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Medical workers screened thousands of travelers at Wuhan train stations for symptoms of 2019-nCoV infection until the Chinese government canceled planes and trains leaving the city.

2019 Novel Coronavirus: What clinicians need to know

BY M. ALEXANDER OTTO

MDedge News

As the 2019 Novel Coronavirus story unfolds, the most important thing for clinicians in the United States to do is ask patients who appear to have the flu if they, or someone they have been in contact with, recently returned from China, according to infectious disease experts.

“We are asking that of everyone with fever and respiratory symptoms who comes to our clinics, hospital, or emergency room. It’s a powerful screening tool,” said William Schaffner, MD, professor of preventive medicine and infectious diseases at Vanderbilt University Medical Center, Nashville, Tenn., and adviser to the Centers for

Disease Control and Prevention (CDC).

In addition to fever, common signs of infection include cough, shortness of breath, and breathing difficulties. A few patients in Wuhan, China, the epicenter of the outbreak, have had diarrhea, vomiting, and other gastrointestinal symptoms. In more severe cases, infection can cause pneumonia, severe acute respiratory syndrome, kidney failure, and death. The incubation period appears to be up to 2 weeks, according to the World Health Organization (WHO).

If patients exhibit symptoms and either they or a close contact has returned from China recently, take standard airborne precautions and send specimens – a serum sample, oral and nasal pharyngeal swabs, and lower respiratory tract

CORONAVIRUS // *continued on page 7*

Fewer lung cancer deaths lead to record drop in overall cancer mortality

BY ANDREW D. BOWSER

MDedge News

Declines in death rates for lung cancer and melanoma have gained momentum in recent years, fueling a record drop in cancer mortality, the American Cancer Society says.

Lung cancer death rates, which were falling by 3% in men and 2% in women annually in 2008 through 2013, dropped by 5% in men and nearly 4% per year in women annually from 2013 to 2017, according to the society’s 2020 statistical report.

Those accelerating reductions in death rates helped fuel the biggest-ever single-year decline in overall cancer mortality, of 2.2%, from 2016 to 2017, their report shows.

According to Rebecca L. Siegel and coauthors, the decline in melanoma death rates escalated to 6.9% per year among 20- to 49-year-olds over 2013-2017, compared with a decline of just 2.9% per year during 2006-2010. Likewise, the melanoma death rate decline was 7.2% annually

MORTALITY // *continued on page 6*

INSIDE HIGHLIGHT



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Neuromuscular blockade for ARDS

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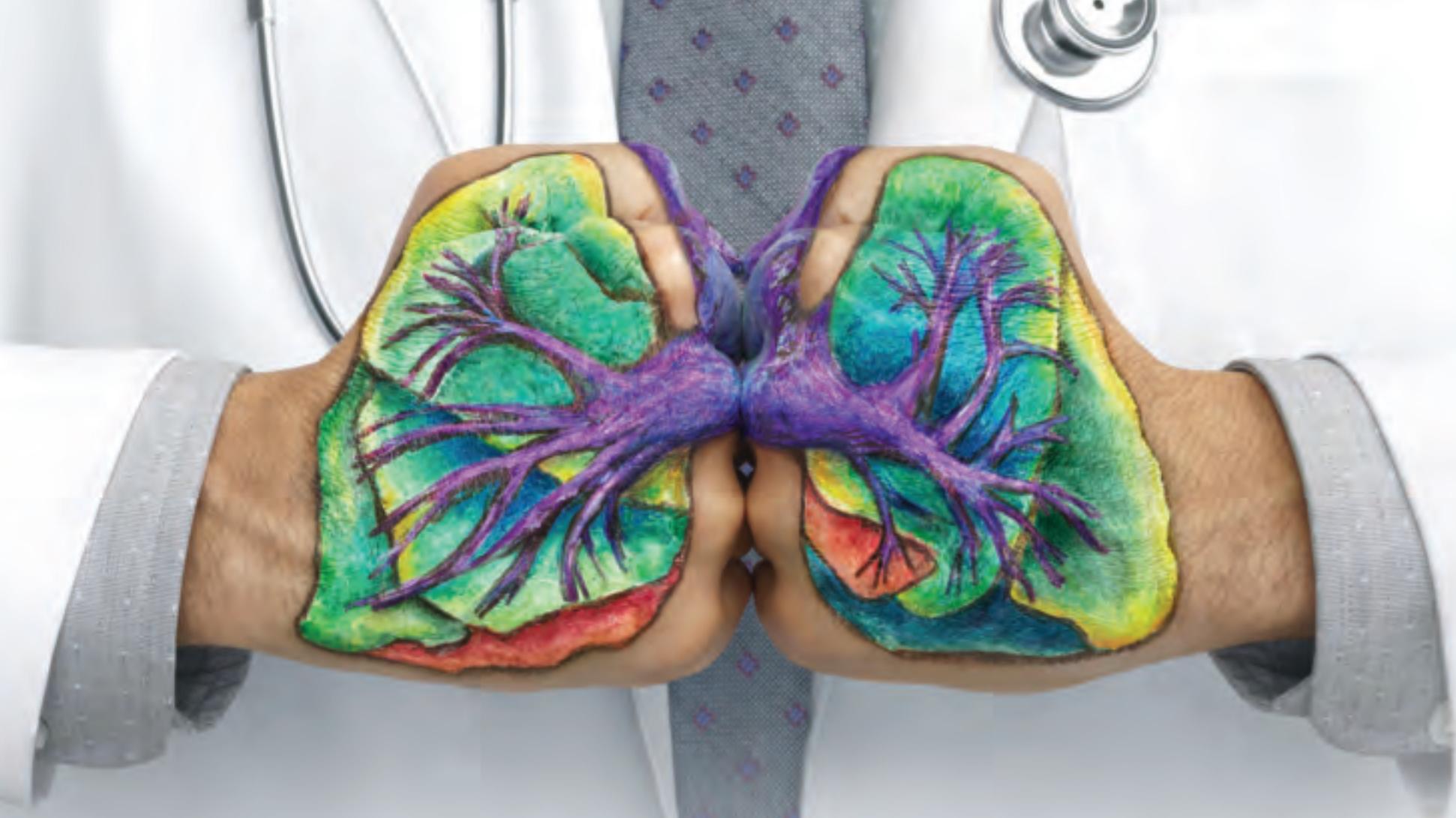
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Indication

