formoterol, and the primary comparison for 1-hour postdose was vs placebo.

COMPARATOR ARMS—Mean improvement in 1-hour postdose FEV_1 (mL/%) over 12 months (serial spirometry subset):

Day of randomization: SYMBICORT 160/4.5 mcg (240 mL/26%), formoterol 4.5 mcg (180 mL/20%), placebo (40 mL/5%).

End of month 12 (last observation carried forward [LOCF]): SYMBICORT 160/4.5 mcg (240 mL/26%), formoterol 4.5 mcg (170 mL/19%), placebo (30 mL/5%).

SYMBICORT 160/4.5 mcg* (n=121)
Formoterol 4.5 mcg* (n=124)
Placebo* (n=125)

Exacerbation Studies

Study 3 (RISE): A 6-month, Phase IIIB, randomized, double-blind, double-dummy, parallel-group, multicenter study of 1219 patients with COPD compared SYMBICORT pMDI 160/4.5 mcg (n=606) with formoterol 4.5 mcg (n=613), each administered as 2 inhalations twice daily. Subjects were current or ex-smokers with a smoking history of ≥10 pack-years, aged ≥40 years with a clinical diagnosis of COPD, COPD symptoms for >1 year, and a history of ≥1 moderate or severe COPD exacerbation in the previous year requiring treatment with systemic corticosteroids or hospitalization. The study included a 4-week run-in period, a 26-week randomized treatment period, and telephone follow-up 2 weeks after end of study completion. This study was designed to assess the annual rate of moderate and severe COPD exacerbations for SYMBICORT vs formoterol.

Study 4: A 12-month, Phase IIIB, randomized, double-blind, double-dummy, parallel-group, multicenter study of 811 patients with COPD compared SYMBICORT pMDI 160/4.5 mcg (n=407) with formoterol 4.5 mcg (n=404), each administered as 2 inhalations twice daily. Subjects were current or ex-smokers with a smoking history of ≥10 pack-years, aged ≥40 years with a clinical diagnosis of COPD, COPD symptoms for >2 years, and a history of ≥1 COPD exacerbation in the previous year treated with a course of systemic corticosteroids and/or antibiotics. The study included a 2-week run-in period, a 12-month randomized treatment period, and telephone follow-up 2 weeks after end of study completion. This study was designed to assess the annual rate of COPD exacerbations for SYMBICORT vs formoterol.

ASTHMA

Study 1: A 12-week, double-blind, placebo-controlled study comparing SYMBICORT 160/4.5 mcg, budesonide 160 mcg, formoterol 4.5 mcg, the free combination of budesonide 160 mcg plus formoterol 4.5 mcg in separate inhalers, and placebo, each administered as 2 inhalations twice daily. A total of 596 patients (124 randomized to receive SYMBICORT) ≥12 years of age were evaluated. The study included a 2-week run-in period with budesonide 80 mcg, 2 inhalations twice daily. Most patients had moderate to severe asthma and were using moderate to high doses of ICS prior to study entry. This study was designed to assess 2 primary endpoints. The first was predose FEV_1 averaged over 12 weeks, and the second was 12-hour average postdose FEV_1 at Week 2. Secondary efficacy variables included daytime and nighttime asthma symptom scores and daily rescue medication use (both recorded by patients in the electronic diary).

COMPARATOR ARMS—Mean change in 2-hour postdose FEV_1 (mL/%) over 12 weeks:

Day of randomization: SYMBICORT 160/4.5 mcg (420 mL/20.0%), budesonide 160 mcg (100 mL/4.4%), formoterol 4.5 mcg (420 mL/19.9%), budesonide 160 mcg + formoterol 4.5 mcg (410 mL/19.4%), placebo (90 mL/4.4%).

End of treatment: SYMBICORT 160/4.5 mcg (420 mL/20.2%), budesonide 160 mcg (140 mL/6.5%), formoterol 4.5 mcg (260 mL/12.3%), budesonide 160 mcg + formoterol 4.5 mcg (410 mL/19.5%), placebo (-10 mL/0.4%).

Mean change from baseline in albuterol use within 1 day of the first dose of study treatment

SYMBICORT 160/4.5 mcg: -70% (n=120)
Budesonide 160 mcg: -14% (n=105)
Formoterol 4.5 mcg: -50% (n=117)
Budesonide 160 mcg + formoterol 4.5 mcg: -70% (n=112)
Placebo: -8% (n=122)

Mean change from baseline in albuterol use over 12 weeks
SYMBICORT 160/4.5 mcg: -57% (n=121)
Budesonide 160 mcg: -19% (n=109)
Formoterol 4.5 mcg: -22% (n=119)
Budesonide 160 mcg + formoterol 4.5 mcg: -67% (n=113)
Placebo: 29% (n=124)

Study 2: A 12-week, randomized, multicenter, double-blind, double-dummy, placebo-controlled study comparing SYMBICORT 80/4.5 mcg, budesonide 80 mcg, formoterol 4.5 mcg, each administered as 2 inhalations twice daily. A total of 480 patients (123 randomized to receive SYMBICORT) ≥12 years of age were evaluated. The study included a 2-week run-in period with placebo and rescue albuterol therapy. Most patients had mild to moderate persistent asthma and were using low to moderate doses of ICS either alone or as part of combination therapy prior to study entry. This study was designed to assess 2 primary endpoints. The first was predose FEV_1 averaged over 12 weeks, and the second was 12-hour average postdose FEV_1 at Week 2. Secondary efficacy variables included daytime and nighttime asthma symptom scores and daily rescue medication use (both recorded by patients in the electronic diary.)

*Administered as 2 inhalations twice daily.

*You are encouraged to report negative side effects of prescription drugs to the FDA. Visit **www.FDA.gov/medwatch** or call 1-800-FDA-1088.*

References: 1. SYMBICORT [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; December 2017. **2.** Rennard SI, Tashkin DP, McElhattan J, et al. Efficacy and tolerability of budesonide/formoterol in one hydrofluoroalkane pressurized metered-dose inhaler in patients with chronic obstructive pulmonary disease: results from a 1-year randomized controlled clinical trial. *Drugs*. 2009;69(5):549-565. **3.** Data on file, REF-4960, AZPLP. **4.** Noonan M, Rosenwasser LJ, Martin P, O'Brien CD, O'Dowd L. Efficacy and safety of budesonide and formoterol in one pressurised metered-dose inhaler in adults and adolescents with moderate to severe asthma: a randomised clinical trial. *Drugs*. 2006;66:2235-2254. **5.** Data on file, REF-4962, AZPLP. **6.** Data on file, REF-35897, AZPLP. **7.** Data on file, REF-16658, AZPLP.

Please see Important Safety Information and Brief Summary of Prescribing Information on adjacent pages.

AstraZeneca

The difference is

Symbicort®
(budesonide/formoterol fumarate dihydrate) Inhalation Aerosol

SYMBICORT® (budesonide and formoterol fumarate dihydrate)
Inhalation Aerosol, for oral inhalation use

BRIEF SUMMARY of PRESCRIBING INFORMATION. For full Prescribing Information, see package insert.

INDICATIONS AND USAGE

Treatment of Asthma

SYMBICORT is indicated for the treatment of asthma in patients 6 years of age and older.

SYMBICORT should be used for patients not adequately controlled on a long-term asthma-control medication such as an inhaled corticosteroid (ICS) or whose disease warrants initiation of treatment with both an inhaled corticosteroid and long-acting beta$_2$-adrenergic agonist (LABA).

Important Limitations of Use:

- SYMBICORT is NOT indicated for the relief of acute bronchospasm.

Maintenance Treatment of Chronic Obstructive Pulmonary Disease

SYMBICORT 160/4.5 is indicated for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema. SYMBICORT 160/4.5 is also indicated to reduce exacerbations of COPD. SYMBICORT 160/4.5 is the only strength indicated for the treatment of COPD.

Important Limitations of Use:

- SYMBICORT is NOT indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS

The use of SYMBICORT is contraindicated in the following conditions:

- Primary treatment of status asthmaticus or other acute episodes of asthma or COPD where intensive measures are required.
- Hypersensitivity to any of the ingredients in SYMBICORT.

WARNINGS AND PRECAUTIONS

Serious Asthma-Related Events – Hospitalizations, Intubations and Death

Use of LABA as monotherapy (without ICS) for asthma is associated with an increased risk of asthma-related death [see *Salmeterol Multicenter Asthma Research Trial (SMART)*]. Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA. When LABA are used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared to ICS alone (see *Serious Asthma-Related Events with ICS/LABA in the full Prescribing Information*).

Serious Asthma-Related Events with ICS/LABA

Four large, 26-week, randomized, blinded, active-controlled clinical safety trials were conducted to evaluate the risk of serious asthma-related events when LABA were used in fixed-dose combination with ICS compared to ICS alone in patients with asthma. Three trials included adult and adolescent patients aged ≥12 years: one trial compared budesonide/formoterol (SYMBICORT) to budesonide *[see Clinical Studies (14.1) in the full Prescribing Information]*; one trial compared fluticasone propionate/salmeterol inhalation powder to fluticasone propionate inhalation powder; and one trial compared mometasone furoate/formoterol to mometasone furoate. The fourth trial included pediatric patients 4 to 11 years of age and compared fluticasone propionate/salmeterol inhalation powder to fluticasone propionate inhalation powder. The primary safety endpoint for all four trials was serious asthma-related events (hospitalizations, intubations and death). A blinded adjudication committee determined whether events were asthma-related.

The three adult and adolescent trials were designed to rule out a risk margin of 2.0, and the pediatric trial was designed to rule out a risk of 2.7. Each individual trial met its pre-specified objective and demonstrated non-inferiority of ICS/LABA to ICS alone. A meta-analysis of the three adult and adolescent trials did not show a significant increase in risk of a serious asthma-related event with ICS/LABA fixed-dose combination compared with ICS alone (Table 1). These trials were not designed to rule out all risk for serious asthma-related events with ICS/LABA compared with ICS.

Table 1. Meta-analysis of Serious Asthma-Related Events in Patients with Asthma Aged 12 Years and Older

	ICS/LABA (N =17,537)[1]	ICS (N =17,552)[1]	ICS/LABA vs ICS Hazard ratio (95% CI)[2]
Serious asthma-related event[3]	116	105	1.10 (0.85, 1.44)
Asthma-related death	2	0	
Asthma-related intubation (endotracheal)	1	2	
Asthma-related hospitalization (≥24-hour stay)	115	105	

ICS = Inhaled Corticosteroid, LABA = Long-acting Beta$_2$-adrenergic Agonist

1. Randomized patients who had taken at least 1 dose of study drug. Planned treatment used for analysis.
2. Estimated using a Cox proportional hazards model of time to first event with baseline hazards stratified by each of the 3 trials.
3. Number of patients with event that occurred within 6 months after the first use of study drug or 7 days after the last date of study drug, whichever date was later. Patients can have one or more events, but only the first event was counted for analysis. A single, blinded, independent adjudication committee determined whether events were asthma-related.

The pediatric safety trial included 6208 pediatric patients 4 to 11 years of age who received ICS/LABA (fluticasone propionate / salmeterol inhalation powder) or ICS (fluticasone propionate inhalation powder). In this trial, 27/3107 (0.9%) patients randomized to ICS/LABA and 21/3101 (0.7%) patients randomized to ICS experienced a serious asthma-related event. There were no asthma-related deaths or intubations. ICS/LABA did not show a significantly increased risk of a serious asthma-related event compared to ICS based on the pre-specified risk margin (2.7), with an estimated hazard ratio of time to first event of 1.29 (95% CI: 0.73, 2.27).

Salmeterol Multicenter Asthma Research Trial (SMART)

A 28-week, placebo-controlled U.S. trial that compared the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13/13,176 in patients treated with salmeterol vs. 3/13,179 in patients treated with placebo; relative risk: 4.37 [95% CI 1.25, 15.34]). Use of background ICS was not required in SMART. The increased risk of asthma-related death is considered a class effect of LABA monotherapy.

Formoterol Monotherapy Studies

Clinical studies with formoterol used as monotherapy suggested a higher incidence of serious asthma exacerbation in patients who received formoterol than in those who received placebo. The sizes of these studies were not adequate to precisely quantify the difference in serious asthma exacerbations between treatment groups.

Deterioration of Disease and Acute Episodes

SYMBICORT should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma or COPD. SYMBICORT has not been studied in patients with acutely deteriorating asthma or COPD. The initiation of SYMBICORT in this setting is not appropriate.

Increasing use of inhaled, short-acting beta$_2$-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate re-evaluation with reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of SYMBICORT with a higher strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids. Patients should not use more than 2 inhalations twice daily (morning and evening) of SYMBICORT.

SYMBICORT should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. An inhaled, short-acting beta$_2$-agonist, not SYMBICORT, should be used to relieve acute symptoms such as shortness of breath.

When beginning treatment with SYMBICORT, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs.

Excessive Use of SYMBICORT and Use with Other Long-Acting Beta$_2$-Agonists

As with other inhaled drugs containing beta$_2$-adrenergic agents, SYMBICORT should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using SYMBICORT should not use an additional LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate) for any reason, including prevention of exercise-induced bronchospasm (EIB) or the treatment of asthma or COPD.

Local Effects

In clinical studies, the development of localized infections of the mouth and pharynx with *Candida albicans* has occurred in patients treated with SYMBICORT. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral antifungal) therapy while treatment with SYMBICORT continues, but at times therapy with SYMBICORT may need to be interrupted. Advise the patient to rinse his/her mouth with water without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.

Pneumonia and Other Lower Respiratory Tract Infections

Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbations frequently overlap. Lower respiratory tract infections, including pneumonia, have been reported following the inhaled administration of corticosteroids.

In a 6-month lung function study of 1704 patients with COPD, there was a higher incidence of lung infections other than pneumonia (e.g., bronchitis, viral lower respiratory tract infections, etc.) in patients receiving SYMBICORT 160/4.5 (7.6%) than in those receiving SYMBICORT 80/4.5 (3.2%), formoterol 4.5 mcg (4.6%) or placebo (3.3%). Pneumonia did not occur with greater incidence in the SYMBICORT 160/4.5 group (1.1 %) compared with placebo (1.3%). In a 12-month lung function study of 1964 patients with COPD, there was also a higher incidence of lung infections other than pneumonia in patients receiving SYMBICORT 160/4.5 (8.1%) than in those receiving SYMBICORT 80/4.5 (6.9%), formoterol 4.5 mcg (7.1%) or placebo (6.2%). Similar to the 6-month study, pneumonia did not occur with greater incidence in the SYMBICORT 160/4.5 group (4.0%) compared with placebo (5.0%).

Immunosuppression

Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated (see the respective package inserts for complete VZIG and IG prescribing information). If chicken pox develops, treatment with antiviral agents may be considered. The immune responsiveness to varicella vaccine was evaluated in pediatric patients with asthma ages 12 months to 8 years with budesonide inhalation suspension.

An open-label, nonrandomized clinical study examined the immune responsiveness to varicella vaccine in 243 asthma patients 12 months to 8 years of age who were treated with budesonide inhalation suspension 0.25 mg to 1 mg daily (n=151) or noncorticosteroid asthma therapy (n=92) (i.e., beta$_2$-agonists, leukotriene receptor antagonists, cromones). The percentage of patients developing a seroprotective antibody titer of ≥5.0 (gpELISA value) in response to the vaccination was similar in patients treated with budesonide inhalation suspension (85%), compared to patients treated with noncorticosteroid asthma therapy (90%). No patient treated with budesonide inhalation suspension developed chicken pox as a result of vaccination.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; untreated systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

Transferring Patients From Systemic Corticosteroid Therapy

Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although SYMBICORT may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress, a severe asthma attack or a severe COPD exacerbation, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress, a severe asthma attack, or a severe COPD exacerbation.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to SYMBICORT. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with SYMBICORT. Lung function (mean forced expiratory volume in 1 second [FEV_1] or morning peak expiratory flow [PEF]), beta-agonist use, and asthma or COPD symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to inhaled corticosteroids or SYMBICORT may unmask conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions). Some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.

Hypercorticism and Adrenal Suppression

Budesonide, a component of SYMBICORT, will often help control asthma and COPD symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since budesonide is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of SYMBICORT in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with SYMBICORT should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients, particularly when budesonide is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of SYMBICORT should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of SYMBICORT with ketoconazole, and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) because adverse effects related to increased systemic exposure to budesonide may occur *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

Paradoxical Bronchospasm and Upper Airway Symptoms

As with other inhaled medications, SYMBICORT can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with SYMBICORT, it should be treated immediately with an inhaled, short-acting bronchodilator, SYMBICORT should be discontinued immediately, and alternative therapy should be instituted.

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of SYMBICORT, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm.

Cardiovascular and Central Nervous System Effects

Excessive beta-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia *[see Overdosage (10) in the full Prescribing Information]*. Therefore, SYMBICORT, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Formoterol, a component of SYMBICORT, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of formoterol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating SYMBICORT and periodically thereafter. If significant reductions in BMD are seen and SYMBICORT is still considered medically important for that patient's COPD therapy, use of medication to treat or prevent osteoporosis should be strongly considered.

Effects of treatment with SYMBICORT 160/4.5, SYMBICORT 80/4.5, formoterol 4.5 mcg, or placebo on BMD was evaluated in a subset of 326 patients (females and males 41 to 88 years of age) with COPD in the 12-month lung function study. BMD evaluations of the hip and lumbar spine regions were conducted at baseline and 52 weeks using dual energy x-ray absorptiometry (DEXA) scans. Mean changes in BMD from baseline to end of treatment were small (mean changes ranged from -0.01 - 0.01 g/cm^2). ANCOVA results for total spine and total hip BMD based on the end of treatment time point showed that all geometric LS Mean ratios for the pairwise treatment group comparisons were close to 1, indicating that overall, BMD for total hip and total spine regions for the 12-month time point were stable over the entire treatment period.

Effect on Growth

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving SYMBICORT routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled

corticosteroids, including SYMBICORT, titrate each patient's dose to the lowest dosage that effectively controls his/her symptoms *[see Dosage and Administration (2.2) and Use in Specific Populations (8.4) in the full Prescribing Information]*.

Glaucoma and Cataracts

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with asthma and COPD following the long-term administration of inhaled corticosteroids, including budesonide, a component of SYMBICORT. Therefore, close monitoring is warranted in patients with a change in vision or with history of increased intraocular pressure, glaucoma, and/or cataracts.

Effects of treatment with SYMBICORT 160/4.5, SYMBICORT 80/4.5, formoterol 4.5 mcg, or placebo on development of cataracts or glaucoma were evaluated in a subset of 461 patients with COPD in the 12-month lung function study. Ophthalmic examinations were conducted at baseline, 24 weeks, and 52 weeks. There were 26 subjects (6%) with an increase in posterior subcapsular score from baseline to maximum value (>0.7) during the randomized treatment period. Changes in posterior subcapsular scores of >0.7 from baseline to treatment maximum occurred in 11 patients (9.0%) in the SYMBICORT 160/4.5 group, 4 patients (3.8%) in the SYMBICORT 80/4.5 group, 5 patients (4.2%) in the formoterol group, and 6 patients (5.2%) in the placebo group.

Eosinophilic Conditions and Churg-Strauss Syndrome

In rare cases, patients on inhaled corticosteroids may present with systemic eosinophilic conditions. Some of these patients have clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of inhaled corticosteroids. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between budesonide and these underlying conditions has not been established.

Coexisting Conditions

SYMBICORT, like all medications containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related $beta_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

Hypokalemia and Hyperglycemia

Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects *[see Clinical Pharmacology (12.2) in the full Prescribing Information]*. The decrease in serum potassium is usually transient, not requiring supplementation. Clinically significant changes in blood glucose and/or serum potassium were seen infrequently during clinical studies with SYMBICORT at recommended doses.

ADVERSE REACTIONS

LABA use may result in the following:

- Serious asthma-related events – hospitalizations, intubations, death *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.
- Cardiovascular and central nervous system effects *[see Warnings and Precautions (5.12) in the full Prescribing Information]*.

Systemic and inhaled corticosteroid use may result in the following:

- *Candida albicans* infection *[see Warnings and Precautions (5.4) in the full Prescribing Information]*
- Pneumonia or lower respiratory tract infections in patients with COPD *[see Warnings and Precautions (5.5) in the full Prescribing Information]*
- Immunosuppression *[see Warnings and Precautions (5.6) in the full Prescribing Information]*
- Hypercorticism and adrenal suppression *[see Warnings and Precautions (5.8) in the full Prescribing Information]*
- Growth effects in pediatric patients *[see Warnings and Precautions (5.14) in the full Prescribing Information]*
- Glaucoma and cataracts *[see Warnings and Precautions (5.15) in the full Prescribing Information]*

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Trials Experience in Asthma

Adult and Adolescent Patients 12 Years of Age and Older

The overall safety data in adults and adolescents are based upon 10 active- and placebo-controlled clinical trials in which 3393 patients ages 12 years and older (2052 females and 1341 males) with asthma of varying severity were treated with SYMBICORT 80/4.5 or 160/4.5 taken 2 inhalations once or twice daily for 12 to 52 weeks. In these trials, the patients on SYMBICORT had a mean age of 38 years and were predominantly Caucasian (82%).

The incidence of common adverse events in Table 2 below is based upon pooled data from three 12-week, double-blind, placebo-controlled clinical studies in which 401 adult and adolescent patients (148 males and 253 females) age 12 years and older were treated with 2 inhalations of SYMBICORT 80/4.5 or SYMBICORT 160/4.5 twice daily. The SYMBICORT group was composed of mostly Caucasian (84%) patients with a mean age of 38 years, and a mean percent predicted FEV_1 at baseline of 76 and 68 for the 80/4.5 mcg and 160/4.5 mcg treatment groups, respectively. Control arms for comparison included 2 inhalations of budesonide HFA metered dose inhaler (MDI) 80 or 160 mcg, formoterol dry powder inhaler (DPI) 4.5 mcg, or placebo (MDI and DPI) twice daily. Table 2 includes all adverse events that occurred at an incidence of ≥3% in any one SYMBICORT group and more commonly than in the placebo group with twice-daily dosing. In considering these data, the increased average duration of patient exposure for SYMBICORT patients should be taken into account, as incidences are not adjusted for an imbalance of treatment duration.

Table 2 Adverse reactions occurring at an incidence of ≥ 3% and more commonly than placebo in the SYMBICORT groups: pooled data from three 12-week, double-blind, placebo-controlled clinical asthma trials in patients 12 years and older

Treatment[1]	SYMBICORT		Budesonide		Formoterol	Placebo
Adverse Event	**80/4.5 N = 277 %**	**160/4.5 N = 124 %**	**80 mcg N = 121 %**	**160 mcg N = 109 %**	**4.5 mcg N = 237 %**	**N = 400 %**
Nasopharyngitis	10.5	9.7	14.0	11.0	10.1	9.0
Headache	6.5	11.3	11.6	12.8	8.9	6.5
Upper respiratory tract infection	7.6	10.5	8.3	9.2	7.6	7.8
Pharyngolaryngeal pain	6.1	8.9	5.0	7.3	3.0	4.8
Sinusitis	5.8	4.8	5.8	2.8	6.3	4.8
Influenza	3.2	2.4	6.6	0.9	3.0	1.3
Back pain	3.2	1.6	2.5	5.5	2.1	0.8
Nasal congestion	2.5	3.2	2.5	3.7	1.3	1.0
Stomach discomfort	1.1	6.5	2.5	4.6	1.3	1.8
Vomiting	1.4	3.2	0.8	2.8	1.7	1.0
Oral Candidiasis	1.4	3.2	0	0	0	0.8
Average Duration of Exposure (days)	**77.7**	**73.8**	**77.0**	**71.4**	**62.4**	**55.9**

1. All treatments were administered as 2 inhalations twice daily.

Long-term safety - asthma clinical trials in patients 12 years and older

Long-term safety studies in adolescent and adult patients 12 years of age and older, treated for up to 1 year at doses up to 1280/36 mcg/day (640/18 mcg twice daily), revealed neither clinically important changes in the incidence nor new types of adverse events emerging after longer periods of treatment. Similarly, no significant or unexpected patterns of abnormalities were observed for up to 1 year in safety measures including chemistry, hematology, ECG, Holter monitor, and HPA-axis assessments.

Pediatric Patients 6 to Less than 12 Years of Age

The safety data for pediatric patients aged 6 to less than 12 years is based on 1 trial of 12 weeks treatment duration. Patients (79 female and 105 male) receiving inhaled corticosteroid at trial entry were randomized to SYMBICORT 80/4.5 (n=92) or budesonide pMDI 80 mcg (n=92), 2 inhalations twice daily. The overall safety profile of these patients was similar to that observed in patients 12 years of age and older who received SYMBICORT 80/4.5 twice daily in studies of similar design. Common adverse reactions that occurred in patients treated with SYMBICORT 80/4.5 with a frequency of ≥3% and more frequently than patients treated only with budesonide pMDI 80 mcg included upper respiratory tract infection, pharyngitis, headache, and rhinitis.