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

Select Important Safety Information

Elevated liver enzymes and drug-induced liver injury (DILI):

DILI has been observed with Esbriet. In the postmarketing period, non-serious and serious cases of DILI, including severe liver injury with fatal outcome, have been reported. Patients treated with Esbriet had a higher incidence of ALT and/or AST elevations of $\geq 3x$ ULN (3.7%) compared with placebo patients (0.8%). Increases in ALT and AST $\geq 3x$ ULN were reversible with dose modification or treatment discontinuation.

Conduct liver function tests (ALT, AST, and bilirubin) prior to the initiation of therapy with Esbriet, monthly for the first 6 months, every 3 months thereafter, and as clinically indicated. Measure liver function promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. Dosage modification or interruption may be necessary for liver enzyme elevations.

Photosensitivity reaction or rash: Patients treated with Esbriet had a higher incidence of photosensitivity reactions (9%) vs placebo (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, vs 1.0% of placebo patients. The most common ($>2\%$) GI events leading to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. Dosage modification may be necessary.

Adverse reactions: The most common adverse reactions ($\geq 10\%$) 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 reduction of Esbriet is 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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WE WON'T BACK DOWN FROM IPF

Help preserve more lung function. Reduce lung function decline.¹⁻³

STUDIED IN A RANGE OF PATIENTS



Clinical trials included patients with IPF with a range of clinical characteristics, select comorbidities, and concomitant medications⁴

DEMONSTRATED EFFICACY



In clinical trials, Esbriet preserved more lung function by delaying disease progression for patients with IPF^{1-4*}

ESTABLISHED SAFETY AND TOLERABILITY



The safety and tolerability of Esbriet were evaluated based on 1247 patients in 3 randomized, controlled trials[†]

COMMITTED TO PATIENTS



Genentech offers a breadth of patient support and assistance services to help your patients with IPF[‡]

WORLDWIDE PATIENT EXPERIENCE



More than 42,000 patients have taken pirfenidone worldwide^{4§}

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 on 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. July 2019. **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. 2019.

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}

[†]Serious adverse reactions, including elevated liver enzymes and drug-induced liver injury, 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

Esbriet[®]
(pirfenidone) tablets 267 mg
801 mg

NTM lung disease incidence, prevalence on the rise

BY STEVE CIMINO

MDedge News

A new study of claims-based data has found that the incidence and prevalence of non-

tuberculous mycobacterial (NTM) lung disease is increasing in most states.

To assess the NTM lung disease burden on a national level, Kevin L. Winthrop, MD, of Oregon Health &

Science University, Portland, and associates analyzed patient data from a U.S. managed care claims database between 2008 and 2015. Their findings were published in the *Annals of the American Thoracic Society*.

A case of NTM lung disease was defined as a patient with at least two medical claims with the disease's diagnostic codes – 031.0 and A31.0 – that were at least 30 days apart. Of the 74,984,596 ben-



BRIEF SUMMARY

The following is a brief summary of the full Prescribing Information for ESBRIET® (pirfenidone). Please review the full Prescribing Information prior to prescribing ESBRIET.

1 INDICATIONS AND USAGE

ESBRIET is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Elevated Liver Enzymes and Drug-Induced Liver Injury

Cases of drug-induced liver injury (DILI) have been observed with ESBRIET. In the postmarketing period, non-serious and serious cases of DILI, including severe liver injury with fatal outcome, have been reported. Patients treated with Esbriet 2403 mg/day in three Phase 3 trials had a higher incidence of elevations in ALT or AST $\geq 3 \times$ ULN than placebo patients (3.7% vs 0.8%, respectively). Elevations $\geq 10 \times$ ULN in ALT or AST occurred in 0.3% of patients in the Esbriet 2403 mg/day group and in 0.2% of patients in the placebo group. Increases in ALT and AST $\geq 3 \times$ ULN were reversible with dose modification or treatment discontinuation.

Conduct liver function tests (ALT, AST, and bilirubin) prior to the initiation of therapy with ESBRIET, monthly for the first 6 months, every 3 months thereafter, and as clinically indicated. Measure liver function tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. Dosage modification or interruption may be necessary for liver enzyme elevations [see *Dosage and Administration* (2.1, 2.3)].

5.2 Photosensitivity Reaction or Rash

Patients treated with ESBRIET 2403 mg/day in the three Phase 3 studies had a higher incidence of photosensitivity reactions (9%) compared with patients treated with placebo (1%). The majority of the photosensitivity reactions occurred during the initial 6 months. Instruct patients to avoid or minimize exposure to sunlight (including sunlamps), to use a sunblock (SPF 50 or higher), and to wear clothing that protects against sun exposure. Additionally, instruct patients to avoid concomitant medications known to cause photosensitivity. Dosage reduction or discontinuation may be necessary in some cases of photosensitivity reaction or rash [see *Dosage and Administration* section 2.3 in full Prescribing Information].

5.3 Gastrointestinal Disorders

In the clinical studies, gastrointestinal events of nausea, diarrhea, dyspepsia, vomiting, gastro-esophageal reflux disease, and abdominal pain were more frequently reported by patients in the ESBRIET treatment groups than in those taking placebo. Dosage reduction or interruption for gastrointestinal events was required in 18.5% of patients in the 2403 mg/day group, as compared to 5.8% of patients in the placebo group; 2.2% of patients in the ESBRIET 2403 mg/day group discontinued treatment due to a gastrointestinal event, as compared to 1.0% in the placebo group. The most common ($>2\%$) gastrointestinal events that led to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. The incidence of gastrointestinal events was highest early in the course of treatment (with highest incidence occurring during the initial 3 months) and decreased over time. Dosage modifications may be necessary in some cases of gastrointestinal adverse reactions [see *Dosage and Administration* section 2.3 in full Prescribing Information].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Liver Enzyme Elevations and Drug-Induced Liver Injury [see *Warnings and Precautions* (5.1)]
- Photosensitivity Reaction or Rash [see *Warnings and Precautions* (5.2)]
- Gastrointestinal Disorders [see *Warnings and Precautions* (5.3)]

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.

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.

ESBRIET was studied in 3 randomized, double-blind, placebo-controlled trials (Studies 1, 2, and 3) in which a total of 623 patients received 2403 mg/day

ESBRIET® (pirfenidone)

of ESBRIET and 624 patients received placebo. Subjects ages ranged from 40 to 80 years (mean age of 67 years). Most patients were male (74%) and Caucasian (95%). The mean duration of exposure to ESBRIET was 62 weeks (range: 2 to 118 weeks) in these 3 trials.

At the recommended dosage of 2403 mg/day, 14.6% of patients on ESBRIET compared to 9.6% on placebo permanently discontinued treatment because of an adverse event. The most common ($>1\%$) adverse reactions leading to discontinuation were rash and nausea. The most common ($>3\%$) adverse reactions leading to dosage reduction or interruption were rash, nausea, diarrhea, and photosensitivity reaction.

The most common adverse reactions with an incidence of $\geq 10\%$ and more frequent in the ESBRIET than placebo treatment group are listed in Table 2.

Table 2. Adverse Reactions Occurring in $\geq 10\%$ of ESBRIET-Treated Patients and More Commonly Than Placebo in Studies 1, 2, and 3

Adverse Reaction	% of Patients (0 to 118 Weeks)	
	ESBRIET 2403 mg/day (N = 623)	Placebo (N = 624)
Nausea	36%	16%
Rash	30%	10%
Abdominal Pain ¹	24%	15%
Upper Respiratory Tract Infection	27%	25%
Diarrhea	26%	20%
Fatigue	26%	19%
Headache	22%	19%
Dyspepsia	19%	7%
Dizziness	18%	11%
Vomiting	13%	6%
Anorexia	13%	5%
Gastro-esophageal Reflux Disease	11%	7%
Sinusitis	11%	10%
Insomnia	10%	7%
Weight Decreased	10%	5%
Arthralgia	10%	7%

¹ Includes abdominal pain, upper abdominal pain, abdominal distension, and stomach discomfort.

Adverse reactions occurring in ≥ 5 to $<10\%$ of ESBRIET-treated patients and more commonly than placebo are photosensitivity reaction (9% vs. 1%), decreased appetite (8% vs. 3%), pruritus (8% vs. 5%), asthenia (6% vs. 4%), dysgeusia (6% vs. 2%), and non-cardiac chest pain (5% vs. 4%).

6.2 Postmarketing Experience

In addition to adverse reactions identified from clinical trials the following adverse reactions have been identified during post-approval use of pirfenidone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Blood and Lymphatic System Disorders

Agranulocytosis

Immune System Disorders

Angioedema

Hepatobiliary Disorders

Drug-induced liver injury [see *Warnings and Precautions* (5.1)]

7 DRUG INTERACTIONS

7.1 CYP1A2 Inhibitors

Pirfenidone is metabolized primarily (70 to 80%) via CYP1A2 with minor contributions from other CYP isoenzymes including CYP2C9, 2C19, 2D6 and 2E1.