Clinical Trials Experience in Chronic Obstructive Pulmonary Disease

The safety data described below reflect exposure to SYMBICORT 160/4.5 in 1783 patients. SYMBICORT 160/4.5 was studied in two placebo-controlled lung function studies (6 and 12 months in duration), and two active-controlled exacerbation studies (6 and 12 months in duration) in patients with COPD.

The incidence of common adverse events in Table 3 below is based upon pooled data from two double-blind, placebo-controlled lung function clinical studies (6 and 12 months in duration) in which 771 adult COPD patients (496 males and 275 females) 40 years of age and older were treated with SYMBICORT 160/4.5, two inhalations twice daily. Of these patients 651 were treated for 6 months and 366 were treated for 12 months. The SYMBICORT group was composed of mostly Caucasian (93%) patients with a mean age of 63 years, and a mean percent predicted FEV_1 at baseline of 33%. Control arms for comparison included 2 inhalations of budesonide HFA (MDI) 160 mcg, formoterol (DPI) 4.5 mcg or placebo (MDI and DPI) twice daily. Table 3 includes all adverse events that occurred at an incidence of ≥3% in the SYMBICORT group and more commonly than in the placebo group. In considering these data, the increased average duration of patient exposure to SYMBICORT should be taken into account, as incidences are not adjusted for an imbalance of treatment duration.

Table 3 Adverse reactions occurring at an incidence of ≥ 3% and more commonly than placebo in the SYMBICORT group: pooled data from two double-blind, placebo-controlled clinical COPD trials

Treatment[1]	SYMBICORT	Budesonide	Formoterol	Placebo
Adverse Event	**160/4.5 N = 771 %**	**160 mcg N = 275 %**	**4.5 mcg N = 779 %**	**N = 781 %**
Nasopharyngitis	7.3	3.3	5.8	4.9
Oral candidiasis	6.0	4.4	1.2	1.8
Bronchitis	5.4	4.7	4.5	3.5
Sinusitis	3.5	1.5	3.1	1.8
Upper respiratory tract infection viral	3.5	1.8	3.6	2.7
Average Duration of Exposure (days)	**255.2**	**157.1**	**240.3**	**223.7**

1. All treatments were administered as 2 inhalations twice daily.

Lung infections other than pneumonia (mostly bronchitis) occurred in a greater percentage of subjects treated with SYMBICORT 160/4.5 compared with placebo (7.9% vs. 5.1%, respectively). There were no clinically important or unexpected patterns of abnormalities observed for up to 1 year in chemistry, hematology, ECG, ECG (Holter) monitoring, HPA-axis, bone mineral density and ophthalmology assessments.

The safety findings from the two double-blind, active-controlled exacerbations studies (6 and 12 months in duration) in which 1012 adult COPD patients (616 males and 396 females) 40 years of age and older were treated with SYMBICORT 160/4.5, two inhalations twice daily were consistent with the lung function studies.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of SYMBICORT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Some of these adverse reactions may also have been observed in clinical studies with SYMBICORT.

Cardiac disorders: angina pectoris, tachycardia, atrial and ventricular tachyarrhythmias, atrial fibrillation, extrasystoles, palpitations
Endocrine disorders: hypercorticism, growth velocity reduction in pediatric patients
Eye disorders: cataract, glaucoma, increased intraocular pressure
Gastrointestinal disorders: oropharyngeal candidiasis, nausea
Immune system disorders: immediate and delayed hypersensitivity reactions, such as anaphylactic reaction, angioedema, bronchospasm, urticaria, exanthema, dermatitis, pruritus
Metabolic and nutrition disorders: hyperglycemia, hypokalemia
Musculoskeletal, connective tissue, and bone disorders: muscle cramps
Nervous system disorders: tremor, dizziness
Psychiatric disorders: behavior disturbances, sleep disturbances, nervousness, agitation, depression, restlessness
Respiratory, thoracic, and mediastinal disorders: dysphonia, cough, throat irritation
Skin and subcutaneous tissue disorders: skin bruising
Vascular disorders: hypotension, hypertension

DRUG INTERACTIONS

In clinical studies, concurrent administration of SYMBICORT and other drugs, such as short-acting $beta_2$-agonists, intranasal corticosteroids, and antihistamines/decongestants has not resulted in an increased frequency of adverse reactions. No formal drug interaction studies have been performed with SYMBICORT.

Inhibitors of Cytochrome P4503A4

The main route of metabolism of corticosteroids, including budesonide, a component of SYMBICORT, is via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4). After oral administration of ketoconazole, a strong inhibitor of CYP3A4, the mean plasma concentration of orally administered budesonide increased. Concomitant administration of CYP3A4 may inhibit the metabolism of, and increase the systemic exposure to, budesonide. Caution should be exercised when considering the coadministration of SYMBICORT with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) *[see Warnings and Precautions (5.9) in the full Prescribing Information]*.

Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

SYMBICORT should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of formoterol, a component of SYMBICORT, on the vascular system may be potentiated by these agents. In clinical trials with SYMBICORT, a limited number of COPD and asthma patients received tricyclic antidepressants, and, therefore, no clinically meaningful conclusions on adverse events can be made.

Beta-Adrenergic Receptor Blocking Agents

Beta-blockers (including eye drops) may not only block the pulmonary effect of beta-agonists, such as formoterol, a component of SYMBICORT, but may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Diuretics

The ECG changes and/or hypokalemia that may result from the administration of non–potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of SYMBICORT with non-potassium-sparing diuretics.

OVERDOSAGE

SYMBICORT

SYMBICORT contains both budesonide and formoterol; therefore, the risks associated with overdosage for the individual components described below apply to SYMBICORT. In pharmacokinetic studies, single doses of 960/54 mcg (12 actuations of SYMBICORT 80/4.5) and 1280/36 mcg (8 actuations of 160/4.5), were administered to patients with COPD. A total of 1920/54 mcg (12 actuations of SYMBICORT 160/4.5) was administered as a single dose to both healthy subjects and patients with asthma. In a long-term active-controlled safety study in adolescent and adult asthma patients 12 years of age and older, SYMBICORT 160/4.5 was administered for up to 12 months at doses up to twice the highest recommended daily dose. There were no clinically significant adverse reactions observed in any of these studies.

Budesonide

The potential for acute toxic effects following overdose of budesonide is low. If used at excessive doses for prolonged periods, systemic corticosteroid effects such as hypercorticism may occur *[see Warnings and Precautions (5) in the full Prescribing Information]*. Budesonide at five times the highest recommended dose (3200 mcg daily) administered to humans for 6 weeks caused a significant reduction (27%) in the plasma cortisol response to a 6-hour infusion of ACTH compared with placebo (+1%). The corresponding effect of 10 mg prednisone daily was a 35% reduction in the plasma cortisol response to ACTH.

Formoterol

An overdose of formoterol would likely lead to an exaggeration of effects that are typical for $beta_2$-agonists: seizures, angina, hypertension, hypotension, tachycardia, atrial and ventricular tachyarrhythmias, nervousness, headache, tremor, palpitations, muscle cramps, nausea, dizziness, sleep disturbances, metabolic acidosis, hyperglycemia, hypokalemia. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of formoterol. No clinically significant adverse reactions were seen when formoterol was delivered to adult patients with acute bronchoconstriction at a dose of 90 mcg/day over 3 hours or to stable asthmatics 3 times a day at a total dose of 54 mcg/day for 3 days.

Treatment of formoterol overdosage consists of discontinuation of the medication together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of formoterol. Cardiac monitoring is recommended in cases of overdosage.

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Vitamin C for sepsis? Experts take sides in debate

BY RANDY DOTINGA
MDedge News

SAN DIEGO – Powerful antibiotics come first to mind when hospitalized patients have sepsis, but a critical care pulmonology specialist urged colleagues to consider another treatment – heavy intravenous doses of vitamin C.

"There is evidence supporting benefit, and ample evidence supporting safety," Michael H. Hooper, MD, who practices in Norfolk, Va., said in a pro-and-con debate over the use of vitamin C in sepsis at the Critical Care Congress sponsored by the Society of Critical Care Medicine.

Randy Dotinga/MDedge News

Dr. Andre Kalil

Dr. Hooper's debate opponent countered by noting the lack of quality research into vitamin C in sepsis and declared that its time has not yet come. "We need more data to know the safety of this drug," said Andre Kalil, MD, professor of internal medicine and director of Transplant Infectious Diseases at the University of Nebraska Medical Center, Omaha.

Dr. Hooper was part of a member of a team led by Paul E. Marik, MD, FCCP, of Eastern Virginia Medical School, Norfolk, that made waves in 2017 with a study in Chest suggesting IV vitamin C has tremendous potential as a treatment for sepsis (Chest. 2017 Jun;151[6]:1229-38).

The retrospective study compared two groups of 47 patients with sepsis – a control group and a group that received treatment with intravenous vitamin C, hydrocortisone, and thiamine. Remarkably, the team found that 9% (4 of 47) of those in the treatment group died in the hospital, compared with 40% (19 of 47) in the control group (*P* less than .001).

The findings make sense, Dr. Hooper said, in light of the fact that "our patients are remarkably deficient" in vitamin C. He pointed to a 2017 study that found nearly 40% of 24 patients with septic shock were deficient in vitamin C – despite getting recommended enteral nutrition, parenteral nutrition, or both – compared with 25% of patients who were not septic. The study authors believe the difference is probably due to "increased metabolism due to the enhanced inflammatory response observed in septic shock" (Crit Care. 2017 Dec 11;21[1]:300).

"We're dealing with a population of patients who need some sort of repletion of this vitamin," Dr. Hooper said.

Why not try oral administration of vitamin C? "Oral administration at regular doses doesn't work," he said. "If you have normal volunteers who are made deficient, then you administer the recommended allowance, it takes days or weeks to return levels to normal."

Dr. Hooper added that the goal of vitamin C therapy isn't simply to restore proper levels in plasma. In addition, he said, "we're trying to restore levels in crucial organs."

He said the cost of treatment with IV vitamin C is low, and no serious adverse events have been seen in studies of the vitamin's use in critical care.

In his comments at the debate, Dr. Kalil pointed to several weaknesses in the 2017 study of vitamin C in sepsis. According to him, it had many problems, including a sample size that lacked statistical power and imbalances in the two groups.

Dr. Kalil raised concerns about the study in a 2017 letter published in Chest titled "Vitamin C Is Not Ready for Prime Time in Sepsis but a Solution Is Close," noting that the control group was sicker and none of those patients had their vitamin C levels measured (Chest. 2017 Sep;152[3]:676).

He added that "acute renal failure is associated with high doses of vitamin C."

As of July 2018, several clinical trials into vitamin C, hydrocortisone, and thiamine for the treatment of septic shock were underway or planned, according to a report that described the current randomized, placebo-controlled, multicenter Ascorbic Acid, Corticosteroids, and Thiamine in Sepsis (ACTS) trial in the United States.

The report notes that "robust evidence" for this approach is lacking, although "the potential effectiveness of this medication combination is rooted in biologic plausibility and supported by small clinical trials of the various individual components" (Crit Care. 2018;22:283).

Dr. Hooper is an executive committee member and principal investigator with the Vitamin C, Thiamine And Steroids in Sepsis (VICTAS) study. Dr. Kalil reports no relevant disclosures.

chestphysiciannews@chestnet.org

VIEW ON THE NEWS

Eric Gartman, MD, FCCP, comments: Research conducted in the treatment of sepsis and septic shock has met many roadblocks over the past several decades and many once-promising approaches have proven to be less effective than initially advertised. As such, it is not surprising that many are in disbelief when approaching the very impressive mortality benefits represented in the limited data available on this therapy. This topic deserves the significant attention it is receiving – and given the vast number of patients who would be eligible to receive it, due diligence regarding its safety and effectiveness is warranted prior to its ubiquitous deployment in millions of ICU patients. At present, worldwide there are multiple well-designed studies aimed at providing the answers that we need to (hopefully) settle this debate.

Sepsis survivors face ongoing immune system challenges

BY JIM KLING
MDedge News

SAN DIEGO – Survivors of sepsis face ongoing challenges, including repeat hospitalizations for infections and repeat sepsis. Although it isn't clear if such episodes result from incomplete resolution of the index infection, or they are due to lingering changes in immune function, they do suggest that physicians should engage sepsis patients in an effort to improve long-term outcomes.

It's also an argument for biomarkers and precision immune modulation in these patients, Hallie Prescott, MD, a critical care physician at the VA Ann Arbor (Mich.) Healthcare System, said during a talk at the Critical Care Congress sponsored by the Society of Critical Care Medicine.

When sepsis was first defined in 1992, physicians tended to focus on the inflammatory component, but it's now understood that multiple pathways become dysregulated, and inflammation is no longer part of the most current definition of sepsis. "We now recognize that there is early activation of both pro- and anti-inflammatory pathways, but over the course of sepsis the balance tips from this proinflammatory state in the first few days toward, for most patients, an anti-inflammatory or immune-suppressed state in the later days," said Dr. Prescott.

As advances in care have increased initial survival rates, more patients go on to the later stages, leaving clinicians to address nosocomial and other secondary infections. Dr. Prescott cited an autopsy study that showed many patients who die of sepsis in the ICU have evidence of immune suppression. Another study of patients at the end of a pneumonia hospitalization found that many patients had elevated inflammatory markers even after hospital discharge, and that such elevation

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was associated with increased mortality as far out as 1 year. The relationship was significant even after adjustment for age, comorbidity, and acute illness. "It suggests that this isn't just identification of patients who had a more severe septic episode," said Dr. Prescott.

The findings may mean that some patients take a long time to return to homeostasis, and other work suggests that about two-thirds of sepsis deaths occur after day 5.

A study by Dr. Prescott's group showed about a 40% 2-year mortality after sepsis hospitalization. When they compared sepsis survivors to matched controls, they found about half the deaths could not be explained by presepsis health status. "Rather, it [seems to be] due to the last sequelae of sepsis, or perhaps this increased risk of secondary infections," Dr. Prescott said.

Studies of the organisms causing secondary infections found increasing incidence of opportunistic infections, from 9% in the first 5 days of sepsis, to 18% in days 16 through 150. The frequency of Candida infection similarly increased, from 13% to 30%. "So in these later phases of sepsis, you're more likely to see [pathogens] that are relatively rare as the initial cause of sepsis," said Dr. Prescott.

Unfortunately, she said, research has not shown that prophylaxis improves outcomes. "My suspicion is that it's because these infections are one marker of a broader problem with immune dysfunction, and we probably need to boost or restore immune function more broadly as opposed to trying to prophylax against very specifically what the patient is at risk for," said Dr. Prescott.

SHAWN LOCKHART/CDC

The problems appear to continue after hospital discharge. A study from Dr. Prescott's group showed that about 40% of sepsis survivors were readmitted at least once within the next 90 days. The most common reason, at 6.4%, was another sepsis episode.

Compared with matched controls, sepsis patients had about a 2.5-fold higher risk for sepsis, and about a 1.5-fold increased risk an infection. "So there seems to be this heightened risk among people surviving sepsis that's not fully explained by the things that put them at risk for developing sepsis in the first place," said Dr. Prescott.

Dr. Prescott cited another study looking at the reason for recurring infections in sepsis survivors that found, in about one in five cases, the readmission was due to the same infectious organism in the same site, suggesting incomplete resolution. In about half of patients, the infection was due to a different organism, or the same organism at a different site, and in about a third of patients, the results were ambiguous due to culture-negative infections.

"I think this suggests a complex picture. Some people perhaps fail to fully eradicate the initial infection, and a larger group of people come back with something else. There's also a very high rate of infection in the same site – about 70% with a new bug have it in the same site as their initial sepsis. Some of this may be just be a reflection of the type of people who get sepsis the first time, but it still tells us that, among the patients we care for who survive sepsis, that they are over the long haul at increased risk of recurrent infections and recurrent episodes of sepsis," said Dr. Prescott.

She argued that real-time assessment of immune function may be needed and there may be a benefit of immune modulation in the later phases of sepsis. Such strategies are not likely to be implemented immediately, however. In the meantime, there are simple steps that clinicians can take, including screening of sepsis survivors and making sure they are up to date on vaccines, and then educating them about the risk of reinfection. "We know that the lay public awareness of sepsis is low. Even people who have sepsis are often unaware that they had it, and they are certainly unaware that they're at risk for having another episode," she said.

Dr. Prescott has no financial disclosures.

chestphysiciannews@chestnet.org

More fiber looks safe, might benefit ICU patients

BY AMY KARON
MDedge News

MIAMI – High-fiber diets in the ICU were well tolerated and led to desirable shifts in the gut microbiome that correlated with decreased abdominal distension, according to the results of an observational cohort study.

"Higher fiber intake was associated with greater preservation of short-chain fatty acid–producing bacteria, even after we adjusted for antibiotics and acute severity of illness," said Yichun Fu, a fourth-year medical student at Columbia University, New York, at the annual Gut Microbiota for Health World Summit.

She explained that, after 72 hours on the high-fiber diet, only 11% of patients had abdominal distension noted in their EMRs, compared with 36% of patients who received no dietary fiber (*P* less than .01). Fiber was not associated with bowel obstruction, high gastric residuals, enteric infections, edema, or diarrhea. She and her associates presented the findings in a poster at the meeting sponsored by the American Gastroenterological Association and the European Society for Neurogastroenterology and Motility.

Dietary fiber is a prebiotic that increases the abundance of short-chain fatty acid (SCFA)–producing bacteria in the gut. Growing evidence links these bacteria and their metabolites – such as acetate, propionate, and butyrate – to immunomodulatory benefits and suggests that they help maintain gut barrier function, glucose homeostasis, adipose tissue lipolysis, and normal blood pressure. Thus, fiber for ICU patients might make sense, but relevant dietary guidelines rarely address the topic. In practice, fiber is often withheld in the ICU because of concerns that it might cause bloating or diarrhea, Ms. Fu said.

For the study, the researchers performed 16s ribosomal RNA sequencing on baseline and 72-hour rectal swabs collected from 129 consecutive adults newly admitted to the ICU. Patients were eligible for the study regardless of whether they received nothing by mouth, enteral feeding, or food by mouth. They were grouped in tertiles based on fiber intake over 72 hours, corrected by caloric intake. The resulting groups were dubbed "no fiber" (median and interquartile range, 0 grams), "low fiber" (median, 11.2 g; IQR, 3.8-18.2 g), and "high fiber" (median, 39.3 g; IQR, 4.7-50.2 g).

Patients in these three groups had a similar relative abundance of SCFA-producing bacteria at baseline. At 72 hours, the high-fiber group had a significantly greater relative abundance of SCFA producers

Amy Karon/MDedge News

Yichun Fu

than the no fiber group (*P* = .01). Compared with no fiber, high-fiber intake also correlated with significantly increased gut bacterial diversity (*P* = .04) and a lower relative abundance of *Enterococcus* bacteria (*P* less than .01). None of these measures differed significantly between the no-fiber and low-fiber groups.

The groups were demographically and clinically similar at baseline, except that the high-fiber group had lower Acute Physiology and Chronic Health Evaluation IV scores (*P* = .02) and was less likely to receive antibiotics, mechanical ventilation, hemodialysis, or vasopressors (*P* less than .01). After correction for these differences, each 10-g increase in fiber intake over 72 hours correlated with a 0.3% median increase in the relative abundance of SCFA-producing bacteria (estimated IQR, 0.10%-0.46%; *P* less than .01).

"Fiber may be a simple candidate therapy for ICU patients," the researchers concluded. The team is now designing a prospective, interventional study to further test whether fiber can modify the gut microbiome to benefit ICU patients, Ms. Fu explained.

Funders included the American Gastroenterological Association, the National Institutes of Health, and the Feldstein Medical Foundation. Ms. Fu reported no competing interests.

chestphysiciannews@chestnet.org

New sleep apnea guidelines offer evidence-based recommendations

BY HEIDI SPLETE
MDedge News

New guidelines on treating obstructive sleep apnea with positive airway pressure include recommendations for using positive airway pressure (PAP) versus no therapy, using either continuous PAP (CPAP) or automatic PAP (APAP) for ongoing treatment, and providing educational interventions to patients starting PAP. The complete guidelines, issued by the American Academy of Sleep Medicine, were published in the Journal of Clinical Sleep Medicine.

The guidelines were driven by improvements in PAP adherence and device technology, wrote lead author Susheel P. Patil, MD, of Johns Hopkins University, Baltimore, and his colleagues.

The guidelines begin with a pair of Good Practice Statements to ensure effective and appropriate management of obstructive sleep apnea (OSA) in adults. First, "Treatment of OSA with PAP therapy should be based on a diagnosis of OSA established using objective sleep apnea testing." Second, "Adequate follow-up, including troubleshooting and monitoring of objective efficacy and usage data to ensure adequate treatment and adherence, should occur following PAP therapy initiation and during treatment of OSA."

The nine recommendations, approved by the AASM board of directors, include four strong recommendations that clinicians should follow under most circumstances, and five conditional recommendations that are suggested but lack strong clinical support for their appropriateness for all patients in all circumstances.

The first of the strong recommendations, for using PAP versus no therapy to treat adults with OSA and excessive sleepiness, was based on a high level of evidence from a meta-analysis of 38 randomized, controlled trials and the conclusion that the benefits of PAP outweighed the harms.

The second strong recommendation for using either CPAP or APAP for ongoing treatment was based on data from 26 trials that showed no clinically significant difference between the two. The third strong recommendation that PAP therapy be initiated using either APAP at home or in-laboratory PAP titration in adults with OSA and no significant comorbidities was supported by a meta-analysis of 10 trials that showed no clinically significant difference between at-home and laboratory initiation, and that each option has its benefits. The authors noted that "the majority of well-informed adult patients with OSA and without significant comorbidities would prefer initiation of PAP using the most rapid, convenient, and cost-effective strategy." This comment supports the fourth strong recommendation for providing educational interventions to patients starting PAP.

The guidelines were developed by a task force commissioned by the AASM that included board-certified sleep specialists and experts in PAP use and will be reviewed and updated as new information surfaces.

The conditional recommendations include using PAP versus no therapy for adults with OSA and impaired quality of life related to poor sleep, such as insomnia, snoring, morning headaches, and daytime fatigue. Other conditional recommendations include using PAP versus no therapy for adults with OSA and comorbid hypertension, choosing CPAP or APAP over bilateral PAP for routine treatment of OSA in adults, providing behavioral interventions or troubleshooting during patients' initial use of PAP, and using telemonitoring-guided interventions to monitor patients during their initial use of PAP.

"The ultimate judgment regarding any specific care must be made by the treating clinician and the patient, taking into consideration the individual circumstances of the patient, available treatment options, and resources," the authors noted.

"When implementing the recommendations, providers should consider additional strategies that will maximize the individual patient's comfort and adherence such as nasal/intranasal over oronasal mask interface and heated humidification," they added.

The guidelines were developed by a task force commissioned by the AASM that included board-certified sleep specialists and experts in PAP use, and will be reviewed and updated as new information surfaces, the authors wrote.

Dr. Patil reported no financial conflicts; several coauthors reported conflicts that were managed by their not voting on guidelines related to those conflicts.

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SOURCE: Patil SP et al. J Clin Sleep Med. 2018 Feb 15;15(2):335-43.

VIEW ON THE NEWS

Octavian C. Ioachimescu, MD, PhD, FCCP, comments: The last guidelines and practice parameters for the use of positive airway pressure (PAP) as therapy for adult patients with obstructive sleep apnea, were published in 2006 and 2008, respectively. Since then, new technological advances, an ever-growing body of literature, and shifting practice patterns led to an acute need for a thorough reassessment, a comprehensive update of the previous recommendations, and the potential of issuing new ones for emerging areas. As such, the American Academy of Sleep Medicine commissioned a task force of content experts to review the existing evidence, to issue new guidelines and to publish an associated systematic review and a meta-analysis of the literature on this topic.

These guidelines show that we still have so many areas insufficiently explored, with very conflicting or suboptimal level of evidence. A publication like this can help us see what our blind spots are in this area. For example, we do not know yet if patients without daytime sleepiness (most of the time defined bluntly by specific cutoffs of the Epworth Sleepiness Scale) benefit in the long term by instituting PAP therapy. Furthermore, impairments of other domains of quality of life have been insufficiently correlated with long-term, hard adverse outcomes. Another example: the utility of Multiple Sleep Latency testing as an objective methodology to assess residual sleepiness after PAP therapy initiation.