Strong CYP1A2 Inhibitors

The concomitant administration of ESBRIET and fluvoxamine or other strong CYP1A2 inhibitors (e.g., enoxacin) is not recommended because it significantly increases exposure to ESBRIET [see *Clinical Pharmacology* section 12.3 in full Prescribing Information]. Use of fluvoxamine or other strong CYP1A2 inhibitors should be discontinued prior to administration of ESBRIET and avoided during

eficiaries in the database, 9,476 met the case definition for NTM lung disease; 69% (n = 6,530) were women.

From 2008 to 2015, the annual incidence of NTM lung disease increased from 3.13 (95% confidence interval, 2.88-3.40) to 4.73 (95% CI, 4.43-5.05) per 100,000 person-years, with the average rate



Dr. George Kubica/CDC

of yearly change being +5.2% (95% CI, 4.0%-6.4%; *P* less than .01). The annual prevalence increased from 6.78 (95% CI, 6.45-7.14) to 11.70 (95% CI, 11.26-12.16) per 100,000 persons, with the average rate of yearly change being +7.5% (95% CI, 6.7-8.2%; *P* less than .01).

The majority of NTM lung disease in the United States is caused by *Mycobacterium avium* complex (17), although other species such as *M. abscessus*, *M. kansasii*, *M. xenopi*, and others contribute to this disease burden.

The authors acknowledged their study's limitations, including the lack of microbiologic or radiographic confirmation of the NTM infection and the inherent shortcomings of claims data-based studies overall. They did note a previous report, however, that "claims-based case identification has a high positive predictive value of approximately 82% for NTM lung disease."

The study was funded by Insmmed; the Intramural Research Programs of the National Institute of Allergy and Infectious Diseases; and the National Heart, Lung, and Blood Institute. The authors reported no conflicts of interest.

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SOURCE: Winthrop KL et al. Ann Am Thorac Soc. 2019 Dec 13. doi: 10.1513/AnnalsATS.201804-236OC.

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ESBRIET treatment. In the event that fluvoxamine or other strong CYP1A2 inhibitors are the only drug of choice, dosage reductions are recommended. Monitor for adverse reactions and consider discontinuation of ESBRIET as needed [see *Dosage and Administration section 2.4 in full Prescribing Information*].

Moderate CYP1A2 Inhibitors

Concomitant administration of ESBRIET and ciprofloxacin (a moderate inhibitor of CYP1A2) moderately increases exposure to ESBRIET [see *Clinical Pharmacology section 12.3 in full Prescribing Information*]. If ciprofloxacin at the dosage of 750 mg twice daily cannot be avoided, dosage reductions are recommended [see *Dosage and Administration section 2.4 in full Prescribing Information*]. Monitor patients closely when ciprofloxacin is used at a dosage of 250 mg or 500 mg once daily.

Concomitant CYP1A2 and other CYP Inhibitors

Agents or combinations of agents that are moderate or strong inhibitors of both CYP1A2 and one or more other CYP isoenzymes involved in the metabolism of ESBRIET (i.e., CYP2C9, 2C19, 2D6, and 2E1) should be discontinued prior to and avoided during ESBRIET treatment.

7.2 CYP1A2 Inducers

The concomitant use of ESBRIET and a CYP1A2 inducer may decrease the exposure of ESBRIET and this may lead to loss of efficacy. Therefore, discontinue use of strong CYP1A2 inducers prior to ESBRIET treatment and avoid the concomitant use of ESBRIET and a strong CYP1A2 inducer [see *Clinical Pharmacology section 12.3 in full Prescribing Information*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The data with ESBRIET use in pregnant women are insufficient to inform on drug associated risks for major birth defects and miscarriage. In animal reproduction studies, pirfenidone was not teratogenic in rats and rabbits at oral doses up to 3 and 2 times, respectively, the maximum recommended daily dose (MRDD) in adults [see *Data*].

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

Data

Animal Data

Animal reproductive studies were conducted in rats and rabbits. In a combined fertility and embryofetal development study, female rats received pirfenidone at oral doses of 0, 50, 150, 450, and 1000 mg/kg/day from 2 weeks prior to mating, during the mating phase, and throughout the periods of early embryonic development from gestation days (GD) 0 to 5 and organogenesis from GD 6 to 17. In an embryofetal development study, pregnant rabbits received pirfenidone at oral doses of 0, 30, 100, and 300 mg/kg/day throughout the period of organogenesis from GD 6 to 18. In these studies, pirfenidone at doses up to 3 and 2 times, respectively, the maximum recommended daily dose (MRDD) in adults (on mg/m² basis at maternal oral doses up to 1000 mg/kg/day in rats and 300 mg/kg/day in rabbits, respectively) revealed no evidence of impaired fertility or harm to the fetus due to pirfenidone. In the presence of maternal toxicity, acyclic/irregular cycles (e.g., prolonged estrous cycle) were seen in rats at doses approximately equal to and higher than the MRDD in adults (on a mg/m² basis at maternal doses of 450 mg/kg/day and higher). In a pre- and post-natal development study, female rats received pirfenidone at oral doses of 0, 100, 300, and 1000 mg/kg/day from GD 7 to lactation day 20. Prolongation of the gestation period, decreased numbers of live newborn, and reduced pup viability and body weights were seen in rats at an oral dosage approximately 3 times the MRDD in adults (on a mg/m² basis at a maternal oral dose of 1000 mg/kg/day).