A welcome recommendation is the endorsement by the task force of the use of telemedicine capabilities in monitoring patients' adherence to PAP therapy. Another interesting aspect is that, while our literature is represented by a mix of both randomized and nonrandomized controlled trials, occasionally there seems to be an interesting dichotomy in the results. Randomized trials tend to point in one direction, while nonrandomized studies pooled in the meta-analysis seem to point to the contrary or to give the impression of more definitive effects. While this is not the place to make an extensive analysis of the strengths and the potential pitfalls of randomized vs nonrandomized studies, this clearly raises some issues. One is that our randomized studies are typically small, underpowered, and, hence, with nonconvincing risk or hazard reduction assessments. Second, the dichotomy in the results may be driven by publication bias, expense, and difficulty in performing adequately powered, long-term trials that essentially may be studying small effects.

Guidelines are not intended to be used in an Occam's razor approach but in a fashion that would allow individualization of therapy while critically appraising the existing evidence for various interventions in specific conditions and maintaining a very stringent and critical view on generalizability, expected results, and adequate management of reasonable expectations. In addition, the areas that are unclear, with conflicting evidence or in which the guidelines allow "too much" latitude to the treating clinician, may be seen as either an invitation to remain "creative," or one for abstaining from action in the name of equipoise. I would advise that both extremes are to be avoided.

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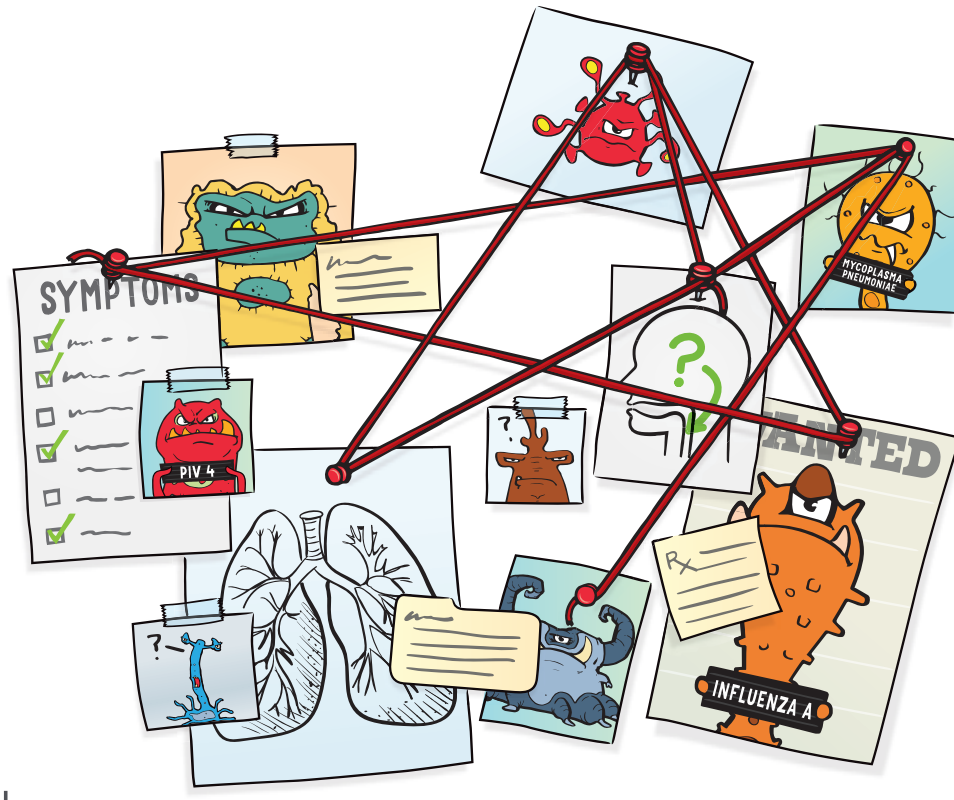

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Study disputes CPAP link to weight gain in OSA patients

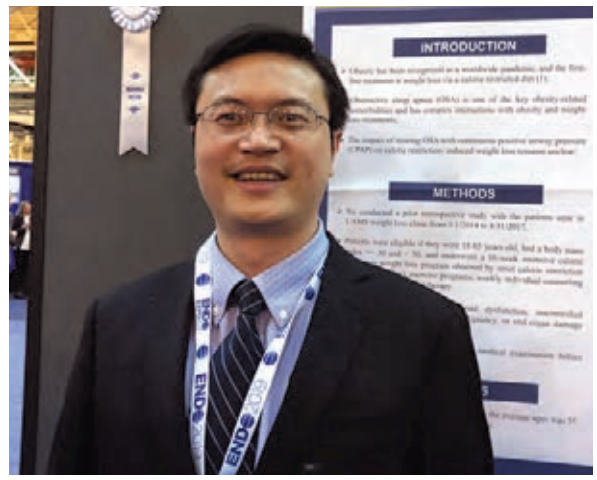
BY TED BOSWORTH
MDedge News

NEW ORLEANS – Contrary to previously published data suggesting continuous positive airway pressure (CPAP) produces weight gain in patients with obstructive sleep apnea (OSA), new study findings presented at the annual meeting of the Endocrine Society provided data supporting the exact opposite conclusion.

"We think the data are strong enough to conclude that combining CPAP with a weight-loss program should be considered for all OSA patients. The weight-loss advantage is substantial," reported Yuanjie Mao, MD, PhD, of the University of Arkansas for Medical Sciences, Little Rock.

Both weight loss and CPAP have been shown to be effective for the treatment of OSA, but concern that CPAP produces a counterproductive gain in weight was raised by findings in a meta-analysis in which CPAP was associated with increased body mass index (Thorax. 2015 Mar;70:258-64). As a result of that finding, some guidelines subsequently advised intensifying a weight-loss program at the time that CPAP is initiated to mitigate the weight-gain effect, according to Dr. Mao. However, he noted that prospective data were never collected, so a causal relationship was never proven. Now, his data support the opposite conclusion.

In the more recent study, 300 patients who had participated in an intensive weight-loss program at his institution were divided into three groups: OSA patients who had been treated with CPAP, symptomatic OSA patients who had not been treated with CPAP, and asymptomatic OSA patients not treated with CPAP. They were compared retrospectively for weight change over a 16-week period.



Ted Bosworth/MDedge News

Dr. Yuanjie Mao

"This was a very simple study," said Dr. Mao, who explained that several exclusions, such as thyroid dysfunction, active infection, and uncontrolled diabetes, were used to reduce variables that might also affect weight change. At the end of 16 weeks, the median absolute weight loss in the CPAP group was 26.7 lb (12.1 kg), compared with 21 lb (9.5 kg) for the symptomatic OSA group and 19.2 lb (8.7 kg) for the asymptomatic OSA group. The weight loss was significantly greater for the CPAP group (*P* less than .01), compared with either of the other two groups, but not significantly different between the groups that were not treated with CPAP.

"The differences remained significant after adjusting for baseline BMI [body mass index], age, and gender," Dr. Mao reported.

Asked why his data contradicted the previously reported data, Dr. Mao said that the previous studies were not evaluating CPAP in the context of a weight-loss program. He contends that when CPAP is combined with a rigorous weight-reduction regimen, there is an additive benefit from CPAP.

According to Dr. Mao, these data bring the value of CPAP for weight loss full circle. Before publication of the 2015 meta-analysis, it was widely assumed that CPAP helped with weight loss based on the expectation that better sleep quality would increase daytime activity. However, in the absence of strong data confirming that effect, Dr. Mao believes the unexpected results of the 2015 study easily pushed the pendulum in the opposite direction.

"The conclusion that CPAP increases weight was drawn from studies not designed to evaluate a weight-loss effect in those participating in a weight-loss program," Dr. Mao said. His study suggests that it is this combination that is important. He believes the observed effect from better sleep quality associated with CPAP is not necessarily related to better daytime function alone.

"Patients who sleep well also have more favorable diurnal changes in factors that might be important to weight change, such as leptin resistance and hormonal secretion," he said. Although more work is needed to determine whether these purported mechanisms are important, he thinks his study has an immediate clinical message.

"Patients with OSA who are prescribed weight loss should also be considered for CPAP for the goal of weight loss," Dr. Mao said. "We think this therapy should be started right away."

chestphysiciannews@chestnet.org

SOURCE: Mao Y et al. ENDO 2019, Session SAT-095.

More sleep can help youth manage type 1 diabetes

BY STEVE CIMINO
MDedge News

More sleep can lead to better glycemic control in youth with type 1 diabetes mellitus, according to a study of sleep duration and quality in young diabetes patients.

"This study adds to the growing body of literature that supports the cascading effects of sleep on multiple aspects of diabetes-related outcomes," wrote lead author Sara S. Frye, PhD, of the University of Arizona, Tucson, and her coauthors, adding that the results "highlight the importance of assessing sleep in this population that appears to be at high risk for insufficient sleep duration." The study was published in Sleep Medicine.


JovanMandic/Getty Images

Dr. Frye and her colleagues recruited 111 children between the ages of 10 and 16 with type 1 diabetes mellitus to participate in their Glucose Regulation and Neurobehavioral Effects of Sleep (GRANES) study. The participants wore wrist actigraphs for an average of 5.5 nights to objectively measure sleep, including duration, quality, timing, and consistency. They completed self-reported sleep diaries each morning of the study. Glycemic control and diabetes management were assessed via hemoglobin A_{1c} (HbA_{1c}) levels and self-monitoring of blood glucose (SMBG) frequency, which were obtained via medical records. The participants and their parents also completed the Diabetes Management Scale.

Based on actigraphy data, the average total sleep time was 7.45 hours (standard deviation, 0.74), below the recommended duration of 9 hours for youths in this age group. All but one participant was recorded as sleeping less than the recommended amount. Average HbA_{1c} of 9.11% (SD, 1.95) indicated poor diabetic control, and the average SMBG frequency was 4.90 (SD, 2.71) with a range of 1-14 checks per day. Per mediation analysis, for every additional hour of sleep, HbA_{1c} was reduced by 0.33% and SMBG frequency went up by 0.88. In addition, SMBG frequency was related to HbA_{1c}, supporting previous findings that "self-management behaviors play a critical role in maintaining diabetes control."

The coauthors acknowledged the limitations of their study, including actigraphy data being logged over a 1-week period instead of the recommended 2 weeks. They also relied on medical records to determine HbA_{1c} and SMBG rather than collecting that information along with the actigraphy data. However, they did note that HbA_{1c} measures glucose levels over a 3-month period, which would have covered their participation in the study.

The study was supported by American Diabetes Association and cosponsored by the Order of the Amaranth Diabetes Foundation. The authors reported no conflicts of interest.

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SOURCE: Frye SS et al. Sleep Med. 2019 Feb 16. doi: 10.1016/j.sleep.2019.01.043.

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Indication

REVATIO is a phosphodiesterase-5 (PDE5) inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) in adults to improve exercise ability and delay clinical worsening. Studies establishing effectiveness were short-term (12 to 16 weeks), and included predominately patients with NYHA Functional Class II-III symptoms. Etiologies were idiopathic (71%) or associated with connective tissue disease (25%).

Limitation of Use: Adding sildenafil to bosentan therapy does not result in any beneficial effect on exercise capacity.

Important Safety Information

REVATIO is contraindicated in patients with concomitant use of organic nitrates in any form, either regularly or intermittently, because of the greater risk of hypotension.

REVATIO is contraindicated in patients with concomitant use of riociguat, a soluble guanylate cyclase (sGC) stimulator medication. PDE5 inhibitors, including sildenafil, may potentiate the hypotensive effects of riociguat.

REVATIO is contraindicated in patients with a known hypersensitivity to sildenafil or any other ingredient in REVATIO. Hypersensitivity, including anaphylactic reaction, anaphylactic shock, and anaphylactoid reaction has been reported in association with the use of sildenafil.

Use of REVATIO, particularly chronic use, is not recommended in children.

Before starting REVATIO, physicians should carefully consider whether their patients with underlying conditions could be adversely affected by the mild and transient vasodilatory effects of REVATIO on blood pressure. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD) and administration of REVATIO to these patients is not recommended. Should signs of pulmonary edema occur when sildenafil is administered, the possibility of associated PVOD should be considered.

Caution is advised when PDE5 inhibitors, such as REVATIO, are administered with α–blockers as both are vasodilators with blood pressure lowering effects.

In PAH patients, the concomitant use of vitamin K antagonists and REVATIO resulted in a greater incidence of reports of bleeding (primarily epistaxis) versus placebo. The incidence of epistaxis was higher in patients with PAH secondary to CTD (sildenafil 13%, placebo 0%) than in PPH patients (sildenafil 3%, placebo 2%).

Co-administration of REVATIO with potent CYP3A4 inhibitors (eg, ketoconazole, itraconazole, and ritonavir) is not recommended as serum concentrations of sildenafil substantially increase. Co-administration of REVATIO with potent CYP3A4 inducers such as barbiturates, carbamazepine, phenytoin, efavirenz, nevirapine, rifampin, and rifabutin is expected to cause substantial decreases in plasma levels of sildenafil. Treatment with doses higher than 20 mg three times a day is not recommended.

Non-arteritic anterior ischemic optic neuropathy (NAION) has been reported post marketing in temporal association with the use of PDE5 inhibitors for the treatment of erectile dysfunction, including sildenafil. Physicians should advise patients to seek immediate medical attention in the event of sudden loss of vision while taking PDE5 inhibitors, including REVATIO. Physicians should also discuss the increased risk of NAION with patients who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE5 inhibitors.

Sudden decrease or loss of hearing has been reported in temporal association with the intake of PDE5 inhibitors, including REVATIO. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE5 inhibitors, including REVATIO.

REVATIO should be used with caution in patients with anatomical deformation of the penis or patients who have conditions which may predispose them to priapism.

The effectiveness of REVATIO in pulmonary hypertension (PH) secondary to sickle cell anemia has not been established. In a small, prematurely terminated study of patients with PH secondary to sickle cell disease, vaso-occlusive crises requiring hospitalization were more commonly reported by patients who received REVATIO than by those randomized to placebo.

Patients with retinitis pigmentosa and patients on bosentan did not participate in the preapproval clinical trial. The safety of REVATIO is unknown in patients with bleeding disorders and patients with active peptic ulceration. In these patients, physicians should prescribe REVATIO with caution.

REVATIO contains sildenafil, the same active ingredient found in VIAGRA®. Combinations of REVATIO with VIAGRA or other PDE5 inhibitors have not been studied. Patients taking REVATIO should not take VIAGRA or other PDE5 inhibitors.

Limited published data from randomized controlled trials, case-controlled trials, and case series do not report a clear association with sildenafil and major birth defects, miscarriage, or adverse maternal or fetal outcomes when sildenafil is used during pregnancy. There are risks to the mother and fetus from untreated PAH.

Limited published data from a case report describe the presence of sildenafil and its active metabolite in human milk. There is insufficient information about the effects of sildenafil on the breastfed infant and no information on the effects of sildenafil on milk production. Limited clinical data during lactation preclude a clear determination of the risk of REVATIO to an infant during lactation.

The most common side effects of REVATIO greater than or equal to 3% were epistaxis, headache, dyspepsia, flushing, insomnia, erythema, dyspnea, and rhinitis. Adverse events of REVATIO injection were similar to those seen with oral tablets.

The most common side effects of REVATIO (placebo-subtracted) as an adjunct to intravenous epoprostenol were headache (23%), edema (14%), dyspepsia (14%), pain in extremity (11%), diarrhea (7%), nausea (7%), and nasal congestion (7%).

At doses higher than the recommended 20 mg TID, there was a greater incidence of some adverse events including flushing, diarrhea, myalgia, and visual disturbances.

No dose adjustment required for renal impaired.

No dose adjustment required for mild to moderate hepatic impaired. Severe impairment has not been studied.

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INDICATION AND USAGE

REVATIO is a phosphodiesterase (PDE-5) indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in adults to improve exercise ability and delay clinical worsening.

Studies establishing effectiveness were short-term (12 to 16 weeks), and included predominately patients with NYHA Functional Class II-III symptoms. Etiologies were idiopathic (71%) or associated with connective tissue disease (CTD) (25%).

Limitation of Use: Adding sildenafil to bosentan therapy does not result in any beneficial effect on exercise capacity.

DOSAGE AND ADMINISTRATION

REVATIO Tablets and Oral Suspension The recommended dose of REVATIO is 5 mg or 20 mg three times a day. Administer REVATIO doses 4–6 hours apart. In the clinical trial no greater efficacy was achieved with the use of higher doses. Treatment with doses higher than 20 mg three times a day is not recommended.

Reconstitution of the Powder for Oral Suspension 1. Tap the bottle to release the powder. 2. Remove the cap. 3. Accurately measure out 60 mL of water and pour the water into the bottle. 4. Replace the cap and shake the bottle vigorously for a minimum of 30 seconds. 5. Remove the cap. 6. Accurately measure out another 30 mL of water and add this to the bottle. You should always add a total of 90 mL of water irrespective of the dose prescribed. 7. Replace the cap and shake the bottle vigorously for a minimum of 30 seconds. 8. Remove the cap. 9. Press the bottle adaptor into the neck of the bottle. The adaptor is provided so that you can fill the oral syringe with medicine from the bottle. Replace the cap on the bottle. 10. Write the expiration date of the constituted oral suspension on the bottle label (the expiration date of the constituted oral suspension is 60 days from the date of constitution).

Incompatibilities Do not mix with any other medication or additional flavoring agent.

CONTRAINDICATIONS

REVATIO is contraindicated in patients with concomitant use of organic nitrates in any form, either regularly or intermittently, because of the greater risk of hypotension [*see Warnings and Precautions*], Concomitant use of riociguat, a guanylate cyclase stimulator. PDE5 inhibitors, including sildenafil, may potentiate the hypotensive effects of riociguat. REVATIO is also contraindicated in patients with known hypersensitivity to sildenafil or any component of the tablet, injection, or oral suspension. Hypersensitivity, including anaphylactic reaction, anaphylactic shock and anaphylactoid reaction, has been reported in association with the use of sildenafil.

WARNINGS AND PRECAUTIONS

Mortality with Pediatric Use In a long-term trial in pediatric patients with PAH, an increase in mortality with increasing REVATIO dose was observed. Deaths were first observed after about 1 year and causes of death were typical of patients with PAH. Use of REVATIO, particularly chronic use, is not recommended in children [*see Use in Specific Populations*].

Hypotension REVATIO has vasodilatory properties, resulting in mild and transient decreases in blood pressure. Before prescribing REVATIO, carefully consider whether patients with certain underlying conditions could be adversely affected by such vasodilatory effects (e.g., patients on antihypertensive therapy or with resting hypotension [BP less than 90/50], fluid depletion, severe left ventricular outflow obstruction, or automatic dysfunction). Monitor blood pressure when co-administering blood pressure lowering drugs with REVATIO.

Worsening Pulmonary Vascular Occlusive Disease Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Since there are no clinical data on administration of REVATIO to patients with veno-occlusive disease, administration of REVATIO to such patients is not recommended. Should signs of pulmonary edema occur when REVATIO is administered, consider the possibility of associated PVOD.

Epistaxis The incidence of epistaxis was 13% in patients taking REVATIO with PAH secondary to CTD. This effect was not seen in idiopathic PAH (REVATIO 3%, placebo 2%) patients. The incidence of epistaxis was also higher in REVATIO-treated patients with a concomitant oral vitamin K antagonist (9% versus 2% in those not treated with concomitant vitamin K antagonist). The safety of REVATIO is unknown in patients with bleeding disorders or active peptic ulceration.

Visual Loss When used to treat erectile dysfunction, non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported postmarketing in temporal association with the use of phosphodiesterase type 5 (PDE-5) inhibitors, including sildenafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. Based on published literature, the annual incidence of NAION is 2.5–11.8 cases per 100,000 males aged ≥ 50 per year in the general population. An observational case-crossover study evaluated risk of NAION when PDE-5 inhibitor use, as a class, occurred immediately before NAION onset (within 5 half-lives), compared to the PDE-5 inhibitor in a prior time period. The results suggest an approximately 2-fold increase in the risk of NAION with a risk estimate of 2.15 (95% CI 1.06, 4.34). A similar study reported a consistent result, with a risk estimate of 2.27 (95% CI 0.99, 5.20). Other risk factors for NAION, such as the presence of "crowded" optic disc, may have contributed to the occurrence of NAION in these studies. Advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes while taking PDE-5 inhibitors, including REVATIO. Physicians should also discuss the increased risk of NAION with patients who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE-5 inhibitors.

There are no controlled clinical data on the safety or efficacy of REVATIO in patients with retinitis pigmentosa, a minority whom have genetic disorders of retinal phosphodiesterases. Prescribe REVATIO with caution in these patients.

Hearing Loss Cases of sudden decrease or loss of hearing, which may be accompanied by tinnitus and dizziness, have been reported in temporal association with the use of PDE-5 inhibitors, including REVATIO. In some of the cases, medical conditions and other factors were reported that may have played a role. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of REVATIO, to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors. Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE-5 inhibitors, including REVATIO.

Combination with Other PDE-5 Inhibitors Sildenafil is also marketed as VIAGRA®. The safety and efficacy of combinations of REVATIO with VIAGRA or other PDE-5 inhibitors have not been studied. Inform patients taking REVATIO not to take VIAGRA or other PDE-5 inhibitors.

Priapism Use REVATIO with caution in patients with anatomical deformation of the penis (e.g., angulation, cavernosal fibrosis, or Peyronie's disease) or in patients who have conditions, which may predispose them to priapism (e.g., sickle cell anemia, multiple myeloma, or leukemia). In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism (painful erection greater than 6 hours in duration) is not treated immediately, penile tissue damage and permanent loss of potency could result.

Vaso-occlusive Crisis in Patients with Pulmonary Hypertension Secondary to Sickle Cell Anemia In a small, prematurely terminated study of patients with pulmonary hypertension (PH) secondary to sickle cell disease, vaso-occlusive crises requiring hospitalization were more commonly reported by patients who received REVATIO than by those randomized to placebo. The effectiveness and safety of REVATIO in the treatment of PAH secondary to sickle cell anemia has not been established.

ADVERSE REACTIONS

Clinical Trials Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Safety data of REVATIO in adults were obtained from the 12-week, placebo-controlled clinical study (Study 1) and an open-label extension study in 277 REVATIO-treated patients with PAH, WHO Group I.

The overall frequency of discontinuation in REVATIO-treated patients on 20 mg three times a day was 3% and was the same for the placebo group. In Study 1, the adverse reactions that were reported by at least 3% of REVATIO-treated patients (20 mg three times a day) and were more frequent in REVATIO-treated patients than in placebo-treated patients are shown in Table 1. Adverse reactions were generally transient and mild to moderate in nature.

Table 1: Most Common Adverse Reactions in Patients with PAH in Study 1 (More Frequent in REVATIO® (sildenafil)-Treated Patients than Placebo-Treated Patients and Incidence ≥3% in REVATIO-Treated Patients)

	Placebo, % (n=70)	REVATIO 20 mg three times a day, % (n=69)	Placebo-Subtracted, %
Epistaxis	1	9	8
Headache	39	46	7
Dyspepsia	7	13	6
Flushing	4	10	6
Insomnia	1	7	6
Erythema	1	6	5
Dyspnea exacerbated	3	7	4
Rhinitis	0	4	4
Diarrhea	6	9	3
Myalgia	4	7	3
Pyrexia	3	6	3
Gastritis	0	3	3
Sinusitis	0	3	3
Paresthesia	0	3	3

At doses higher than the recommended 20 mg three times a day, there was a greater incidence of some adverse reactions including flushing, diarrhea, myalgia and visual disturbances. Visual disturbances were identified as mild and transient, and were predominately color-tinge to vision, but also increased sensitivity to light or blurred vision.

The incidence of retinal hemorrhage with REVATIO 20 mg three times a day was 1.4% versus 0% placebo and for all REVATIO doses studied was 1.9% versus 0% placebo. The incidence of eye hemorrhage at both 20 mg three times a day and at all doses studied was 1.4% for REVATIO versus 1.4% for placebo. The patients experiencing these reactions had risk factors for hemorrhage including concurrent anticoagulant therapy.

In a placebo-controlled fixed dose titration study (Study 2) of REVATIO (starting with recommended dose of 20 mg and increased to 40 mg and then 80 mg all three times a day) as an adjunct to intravenous epoprostenol in patients with PAH, the adverse reactions that were more frequent in the REVATIO + epoprostenol group than in the epoprostenol group (greater than 6% difference) are shown in Table 2.

Table 2: Adverse Reactions (%) in patients with PAH in Study 2 (incidence in REVATIO + Epoprostenol group at least 6% greater than Epoprostenol group)

	REVATIO + Epoprostenol (n=134)	Epoprostenol (n=131)	(REVATIO + Epoprostenol) minus Epoprostenol
Headache	57	34	23
Edema^	25	13	14
Dyspepsia	16	2	14
Pain in extremity	17	6	11
Diarrhea	25	18	7
Nausea	25	18	7
Nasal congestion	9	2	7

^includes peripheral edema

Postmarketing Experience The following adverse reactions have been identified during post approval use of sildenafil (marketed for both PAH and erectile dysfunction). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiovascular Events In postmarketing experience with sildenafil at doses indicated for erectile dysfunction, serious cardiovascular, cerebrovascular, and vascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension, pulmonary hemorrhage, and subarachnoid and intracerebral hemorrhages have been reported in temporal association with the use of the drug. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of sildenafil without sexual activity. Others were reported to have occurred hours to days after use concurrent with sexual activity. It is not possible to determine whether these events are related directly to sildenafil, to sexual activity, to the patient's underlying cardiovascular disease, or to a combination of these or other factors.

Nervous system Seizure, seizure recurrence.

Clinical depression found in a quarter of OSA patients

BY JEFF CRAVEN
MDedge News

About a quarter of patients with obstructive sleep apnea also had clinical depression and used antidepressants, recent research has shown.

Although patients in the study associated their sleep disorder with poorer quality of life as well as symptoms of anxiety and depression, it is unclear whether treating their obstructive sleep apnea (OSA) with continuous positive airway pressure (CPAP) would alleviate these symptoms, said Melinda L. Jackson, PhD, from Monash University in Clayton, Victoria, Australia, and her colleagues.

"OSA is a modifiable factor that, if treated, may reduce the economic, health care, and personal burden of depression," Dr. Jackson and her colleagues wrote in their study, recently published in the journal Sleep Medicine. "Findings from the treatment phase of this study will help us determine whether clinical depression is alleviated with CPAP use, taking into account antidepressant use; whether there are subgroups of patients who respond better to treatment; and what are the characteristics of patients who respond compared to those who remain depressed."

The researchers used baseline data from 109 patients in the CPAP for OSA and Depression trial who were diagnosed with OSA. Participants (mean age, 52.6 years; 43.1% female) consecutively presented to a sleep laboratory where they answered interview questions to assess clinical depression and sleep habits. Data were collected using the structured clinical interview for depression (SCID-IV), Hospital Anxiety and Depression Scale, Pittsburgh Sleep Quality Index (PSQI), Functional Outcomes of Sleep Questionnaire (FOSQ), Epworth Sleepiness Scale, and Assessment of Quality of Life questionnaire. In addition, the researchers performed a meta-analysis of seven studies, including the current study, to determine the prevalence of clinical depression among patients with untreated OSA.

Overall, SCID-IV scores identified clinical depression in 25 participants (22.7%), and these participants said they had greater sleep disturbance and reported higher depressive, anxiety and stress as well as lower quality of life as a result of their clinical depression. Researchers found these participants also had significantly worse quality of sleep (*P* less than .05) and daytime dysfunction (*P* less than .05) as identified by PSQI scores, while FOSQ results showed participants with clinical depression had significantly lower activity levels, social outcomes, and general productivity, compared with patients without clinical depression (*P* less than .05). In a meta-analysis, Dr. Jackson and her colleagues found a pooled prevalence of 23% for clinical depression among participants with OSA.

Participants using antidepressants were examined separately from participants who had clinical depression. The researchers found 27 participants (24.8%) using antidepressants who also had reported higher symptoms of anxiety, depression, and stress; lower quality of life; and poorer sleep outcomes. Participants using antidepressants also were more likely to have bipolar disorder or a condition such as hypertension, chronic obstructive pulmonary disease, high cholesterol, or type 2 diabetes, and 75% of these participants reported having some type of comorbid condition.

The investigators noted they were uncertain whether depression or OSA occurred first, or whether depression exacerbated symptoms of OSA through other factors such as weight gain, sleep disruption, inactivity, or alcohol use. Depression and OSA may also present independently of one another, they added.

"Development of scales to better capture information about when symptoms commenced and the length of time an individual has experienced OSA will provide a clearer understanding of the consequences of OSA on psychological and medical conditions," the researchers said.

This study was funded by the Austin Medical Research Fund, and one authors reported support from an National Health and Medical Research Council Early Career Fellowship. The authors report no relevant conflicts.

chestphysician@chestnet.org

SOURCE: Jackson ML et al. Sleep Med. 2019 Mar 27. doi: 10.1016/j.sleep.2019.03.011.

Five pitfalls in optimizing heart failure management

BY BRUCE JANCIN
MDedge News

SNOWMASS, COLO. – Many of the abundant missed opportunities to optimize pharmacotherapy for heart failure with reduced ejection fraction revolve around not getting fully on board with the guideline-directed medical therapy shown to be highly effective at improving clinical outcomes, Akshay S. Desai, MD, asserted at the Annual Cardiovascular Conference at Snowmass sponsored by the American College of Cardiology.


Dr. Desai

"If you take nothing else away from this talk, the opportunity to improve clinical outcomes in your population through both optimization of selection of therapies and optimization of dose is really quite profound," declared Dr. Desai, director of the cardiomyopathy and heart failure program at Brigham and Women's Hospital, and a cardiologist at Harvard Medical School, Boston.

He highlighted five common traps or pitfalls for physicians with regard to medical therapy of patients with heart failure with reduced ejection fraction (HFrEF):

Underutilizing guideline-directed medical therapy

The current ACC/American Heart Association/Heart Failure Society of America guidelines on heart failure management (Circulation. 2017 Aug 8;136[6]:e137-61) reflect 20 years of impressive progress in improving heart failure outcomes through the use of increasingly effective guideline-directed medical therapy (GDMT). The magnitude of this improvement was nicely captured in a meta-analysis of 57 randomized controlled trials published during 1987-2015. The meta-analysis showed that, although ACE inhibitor therapy alone had no significant impact on all-cause mortality compared to placebo in patients with HFrEF, the sequential addition of guideline-directed drugs conferred stepwise improvements in survival. This approach culminated in a 56% reduction in all-cause mortality with the combination of an ACE inhibitor, beta-blocker, and mineralocorticoid receptor antagonist (MRA), compared with placebo, and a 63% reduction with an angiotensin receptor-neprilysin inhibitor (ARNI), beta-blocker, and MRA (Circ Heart Fail. 2017 Jan;10[1]. pii: e003529).

Moreover, the benefits of contemporary GDMT extend beyond reductions in all-cause mortality, death due to heart failure, and heart failure–related hospitalizations into areas where one wouldn't necessarily have expected to see much benefit. For example, an analysis of data on more than 40,000 HFrEF patients in 12 clinical trials showed a sharp decline in the rate of sudden death over the years as new agents were incorporated into GDMT. The cumulative incidence of sudden death within 90 days after randomization plunged from 2.4% in the earliest trial to 1.0% in the most recent one (N Engl J Med. 2017 Jul 6;377[1]:41-51).

"We're at the point where we now question whether routine use of implantable cardioverter-defibrillators in primary prevention patients with nonischemic heart failure is really worthwhile on the backdrop of effective medical therapy," Dr. Desai observed.

But there's a problem: "We don't do a great job with GDMT, even with this incredible evidence base that we have," the cardiologist said.

He cited a report from the CHAMP-HF registry that scrutinized the use of GDMT in more than 3,500 ambulatory HFrEF patients in 150 U.S. primary care and cardiology practices. It found that 67% of patients deemed eligible for an MRA weren't on one. Neither were 33% with no contraindications to beta-blocker therapy and 27% who were eligible for an ACE inhibitor, angiotensin receptor blocker (ARB), or ARNI (J Am Coll Cardiol. 2018 Jul 24;72[4]:351-66).

Underdosing GDMT

The CHAMP-HF registry contained further disappointing news regarding the state of treatment of patients with HFrEF in ambulatory settings: Among those patients who were on GDMT, very few were receiving the recommended target doses of the medications as established in major clinical trials and specified in the guidelines. Only 14% of patients on an ARNI were on the target dose, as were 28% on a beta-blocker, and 17% of those on an ACE inhibitor or ARB. And among patients who were eligible for all classes of GDMT, just 1% were simultaneously on the target doses of an MRA, beta-blocker, and ARNI, ACE inhibitor, or ARB. This despite solid evidence that, although some benefit is derived from initiating these medications, incremental benefit comes from dose titration.

"Even for those of us who feel like we do this quite well, if we examine our practices systematically – and we've done this in our own practices at Brigham and Women's – you see that a lot of eligible patients aren't on optimal therapy. And you might argue that many of them have contraindications, but even when you do a deep dive into the literature or the electronic medical record and ask the question – Why is this patient with normal renal function and normal potassium with class II HFrEF not on an MRA? – sometimes it's hard to establish why that's the case," said Dr. Desai.

Interrupting GDMT during hospitalizations

This is common practice. But in fact, continuation of GDMT is generally well tolerated in the setting of acute decompensated heart failure in the absence of severe hypotension and cardiogenic shock. Moreover, in-hospital discontinuation or dose reduction is associated with increased risks of readmission and mortality.

And in treatment-naive HFrEF patients, what better place to introduce a medication and assess its tolerability than the hospital? Plus, medications prescribed at discharge are more likely to be continued in the outpatient setting, he noted.

Being seduced by the illusion of stability

The guidelines state that patients with NYHA class II or III HFrEF who tolerate an ACE inhibitor or ARB should be transitioned to an ARNI to further reduce their risk of morbidity and mortality. Yet many physicians wait to make the switch until clinical decompensation occurs. That's a mistake, as was demonstrated in the landmark PARADIGM-HF trial. Twenty percent of study participants without a prior hospitalization for heart failure experienced cardiovascular death or heart failure hospitalization during the follow-up period. Patients who were clinically stable as defined by no prior heart failure hospitalization or none within 3 months prior to enrollment were as likely to benefit from ARNI therapy with sacubitril/valsartan (Entresto) as were those with a recent decompensation (JACC Heart Fail. 2016 Oct;4[10]:816-22). "A key message is that stability is an illusion in patients with symptomatic heart failure," said Dr. Desai. "In PARADIGM-HF, the first event for about half of patients was not heralded by a worsening of symptoms or a heart failure hospitalization, it was an abrupt death at home. This may mean that a missed opportunity to optimize treatment may not come back to you down the road, so waiting until patients get worse in order to optimize their therapy may not be the best strategy."

Inadequately monitoring lab levels

The MRAs, spironolactone and eplerenone (Inspra), are the GDMT drugs for which laboratory surveillance takes on the greatest importance because of their potential to induce hyperkalemia. The guidelines are clear that a potassium level and measurement of renal function should be obtained within a week of initiating therapy with an MRA, again at 4 weeks, and periodically thereafter. "In general, this is done in clinical practice almost never," he said.

These agents should be avoided in patients with prior hyperkalemia or advanced chronic kidney disease, and used with care in groups known to be at increased risk for hyperkalemia, including the elderly and patients with diabetes.

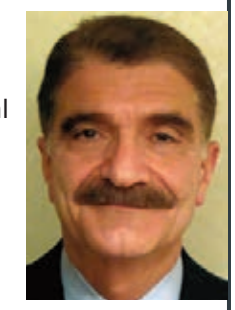
He considers spironolactone equivalent to eplerenone so long as the dosing is adequate. He generally reserves eplerenone for patients with poorly tolerated antiandrogenic effects on spironolactone.

Dr. Desai reported serving as a paid consultant to more than half a dozen pharmaceutical or medical device companies.

bjancin@mdedge.com

VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments:



The stepwise institution of guideline-directed medical therapy for patients with HFrEF as suggested by the author should improve the clinical outcomes in this high-risk patient population.

PIONEER-HF extension: For heart failure patients, don't delay starting sacubitril/valsartan

BY BRUCE JANCIN
MDedge News

NEW ORLEANS – Waiting a few months after a patient has been hospitalized for acute decompensated heart failure before launching a switch from enalapril to sacubitril/valsartan imposes a steep price in terms of extra major cardiovascular events, compared with starting the angiotensin-neprilysin inhibitor during the initial hospitalization, according to the open-label extension of the PIONEER-HF trial.

"We think these data have important clinical implications: While sacubitril/valsartan decreases NT-proBNP compared with enalapril regardless of when it is initiated, the early improvement in postdischarge outcomes supports the in-hospital initiation of sacubitril/valsartan in stabilized patients with acute decompensated heart failure," Adam D. DeVore, MD, declared in presenting the PIONEER-HF Extension results at the annual meeting of the American College of Cardiology.

PIONEER-HF was a landmark, practice-changing, double-blind clinical trial in which 881 patients were randomized to initiation of sacubitril/valsartan (Entresto) or enalapril during hospitalization for acute decompensated heart failure. In the previously reported main outcome, 8 weeks after discharge the sacubitril/valsartan group had a 29% greater reduction in NT-proBNP (the N-terminal prohormone of brain natriuretic peptide) and a 42% lower rate of the composite clinical endpoint of cardiovascular death or heart failure rehospitalization than the enalapril group (N Engl J Med. 2019 Feb 7;380[6]:539-48).

The 4-week open-label extension of PIONEER-HF began at week 8, when participants initially randomized to enalapril during the double-blind phase were switched

Bruce Jancin/MDedge News

Dr. Adam D. DeVore

to sacubitril/valsartan, while those assigned to in-hospital initiation of the angiotensin receptor-neprilysin inhibitor (ARNI) stayed the course.

At week 12, after 4 weeks of open-label treatment, patients on sacubitril/valsartan from the start experienced an additional 18.5% drop in NT-proBNP from their week 8 baseline of 1,218 pg/mL. Meanwhile, the NT-proBNP level in the switch group plunged by 35.8% from a week 8 baseline of 1,630 pg/mL. As a result, both groups ended up at the same much-improved biomarker level at week 12, observed Dr. DeVore, a cardiologist at Duke University in Durham, N.C.

Clinical event rates, however, were another story altogether. The clinical event gap between the two study arms documented at week 8 in the double-blind phase of the trial didn't close significantly in the 4 weeks after the enalapril group crossed over to open-label sacubitril/valsartan. Indeed, the relative risk of the composite endpoint of cardiovascular death, heart failure rehospitalization, or left ventricular assist device implantation during the 4-week extension phase was 33% lower in the continuous sacubitril/valsartan group than in the switchers. The absolute risk reduction was 5.6%, with a favorable number needed to treat of 18.

This difference was driven mainly by less rehospitalization for heart failure.

"But this is an important thing as we think about what we're trying to accomplish in heart failure: trying to find tools that improve rehospitalization rates after people leave the hospital is extremely important," Dr. DeVore said. "We do know that the really vulnerable period for rehospitalization is early on, so my suspicion – though I can't prove it – is that's the important part. That's when we need to have patients on the best therapy."

He was asked how practical it is to initiate sacubitril/valsartan during hospitalization for acute decompensated heart failure in real-world clinical practice, given that it can be done only after patients achieve hemodynamic stability.

"I think the definition of hemodynamic stability we used in the trial was a fairly straightforward one, very clinical, and one we can translate to the bedside," Dr. DeVore replied. "Patients had to have a systolic blood pressure of 100 mm Hg or greater for 6 hours, which is easily documented in the hospital, no changes in IV diuretics or IV vasodilators for 6 hours, and no IV inotropes for the last 24 hours. That's how we defined hemodynamic stability. I think we should be able to find these patients."

Average length of stay in the index hospitalization in PIONEER-HF was just over 5 days, but the study protocol actually resulted in longer-than-needed hospitalization because it required that patients had to receive three double-blind doses of their study medication before discharge. In routine practice, it's unlikely that in-hospital initiation of sacubitril/valsartan will result in a length of stay greater than the national average of about 4.5 days, according the cardiologist.

Current ACC/American Heart Association/Heart Failure Society of American guidelines on management of heart failure include a Class Ia recommendation to switch patients from an ACE inhibitor or angiotensin inhibitor to sacubitril/valsartan (Circulation. 2017 Aug 8;136[6]:e137-61). But heart failure specialists are concerned by national data showing that sacubitril/valsartan remains widely underprescribed.

Dr. DeVore reported serving as a consultant to Novartis and receiving research grants from a half dozen pharmaceutical companies as well as the American Heart Association, National Heart, Lung, and Blood Institute, and the Patient-Centered Outcomes Research Institute.

bjancin@mdedge.com

FDA: Programmable heart failure device approved

BY CHRISTOPHER PALMER
MDedge News

The Food and Drug Administration has approved the Optimizer Smart system for patients with chronic, moderate to severe heart failure. Specifically, these patients are unsuited for other treatments, have marked physical limitations related to their heart failure, and have remained symptomatic despite optimal medical therapy. They also have a regular heart rhythm, are not candidates for resynchronization, and possess a left ventricular ejection fraction of 25%-45%.

The cardiac contractility modulation system is indicated to improve 6-minute hall walk distance, quality of life, and functional status in these patients.

The system is made up of several components, including the implantable pulse generator, a programmer, and software. The pulse generator is connected to three leads that have been implanted in the heart, after which the device is tested and programmed to deliver pulses during normal heartbeats, which improves the heart's squeezing capability. In randomized, multicenter clinical trials, the system plus optimal medical therapy demonstrated improvements in distance during 6-minute walking tests and standard assessments of heart failure symptoms when compared with optimal medical therapy alone.

The Breakthrough Device designation means this system treats a life-threatening disease and addresses unmet medical needs among some patients. "The FDA recognized the unmet need for these patients and worked with the manufacturer through our Breakthrough Device Program to efficiently bring this product to market, while ensuring it meets our regulatory requirements for safety and effectiveness," Bram Zuckerman, MD, the director of the division of cardiovascular devices in the FDA's Center for Devices and Radiological Health said in a news release from the agency.

cpalmer@mdedge.com

BP control slowed white-matter lesion progression

BY MITCHEL L. ZOLER
MDedge News

NEW ORLEANS – Hypertensive elderly patients treated to maintain an ambulatory systolic blood pressure of 130 mm Hg had significantly slower progression of white-matter lesions in their brains than did control hypertensive patients maintained at an ambulatory systolic pressure of about 145 mm Hg during 3 years of follow-up in a randomized, single-center study with 199 patients.

The results also showed similar rates of death, syncope episodes, and falls in the intensively and less rigorously treated subgroups, and the patients treated to a systolic of 130 mm Hg also had significantly fewer nonfatal cardiovascular disease events, further documenting the safety and efficacy in elderly patients of a more aggressive blood pressure goal like the one promoted in current guidelines from the American College of Cardiology and American Heart Association, William B. White, MD, said at the annual meeting of the American College of Cardiology.

Courtesy Dr. William B. White

Dr. William B. White

The study's findings also showed that, in one measure of cognitive function, the serial reaction time task, the patients treated to a systolic pressure of 130 mm Hg had an average 23-millisecond improvement in their reaction time from baseline to their 3-year follow-up, while patients in the control group treated to a systolic pressure of 145 mm Hg had a 33-millisecond increase in their average reaction time during follow-up. This 56-millisecond between-group difference from baseline in average change in reaction time over 3 years was both statistically significant and represents a clinically meaningful difference for a measure of both processing speed and executive function, said Dr. White, professor of medicine at the University of Connecticut in Farmington. However, the participants also underwent assessment by five other clinical measures of cognitive function and in none of the other five tests did more intensive blood pressure control link with an improvement, compared with the results in control patients.

The study had two primary endpoints. One was progression

of white-matter hyperintensity on brain MR images, which is a measure of neuron necrosis in the brain, and this analysis showed that the growth of white matter occurred at a 40% reduced rate among 99 patients treated to an average ambulatory systolic blood pressure of 130 mm Hg, compared with the average progression among 100 controls treated to an average ambulatory systolic of 145 mm Hg. The second measure was improvement during 3 years, compared with controls, in any of six different measures of mobility, including gait speed. The results showed no significant differences between the treatment arms in any of these measures. The average progression of white-matter disease among control patients after 3 years was of a magnitude that would trigger concern in a neurologist who saw these scans, said Dr. White. The researchers could already begin to see a between-group difference in the accumulation of white-matter hyperintensity on the MR scans of patients at 18 months in the study, he added.

During his presentation, Dr. White suggested that the absence of discerned improvements in mobility from more aggressive blood pressure control despite the observed slowed progression of white-matter disease may have resulted from the study's relatively brief follow-up.

Continued on following page

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The INFINITY (Intensive versus Standard Ambulatory Blood Pressure Lowering to Prevent Functional Decline in the Elderly) study enrolled hypertensive patients at least 75 years old who already showed visible evidence of white-matter hypertrophy on their brain MR scan at baseline but also had normal mobility and mental function (their baseline score on the mini mental state examination had to be within the normal range, with an average score of 28 among enrolled patients), and they had no history of any chronic neurological condition (Am Heart J. 2013 Mar;165[3]:258-65). The median age of enrolled patients was 80 years. They had an average of 15 years of education, indicating a study cohort with a high level of education and function, Dr. White noted. The inclusion and exclusion criteria led to a study population

The growth of white matter occurred at a 40% reduced rate among 99 patients treated to an average ambulatory systolic blood pressure of 130 mm Hg, compared with the average progression among 100 controls treated to an average ambulatory systolic of 145 mm Hg.

that was substantially older but without as much comorbidity as patients enrolled in the SPRINT MIND study (JAMA. 2019 Jan 28;321[6]:553-61), he said. The study exclusively used 24-hour ambulatory monitoring for baseline and follow-up blood pressure measurements.

The participating clinicians successfully maintained patients in each of the treatment groups at close to their goal systolic blood pressures. At 18 months, the actual average systolic pressures among patients in the two study groups were 132 mm Hg and 146 mm Hg, and at 36 months their pressures averaged 131 mm Hg and 146 mm Hg for 163 patients who remained in the study out to 36 months. Maintenance of the lower pressure generally required treatment with one additional antihypertensive medication, compared with the control patients' treatment, Dr. White said.

The rates of total falls and falls causing injury were virtually identical in the two treatment groups. The incidence of nonfatal cardiovascular disease events over 3 years, including MI, strokes, and cardiovascular disease hospitalizations, was 4 cases in the intensively treated patients and 17 among those treated to a higher systolic pressure, a statistically significant and unexpected difference, Dr. White reported.

mzoler@mdedge.com

Pembrolizumab approved for 1st-line stage III NSCLC

BY LAURA NIKOLAIDES
MDedge News

The Food and Drug Administration has approved pembrolizumab (Keytruda) for the first-line treatment of patients with stage III non–small cell lung cancer (NSCLC) who are not candidates for surgical resection or definitive chemoradiation, and for stage IV NSCLC.

Patients' tumors must express programmed death-ligand 1 (PD-L1) as determined by an FDA-approved test (tumor proportion score ≥ 1%) and have no epidermal growth factor receptor or anaplastic lymphoma kinase mutations.

The checkpoint inhibitor was previously approved as a single agent for the first-line treatment of patients with metastatic disease with PD-L1 expression at a higher level (TPS ≥ 50%), the FDA stated.

Approval was based on statistically significant overall survival improvement with pembrolizumab, compared with investigator's choice of a carboplatin-containing regimen with either pemetrexed or paclitaxel in KEYNOTE-042. The trial enrolled 1,274 patients with stage III or IV NSCLC who had not received prior systemic treatment for metastatic NSCLC and whose tumors expressed PD-L1 (TPS ≥ 1%).

Overall survival was improved in all three subgroups for pembrolizumab, compared with chemotherapy: in the TPS ≥ 50% subgroup, the TPS ≥ 20% subgroup, and the overall population (TPS ≥ 1%). The median overall survival in the TPS ≥ 1% population was 16.7 for pembrolizumab and 12.1 months for the chemotherapy arms (hazard ratio, 0.81; 95% confidence interval, 0.71-0.93; $P = .0036$). For the TPS ≥ 50% subgroup, the estimated median overall survival was 20 months for pembrolizumab and 12.2 months for the chemotherapy arm (HR, 0.69; 95% CI, 0.56-0.85; $P = .0006$).

The most common adverse reactions reported for patients who received pembrolizumab included fatigue, decreased appetite, dyspnea, cough, rash, constipation, diarrhea, nausea, hypothyroidism, pneumonia, pyrexia, and weight loss.

The most common adverse reactions reported for patients who received pembrolizumab included fatigue, decreased appetite, dyspnea, cough, rash, constipation, diarrhea, nausea, hypothyroidism, pneumonia, pyrexia, and weight loss, the FDA said.