8.2 Lactation

Risk Summary

No information is available on the presence of pirfenidone in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. The lack of clinical data during lactation precludes clear determination of the risk of ESBRIET to an infant during lactation; therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ESBRIET and the potential adverse effects on the breastfed child from ESBRIET or from the underlying maternal condition.

Data

Animal Data

A study with radio-labeled pirfenidone in rats has shown that pirfenidone or its metabolites are excreted in milk. There are no data on the presence of pirfenidone or its metabolites in human milk, the effects of pirfenidone on the breastfed child, or its effects on milk production.

ESBRIET® (pirfenidone)

8.4 Pediatric Use

Safety and effectiveness of ESBRIET in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of subjects in the clinical studies receiving ESBRIET, 714 (67%) were 65 years old and over, while 231 (22%) were 75 years old and over. No overall differences in safety or effectiveness were observed between older and younger patients. No dosage adjustment is required based upon age.

8.6 Hepatic Impairment

ESBRIET should be used with caution in patients with mild (Child Pugh Class A) to moderate (Child Pugh Class B) hepatic impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed [see *Dosage and Administration section 2.3 in full Prescribing Information*].

The safety, efficacy, and pharmacokinetics of ESBRIET have not been studied in patients with severe hepatic impairment. ESBRIET is not recommended for use in patients with severe (Child Pugh Class C) hepatic impairment [see *Clinical Pharmacology section 12.3 in full Prescribing Information*].

8.7 Renal Impairment

ESBRIET should be used with caution in patients with mild (CL_{cr} 50-80 mL/min), moderate (CL_{cr} 30-50 mL/min), or severe (CL_{cr} less than 30 mL/min) renal impairment [see *Clinical Pharmacology section 12.3 in full Prescribing Information*]. Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed [see *Dosage and Administration section 2.3 in full Prescribing Information*]. The safety, efficacy, and pharmacokinetics of ESBRIET have not been studied in patients with end-stage renal disease requiring dialysis. Use of ESBRIET in patients with end-stage renal diseases requiring dialysis is not recommended.

8.8 Smokers

Smoking causes decreased exposure to ESBRIET [see *Clinical Pharmacology section 12.3 in full Prescribing Information*], which may alter the efficacy profile of ESBRIET. Instruct patients to stop smoking prior to treatment with ESBRIET and to avoid smoking when using ESBRIET.

10 OVERDOSAGE

There is limited clinical experience with overdosage. Multiple dosages of ESBRIET up to a maximum tolerated dose of 4005 mg per day were administered as five 267 mg capsules three times daily to healthy adult volunteers over a 12-day dose escalation.

In the event of a suspected overdosage, appropriate supportive medical care should be provided, including monitoring of vital signs and observation of the clinical status of the patient.

17 PATIENT COUNSELING INFORMATION

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

Liver Enzyme Elevations

Advise patients that they may be required to undergo liver function testing periodically. Instruct patients to immediately report any symptoms of a liver problem (e.g., skin or the white of eyes turn yellow, urine turns dark or brown [tea colored], pain on the right side of stomach, bleed or bruise more easily than normal, lethargy) [see *Warnings and Precautions (5.1)*].

Photosensitivity Reaction or Rash

Advise patients to avoid or minimize exposure to sunlight (including sunlamps) during use of ESBRIET because of concern for photosensitivity reactions or rash. Instruct patients to use a sunblock and to wear clothing that protects against sun exposure. Instruct patients to report symptoms of photosensitivity reaction or rash to their physician. Temporary dosage reductions or discontinuations may be required [see *Warnings and Precautions (5.2)*].

Gastrointestinal Events

Instruct patients to report symptoms of persistent gastrointestinal effects including nausea, diarrhea, dyspepsia, vomiting, gastro-esophageal reflux disease, and abdominal pain. Temporary dosage reductions or discontinuations may be required [see *Warnings and Precautions (5.3)*].

Smokers

Encourage patients to stop smoking prior to treatment with ESBRIET and to avoid smoking when using ESBRIET [see *Clinical Pharmacology section 12.3 in full Prescribing Information*].

Take with Food

Instruct patients to take ESBRIET with food to help decrease nausea and dizziness.

Distributed by:

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VIEW ON THE NEWS

Sachin Gupta, MD, FCCP,
comments: It's a classic

chicken-or-egg scenario in regard to the rising numbers.

Increased awareness of NTM lung disease is, in part, why

we're seeing prevalence and incidence go up. And yet the disease itself may also be growing in clusters and pockets, as the data show, in various places across the country. The worrisome aspect here is that future studies will likely show that, as incidence is increasing, mortality is increasing as well. That speaks to the challenges with these bugs: very hard to diagnose, very hard to treat.



for the more recent time period, compared with just 1.3% annually in the earlier time period. The finding was even more remarkable for those 65 years of age and older, according to investigators, since the declines in melanoma death rates reached 6.2% annually, compared with a 0.9% annual increase in the years before immunotherapy.