The recommended dose for NSCLC is 200 mg as an IV infusion over 30 minutes every 3 weeks.

chestphysiciannews@chestnet.org

Prior antibiotics exposure may hamper checkpoint inhibitor efficacy

BY NEIL OSTERWEIL
MDedge News

SAN FRANCISCO – Antibiotic exposure in the month before cancer immunotherapy starts may hamper the efficacy of immune checkpoint inhibitors, investigators caution.

A prospective study of 196 patients treated with immune checkpoint inhibitors for various cancers showed that the 29 patients who received antibiotics within 30 days of starting immunotherapy had significantly worse overall survival than patients without antibiotic exposure; this effect was seen across cancer types, reported David James Pinato, MD, PhD, from Imperial College London.

In contrast, concurrent antibiotic and checkpoint inhibitor use was not significantly associated with overall survival differences, he said at the American Society of Clinical Oncology (ASCO) – Society for Immunotherapy of Cancer (SITC): Clinical Immuno-Oncology Symposium.

"I think these data are quite interesting in showing an independent detrimental effect, both on response and survival, in unselected patients treated with immune checkpoint inhibitors in routine clinical practice," Dr. Pinato said.

The data also suggest "the timing of antibiotic exposure is crucial," he added. Antibiotic treatment concurrent with immunotherapy did not appear to affect prognosis. Alternatively, prior antibiotic therapy appeared to have "a sort of a priming effect towards the immune system."


Neil Osterweil/MDedge News

Dr. David James Pinato

Broad-spectrum antibiotics can affect the diversity of the gut microbiome, which influences mucosal immunity, dendritic cell function, and antigen presentation. Alternatively, enrichment of the microbiome with several bacterial species can enhance the potency of checkpoint inhibitors by facilitating the process of tumor rejection, Dr. Pinato explained.

To see whether antibiotic disruption, or "dysbiosis" of the gut microbiome, could hinder responsiveness to checkpoint inhibitors regardless of the tumor site and whether there were time-dependent effects of antibiotic exposure on response to checkpoint inhibitors, the investigators conducted a prospective, observational study in 196 patients treated with checkpoint inhibitors for non–small cell lung cancer (NSCLC), melanoma, renal cell carcinoma, head and neck cancer, transitional cell carcinoma of the bladder, and other cancers.

The researchers defined prior antibiotic exposure as more than 30 days before the start of checkpoint inhibitor therapy and concurrent exposure as antibiotics begun on the first day of the first cycle of checkpoint inhibitor dosing.

Of the 196 patients, 29 had previously received antibiotics, and 68 received them concurrently. The most frequently prescribed antibiotics were beta-lactam agents given in a single, short course. Other classes of drugs, used in eight or fewer patients each, included quinolones, macrolides, sulfonamides, tetracyclines, aminoglycosides, and nitroimidazole.

Median overall survival for the entire cohort, one of two primary outcomes, was 2 months for patients who had received prior antibiotics and 26 months for patients with no prior exposure. This difference was similar for patients with NSCLC (2.5 vs. 26 months), melanoma (3.9 vs. 14 months), and other cancers combined (1.1 vs. 11.0 months; log-rank *P* less than .01 for all comparisons).

In multivariate analysis, only response to checkpoints inhibitors (complete vs. partial response, stable disease, or progression) and prior antibiotic exposure were significantly associated with survival. The hazard ratio for survival for patients who had not previously received antibiotics was 3.5 (*P* less than .001).

In contrast, concurrent antibiotic and checkpoint inhibitor use did not have a significant effect on survival.

An analysis of radiologic responses also showed that patients with prior antibiotic exposure had a significantly higher probability of primary disease progression than those without (81% vs. 44%; *P* less than .001). There were no associations, however, between specific classes of antibiotics or corticosteroid use.

The findings indicate that "certainly, mechanistic studies are required here, not just to investigate the prognostic role of antibiotic-mediated dysbiosis, but perhaps transform this into an actual driver of antitumor immunity," Dr. Pinato concluded.

The study was internally supported. Dr. Pinato reported receiving grant funding from Merck and Bristol-Myers Squibb unrelated to the study, as well as honoraria from ViiV Healthcare.

chestphysiciannews@chestnet.org

SOURCE: Pinato DJ et al. ASCO-SITC, Abstract 147.

Data from routine lung cancer visits yield research insights

BY HEIDI SPLETE
MDedge News

A continuously updating database of clinical and genomic details on patients with non–small cell lung cancer accurately represented correlations between genomics and outcomes, based on an analysis of more than 4,000 patients.

"Most efforts to identify clinicogenomic associations currently rely on clinical trials, single-institution series, or national registries," wrote Gaurav Singal, MD, of Foundation Medicine in Cambridge, Mass., and colleagues in JAMA.

To explore the feasibility of a clinicogenomic database, the researchers combined clinical data from electronic health records with comprehensive genetic profiling data from 28,889 patients; 4,064 adults with non–small cell lung cancer were included in the analysis of associations among tumor genomics, patient characteristics, and clinical outcomes. The data were collected between Jan. 1, 2011, and Jan. 1, 2018, from 275 U.S. oncology practices.

The researchers examined implications of clinical and genomic features for 3,522 patients with advanced disease. Among these, the median overall survival was 10.3 months and the 5-year survival rate was 3.8%. Factors influencing a longer overall survival included never smoking and having nonsquamous pathology; the presence of mutations in genes TP53 and RB1 were associated with shorter survival.

For each patient, researchers calculated the tumor mutational burden (TMB), defined as "a measure of the number of somatic mutations identified per megabase of DNA sequenced." TMB was significantly higher among smokers, compared with nonsmokers, and "alterations in EGFR, ALK, ROS1, and RET were associated with significantly lower TMB than wild-type cases," the researchers wrote. Overall, the results "replicated previously described associations between clinical and genomic characteristics, driver mutations and response to targeted therapy, and TMB and response to immunotherapy," the researchers wrote.

The findings were limited by several factors, notably the quality and completeness of mortality data, as well as potential biases from the inclusion of comprehensive genetic profiling results and analysis of therapeutic exposures in an unrandomized trial, as well as a study population limited to patients with advanced stage disease, the researchers noted.

However, the results support data from similar studies and further show that clinicogenomic databases can be used in research to augment drug development and improve the design of clinical trials, they wrote.

The study was supported by Flatiron Health and Foundation Medicine, which are both owned by the Roche Group. Dr. Singal and several coauthors are employees of Foundation Medicine.

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SOURCE: Singal G et al. JAMA. 2019;321:1391-9.

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The safety and efficacy of ANORO in patients with asthma have not been established. ANORO is not indicated for the treatment of asthma.

CONTRAINDICATIONS

- ANORO is contraindicated in patients with severe hypersensitivity to milk proteins or with hypersensitivity to umeclidinium, vilanterol, or any of the excipients.

WARNINGS AND PRECAUTIONS

- ANORO should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD.
- ANORO is NOT a rescue medication and should NOT be used for the relief of acute bronchospasm or symptoms. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist.

Please see additional Important Safety Information for ANORO ELLIPTA on the following pages.
Please see Brief Summary of Prescribing Information, including Boxed Warning, for ANORO ELLIPTA following this ad.

START WITH ANORO FOR SUPERIOR IMPROVEMENT IN LUNG FUNCTION VS AN ESTABLISHED ICS/LABA[2]

Nearly 2x the lung function improvement vs ADVAIR[2]

LS mean change from baseline in weighted mean FEV_1 (0-24 hours) on Day 84

1.8x IMPROVEMENT

Study DB2114930[2]

74 mL Difference (*P*<0.001)
ANORO **165 mL (n=353)**
ADVAIR **91 mL (n=353)**

1.9x IMPROVEMENT

Study DB2114951[2]

101 mL Difference (*P*<0.001)
ANORO **213 mL (n=349)**
ADVAIR **112 mL (n=348)**

The indication for ANORO differs from the indication for ADVAIR in that ANORO is not indicated for reducing COPD exacerbations.

Studied in patients with moderate to severe COPD (GOLD 2 or 3).[2]

What would almost 2x the lung function improvement mean for your patients?

Learn more at **StartWithANORO.com**

Description of studies[2,3]: The efficacy and safety of a once-daily dose of ANORO ELLIPTA and a twice-daily dose of ADVAIR 250 mcg/50 mcg (administered via the DISKUS inhaler) were evaluated in two 12-week, multicenter, randomized, double-blind, double-dummy, parallel-group studies in patients (mean age range: 63 to 64 years) with COPD with no exacerbations (COPD symptoms requiring oral corticosteroids, antibiotics, and/or hospitalization) in the previous year. At screening, patients had a mean postbronchodilator FEV_1 range of 49.4% to 49.5% predicted. The studies were not powered to compare the safety profiles of the products.

Primary endpoint: Weighted mean FEV_1 (0-24 hours postdose) on Day 84.

COPD=chronic obstructive pulmonary disease; FEV_1=forced expiratory volume in 1 second; GOLD=Global Initiative for Chronic Obstructive Lung Disease; ICS=inhaled corticosteroid; LAMA=long-acting muscarinic antagonist; LS=least squares.

Important Safety Information for ANORO ELLIPTA (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- ANORO should not be used more often or at higher doses than recommended or with another LABA (eg, salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs, like LABA.
- Caution should be exercised when considering the coadministration of ANORO with long-term ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur.
- If paradoxical bronchospasm occurs, discontinue ANORO and institute alternative therapy.
- Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of ANORO. Discontinue ANORO if such reactions occur.

ANORO ELLIPTA
(umeclidinium 62.5 mcg and vilanterol 25 mcg inhalation powder)

Important Safety Information for ANORO ELLIPTA (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- Vilanterol can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms. If such effects occur, ANORO may need to be discontinued. ANORO should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.
- Use with caution in patients with narrow-angle glaucoma. Instruct patients to contact a healthcare provider immediately if signs or symptoms of acute narrow-angle glaucoma develop.
- Use with caution in patients with urinary retention, especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to contact a healthcare provider immediately if signs or symptoms of urinary retention develop.
- Be alert to hypokalemia and hyperglycemia.

ADVERSE REACTIONS

- The most common adverse reactions (≥1% and more common than placebo) reported in four 6-month clinical trials with ANORO (and placebo) were: pharyngitis, 2% (<1%); sinusitis, 1% (<1%); lower respiratory tract infection, 1% (<1%); constipation, 1% (<1%); diarrhea, 2% (1%); pain in extremity, 2% (1%); muscle spasms, 1% (<1%); neck pain, 1% (<1%); and chest pain, 1% (<1%).
- In addition to the 6-month efficacy trials with ANORO, a 12-month trial evaluated the safety of umeclidinium/vilanterol 125 mcg/25 mcg in subjects with COPD. Adverse reactions (incidence ≥1% and more common than placebo) in subjects receiving umeclidinium/vilanterol 125 mcg/25 mcg were: headache, back pain, sinusitis, cough, urinary tract infection, arthralgia, nausea, vertigo, abdominal pain, pleuritic pain, viral respiratory tract infection, toothache, and diabetes mellitus.

DRUG INTERACTIONS

- Caution should be exercised when considering the coadministration of ANORO with ketoconazole and other known strong CYP3A4 inhibitors as increased systemic exposure to vilanterol and cardiovascular adverse effects may occur. See prior Warning and Precaution regarding CYP3A4 inhibitors.
- ANORO should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval, or within 2 weeks of discontinuation of such agents, because they may potentiate the effect of vilanterol on the cardiovascular system.
- Use beta-blockers with caution as they not only block the pulmonary effect of beta-agonists, such as vilanterol, but may produce severe bronchospasm in patients with COPD.
- Use with caution in patients taking non–potassium-sparing diuretics, as ECG changes and/or hypokalemia associated with these diuretics may worsen with concomitant beta-agonists.
- Avoid coadministration of ANORO with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects.

Please see additional Important Safety Information for ANORO ELLIPTA on the previous pages.
Please see Brief Summary of Prescribing Information, including Boxed Warning, for ANORO ELLIPTA following this ad.

References: 1. Global Initiative for Chronic Obstructive Lung Disease. *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease*. 2019 report. www.goldcopd.org. Accessed November 27, 2018. **2.** Donohue JF, Worsley S, Zu C-Q, et al. Improvements in lung function with umeclidinium/vilanterol versus fluticasone propionate/salmeterol in patients with moderate-to-severe COPD and infrequent exacerbations. *Respir Med.* 2015; 109(7):870-881. **3.** Data on file, GSK.

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ANORO ELLIPTA was developed in collaboration with INNOVIVA

PM-US-UCV-ADVT-180001 December 2018. Produced in USA.

ANORO ELLIPTA
(umeclidinium 62.5 mcg and vilanterol 25 mcg inhalation powder)

ANORO ELLIPTA **BRIEF SUMMARY**

(umeclidinium and vilanterol inhalation powder), for oral inhalation

The following is a brief summary only; see full prescribing information for complete product information.

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of LABA *[see Warnings and Precautions (5.1)]*.

The safety and efficacy of ANORO ELLIPTA in patients with asthma have not been established. ANORO ELLIPTA is not indicated for the treatment of asthma.

1 INDICATIONS AND USAGE

ANORO ELLIPTA is a combination anticholinergic/long-acting beta$_2$-adrenergic agonist (anticholinergic/LABA) indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

Important Limitations of Use: ANORO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

4 CONTRAINDICATIONS

The use of ANORO ELLIPTA is contraindicated in patients with severe hypersensitivity to milk proteins or who have demonstrated hypersensitivity to umeclidinium, vilanterol, or any of the excipients *[see Warnings and Precautions (5.6), Description (11) of full prescribing information]*.

5 WARNINGS AND PRECAUTIONS

5.1 Asthma-Related Death

Data from a large placebo-controlled trial in subjects with asthma showed that LABA may increase the risk of asthma-related death. Data are not available to determine whether the rate of death in patients with COPD is increased by LABA.

A 28-week, placebo-controlled, US trial comparing the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol vs. 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 1 5.34]). The increased risk of asthma-related death is considered a class effect of LABA, including vilanterol, one of the active ingredients in ANORO ELLIPTA.

No trial adequate to determine whether the rate of asthma-related death is increased in subjects treated with ANORO ELLIPTA has been conducted. The safety and efficacy of ANORO ELLIPTA in patients with asthma have not been established. ANORO ELLIPTA is not indicated for the treatment of asthma.

5.2 Deterioration of Disease and Acute Episodes

ANORO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD. ANORO ELLIPTA has not been studied in subjects with acutely deteriorating COPD. The initiation of ANORO ELLIPTA in this setting is not appropriate.

ANORO ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. ANORO ELLIPTA has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist.

When beginning treatment with ANORO ELLIPTA, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms. When prescribing ANORO ELLIPTA, the healthcare provider should also prescribe an inhaled, short-acting beta$_2$-agonist and instruct the patient on how it should be used. Increasing inhaled, short-acting beta$_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If ANORO ELLIPTA no longer controls symptoms of bronchoconstriction; the patient's inhaled, short-acting beta$_2$-agonist becomes less effective; or the patient needs more short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting a reevaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dose of ANORO ELLIPTA beyond the recommended dose is not appropriate in this situation.

5.3 Excessive Use of ANORO ELLIPTA and Use with Other Long-acting Beta$_2$-agonists

ANORO ELLIPTA should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using ANORO ELLIPTA should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

5.4 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of ANORO ELLIPTA with long-term ketoconazole and other known strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3) of full prescribing information]*.

5.5 Paradoxical Bronchospasm

As with other inhaled medicines, ANORO ELLIPTA can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with ANORO ELLIPTA, it should be treated immediately with an inhaled, short-acting bronchodilator; ANORO ELLIPTA should be discontinued immediately; and alternative therapy should be instituted.

5.6 Hypersensitivity Reactions

Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of ANORO ELLIPTA. Discontinue ANORO ELLIPTA if such reactions occur. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder products containing lactose; therefore, patients with severe milk protein allergy should not use ANORO ELLIPTA *[see Contraindications (4)]*.

5.7 Cardiovascular Effects

Vilanterol, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms *[see Clinical Pharmacology (12.2) of full prescribing information]*. If such effects occur, ANORO ELLIPTA may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Therefore, ANORO ELLIPTA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

5.8 Coexisting Conditions

ANORO ELLIPTA, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta$_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.9 Worsening of Narrow-Angle Glaucoma

ANORO ELLIPTA should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a healthcare provider immediately if any of these signs or symptoms develops.

5.10 Worsening of Urinary Retention

ANORO ELLIPTA should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a healthcare provider immediately if any of these signs or symptoms develops.

5.11 Hypokalemia and Hyperglycemia

Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Beta-agonist medicines may produce transient hyperglycemia in some patients. In 4 clinical trials of 6-month duration evaluating ANORO ELLIPTA in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium.

6 ADVERSE REACTIONS

LABA, such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related death. ANORO ELLIPTA is not indicated for the treatment of asthma. *[See Boxed Warning and Warnings and Precautions (5.1).]*

The following adverse reactions are described in greater detail in other sections:

- Paradoxical bronchospasm *[see Warnings and Precautions (5.5)]*
- Cardiovascular effects *[see Warnings and Precautions (5.7)]*
- Worsening of narrow-angle glaucoma *[see Warnings and Precautions (5.9)]*
- Worsening of urinary retention *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The clinical program for ANORO ELLIPTA included 8,138 subjects with COPD in four 6-month lung function trials, one 12-month long-term safety study, and 9 other trials of shorter duration. A total of 1,124 subjects have received at least 1 dose of ANORO ELLIPTA (umeclidinium/vilanterol 62.5 mcg/25 mcg), and 1,330 subjects have received a higher dose of umeclidinium/vilanterol (125 mcg/25 mcg). The safety data described below are based on the four 6-month and the one 12-month trials. Adverse reactions observed in the other trials were similar to those observed in the confirmatory trials.

6-Month Trials

The incidence of adverse reactions associated with ANORO ELLIPTA in Table 1 is based on four 6-month trials: 2 placebo-controlled trials (Trials 1 and 2; n = 1,532 and n = 1,489, respectively) and 2 active-controlled trials (Trials 3 and 4; n = 843 and n = 869, respectively). Of the 4,733 subjects, 68% were male and 84% were white. They had a mean age of 63 years and an average smoking history of 45 pack-years, with 50% identified as current smokers. At screening, the mean postbronchodilator percent predicted forced expiratory volume in 1 second (FEV_1) was 48% (range: 13% to 76%), the mean postbronchodilator FEV_1/forced vital capacity (FVC) ratio was 0.47 (range: 0.13 to 0.78), and the mean percent reversibility was 14% (range: -45% to 109%). Subjects received 1 dose once daily of the following: ANORO ELLIPTA, umeclidinium/vilanterol 125 mcg/25 mcg, umeclidinium 62.5 mcg, umeclidinium 125 mcg, vilanterol 25 mcg, active control, or placebo.

Table 1. Adverse Reactions with ANORO ELLIPTA with ≥1% Incidence and More Common than Placebo in Subjects with Chronic Obstructive Pulmonary Disease

Adverse Reaction	ANORO ELLIPTA (n = 842) %	Umeclidinium 62.5 mcg (n = 418) %	Vilanterol 25 mcg (n = 1,034) %	Placebo (n = 555) %
Infections and infestations				
Pharyngitis	2	1	2	<1
Sinusitis	1	<1	1	<1
Lower respiratory tract infection	1	<1	<1	<1
Gastrointestinal disorders				
Constipation	1	<1	<1	<1
Diarrhea	2	<1	2	1
Musculoskeletal and connective tissue disorders				
Pain in extremity	2	<1	2	1
Muscle spasms	1	<1	<1	<1
Neck pain	1	<1	<1	<1
General disorders and administration site conditions				
Chest pain	1	<1	<1	<1

Other adverse reactions with ANORO ELLIPTA observed with an incidence less than 1% but more common than placebo included the following: productive cough, dry mouth, dyspepsia, abdominal pain, gastroesophageal reflux disease, vomiting, musculoskeletal chest pain, chest discomfort, asthenia, atrial fibrillation, ventricular extrasystoles, supraventricular extrasystoles, myocardial infarction, pruritus, rash, and conjunctivitis.

12-Month Trial

In a long-term safety trial, 335 subjects were treated for up to 12 months with umeclidinium/vilanterol 125 mcg/25 mcg or placebo. The demographic and baseline characteristics of the long-term safety trial were similar to those of the placebo-controlled efficacy trials described above. Adverse reactions that occurred with a frequency of greater than or equal to 1% in the group receiving umeclidinium/vilanterol 125 mcg/25 mcg that exceeded that in placebo in this trial were: headache, back pain, sinusitis, cough, urinary tract infection, arthralgia, nausea, vertigo, abdominal pain, pleuritic pain, viral respiratory tract infection, toothache, and diabetes mellitus.

6.2 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval use of ANORO ELLIPTA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to ANORO ELLIPTA or a combination of these factors.

Cardiac Disorders

Palpitations.

Eye Disorders

Blurred vision, glaucoma, increased intraocular pressure.

Immune System Disorders

Hypersensitivity reactions, including anaphylaxis, angioedema, and urticaria.

Nervous System Disorders

Dysgeusia, tremor.

Psychiatric Disorders

Anxiety.

Renal and Urinary Disorders

Dysuria, urinary retention.

Respiratory, Thoracic, and Mediastinal Disorders

Dysphonia, paradoxical bronchospasm.

(continued on next page)

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4

Vilanterol, a component of ANORO ELLIPTA, is a substrate of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to vilanterol. Caution should be exercised when considering the coadministration of ANORO ELLIPTA with ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) *[see Warnings and Precautions (5.4), Clinical Pharmacology (12.3) of full prescribing information]*.

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

Vilanterol, like other beta$_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

7.3 Beta-adrenergic Receptor Blocking Agents

Beta-blockers not only block the pulmonary effect of beta-agonists, such as vilanterol, a component of ANORO ELLIPTA, but may also produce severe bronchospasm in patients with COPD. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

7.4 Non–Potassium-Sparing Diuretics

The electrocardiographic changes and/or hypokalemia that may result from the administration of non–potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, such as vilanterol, a component of ANORO ELLIPTA, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of ANORO ELLIPTA with non–potassium-sparing diuretics.

7.5 Anticholinergics

There is potential for an additive interaction with concomitantly used anticholinergic medicines. Therefore, avoid coadministration of ANORO ELLIPTA with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects *[see Warnings and Precautions (5.9, 5.10), Adverse Reactions (6)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

Pregnancy Category C. There are no adequate and well-controlled trials of ANORO ELLIPTA or its individual components, umeclidinium and vilanterol, in pregnant women. Because animal reproduction studies are not always predictive of human response, ANORO ELLIPTA should be used during pregnancy only if the potential benefit justifies the potential risk to fetus. Women should be advised to contact their heathcare providers if they become pregnant while taking ANORO ELLIPTA.

Umeclidinium: There was no evidence of teratogenic effects in rats and rabbits at approximately 50 and 200 times, respectively, the MRHDID (maximum recommended human daily inhaled dose) in adults (on an AUC basis at maternal inhaled doses up to 278 mcg/kg/day in rats and at maternal subcutaneous doses up to 180 mcg/kg/day in rabbits).

Vilanterol: There were no teratogenic effects in rats and rabbits at approximately 13,000 and 70 times, respectively, the MRHDID in adults (on a mcg/m^2 basis at maternal inhaled doses up to 33,700 mcg/kg/day in rats and on an AUC basis at maternal inhaled doses up to 591 mcg/kg/day in rabbits). However, fetal skeletal variations were observed in rabbits at approximately 450 times the MRHDID in adults (on an AUC basis at maternal inhaled or subcutaneous doses of 5,740 or 300 mcg/kg/day, respectively). The skeletal variations included decreased or absent ossification in cervical vertebral centrum and metacarpals.

Nonteratogenic Effects

Umeclidinium: There were no effects on perinatal and postnatal developments in rats at approximately 80 times the MRHDID in adults (on an AUC basis at maternal subcutaneous doses up to 180 mcg/kg/day).

Vilanterol: There were no effects on perinatal and postnatal developments in rats at approximately 3,900 times the MRHDID in adults (on a mcg/m^2 basis at maternal oral doses up to 10,000 mcg/kg/day).

8.2 Labor and Delivery

There are no adequate and well-controlled human trials that have investigated the effects of ANORO ELLIPTA during labor and delivery.

Because beta-agonists may potentially interfere with uterine contractility, ANORO ELLIPTA should be used during labor only if the potential benefit justifies the potential risk.

8.3 Nursing Mothers

ANORO ELLIPTA

It is not known whether ANORO ELLIPTA is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when ANORO ELLIPTA is administered to a nursing woman. Since there are no data from well-controlled human studies on the use of ANORO ELLIPTA by nursing mothers, based on the data for the individual components, a decision should be made whether to discontinue nursing or to discontinue ANORO ELLIPTA, taking into account the importance of ANORO ELLIPTA to the mother.