Smoking cessation has been the main driver of progress in cutting lung cancer death

rates, according to the report, while in melanoma, death rates have dropped after the introduction of immune checkpoint inhibitors and targeted therapies.

By contrast, reductions in death rates have slowed for colorectal cancers and female breast cancers, and have stabilized for prostate cancer, Ms. Siegel and coauthors stated, adding that racial and geographic disparities persist in preventable cancers, including those of the lung and cervix.

“Increased investment in both the equitable application of existing cancer control interventions and basic and clinical research to further advance treatment options would undoubtedly accelerate progress against cancer,” said the investigators. The report appears in *CA: A Cancer Journal for Clinicians*.

While the decline in lung cancer death rates is good news, the disease remains a major killer, responsible for more deaths than breast, colorectal, and ovarian cancer combined, said Jacques P. Fontaine, MD, FCCP, a thoracic surgeon at Moffitt Cancer Center in Tampa.

“Five-year survival rates are still around the 18%-20% range, which is much lower than breast and prostate cancer,” Dr. Fontaine said in an interview. “Nonetheless, we’ve made a little dent in that, and we’re improving.”

Two other factors that have helped spur that improvement, according to Dr. Fontaine, are the reduced incidence of squamous cell carcinomas, which are linked to smoking, and the increased use of lung cancer screening with low-dose computed tomography.

Squamous cell carcinomas tend to be central rather than peripheral, which makes the tumors harder to resect: “Surgery is sometimes not an option, and even to this day in 2020, the single most effective treatment for lung cancer remains surgical re-

section,” said Dr. Fontaine.

Likewise, centrally located tumors may preclude giving high-dose radiation and may result in more “collateral damage” to healthy tissue, he added.

Landmark studies show that low-dose CT scans reduce lung cancer deaths by 20% or more; however, screening can have false-positive results that lead to unnecessary biopsies and other harms, suggesting that the procedures should be done in centers of

excellence that provide high-quality, responsible screening for early lung cancer, Dr. Fontaine said.

While the drop in melanoma death rates is encouraging and, not surprising in light of new cutting-edge therapies, an ongoing unmet treatment need still exists, according to Vishal Anil Patel, MD, director of cutaneous oncology at the George Washington Cancer Center.

Response rates remain lower from other cancers, sparking interest in combining current immunotherapies with costimulatory molecules that may further improve survival rates, according to Dr. Patel.

In 2020, 606,000 cancer deaths are projected, according to the report. Of those deaths, nearly 136,000 are attributable to cancers of the lung and bronchus, while melanoma accounts for nearly 7,000 deaths.

The report notes that variation in cancer incidence reflects geographical differences in medical detection practices and the prevalence of risk factors, such as smoking, obesity, and other health behaviors. “For example, lung cancer incidence and mortality rates in Kentucky, where smoking prevalence was historically highest, are 3 to 4 times higher than those in Utah, where it was lowest,” the investigators wrote.

Cancer mortality rates have fallen 29% since 1991, translating into 2.9 million fewer cancer deaths, the report says.

Ms. Siegel and coauthors are employed by the American Cancer Society, which receives grants from private and corporate foundations, and their salaries are solely funded through the American Cancer Society, according to the report.

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SOURCE: Siegel RL et al. *CA Cancer J Clin.* 2020;70(1):7-30. doi: 10.3322/caac.21590.



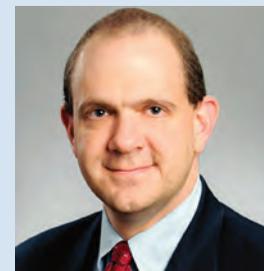
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Dr. Patel

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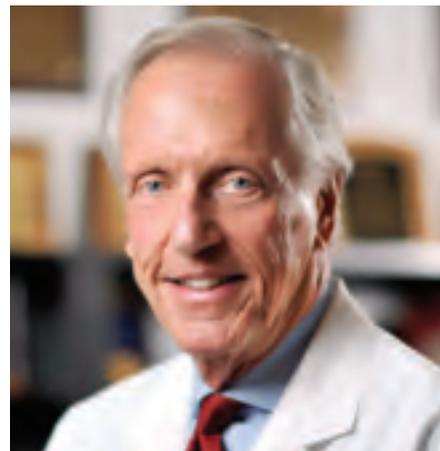
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specimens if available – to the local health department, which will forward them to the CDC for testing. Turnaround time is 24-48 hours.

The 2019 Novel Coronavirus (2019-nCoV), identified as the



Dr. William Shaffner

cause of an outbreak of respiratory illness first detected in December in association with a live-animal market in Wuhan, has been implicated in almost 2,000 cases and 56 deaths in that country. Cases have been reported in 13 countries besides China. Five cases of 2019-nCoV infection have been confirmed in the United States, all in people recently returned from Wuhan. As the virus spreads in China, however, it's almost certain more cases will show up in the United States. Travel history is key, Dr. Schaffner and others said.