Umeclidinium

It is not known whether umeclidinium is excreted in human breast milk. However, administration to lactating rats at approximately 25 times the MRHDID in adults resulted in a quantifiable level of umeclidinium in 2 pups, which may indicate transfer of umeclidinium in milk.

Vilanterol

It is not known whether vilanterol is excreted in human breast milk. However, other beta$_2$-agonists have been detected in human milk.

8.4 Pediatric Use

ANORO ELLIPTA is not indicated for use in children. The safety and efficacy in pediatric patients have not been established.

8.5 Geriatric Use

Based on available data, no adjustment of the dosage of ANORO ELLIPTA in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.

Clinical trials of ANORO ELLIPTA for COPD included 2,143 subjects aged 65 years and older and 478 subjects aged 75 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

8.6 Hepatic Impairment

Patients with moderate hepatic impairment (Child-Pugh score of 7-9) showed no relevant increases in C_{max} or AUC, nor did protein binding differ between subjects with moderate hepatic impairment and their healthy controls. Studies in subjects with severe hepatic impairment have not been performed *[see Clinical Pharmacology (12.3) of full prescribing information]*.

8.7 Renal Impairment

There were no significant increases in either umeclidinium or vilanterol exposure in subjects with severe renal impairment (CrCl less than 30 mL/min) compared with healthy subjects. No dosage adjustment is required in patients with renal impairment *[see Clinical Pharmacology (12.3) of full prescribing information]*.

10 OVERDOSAGE

No case of overdose has been reported with ANORO ELLIPTA.

ANORO ELLIPTA contains both umeclidinium and vilanterol; therefore, the risks associated with overdosage for the individual components described below apply to ANORO ELLIPTA. Treatment of overdosage consists of discontinuation of ANORO ELLIPTA together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medicine can produce bronchospasm. Cardiac monitoring is recommended in cases of overdosage.

10.1 Umeclidinium

High doses of umeclidinium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a once-daily inhaled dose of up to 1,000 mcg umeclidinium (16 times the maximum recommended daily dose) for 14 days in subjects with COPD.

10.2 Vilanterol

The expected signs and symptoms with overdosage of vilanterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms of beta-adrenergic stimulation (e.g., angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, seizures, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia, hyperglycemia, hypokalemia, metabolic acidosis). As with all inhaled sympathomimetic medicines, cardiac arrest and even death may be associated with an overdose of vilanterol.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

ANORO ELLIPTA

No studies of carcinogenicity, mutagenicity, or impairment of fertility were conducted with ANORO ELLIPTA; however, studies are available for the individual components, umeclidinium and vilanterol, as described below.

Umeclidinium

Umeclidinium produced no treatment-related increases in the incidence of tumors in 2-year inhalation studies in rats and mice at inhaled doses up to 137 and 295/200 mcg/kg/day (male/female), respectively (approximately 20 and 25/20 times the MRHDID in adults on an AUC basis, respectively).

Umeclidinium tested negative in the following genotoxicity assays: the in vitro Ames assay, in vitro mouse lymphoma assay, and in vivo rat bone marrow micronucleus assay.

No evidence of impairment of fertility was observed in male and female rats at subcutaneous doses up to 180 mcg/kg/day and inhaled doses up to 294 mcg/kg/day, respectively (approximately 100 and 50 times, respectively, the MRHDID in adults on an AUC basis).

Vilanterol

In a 2-year carcinogenicity study in mice, vilanterol caused a statistically significant increase in ovarian tubulostromal adenomas in females at an inhalation dose of 29,500 mcg/kg/day (approximately 7,800 times the MRHDID in adults on an AUC basis). No increase in tumors was seen at an inhalation dose of 615 mcg/kg/day (approximately 210 times the MRHDID in adults on an AUC basis).

In a 2-year carcinogenicity study in rats, vilanterol caused statistically significant increases in mesovarian leiomyomas in females and shortening of the latency of pituitary tumors at inhalation doses greater than or equal to 84.4 mcg/kg/day (greater than or equal to approximately 20 times the MRHDID in adults on an AUC basis). No tumors were seen at an inhalation dose of 10.5 mcg/kg/day (approximately 1 time the MRHDID in adults on an AUC basis).

These tumor findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Vilanterol tested negative in the following genotoxicity assays: the in vitro Ames assay, in vivo rat bone marrow micronucleus assay, in vivo rat unscheduled DNA synthesis (UDS) assay, and in vitro Syrian hamster embryo (SHE) cell assay. Vilanterol tested equivocal in the in vitro mouse lymphoma assay.

No evidence of impairment of fertility was observed in reproductive studies conducted in male and female rats at inhaled vilanterol doses up to 31,500 and 37,100 mcg/kg/day, respectively (approximately 12,000 and 14,500 times, respectively, the MRHDID in adults on a mcg/m^2 basis).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Asthma-Related Death

Inform patients that LABA, such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related death. ANORO ELLIPTA is not indicated for the treatment of asthma.

Not for Acute Symptoms

Inform patients that ANORO ELLIPTA is not meant to relieve acute symptoms of COPD and extra doses should not be used for that purpose. Advise patients to treat acute symptoms with an inhaled, short-acting beta$_2$-agonist such as albuterol. Provide patients with such medicine and instruct them in how it should be used.

Instruct patients to seek medical attention immediately if they experience any of the following:

- Decreasing effectiveness of inhaled, short-acting beta$_2$-agonists
- Need for more inhalations than usual of inhaled, short-acting beta$_2$-agonists
- Significant decrease in lung function as outlined by the physician

Tell patients they should not stop therapy with ANORO ELLIPTA without healthcare provider guidance since symptoms may recur after discontinuation.

Do Not Use Additional Long-acting Beta$_2$-agonists

Instruct patients not to use other medicines containing a LABA. Patients should not use more than the recommended once-daily dose of ANORO ELLIPTA.

Instruct patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis to discontinue the regular use of these products and use them only for the symptomatic relief of acute symptoms.

Paradoxical Bronchospasm

As with other inhaled medicines, ANORO ELLIPTA can cause paradoxical bronchospasm. If paradoxical bronchospasm occurs, instruct patients to discontinue ANORO ELLIPTA and contact their healthcare provider right away.

Risks Associated with Beta-agonist Therapy

Inform patients of adverse effects associated with beta$_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

Worsening of Narrow-Angle Glaucoma

Instruct patients to be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a healthcare provider immediately if any of these signs or symptoms develops.

Worsening of Urinary Retention

Instruct patients to be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination). Instruct patients to consult a healthcare provider immediately if any of these signs or symptoms develops.

ANORO ELLIPTA was developed in collaboration with INNOVIVA

GlaxoSmithKline
Research Triangle Park, NC 27709

Revised 10/2017 ANR:5BRS

PM-US-UCV-ADVT-180001 December 2018. Produced in USA.

FROM THE PRESIDENT

Expanding our educational reach

BY CLAYTON T. COWL, MD, FCCP

CHEST Congress Thailand concluded in Bangkok last month with more than 1,000 attendees from 56 countries. Attendees heard experts speak on several clinical tracks, including lung cancer, severe airway disease, pulmonary infections, interventional pulmonary management, and sleep-related disordered breathing. Panel discussions were held covering controversial topics across pulmonary, critical care, and sleep medicine, and close to 400 submitted abstracts were presented. Registration continues to build for the next CHEST international meeting to be held in conjunction with the Hellenic Thoracic Society in Athens, Greece, June 25-27. This meeting will feature clinicians and academicians providing relevant clinical updates to providers throughout that region in more of a "board review-like" format.


Dr. Cowl

Why is it so important that CHEST spread its brand of education to an international audience?

Clinicians are yearning for up-to-date information regardless of geography

Having the opportunity to visit with clinicians from Southeast Asia and Australia, it became clear to me that there is a need for high quality educational opportunities to be shared across the globe. Many attendees in Bangkok had never had the opportunity to attend a CHEST annual meeting within North America; their exposure to state-of-the-art reviews using interactive audience participation was a format that was clearly appreciated. Hands-on educational opportunities through simulation, as well as novel interactive tools such as serious gaming, were modalities not previously available to many attendees, and the reviews received were overwhelmingly positive.

Access to cutting-edge training in certain areas in the world has become more limited

Resources for international travel have become more limited. Industry sponsorship in certain regions has dwindled and, for certain countries, the ability to access medical meetings within the United States or other areas in Europe or North America has become burdensome, if not logistically impossible. Bringing the CHEST brand of education to members and other practicing providers outside North America within the represented specialties has allowed access to experts and the most effective formats for education without extended travel and excess cost.

Having the opportunity to visit with clinicians from Southeast Asia and Australia, it became clear to me that there is a need for high quality educational opportunities to be shared across the globe.

Smaller international meetings allow for more tailored curricula designed to meet local needs

The ability to build the curriculum around specific requests of a national society has allowed for a more focused educational platform designed to meet the needs of what regional leaders feel is the most critical for the highest prevalence of patients seen in that specific area. The international strategy of CHEST calls for an annual congress outside of North America and at least one smaller "board review-type" meeting in a different region elsewhere across the world each academic year. Co-hosting more meetings will not only help address unmet educational needs outside of the United States and Canada but also extend our reach to participants who may not have otherwise had the ability to participate in the CHEST brand of education. During multiple sessions, there were literally dozens of questions for which there was time to address each in real time. The panel discussions were lively, well-moderated, and also stimulated multiple questions and comments from the audience.

Education by podium lecture is fast becoming outdated

Although a compelling lecture using a didactic format from a podium at the front of a room is not going to be replaced completely any time soon, educational delivery trends are moving toward virtual classrooms, use of simulation, problem solving online, serious gaming, and hands-on experiential education. As an innovator and leader in medical education, CHEST will continue to provide a variety of options for delivering education utilizing a variety of platforms. By opening a multimedia production studio at CHEST Global Headquarters in Glenview, Illinois, this past February, the organization is positioning itself to continue to refine its ability to produce and distribute a variety of courses available to all CHEST members in an archivable, easily accessible format. The Board of Regents has doubled down on its digital strategy toward improving communication across the entire user experience, and offering courses to our international members closer to home is one way to execute this strategy.

Networking and new friendships underscore what's important

Meeting new colleagues from across the globe has made me realize that we are all focused on providing the very best care possible to our patients every day. Ultimately, education is communication. The ability to share how CHEST educates its membership will improve patient care worldwide and foster lifelong friendships with those we meet in other lands. Those opportunities to share ideas on health-care delivery will keep us on the cutting edge technologically and keep us focused on how to use resources responsibly and in a way that best serves the communities where we practice.

NEWS FROM THE BOARDS AND CHEST LEADERSHIP

Highlights from the spring leadership meeting

BY VICTOR J. TEST, MD, FCCP

CHEST leadership meets quarterly in person, but the fall and spring meetings include all of the combined committees of CHEST. As the fall meeting takes place during the CHEST Annual Scientific Meeting, the spring meeting takes on a particular importance in providing the impetus of the upcoming year. The meeting spanned from March 27 to March 30. Traditionally, the first day consists of committee meetings, such as the Council of Networks, Training and Transition, Education, Membership, Guideline Oversight, and Professional Standards. On the morning of the second day, the following committees met: Finance, Diversity, and the Governance Committee. The afternoon of the second day was a combined boards meeting with all members of the Board of Trustees and the Board of Regents, where we received updates from each of the committees. In addition, all of the board members underwent professional media training as professional development.

On the 29th, the Foundation Board of Trustees had their meeting, which was attended by several of the members of the Board of Regents (highlights listed below). In the afternoon, we had the biannual meeting of the CHEST Industry Advisory Council, where CHEST leadership meets with our industry partners, working together to anticipate the needs of our members and our patients. The Board of Regents convened on March 30 for our formal board meeting.

Highlights of the spring combined meeting: CHEST leadership committees

Education Committee: Under the leadership of the Chair, Dr. Alex Niven, the Education Committee

Continued on following page

Continued from previous page

has grown in scope and focus with the increasing strength of their subcommittees, including Live Learning, Simulation, Peer Review, Outcomes, Innovations, and Educator Development.

The Education Committee is now working to develop a revolving education curriculum to ensure that our members have a solid base at the annual meeting, as well as in online learning. The committee is working to increase coordination with the APCCMPD, as well.

Membership Committee: The Membership Committee reported on several accomplishments during the year, including an increase in nonphysician membership and rolling out several new programs, including automatic membership renewal option and adjusted membership fees for international members and retired members.

Finance Committee: The financial report for the last quarter of the CHEST fiscal year was robust with solid outlook for the year.

Training and Transitions

The T & T Committee has had marked success with a dramatic increase in fellow education programs and learners at the CHEST annual meeting. This year will bring new fellow courses in pulmonary nodules and lung transplantation. In addition, the committee is also reviewing abstract submissions for trainees at a record pace, with case report submissions exceeding last year's record number of 1,015 submissions.

CHEST leadership meets quarterly in person, but the fall and spring meetings include all of the combined committees of CHEST. As the fall meeting takes place during the CHEST Annual Scientific Meeting, the spring meeting takes on a particular importance in providing the impetus of the upcoming year.

Guideline Oversight

There are currently 12 guidelines in development, in addition to the 6 guidelines that were completed last fiscal year. This committee updated us regarding the ongoing development of "living guidelines."

Scientific Program Committee

Dr. Bill Kelly, chairman of CHEST 2019 in New Orleans, reported on the meeting, including the record number of submissions in all curriculum areas. He updated us regarding the ongoing maintenance of certification (MOC) credits for the meeting, as well as important new initiatives, such as child care and innovative electronic options for the meeting, designed to make the experience "easy" on attendees in New Orleans - The Big Easy.

CHEST Foundation Board of Trustees

Doreen Addrizzo-Harris, MD, FCCP, President of the Foundation, updated us on the quarterly activities of the foundation and guided the board through some of the novel fundraising opportunities, including the 6th Annual Irv Feldman Poker Night, the Inaugural CHEST Foundation Derby Dinner and Auction in New York, and the Popovich Endowment Dinner and future gala. The Foundation is sponsoring a number of activities at CHEST in New Orleans, including a Lung Health Experience, Breakfast of Champions, Women & Pulmonary Luncheon, the Young Professionals Reception, and the Foundation Reception.

CHEST Board of Regents (BoR)

The Board of Regents, led by Clayton Cowl, MD, FCCP, President of CHEST, had a packed session. The session started off with a unique team building exercise. The Board approved the Master Fellow Award selection that will honor Dr. Darcy Marciniuk. The Digital Strategy Task Force, led by Dr. Chris Carroll, Nicki Augustyn, and Ron Moen, reported on their findings, which led to a lively discussion on how to move forward with an innovative and successful digital plan. A report was also given on the membership recruitment and retention initiative. Finally, the BoR approved a new agreement with PA Consulting to assist in the ongoing CHEST Analytics program.

CHEST 2019 and southern culture

CHEST Annual Meeting 2019

Get a glimpse of the rich southern culture of New Orleans this October by checking out a few of these locations and events.

Visit a museum – Backstreet Cultural Museum

The Backstreet Cultural Museum is located in a small, former funeral home in the historic Treme neighborhood. The museum displays the permanent collection of Mardi Gras Indians costumes, second-line parade outfits, jazz funeral photos, and music memorabilia from curator Sylvester Francis. Interested in upcoming parades and festivals happening nearly every weekend in New Orleans? Learn about these at the museum, as well as more NOLA arts and traditions.

View the local art in Jackson Square

Jackson Square is an area where you'll see tarot readers, street performers, and artists. It has an open-air artist community where their works are hung on the iron railings around the square. Spend time getting your portrait done, buy a new art piece from a local, or have fun watching a street performance.

Diego Delso, delso.photo/CC-BY-SA

Jackson Square

Enjoy the architecture of the French Quarter

Explore New Orleans' oldest neighborhood, The French QuaSrter, with its mix of French Creole and Spanish influenced architecture. You'll find hints of this on old tiled street names and the French Fleur de Lys emblem noticeable all around the city. There are also Caribbean, African, and other European influences throughout the area. Take in the gorgeous mansions, the colorful Creole houses with their porches and swing chairs, the townhouses with beautiful ironwork balconies, and more!

Head to Oktoberfest

New Orleans also has a rich German history. You can celebrate this October with the city's own version of Oktoberfest, which takes place the first three weekends in the month. Experience some of the best of German culture by drinking a rare beer, trying authentic cuisine, and listening to live music during this celebration.

New Orleans Film Festival

From October 16-24, the New Orleans Film Society will be hosting the 2019 New Orleans Film Festival (NOFF). You can check out showings in different venues throughout the city. Local filmmakers are showcased during the festival, and their films and any shown during NOFF can qualify for the Oscars in all three Academy-accredited categories: Narrative Short, Documentary Short, and Animated Short.

Check out more things you can do in NOLA (https://tinyurl.com/yxnqswv5).

CMS proposal threatens home mechanical ventilators access

BY PHIL PORTE

Executive director, NAMDRC

CMS announced in a press release in mid-March that as it revamped the competitive bidding program for durable medical equipment, it would move to include no invasive ventilation (NIV) in the revamped program, slated to take effect January 1, 2021.

While the implementation date is still more than 18 months in the future, the regulatory timetable for a formal announcement, as well as time for CMS to introduce its revamped bidding process, actually creates a relatively short window for aggressive action to thwart the CMS proposal.

In late November 2018, when CMS was seeking public comment on the idea of such a move, CHEST, NAMDRC and numerous other societies submitted strongly worded comments opposed to the recommendation, citing a wide array of clinical risks associated with such a proposal. The comments also highlighted CMS' total failure to revamp its own coverage policies, frequently cited by the pulmonary medicine community and the Office of the Inspector General as the primary root cause for significant problems.

Background: Under current law, Medicare is required to pay for certain ventilators under a "frequent and substantial servicing" payment methodology, with payment continuing as long as medical necessity is documented. Nearly 2 decades ago, CMS (then HCFA) sought to circumvent those statutory requirements by declaring that some ventilators are really not ventilators (as FDA classifications indicate) but are actually "respiratory assist devices."

The long-term impact of that unilateral policy decision has been ongoing chaos, as well as flawed coverage policies. For example, it is much more challenging for a physician to order a cheaper bi-level device than to order a ventilator for treatment of "respiratory failure." As there are no limitations or qualifying criteria tied to "respiratory failure," the community has responded with the path of least resistance while pleading with CMS to restructure their coverage policies to reflect the standards of care for home mechanical ventilation.

Since 2014, the community has repeatedly tried to convince CMS of the importance, and cost savings, associated with such a revamp, to no avail. Given 5 years of well documented efforts, it is likely that the only genuine solution will be a legislative one that forces CMS to behave in certain ways.

The challenges: There are complicating variables that the clinical community will need to address:

1. If the term "ventilator" is included in any legislative effort, CMS could expand its infamous concept "just because FDA calls a device a ventilator doesn't make it one." Using particular CPT or HCPCS codes would open the door for CMS to simply change coding to circumvent legislative intent.

2. If a legislative effort receives serious support, it ought to include specific guidance to CMS to force it to change its coverage policies for home mechanical ventilation to reflect standards of care and state-of-the-art devices.

For example, because devices are designed today to serve a wide range of respiratory issues, one device may be used to provide critical life support for an ALS patient, while *that same device* could also be used to provide nocturnal or intermittent support for other neuromuscular or COPD patients. Because the durable medical equipment benefit is focused on devices, CMS' move to change to focus from a device to a patient is questionable.

3. Forcing CMS to move in a particular direction regarding coverage and device usage must be flexible enough to allow for technological and medical innovations; after all, no one wants to recommend legislative policies that would have to be revisited to address potential/likely advances in this field.

Broad strategies: While the durable medical equipment community is also challenging this proposal, they agreed that the medical and patient communities should take the lead. And, in principle, we agree. But implementation of that effort is a bit of a challenge as it requires a significant grassroots effort from concerned physicians, as well as patient groups to contact their legislators in Congress. After all, the worst case scenario is for a Senator to say, "How come I haven't heard from any constituents about this problem if it is as bad as you say it is?" That is a fair and common refrain, and we must be prepared to engage the broad physician and patient communities to ensure success in this effort.

Once there is formal introduction of a proposal to move this matter forward, there will be outreach to physicians and respiratory therapists across the country to urge support of the legislation. *Keep watching for such requests for action!*

As add-on maintenance treatment for patients (12+ years) with moderate-to-severe asthma with an eosinophilic phenotype, or with OCS-dependent asthma regardless of phenotype

A PATH TO **ASTHMA CONTROL**

DUPIXENT AFFECTS IL-4 AND IL-13 SIGNALING, IMPACTING TWO OF THE SOURCES THAT MEDIATE ALLERGIC AND EOSINOPHILIC INFLAMMATION[1]

The mechanism of dupilumab action in asthma has not been established.[1]

INDICATION

DUPIXENT is indicated as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma.

LIMITATION OF USE

DUPIXENT is not indicated for the relief of acute bronchospasm or status asthmaticus.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATION: DUPIXENT is contraindicated in patients with known hypersensitivity to dupilumab or any of its excipients.

WARNINGS AND PRECAUTIONS

Hypersensitivity: Hypersensitivity reactions, including generalized urticaria, rash, erythema nodosum, anaphylaxis and serum sickness or serum sickness-like reactions, were reported in <1% of subjects who received DUPIXENT in clinical trials. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue DUPIXENT.

Eosinophilic Conditions: Patients being treated for asthma may present with serious systemic eosinophilia sometimes presenting with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis. Be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in patients with eosinophilia, which may be associated with a reduction of oral corticosteroids. Cases of eosinophilic pneumonia and of vasculitis consistent with eosinophilic granulomatosis with polyangiitis have been reported in adult patients who participated in the asthma development program. A causal association between DUPIXENT and these conditions has not been established.

Acute Asthma Symptoms or Deteriorating Disease: Do not use DUPIXENT to treat acute asthma symptoms, acute exacerbations, acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of DUPIXENT.

LEARN MORE AT *DUPIXENTASTHMAHCP.COM*

TRIAL 1: BASELINE EOS ≥300 CELLS/µL

UP TO **81%** **REDUCTION IN ANNUALIZED RATE OF SEVERE EXACERBATIONS through Week 24**[1,a]

- **71% REDUCTION** with DUPIXENT 200 mg + SOC (n=65) vs placebo + SOC (n=68) (0.30 vs 1.04; rate ratio: 0.29 [95% CI: 0.11, 0.76])
- **81% REDUCTION** with DUPIXENT 300 mg + SOC (n=64) vs placebo + SOC (n=68) (0.20 vs 1.04; rate ratio: 0.19 [95% CI: 0.07, 0.56])

TRIAL 1: BASELINE EOS ≥300 CELLS/µL

UP TO **430 mL** **IMPROVEMENT IN PRE-BRONCHODILATOR FEV_1 from baseline at Week 12**[1]

- **430 mL IMPROVEMENT** with DUPIXENT 200 mg + SOC (n=65) vs **180 mL** with placebo + SOC (n=68) (LSM difference: 260 mL [95% CI: 110, 400 mL])
- **390 mL IMPROVEMENT** with DUPIXENT 300 mg + SOC (n=64) vs **180 mL** with placebo + SOC (n=68) (LSM difference: 210 mL [95% CI: 60, 360 mL])

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

Reduction of Corticosteroid Dosage: Do not discontinue systemic, topical, or inhaled corticosteroids abruptly upon initiation with DUPIXENT. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Parasitic (Helminth) Infections: It is unknown if DUPIXENT will influence the immune response against helminth infections. Treat patients with pre-existing helminth infections before initiating therapy with DUPIXENT. If patients become infected while receiving treatment with DUPIXENT and do not respond to anti-helminth treatment, discontinue treatment with DUPIXENT until the infection resolves.

TRIAL 1: 24-WEEK STUDY–776 adults (≥18 years) with moderate-to-severe asthma on a standard of care of medium- or high-dose ICS and a LABA were randomized to either DUPIXENT 200 mg Q2W[b] + SOC (n=150), DUPIXENT 300 mg Q2W[c] + SOC (n=157), or placebo + SOC (n=158). Subjects enrolled in Trial 1 were required to have a history of 1 or more asthma exacerbations that required treatment with systemic corticosteroids or emergency department visit or hospitalization for the treatment of asthma in the year prior to trial entry. DUPIXENT was administered as an add-on to background asthma treatment. **Primary endpoint:** Mean change from baseline to Week 12 in FEV_1 in patients with baseline eosinophils ≥300 cells/µL. **Other endpoint:** Annualized rate of severe exacerbation events during the 24-week treatment period.[d] **Selected baseline demographics:** Mean duration of asthma: 22 years; mean exacerbations in previous year: 2.2; high-dose ICS use: 50%; pre-dose FEV_1 at baseline: 1.84 L; mean FeNO: 39 ppb; mean total IgE: 435 IU/mL; and mean baseline blood eosinophil count: 350 cells/µL.