Plan and rehearse

The first step to prepare is to use the CDC's Interim Guidance for Healthcare Professionals to make a written plan specific to your practice to respond to a potential case. The plan must include notifying the local health department, the CDC liaison for testing, and tracking down patient contacts.

"It's not good enough to just download CDC's guidance. Use it to make your own local plan and know what to do 24/7," said Daniel Lucey, MD, an infectious disease expert at Georgetown University Medical Center, Washington.

Know who is on call at the health department on weekends and nights, he recommended. Know where the patient is going to be isolated; figure out what to do if there's more than one, and tests come back positive. Have masks on hand, and rehearse the response. "Make a coronavirus team, and absolutely have the nurses involved," as well as other providers who may come into contact with a case, he added.

"You want to be able to do as well

as your counterparts in Washington state and Chicago," where the two U.S. cases emerged. "They were prepared. They knew what to do," Dr. Lucey said.

Those first two U.S. patients – a

What we know today might change tomorrow, so we have to keep tuned in to new information, but we learned a lot from SARS.

man in Everett, Wash., and a Chicago woman – developed symptoms after returning from Wuhan, a city of 11 million just over 400 miles inland from the port city of Shanghai. On Jan. 26 three more cases were confirmed by the CDC, two in California and one in Arizona, and each had recently traveled to Wuhan. All five patients remain hospitalized, and there's no evidence they spread the infection further. There is also no evidence of human-to-human transmission of other cases exported from China to any other countries, according to the WHO.

WHO declined to declare a global health emergency – a Public Health Emergency of International Concern, in its parlance – on Jan. 23. The step would have triggered travel and trade restrictions in member states, including the United States. For now, at least, the group said it wasn't warranted.

Fatality rates

The focus right now is China. The outbreak has spread beyond Wuhan to other parts of the country, and there's evidence of fourth-generation spread.

Transportation into and out of Wuhan and other cities has been

curtailed, Lunar New Year festivals have been canceled, and the Shanghai Disneyland has been closed, among other measures taken by Chinese officials.

The government could be taking drastic measures in part to prevent the public criticism it took in the early 2000s for the delayed response and lack of transparency during the global outbreak of another wildlife-market coronavirus epidemic, severe acute respiratory syndrome (SARS). In a press conference Jan. 22, WHO officials commended the government's containment efforts but did not say they recommended them.

According to WHO, serious cases in China have mostly been in people over 40 years old with significant comorbidities and have skewed toward men. Spread seems to be lim-



Dr. Daniel Lucey

ited to family members, health care providers, and other close contacts, probably by respiratory droplets. If that pattern holds, WHO officials said, the outbreak is containable.

The fatality rate appears to be around 3%, a good deal lower than the 10% reported for SARS and much lower than the nearly 40% reported for Middle East respiratory

syndrome (MERS), another recent coronavirus mutation from the animal trade.

The 2019-nCoV fatality rate might drop as milder cases are detected and added to the denominator. "It definitely appears to be less severe than SARS and MERS," said Amesh Adalja, MD, an infectious disease physician in Pittsburgh and emerging infectious disease researcher at Johns Hopkins University, Baltimore.

SARS: Lessons learned

In general, the world is much better equipped for coronavirus outbreaks than when SARS, in particular, emerged in 2003.

WHO officials in their press conference lauded China for its openness with the current outbreak, and for isolating and sequencing the virus

Know who is on call at the health department on weekends and nights. Know where the patient is going to be isolated; figure out what to do if there's more than one.

immediately, which gave the world a diagnostic test in the first days of the outbreak, something that wasn't available for SARS. China and other countries also are cooperating and working closely to contain the 2019-nCoV.

"What we know today might change tomorrow, so we have to keep tuned in to new information, but we learned a lot from SARS," Dr. Shaffner said. Overall, it's likely "the impact on the United States of this new coronavirus is going to be trivial," he predicted.

Dr. Lucey, however, recalled that the SARS outbreak in Toronto in 2003 started with one missed case. A woman returned asymptomatic from Hong Kong and spread the infection to her family members before she died. Her cause of death wasn't immediately recognized, nor was the reason her family members were sick, since they hadn't been to Hong Kong recently.

The infection ultimately spread to more than 200 people, about half of them health care workers. A few people died.

If a virus is sufficiently contagious, "it just takes one. You don't want to be the one who misses that first patient," Dr. Lucey said.

Currently, there are no antivirals or vaccines for coronaviruses; researchers are working on both, but for now, care is supportive.

Symptoms of the 2019 Novel Coronavirus

Common symptoms	Respiratory symptoms Fever Cough Shortness of breath Breathing difficulties
Less common symptoms	Diarrhea Gastrointestinal symptoms
Severe cases	Pneumonia Severe acute respiratory syndrome Kidney failure Death

Source: World Health Organization, Lancet 2020 Jan 24. doi: 10.1016/S0140-6736(20)30183-5

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Dual e-cigarette and combustible tobacco use: Common, linked to extra respiratory disease risk

BY JEFF CRAVEN

MDedge News

E-cigarette use is significantly and independently associated with an increased risk of respiratory disease, according to a recent longitudinal analysis published in the *American Journal of Preventive Medicine*.