[a] Severe exacerbations were defined as deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or hospitalization or emergency department visit due to asthma that required systemic corticosteroids.
[b] With 400 mg loading dose.
[c] With 600 mg loading dose.
[d] Results were evaluated in the overall population and subgroups based on baseline blood eosinophil count.

EOS, eosinophils; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LSM, least squares mean; OCS, oral corticosteroid; Q2W, once every 2 weeks; SOC, standard of care.

Please see additional Important Safety Information throughout and brief summary of full Prescribing Information on the following pages.

DUPIXENT® (dupilumab) Injection
200mg · 300mg

MORE PATIENTS STOPPED USING OCS WITH DUPIXENT WHILE IMPROVING ASTHMA CONTROL[1,2]

TRIAL 3: NO BIOMARKER REQUIREMENT (ITT POPULATION)[a]

70%

REDUCTION IN OCS DOSE

(median 100%) from baseline at Week 24 with DUPIXENT 300 mg + SOC (n=103) (95% CI: 60%, 80%) vs **42%** (median 50%) with placebo + SOC (n=107)

86% OF PATIENTS REDUCED OR ELIMINATED THEIR OCS DOSE with DUPIXENT 300 mg + SOC (n=103) vs **68%** with placebo + SOC (n=107)

IMPROVE LUNG FUNCTION AND REDUCE SEVERE EXACERBATIONS WITH THE ONLY BIOLOGIC INDICATED FOR OCS-DEPENDENT ASTHMA PATIENTS, REGARDLESS OF PHENOTYPE[b]

TRIAL 3: NO BIOMARKER REQUIREMENT (ITT POPULATION)[a]

59%
REDUCTION

IN ANNUALIZED RATE OF SEVERE EXACERBATIONS
at Week 24 with DUPIXENT 300 mg + SOC (n=103) vs placebo + SOC (n=107) (0.65 vs 1.60; rate ratio: 0.41 [95% CI: 0.26, 0.63])

220 mL
IMPROVEMENT

IN PRE-BRONCHODILATOR FEV_1
at Week 24 with DUPIXENT 300 mg + SOC (n=103) vs **10 mL** with placebo + SOC (n=107) (LSM difference: 220 mL [95% CI: 90, 340 mL])

IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS: The most common adverse reactions (incidence ≥1%) in asthma patients are injection site reactions, oropharyngeal pain, and eosinophilia.

DRUG INTERACTIONS: Avoid use of live vaccines in patients treated with DUPIXENT.

TRIAL 3: 24-WEEK STUDY–210 subjects (≥12 years) with asthma who required daily OCS in addition to regular use of standard of care of high-dose ICS plus an additional controller medication were randomized to either DUPIXENT 300 mg Q2W[c] + SOC + OCS (n=103) or placebo + SOC + OCS (n=107); the baseline mean OCS dose was 11 mg in the DUPIXENT group and 12 mg in the placebo group. **Primary endpoint:** Percent reduction from baseline in OCS dose at Week 24, while maintaining asthma control, in the overall population. **Selected baseline demographics:** Mean duration of asthma: 20 years; mean exacerbations in previous year: 2.1; high-dose ICS use: 89%; pre-dose FEV_1 at baseline: 1.58 L; mean FeNO: 38 ppb; mean total IgE: 431 IU/mL; and mean baseline blood eosinophil count: 350 cells/μL.

[a] Intention-to-treat (ITT) population was unrestricted by minimum baseline eosinophils or other Type 2 biomarkers (eg, FeNO or IgE).
[b] Asthma exacerbation was defined as a temporary increase in OCS dose for at least 3 days.
[c] With 600 mg loading dose.

DUPIXENT® (dupilumab) Injection
200mg · 300mg

DUPIXENT OFFERS A PATH TO ASTHMA CONTROL

	DUPIXENT (dupilumab)[1]	XOLAIR® (omalizumab)[3]	NUCALA® (mepolizumab)[4]	FASENRA™ (benralizumab)[5]	CINQAIR® (reslizumab)[6]
Moderate asthma (eosinophilic phenotype)	✓				
Severe asthma (eosinophilic phenotype)	✓		✓	✓	✓
OCS-dependent asthma	✓				
Pre-filled syringe	✓	✓		✓	
At-home self-administration	✓				
In-office administration	✓	✓	✓	✓	✓

This presentation includes the fixed properties of these biologics. It is not intended to compare their safety, effectiveness, or uses. Please refer to each product's Prescribing Information for approved indication and dosing and administration information.

Xolair is indicated for moderate to severe persistent asthma in patients 6 years of age and older who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids.[3]

DUPIXENT IS THE FIRST ASTHMA BIOLOGIC TO OFFER THE CHOICE OF AT-HOME SELF-ADMINISTRATION OR IN-OFFICE ADMINISTRATION

DUPIXENT can be administered in the office under the guidance of a healthcare provider if the patient is not an appropriate candidate for self-administration. A patient may self-inject DUPIXENT after training in subcutaneous injection technique using the pre-filled syringe.

IMPORTANT SAFETY INFORMATION

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** Available data from case reports and case series with DUPIXENT use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, DUPIXENT may be transmitted from the mother to the developing fetus.
- **Lactation:** There are no data on the presence of DUPIXENT in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DUPIXENT and any potential adverse effects on the breastfed child from DUPIXENT or from the underlying maternal condition.

Please see brief summary of full Prescribing Information on the following pages.

References: 1. DUPIXENT Prescribing Information. March 2019. **2.** Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med.* 2018;378(26):2475-2485. **3.** Xolair Prescribing Information. September 2018. **4.** Nucala Prescribing Information. December 2017. **5.** Fasenra Prescribing Information. November 2017. **6.** Cinqair Prescribing Information. May 2016.

SANOFI GENZYME

REGENERON

US-DAS-1450

DUPIXENT® (dupilumab) injection, for subcutaneous use **Rx Only**
Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE

1.1 Atopic Dermatitis

DUPIXENT is indicated for the treatment of patients aged 12 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical corticosteroids.

1.2 Asthma

DUPIXENT is indicated as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma.

Limitation of Use

DUPIXENT is not indicated for the relief of acute bronchospasm or status asthmaticus.

4 CONTRAINDICATIONS

DUPIXENT is contraindicated in patients who have known hypersensitivity to dupilumab or any of its excipients *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Hypersensitivity reactions, including generalized urticaria, rash, erythema nodosum and serum sickness or serum sickness-like reactions, were reported in less than 1% of subjects who received DUPIXENT in clinical trials. Two subjects in the atopic dermatitis development program experienced serum sickness or serum sickness-like reactions that were associated with high titers of antibodies to dupilumab. One subject in the asthma development program experienced anaphylaxis *[see Adverse Reactions (6.2)]*. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue DUPIXENT *[see Adverse Reactions (6.1, 6.2)]*.

5.2 Conjunctivitis and Keratitis

Conjunctivitis and keratitis occurred more frequently in atopic dermatitis subjects who received DUPIXENT. Conjunctivitis was the most frequently reported eye disorder. Most subjects with conjunctivitis recovered or were recovering during the treatment period. Among asthma subjects the frequency of conjunctivitis was similar between DUPIXENT and placebo *[see Adverse Reactions (6.1)]*. Keratitis was reported in <1% of the DUPIXENT group (1 per 100 subject-years) and in 0% of the placebo group (0 per 100 subject-years) in the 16-week atopic dermatitis monotherapy trials. In the 52-week DUPIXENT + topical corticosteroids (TCS) atopic dermatitis trial, keratitis was reported in 4% of the DUPIXENT + TCS group (12 per 100 subject-years) and in 0% of the placebo + TCS group (0 per 100 subject-years). Most subjects with keratitis recovered or were recovering during the treatment period. Among asthma subjects the frequency of keratitis was similar between DUPIXENT and placebo *[see Adverse Reactions (6.1)]*. Advise patients to report new onset or worsening eye symptoms to their healthcare provider.

5.3 Eosinophilic Conditions

Patients being treated for asthma may present with serious systemic eosinophilia sometimes presenting with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis, conditions which are often treated with systemic corticosteroid therapy. These events may be associated with the reduction of oral corticosteroid therapy. Physicians should be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients with eosinophilia. Cases of eosinophilic pneumonia and cases of vasculitis consistent with eosinophilic granulomatosis with polyangiitis have been reported with DUPIXENT in adult patients who participated in the asthma development program. A causal association between DUPIXENT and these conditions has not been established.

5.4 Acute Asthma Symptoms or Deteriorating Disease

DUPIXENT should not be used to treat acute asthma symptoms or acute exacerbations. Do not use DUPIXENT to treat acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with DUPIXENT.

5.5 Reduction of Corticosteroid Dosage

Do not discontinue systemic, topical, or inhaled corticosteroids abruptly upon initiation of therapy with DUPIXENT. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

5.6 Atopic Dermatitis Patients with Comorbid Asthma

Advise atopic dermatitis patients with comorbid asthma not to adjust or stop their asthma treatments without consultation with their physicians.

5.7 Parasitic (Helminth) Infections

Patients with known helminth infections were excluded from participation in clinical studies. It is unknown if DUPIXENT will influence the immune response against helminth infections. Treat patients with pre-existing helminth infections before initiating therapy with DUPIXENT. If patients become infected while receiving treatment with DUPIXENT and do not respond to antihelminth treatment, discontinue treatment with DUPIXENT until the infection resolves.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail elsewhere in the labeling:

- Hypersensitivity *[see Warnings and Precautions (5.1)]*
- Conjunctivitis and Keratitis *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adults with Atopic Dermatitis

Three randomized, double-blind, placebo-controlled, multicenter trials (Trials 1, 2, and 3) and one dose-ranging trial (Trial 4) evaluated the safety of DUPIXENT in subjects with moderate-to-severe atopic dermatitis. The safety population had a mean age of 38 years; 41% of subjects were female, 67% were white, 24% were Asian, and 6% were black; in terms of comorbid conditions, 48% of the subjects had asthma, 49% had allergic rhinitis, 37% had food allergy, and 27% had allergic conjunctivitis. In these 4 trials, 1472 subjects were treated with subcutaneous injections of DUPIXENT, with or without concomitant topical corticosteroids (TCS).

A total of 739 subjects were treated with DUPIXENT for at least 1 year in the development program for moderate-to-severe atopic dermatitis.

Trials 1, 2, and 4 compared the safety of DUPIXENT monotherapy to placebo through Week 16. Trial 3 compared the safety of DUPIXENT plus TCS to placebo plus TCS through Week 52.

Weeks 0 to 16 (Trials 1 to 4)

In DUPIXENT monotherapy trials (Trials 1, 2, and 4) through Week 16, the proportion of subjects who discontinued treatment because of adverse events was 1.9% in both the DUPIXENT 300 mg Q2W and placebo groups.

Table 1 summarizes the adverse reactions that occurred at a rate of at least 1% in the DUPIXENT 300 mg Q2W monotherapy groups, and in the DUPIXENT + TCS group, all at a higher rate than in their respective comparator groups during the first 16 weeks of treatment.

Table 1: Adverse Reactions Occurring in ≥1% of the DUPIXENT Monotherapy Group or the DUPIXENT + TCS Group in the Atopic Dermatitis Trials through Week 16

Adverse Reaction	DUPIXENT Monotherapy[a]		DUPIXENT + TCS[b]	
	DUPIXENT 300 mg Q2W[c] N=529 n (%)	Placebo N=517 n (%)	DUPIXENT 300 mg Q2W[c] + TCS N=110 n (%)	Placebo + TCS N=315 n (%)
Injection site reactions	51 (10)	28 (5)	11 (10)	18 (6)
Conjunctivitis[d]	51 (10)	12 (2)	10 (9)	15 (5)
Blepharitis	2 (<1)	1 (<1)	5 (5)	2 (1)
Oral herpes	20 (4)	8 (2)	3 (3)	5 (2)
Keratitis[e]	1 (<1)	0	4 (4)	0
Eye pruritus	3 (1)	1 (<1)	2 (2)	2 (1)
Other herpes simplex virus infection[f]	10 (2)	6 (1)	1 (1)	1 (<1)
Dry eye	1 (<1)	0	2 (2)	1 (<1)

[a] Pooled analysis of Trials 1, 2, and 4.

[b] Analysis of Trial 3 where subjects were on background TCS therapy.

[c] DUPIXENT 600 mg at Week 0, followed by 300 mg every two weeks.

[d] Conjunctivitis cluster includes conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, giant papillary conjunctivitis, eye irritation, and eye inflammation.

[e] Keratitis cluster includes keratitis, ulcerative keratitis, allergic keratitis, atopic keratoconjunctivitis, and ophthalmic herpes simplex.

[f] Other herpes simplex virus infection cluster includes herpes simplex, genital herpes, herpes simplex otitis externa, and herpes virus infection, but excludes eczema herpeticum.

Safety through Week 52 (Trial 3)

In the DUPIXENT with concomitant TCS trial (Trial 3) through Week 52, the proportion of subjects who discontinued treatment because of adverse events was 1.8% in DUPIXENT 300 mg Q2W + TCS group and 7.6% in the placebo + TCS group. Two subjects discontinued DUPIXENT because of adverse reactions: atopic dermatitis (1 subject) and exfoliative dermatitis (1 subject). The safety profile of DUPIXENT + TCS through Week 52 was generally consistent with the safety profile observed at Week 16.

Adolescents with Atopic Dermatitis

The safety of DUPIXENT was assessed in a trial of 250 subjects 12 to 17 years of age with moderate-to-severe atopic dermatitis (Trial 6). The safety profile of DUPIXENT in these subjects through Week 16 was similar to the safety profile from studies in adults with atopic dermatitis.

The long-term safety of DUPIXENT was assessed in an open-label extension study in subjects 12 to 17 years of age with moderate-to-severe atopic dermatitis (Trial 7). The safety profile of DUPIXENT in subjects followed through Week 52 was similar to the safety profile observed at Week 16 in Trial 6. The long-term safety profile of DUPIXENT observed in adolescents was consistent with that seen in adults with atopic dermatitis.

Asthma

A total of 2888 adult and adolescent subjects with moderate-to-severe asthma (AS) were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks duration (AS Trials 1, 2, and 3). Of these, 2678 had a history of 1 or more severe exacerbations in the year prior to enrollment despite regular use of medium- to high-dose inhaled corticosteroids plus an additional controller(s) (AS Trials 1 and 2). A total of 210 subjects with oral corticosteroid-dependent asthma receiving high-dose inhaled corticosteroids plus up to two additional controllers were enrolled (AS Trial 3). The safety population (AS Trials 1 and 2) was 12-87 years of age, of which 63% were female, and 82% were white. DUPIXENT 200 mg or 300 mg was administered subcutaneously Q2W, following an initial dose of 400 mg or 600 mg, respectively.

In AS Trials 1 and 2, the proportion of subjects who discontinued treatment due to adverse events was 4% of the placebo group, 3% of the DUPIXENT 200 mg Q2W group, and 6% of the DUPIXENT 300 mg Q2W group.

Table 2 summarizes the adverse reactions that occurred at a rate of at least 1% in subjects treated with DUPIXENT and at a higher rate than in their respective comparator groups in Asthma Trials 1 and 2.

Table 2: Adverse Reactions Occurring in ≥1% of the DUPIXENT Groups in Asthma Trials 1 and 2 and Greater than Placebo (6-Month Safety Pool)

Adverse Reaction	AS Trials 1 and 2		
	DUPIXENT 200 mg Q2W N=779 n (%)	DUPIXENT 300 mg Q2W N=788 n (%)	Placebo N=792 n (%)
Injection site reactions[a]	111 (14%)	144 (18%)	50 (6%)
Oropharyngeal pain	13 (2%)	19 (2%)	7 (1%)
Eosinophilia[b]	17 (2%)	16 (2%)	2 (<1%)

[a] Injection site reactions cluster includes erythema, edema, pruritus, pain, and inflammation.

[b] Eosinophilia = blood eosinophils ≥3,000 cells/mcL, or deemed by the investigator to be an adverse event. None met the criteria for serious eosinophilic conditions *[see Section 5.3 Warnings and Precautions]*.

Injection site reactions were most common with the loading (initial) dose. The safety profile of DUPIXENT through Week 52 was generally consistent with the safety profile observed at Week 24.

Specific Adverse Reactions

Conjunctivitis

During the 52-week treatment period of concomitant therapy trial (Trial 3), conjunctivitis was reported in 16% of the DUPIXENT + TCS group (20 per 100 subject-years) and in 9% of the placebo + TCS group (10 per 100 subject-years). Among asthma subjects, the frequency of conjunctivitis was similar between DUPIXENT and placebo *[see Warnings and Precautions (5.2)]*.

Eczema Herpeticum and Herpes Zoster

The rate of eczema herpeticum was similar in the placebo and DUPIXENT groups in the atopic dermatitis trials. Herpes zoster was reported in <0.1% of the DUPIXENT groups (<1 per 100 subject-years) and in <1% of the placebo group (1 per 100 subject-years) in the 16-week atopic dermatitis monotherapy trials. In the 52-week DUPIXENT + TCS atopic dermatitis trial, herpes zoster was reported in 1% of the DUPIXENT + TCS group

(1 per 100 subject-years) and 2% of the placebo + TCS group (2 per 100 subject-years). Among asthma subjects the frequency of herpes zoster was similar between DUPIXENT and placebo.

Hypersensitivity Reactions

Hypersensitivity reactions were reported in <1% of DUPIXENT-treated subjects. These included serum sickness reaction, serum sickness-like reaction, generalized urticaria, rash, erythema nodosum, and anaphylaxis *[see Contraindications (4), Warnings and Precautions (5.1), and Adverse Reactions (6.2)]*.

Eosinophils

DUPIXENT-treated subjects had a greater initial increase from baseline in blood eosinophil count compared to subjects treated with placebo. In subjects with atopic dermatitis, the mean and median increases in blood eosinophils from baseline to Week 4 were 100 and 0 cells/mcL respectively. In subjects with asthma, the mean and median increases in blood eosinophils from baseline to Week 4 were 130 and 10 cells/mcL respectively. The incidence of treatment-emergent eosinophilia (≥500 cells/mcL) was similar in DUPIXENT and placebo groups. Treatment-emergent eosinophilia (≥5,000 cells/mcL) was reported in <2% of DUPIXENT-treated patients and <0.5% in placebo-treated patients. Blood eosinophil counts declined to near baseline levels during study treatment *[see Warnings and Precautions (5.3)]*.

Cardiovascular (CV)

In the 1-year placebo controlled trial in subjects with asthma (AS Trial 2), CV thromboembolic events (CV deaths, non-fatal myocardial infarctions [MI], and non-fatal strokes) were reported in 1 (0.2%) of the DUPIXENT 200 mg Q2W group, 4 (0.6%) of the DUPIXENT 300 mg Q2W group, and 2 (0.3%) of the placebo group.

In the 1-year placebo controlled trial in subjects with atopic dermatitis (Trial 3), CV thromboembolic events (CV deaths, non-fatal MIs, and non-fatal strokes) were reported in 1 (0.9%) of the DUPIXENT + TCS 300 mg Q2W group, 0 (0.0%) of the DUPIXENT + TCS 300 mg QW group, and 1 (0.3%) of the placebo + TCS group.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to dupilumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Approximately 6% of subjects with atopic dermatitis or asthma who received DUPIXENT 300 mg Q2W for 52 weeks developed antibodies to dupilumab; ~2% exhibited persistent ADA responses and ~2% had neutralizing antibodies.

Approximately 9% of subjects with asthma who received DUPIXENT 200 mg Q2W for 52 weeks developed antibodies to dupilumab; ~4% exhibited persistent ADA responses, and ~4% had neutralizing antibodies.

Approximately 5% of subjects in the placebo groups in the 52-week studies were positive for antibodies to DUPIXENT; ~2% exhibited persistent ADA responses, and ~1% had neutralizing antibodies.

Approximately 16% of adolescent subjects with atopic dermatitis who received DUPIXENT 300 mg or 200 mg Q2W for 16 weeks developed antibodies to dupilumab; approximately 3% exhibited persistent ADA responses, and approximately 5% had neutralizing antibodies.

Approximately 4% of adolescent subjects with atopic dermatitis in the placebo group were positive for antibodies to DUPIXENT; approximately 1% exhibited persistent ADA responses, and approximately 1% had neutralizing antibodies.

The antibody titers detected in both DUPIXENT and placebo subjects were mostly low. In subjects who received DUPIXENT, development of high titer antibodies to dupilumab was associated with lower serum dupilumab concentrations *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

Two subjects who experienced high titer antibody responses developed serum sickness or serum sickness-like reactions during DUPIXENT therapy *[see Warnings and Precautions (5.1)]*.

7 DRUG INTERACTIONS

7.1 Live Vaccines

Avoid use of live vaccines in patients treated with DUPIXENT.

7.2 Non-Live Vaccines

Immune responses to vaccination were assessed in a study in which subjects with atopic dermatitis were treated once weekly for 16 weeks with 300 mg of dupilumab (twice the recommended dosing frequency). After 12 weeks of DUPIXENT administration, subjects were vaccinated with a Tdap vaccine (Adacel®) and a meningococcal polysaccharide vaccine (Menomune®). Antibody responses to tetanus toxoid and serogroup C meningococcal polysaccharide were assessed 4 weeks later. Antibody responses to both tetanus vaccine and meningococcal polysaccharide vaccine were similar in dupilumab-treated and placebo-treated subjects. Immune responses to the other active components of the Adacel and Menomune vaccines were not assessed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DUPIXENT during pregnancy.

Please contact 1-877-311-8972 or go to https://mothertobaby.org/ongoing-study/dupixent/ to enroll in or to obtain information about the registry.

Risk Summary

Available data from case reports and case series with DUPIXENT use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, DUPIXENT may be transmitted from the mother to the developing fetus. There are adverse effects on maternal and fetal outcomes associated with asthma in pregnancy *(see Clinical Considerations)*. In an enhanced pre- and post-natal developmental study, no adverse developmental effects were observed in offspring born to pregnant monkeys after subcutaneous administration of a homologous antibody against interleukin-4-receptor alpha (IL-4Rα) during organogenesis through parturition at doses up to 10-times the maximum recommended human dose (MRHD) *(see Data)*. The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-fetal Risk

In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

Data

Animal Data

In an enhanced pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of homologous antibody against IL-4Rα up to 10 times the MRHD (on a mg/kg basis of 100 mg/kg/week) from the beginning of organogenesis to parturition. No treatment-related adverse effects on embryofetal toxicity or malformations, or on morphological, functional, or immunological development were observed in the infants from birth through 6 months of age.

8.2 Lactation

Risk Summary

There are no data on the presence of dupilumab in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal and limited systemic exposure to dupilumab on the breastfed infant are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DUPIXENT and any potential adverse effects on the breastfed child from DUPIXENT or from the underlying maternal condition.

8.4 Pediatric Use

Atopic Dermatitis

The safety and efficacy of DUPIXENT have been established in pediatric patients 12 years of age and older with moderate-to-severe atopic dermatitis. A total of 251 adolescents ages 12 to 17 years old with moderate-to-severe atopic dermatitis were enrolled in Trial 6. The safety and efficacy were generally consistent between adolescents and adults *[see Adverse Reactions (6.1) and Clinical Studies (14.2) in the full prescribing information]*. Safety and efficacy in pediatric patients (<12 years of age) with atopic dermatitis have not been established.

Asthma

A total of 107 adolescents aged 12 to 17 years with moderate to severe asthma were enrolled in AS Trial 2 and received either 200 mg (N=21) or 300 mg (N=18) DUPIXENT (or matching placebo either 200 mg [N=34] or 300 mg [N=34]) Q2W. Asthma exacerbations and lung function were assessed in both adolescents and adults. For both the 200 mg and 300 mg Q2W doses, improvements in FEV_1 (LS mean change from baseline at Week 12) were observed (0.36 L and 0.27 L, respectively). For the 200 mg Q2W dose, subjects had a reduction in the rate of severe exacerbations that was consistent with adults. Safety and efficacy in pediatric patients (<12 years of age) with asthma have not been established. Dupilumab exposure was higher in adolescent patients than that in adults at the respective dose level which was mainly accounted for by difference in body weight *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

The adverse event profile in adolescents was generally similar to the adults *[see Adverse Reactions (6.1)]*.

8.5 Geriatric Use

Of the 1472 subjects with atopic dermatitis exposed to DUPIXENT in a dose-ranging study and placebo-controlled trials, 67 subjects were 65 years or older. Although no differences in safety or efficacy were observed between older and younger subjects, the number of subjects aged 65 and over is not sufficient to determine whether they respond differently from younger subjects.

Of the 1977 subjects with asthma exposed to DUPIXENT, a total of 240 subjects were 65 years or older. Efficacy and safety in this age group was similar to the overall study population.

10 OVERDOSE

There is no specific treatment for DUPIXENT overdose. In the event of overdosage, monitor the patient for any signs or symptoms of adverse reactions and institute appropriate symptomatic treatment immediately.

17 PATIENT COUNSELING INFORMATION

Advise the patients and/or caregivers to read the FDA-approved patient labeling (Patient Information and Instructions for Use) before the patient starts using DUPIXENT and each time the prescription is renewed as there may be new information they need to know.

Pregnancy Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DUPIXENT during pregnancy. Encourage participation in the registry *[see Use in Specific Populations (8.1)]*.

Administration Instructions

Provide proper training to patients and/or caregivers on proper subcutaneous injection technique, including aseptic technique, and the preparation and administration of DUPIXENT prior to use. Advise patients to follow sharps disposal recommendations.

Hypersensitivity

Advise patients to discontinue DUPIXENT and to seek immediate medical attention if they experience any symptoms of systemic hypersensitivity reactions *[see Warnings and Precautions (5.1)]*.

Conjunctivitis and Keratitis

Advise patients to consult their healthcare provider if new onset or worsening eye symptoms develop *[see Warnings and Precautions (5.2)]*.

Eosinophilic Conditions

Advise patients to notify their healthcare provider if they present with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis *[see Warnings and Precautions (5.3)]*.

Not for Acute Asthma Symptoms or Deteriorating Disease

Inform patients that DUPIXENT does not treat acute asthma symptoms or acute exacerbations. Inform patients to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with DUPIXENT *[see Warnings and Precautions (5.4)]*.

Reduction in Corticosteroid Dosage

Inform patients to not discontinue systemic or inhaled corticosteroids except under the direct supervision of a physician. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy *[see Warnings and Precautions (5.5)]*.

Atopic Dermatitis Patients with Comorbid Asthma

Advise atopic dermatitis patients with comorbid asthma not to adjust or stop their asthma treatment without talking to their physicians *[see Warnings and Precautions (5.6)]*.

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SLEEP STRATEGIES

The burgeoning role of sleep-related chronic hypoxia in long-term outcomes

BY KRISHNA M. SUNDAR, MD, FCCP

Clinicians are well aware of the acute effects of hypoxemia when encountered in conditions such as pulmonary embolism, pulmonary edema, COPD exacerbation, and others, whereas effects of chronic hypoxemia, such as pulmonary hypertension and polycythemia, are more difficult to recognize. Chronic hypoxemia is frequent in chronic lung diseases, such as COPD, but how it leads to increased mortality in severe COPD is unknown (NHLBI Working Group for LTOT in COPD. *Am J Respir Crit Care Med*. 2006;174:373). Chronic hypoxemia following high altitude exposure tends to have more unpredictable effects. Chronic hypoxemia, greater than that expected for the altitude of residence, is encountered frequently in high altitude dwellers. Here it has been implicated in the pathophysiology of chronic mountain sickness (Villafeurte and Corante. *High Alt Med Biol*. 2016;17[2]:61) and low birth weights (Maatta J, et al. *Sci Rep*. 2018;8[1]:13583), even though high altitude residence has been linked to better cardiovascular outcomes and reduced cancer-related deaths (Burstcher M. *Aging Dis*. 2013;5[4]:274). Chronic hypoxia effects at high altitude may, therefore, be variegated depending on a number of factors that include organ-system-specific effects, severity of chronic hypoxia, and a propensity to disease determined by genetic background and generations of residence.


Dr. Sundar

Such diverse effects of chronic sleep-related hypoxemia are also being reported with obstructive sleep apnea (OSA). While sleep can result in sustained drops in ventilation and consequent hypoxemia similar to what is seen in COPD, OSA is typified by a form of sleep-related hypoxemia in a pattern termed as chronic intermittent hypoxia (CIH). CIH is characterized by rapid fluctuations in oxygen saturations (Figure 1) that are virtually pathognomonic of sleep apnea either from recurrent upper airway obstructions (as in OSA) or pauses in respiratory generator firing (as in central sleep apnea). OSA-driven CIH has received most attention, given its purported role in in the causation of the wide range of pathologic conditions associated with OSA. Outcomes from cross-sectional and longitudinal studies have correlated time spent below 90% or recurrent oxygen desaturations to a number of OSA-related outcomes such as cardiovascular disease, diabetes, and cognitive dysfunction (Dewan et al. *Chest*. 2015;147[1]:266). While these effects of OSA-related intermittent hypoxemia occur over long periods of time, as with other forms of chronic hypoxia, some effects, such as hypertension, are demonstrable in animal models after much shorter durations of sleep-related intermittent hypoxia exposure. As seen with other forms of chronic hypoxemia, an opposing beneficial effect has also been demonstrated on the size of myocardial infarct during acute coronary events and from mild OSA-related mortality in elderly subjects (Javaheri et al. *J Am Coll Cardiol*. 2017;69[7]:841).

Given how common sleep-related hypoxemia and OSA are, it is important to understand the implications of different patterns of sleep-related hypoxemia that a vast segment of the population experiences on a nightly basis. A number of factors may determine chronic outcomes with sleep-related hypoxemia that include the pattern of sleep-related hypoxemia (chronic sustained hypoxemia associated with sleep-related hypoventilation vs chronic intermittent hypoxemia of OSA), degree of hypoxemia, presence of underlying disease, and hitherto undescribed individual factors. While a correlation between hypoxemic burden secondary to sleep-disordered breathing and cardiovascular outcomes has been shown (Azabarzin A, et al. *Eur Heart J*. 2018 Oct 30), CPAP interventional studies that address OSA-related CIH have shown mixed results for prevention of cardiovascular disease (McEvoy RD, et al. *N Engl J Med*. 2016;375[10]:919). It has also been difficult to draw upon results of oxygen supplementation in other forms of hypoxemia, such as COPD, when specifically targeted to addressing the hypoxemia seen only at night or with exercise (LOTT Research Group. *N Engl J Med*. 2016;375:1617). To complicate this further, high altitude residence (that may result in similar levels of sleep-related hypoxemia) is not associated with any differences in life-expectancy but may provide a reduction in cardiovascular outcomes (Ezzati, et al. J *Epidemiol Community Health*. 2012;66[7]:e17).

Chronic hypoxemia is frequent in chronic lung diseases, such as COPD, but how it leads to increased mortality in severe COPD is unknown.

How do we reconcile such disparate effects of chronic hypoxemia? Part of the difference may be in the pattern of chronic intermittent hypoxemia noted with OSA characterized not only by rapid drops in oxygen but also rapid reoxygenation events secondary to arousals terminating an apnea – these reoxygenation events have been attributed to the increased oxidant stress demonstrable in multiple tissues. While chronic hypoxia itself may cause increased oxidant stress, such effects seen with sustained forms of hypoxia, such as sleep-related hypoventilation or high altitude residence, may be more gradual resulting in lesser degrees of tissue effects and regulation of antioxidant defenses with sustained exposure. Herein lies the importance of understanding physiologic and biological effects stemming from chronic hypoxia to explain its variegated effects on different organ systems. In this regard, the role of the carotid body, a structure with unique vascular supply and with the ability to respond to minor changes in oxygen saturation as is seen in patients with OSA is key to the causation of hypertension associated with OSA (Shell et al. *Curr Hyperten Rep*. 2016;18[3]:19). Carotid body activation by intermittent hypoxia and long-term sensory facilitation drive the elevated sympathetic activity and consequent increases in blood pressure that can be improved by supplemental oxygen (Turnbull CD, et al. *Am J Respir Crit Care Med*. 2019;199[2]:211).

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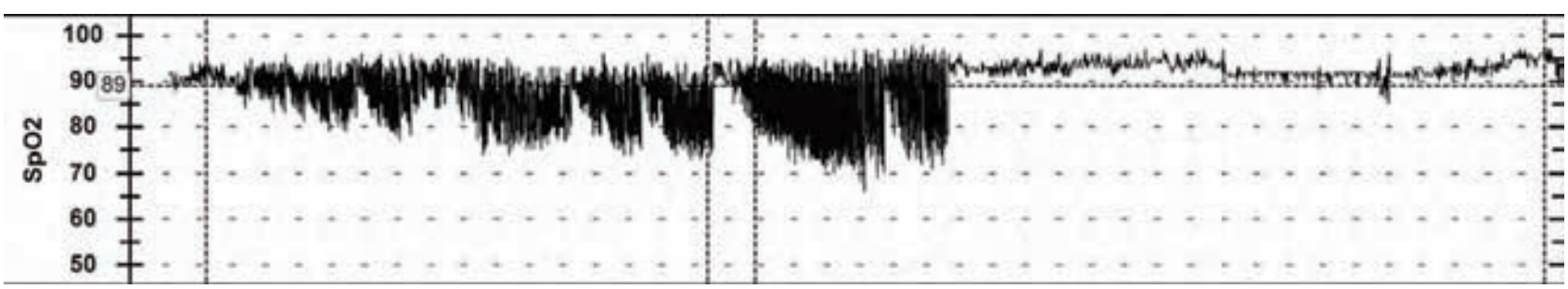

Figure 1: Demonstration of the pattern of intermittent hypoxemia in OSA characterized by oximetric desaturations and re-saturations that resolve with CPAP application.

Continued from previous page

While carotid body responses are key to the pathophysiology of OSA, every organ in the body (in fact, every cell within the body) has the ability to sense and respond to hypoxia. This ability to sense oxygen tensions is ingrained in every cell by virtue of oxygen's critical role in the genesis of life and evolution. These cellular responses to hypoxia are mediated by hypoxia-inducible factors (HIFs), isoforms of which include the more ubiquitous HIF-1 found in all parenchymal cells and HIF-2 found in specialized erythropoietin-producing cells of the kidney and the pulmonary circulation (the polycythemia and pulmonary vasoconstrictive responses from hypoxia are mediated through HIF-2). HIFs mediate the transcription of hundreds of genes, and they have been implicated in the pathobiology of a wide range of phenomena, from cancer to atherosclerotic vascular disease, metabolic syndrome, neurodegenerative disorders, pulmonary hypertension, and nonalcoholic fatty liver disease (Prabhakar and Semenza. *Physiol Rev*. 2012;92[3]:967). While HIF activation is an attractive target for examining the effects of chronic hypoxia of high altitude and sleep-disordered breathing, HIF activation varies from tissue to tissue and interacts with a number of other cellular systems in leading to differential effects. The short half-life of HIF proteins make them difficult to detect in tissues, so a number of secondary HIF-effects has been measured with mixed results depending on animal model utilized, pattern and degree of hypoxia studied, and the target effect measured. Comparative effects of intermittent vs sustained hypoxemia need to be systematically studied in different organ systems in different species, given the differing oxygen thresholds of individual cells due to unique blood flows and variations in the system of co-factors and prolyl hydroxylases that regulate the activation of HIFs. While the thrust of the work has been centered on HIF-related effects and the role of NF-kB-driven inflammation seen in OSA, there is substantial evidence to the role of oxidant stress that may be directly related to reoxygenation events occurring with CIH (Lavie L. *Sleep Med Rev*. 2015;20:27).

Chronic intermittent hypoxia is characterized by rapid fluctuations in oxygen saturations that are virtually pathognomonic of sleep apnea.

For life that has been intricately involved with oxygen from its genesis, it is not unreasonable to expect adaptations of cells, organs, and the whole individual to a wide range of oxygen tensions. Attempts to understand the import of sleep-disordered breathing has led to a need to unravel the implications of OSA-related chronic intermittent hypoxia and sleep-hypoventilation. This has led to a resurgence of interest in hypoxia-related research. Whether such chronic sleep-related sustained and intermittent hypoxemia is a harbinger of chronic disease is still not fully clear. A number of challenges exist with the understanding of these chronic hypoxia effects that include the long time needed for disease occurrence, its differential effects on organ systems, the role of hypoxia vs reoxygenation injury, importance of local blood flow, etc. Understanding these pathways will be crucial in prognosticating the role of sleep-related hypoxemia, the recognition of which has become part and parcel of routine management in sleep medicine.

Dr. Sundar is Medical Director, Sleep-Wake Center, Clinical Professor, Pulmonary, Critical Care & Sleep Medicine, Department of Medicine, University of Utah, Salt Lake City, Utah.

This month in the journal *CHEST*®

Editor's Picks

BY RICHARD S. IRWIN, MD, MASTER FCCP

Giants in Chest Medicine
John Heffner, MD, FCCP

ORIGINAL RESEARCH
The Landscape of US Lung Cancer Screening Services-Figure 1
By M. S. Kale, et al.

Systemic Markers of Inflammation in Smokers With Symptoms Despite Preserved Spirometry in SPIROMICS
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Prevalence of Atrial Fibrillation in Hospital Encounters With End-Stage COPD on Home Oxygen: National Trends in the United States
By X. Xiao, et al.

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NetWorks

LC screening. microRNAs. Impulse oscillometry. PH definition change. LC & women.

Interventional Chest/ Diagnostic Procedures

Complications and economic burden of diagnostic procedures for lung abnormalities in the community setting

The influential National Lung Screening Trial (NLST) reported a 20% reduction in lung cancer-related deaths using low-dose CT scan when compared with plain chest radiography (Aberle et al. *N Engl J Med*. 2011;365[5]:395). Many medical societies responded by recommending screening individuals at high-risk for lung cancer, and community-based lung cancer screening programs were developed across the United States. A concerning feature of the study was the rate (23.3%) of false-positive findings after three rounds of screening and the potential for complications secondary to diagnostic invasive procedures.

Using a 2008-2013 cohort of community inpatient and outpatient practice settings, Hou and colleagues searched administrative databases for procedure and diagnostic codes used in the NLST (Hou et al. *JAMA Intern Med*. 2019;179 [3]:324). The study team created an age-matched control cohort that did not have an invasive procedure and used the difference in complications rates as an indicator of a procedure-related complication. Additionally, they estimated 1-year medical costs associated with complications. More than 340,000 patients were included in the study, and the overall complication rate was far higher than what was reported in the NLST. This difference was more pronounced in the older group in the study cohort (23.8% vs 8.5%). The associated economic burden of complications was substantial, and cost more than the initial procedure itself.

Dr. Cardenas-Garcia

Although this was not a lung cancer screening cohort and used an administrative database, some valuable lessons can be offered from this study. First, complication rates of procedures like those performed in the NLST are likely to be higher in low-volume centers. Second, in order to minimize procedures, associated complications, and costs, we should be cognizant of the diagnostic limitations of each type of intervention when evaluating patients with lung nodules, wisely choosing the correct procedure for the correct patient after multidisciplinary discussion. We should seek to minimize biopsies of lesions that are likely benign.

Third, it is evident that more research is needed regarding this topic. The ideal study would need to include both academic and community-based lung cancer screening programs, and, prospectively, analyze the diagnostic yield and complication rates, as well as downstream costs. Finally, the results of this study call all of us to properly follow the lung cancer screening guidelines and reconcile them with our common sense when evaluating a patient with a screen-detected nodule. Injudicious testing invites unnecessary complications, increases the cost of care, and diverts resources from those more likely to benefit from appropriate interventions.

Jose Cardenas-Garcia, MD, FCCP
Steering Committee Member
Douglas Arenberg, MD, FCCP
NetWork Member

Pediatric Chest Medicine

microRNAs: A New Biomarker

Biomarkers are essential tools in a clinician's armamentarium. Biomarkers have multiple uses being indicators of a pathologic or physiologic process. One promising biomarker, now studied across multiple disorders, is microRNA (miRNA).

miRNAs are short (18–22 nucleotide) regulatory RNAs that bind mRNAs and decrease protein translation. miRNAs are generally co-transcribed with neighboring genes or co-transcribed within a cluster of miRNAs (a polycistronic cluster). Over 2,000 miRNAs are listed on miRBase (http://www.mirbase.org/), considered the central repository.

Function and biomarker utility of miRNAs are specific to the cells in which they are expressed. miRNAs isolated from circulating plasma exosomes have been shown to be stable over time, which is key in establishing their utility (Sanz-Rubio, et al. *Sci Rep*. 2018;8[1]:10306). miRNAs have been credited with the function of micromanaging the circadian clock and sleep homeostasis in virtually all living organisms (Goodwin, et al. *Cell Rep*. 2018;23[13]:3776; Mehta, et al. *J Mol Biol*. 2013;425[19]:3609).

Dr. Rao

Preliminary work has identified dysregulated miRNAs in patients with obstructive sleep apnea (Li, et al. *Medicine (Baltimore)*. 2017;96[34]:e7917). Exosomal miRNA has been shown to predict and protect against severe bronchopulmonary dysplasia (Lal, et al. *JCI Insight*. 2018;3[5]. pii: 93994).

Circadian miRNAs in salivary samples were found to have "altered" expression in autistic children with disordered sleep relative to peers with typical sleep (Hicks, et al. *PLoS One*. 2018;13[7]:e0198288). Collection from salivary samples facilitates multiple timed collection feasible at home and has multiple benefits.

Work on miRNAs, though preliminary, appears promising in providing a much-needed new perspective on pathophysiology and treatment in many disease processes.

Harish Rao, MD
Steering Committee Member

Pulmonary Physiology, Function, and Rehabilitation

Using impulse oscillometry in clinical practice

Impulse oscillometry (iOS) is an effort-independent test that requires minimal cooperation from the patient. It provides measures of respiratory mechanics during normal tidal breathing, including resistance (R), reactance (X), and impedance (Z) (Oostveen E, et al. *Eur Respir J*. 2003;22[6]:1026).

Airway R is largely, but not entirely, determined by cross-sectional area

(Poiseuille's Law). X is a surrogate for lung elastance, which is the inverse of compliance. Z is the combination of R and X and isn't used clinically.

There are several benefits to using iOS, as opposed to or in conjunction with standard spirometry. First, iOS yields respiratory function measurements for patients, like the elderly and young children, who cannot provide acceptable and reproducible spirometry (Pezzoli L, et al. *Age Ageing*. 2003;32[1]:43). Second, it provides a real-world assessment of lung function because R and X values are obtained during tidal breathing. Humans don't use the forced maneuvers needed for spirometry during normal daily activities, which weakens the correlation of FEV_1 with respiratory symptoms. Forced maneuvers also create artifacts from gas compression and cause small airway closure, which limits inferences made from standard spirometry (Brusasco V, et al. *Eur Respir J.* 2005;26[5]:948). Lastly, R and X provide information not available from spirometry, and iOS is particularly sensitive for detecting small airway dysfunction (Berger K, et al. *Chest*. 2015;148[5]:1131).


Dr. Holley

Clinical and disease-specific indications for iOS are still being established. As discussed above, iOS is appropriate for any patient unable to perform spirometry. As new inhalers designed to deliver medication to the distal airways become available, subtle abnormalities detected via iOS will provide a target for specific therapies (Lipworth B. *Ann Allergy Asthma Immunol.* 2013;110[4]:233). iOS shows significant promise as a noninvasive assessment for supraglottic diseases, like vocal cord dysfunction, and can quantify changes over time following invasive intervention to relieve upper airway obstruction (Bikov A, et al. *Chest*. 2015;148[3]:731; Horan T, et al. *Chest*. 2001:120[1]:69). As their comfort level with interpretation improves, pulmonologists will find iOS is an important tool for disease diagnosis and treatment.

Aaron Holley, MD, FCCP
Steering Committee Member

Pulmonary Vascular Disease
Hemodynamic definition of pulmonary hypertension changed

Many patients worldwide went to bed February 26, 2018, with normal pulmonary pressures and woke up the next morning with pulmonary hypertension (PH). That day, experts met at the World Symposium on PH in Nice, France, and changed the definition of resting PH from a mean pulmonary artery pressure (mPAP) of greater than or equal to 25 mm Hg to a mPAP greater than 20 mm Hg (Simmoneau, et al. *Eur Respir J*. 2019;53:1801913). The First World Health Organization symposium on PH in 1973 established the 25 mm Hg cutoff to distinguish primary PH from what was then considered less severe forms of PH. This definition, acknowledged as arbitrary and conservative at the time, has persisted due to a paucity of data establishing a definitively abnormal mPAP threshold.


Dr. Kingrey

Two contemporary findings provide justification for the definition change: (1)Normal mPAP is 14 ± 3.3 mm Hg in healthy subjects (Kovacs, et al. *Eur Respir J.* 2009;34[4]:888). (2) Patients with mPAP greater than 20 mm Hg suffer worse outcomes compared with control subjects (Maron, et al. *Circulation*. 2016;133[13]:1240).

Preserving the other hemodynamic criteria for group 1 PH, pulmonary artery wedge pressure less than or equal to 15 mm Hg and pulmonary vascular resistance greater than or equal to 3 Wood units, experts also recommend applying the new definition to all pre-capillary PH, including groups 3, 4, and applicable group 5 diagnoses.

Importantly, new guidelines do not recommend treating PH patients with mPAP 21-24 mm Hg: "A change in the hemodynamic definition of PH due to [pulmonary vascular diseases] does not imply treating these additional patients, but highlights the importance of close monitoring in this population."

John Kingrey, MD
Steering Committee Member

Thoracic Oncology
Lung Cancer and Women

While the overall incidence of lung cancer (LC) has decreased among both men and women, the decline among men has been steeper compared with women. Further, in women born in the 1950s to 1960s, the incidence has actually increased and cannot be fully explained by sex differences in smoking behavior (Jemal, et al. *N Engl J Med.* 2018;378[21]:1999). Data suggest that women may be more susceptible to the harmful effects of tobacco and that the biology of LC may be different in women. In addition, LC in nonsmokers is more likely to occur in women.


Dr. Gonzalez

LC is the leading cause of cancer death in both women and men worldwide, but the dramatic rise in the mortality rate from LC in women was qualified as a "full blown epidemic" in the Surgeon General's 2001 Women and Smoking report (*MMWR*. 2002;51[RR12]:1-30).

The benefits of lung cancer screening (LCS) in the National Lung Screening Trial (NLST) were higher in women than in men and significantly greater in the subset of women (16%) who entered the Nelson trial – reduction in 10-year LC mortality of 61% vs 26% in men (De Koning, et al. IASLC. 19th World Congress on Lung Cancer. 2018. Abstract PL02.05). A retrospective review of patients diagnosed with LC between 2005 and 2011 showed that only 37% of women vs 50% of men met LCS criteria (Wang, et al. *JAMA*. 2015;313[8]:853).

Lung cancer needs to be recognized as an important women's health issue, and there is need for continued attention to sex differences in LC risk, LCS criteria, and outcomes.

Anne Gonzalez, MD, FCCP
Steering Committee Member

CHEST Regional Congress 2019 Athens

Athens, Greece, one of the oldest cities in the world, will set a perfect backdrop for our upcoming CHEST Regional Congress, hosted by the Hellenic Thoracic Society and CHEST. Athens attracts millions of people from all over the world every year and has both historical and modern features including the Acropolis of Athens, which contains the remains of ancient buildings of great architectural significance such as the Parthenon; the Theatre of Dionysus, the oldest theater in Greece; and the National Archaeological Museum, which houses a large collection of artwork dating back to the Neolithic Age. The historic scenery and infectious energy will invigorate you as you partake in the top pulmonary medicine review courses.

This pulmonary review will give attendees access to world-class faculty from regional and international centers of excellence. A group of exceptional CHEST and Hellenic Thoracic Society faculty, including Drs. Kevin Brown Stephanie Levine, Nicholas Pastis, and Doreen Addrizzo-Harris, Vasilis Skouras, and Vlasis Poylchronopoulos, will come together to host outstanding sessions covering a multitude of topics, including interstitial lung disease, COPD, asthma, lung cancer, pleural disease, sarcoid, and pulmonary hypertension, among others. Also experience innovative and diverse education opportunities incorporating the best of the CHEST Pulmonary Medicine Board Review courses, CHEST Games, and a simulation demonstration opportunity on the final day of the meeting.

Information at athens.chestnet.org.

Our host city of Athens offers a great opportunity to include your family in your plans. It offers adventure at every turn: visit the historic landmarks, exciting markets, and historic architecture—some of which dates back to before 400 BC. On the final day of CHEST Regional Congress, you will have additional time to explore and take in the history of this beautiful city.

We look forward to seeing you 27-29 June at CHEST Regional Congress Athens!

Gerard A. Silvestri, MD, MS, FCCP
Hillenbrand Professor of Thoracic Oncology
Division of Pulmonary and Critical Care Medicine
Medical University of South Carolina
Charleston, SC

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