E-cigarettes have been promoted as a safer alternative to combustible tobacco, and until recently, there has been little and conflicting evidence by which to test this hypothesis. This study conducted by Dharma N. Bhatta, PhD, and Stanton A. Glantz, PhD, of the Center for Tobacco Control Research and Education at the University of California, San Francisco, is one of the first longitudinal examinations of e-cigarette use that controls for combustible tobacco use.

Dr. Bhatta and Dr. Glantz performed a multivariable, logistic regression analysis of adults enrolled in the nationally representative, population-based, longitudinal Population Assessment of Tobacco and Health study. The researchers analyzed the tobacco use of adults in the study in three waves, following them through wave 1 (September 2013 to December 2014), wave 2 (October 2014 to October 2015), and wave 3 (October 2015 to October 2016), analyzing the data between 2018 and 2019. Overall, wave 1 began with 32,320 participants, and 15.1% of adults reported respiratory disease at baseline.

Lung or respiratory disease was assessed by asking participants whether they had been told by a health professional that they had chronic obstructive pulmonary disease, chronic bronchitis, emphysema, or asthma. The researchers defined e-cigarette and combustible tobacco use as participants who never, currently, or formerly used e-cigarettes or smoked combustible tobacco. Participants who indicated they used e-cigarettes or combustible tobacco frequently or infrequently were placed in the current-user group, while past users were those participants who said they used to, but no longer use e-cigarettes or combustible tobacco.

The results showed former e-cigarette use (adjusted odds ratio, 1.34; 95% confidence interval, 1.23-1.46) and current e-cigarette use (aOR, 1.32; 95% CI, 1.17-1.49) were associated with an increased risk of having incident respiratory disease.

The data showed a not unexpected statistically significant association between former combustible tobacco use (aOR, 1.29; 95% CI, 1.14-1.47) as well as current combustible tobacco use (aOR, 1.61; 95% CI, 1.42-1.82) and incident respiratory disease risk.

There was a statistically significant association between respiratory disease and former or current e-cigarette use for adults who did not have respiratory disease at baseline, after adjusting for factors such as current combustible tobacco use, clinical variables, and demographic differences. Participants in wave 1 who reported former (aOR, 1.31;



AndreyPopov/Getty Images



Dr. Farber

95% CI, 1.07-1.60) or current (aOR, 1.29; 95% CI, 1.03-1.61) e-cigarette use had a significantly higher risk of developing incident respiratory disease in subsequent waves. There was also a statistically significant association between use of combustible tobacco and subsequent respiratory disease in later waves of the study (aOR, 2.56; 95% CI, 1.92-3.41), which the researchers noted was independent of the usual risks associated with combustible tobacco.

The investigators also looked at the link between dual use of e-cigarettes and combustible tobacco and respiratory disease risk. “The much more common pattern is dual use, in which an e-cigarette user continues to smoke combustible tobacco products at the same time (93.7% of e-cigarette users at wave 2 and

91.2% at wave 3 also used combustible tobacco; 73.3% of e-cigarette users at wave 2 and 64.9% at wave 3 also smoked cigarettes),” they wrote.

The odds of developing respiratory disease for participants who used both e-cigarettes and combustible tobacco were 3.30, compared with a participant who never used e-cigarettes, with similar results seen when comparing e-cigarettes and cigarettes.

“Although switching from combustible tobacco, including cigarettes, to e-cigarettes theoretically could reduce the risk of developing respiratory disease, current evidence indicates a high prevalence of dual use, which is associated with increased risk beyond combustible tobacco use,” the investigators wrote.

Harold J. Farber, MD, FCCP, professor of pediatrics in the pulmonary section at Baylor College of Medicine and Texas Children’s Hospital, both in Houston, said in an interview that the increased respiratory risk among dual users, who are likely using e-cigarettes and combustible tobacco together as a way to quit smoking, is particularly concerning.

“There is substantial reason to be concerned about efficacy of electronic cigarette products. Real-world observational studies have shown that, on average, tobacco smokers who use elec-

tronic cigarettes are less likely to stop smoking than those who do not use electronic cigarettes,” he said. “People who have stopped tobacco smoking but use electronic cigarettes are more likely to relapse to tobacco smoking than those who do not use electronic cigarettes.”

Dr. Farber noted that there are other Food and Drug Administration–approved medications for treating tobacco addiction. In addition, the World Health Organization, American Medical Association, Centers for Disease Control and Prevention, and FDA have all advised that e-cigarettes should not be used as smoking cessation aids, he said, especially in light of current outbreak of life-threatening e-cigarette and vaping lung injuries currently being investigated by the CDC and FDA.

“These study results suggest that the CDC reports of e-cigarette, or vaping, product use–associated lung injury are likely to be just the tip of the iceberg,” he said. “Although the CDC has identified vitamin E acetate–containing products as an important culprit, it is unlikely to be the only one. There are many substances in the emissions of e-cigarettes that have known irritant and/or toxic effects on the airways.”

Dr. Bhatta and Dr. Glantz acknowledged several limitations in their analysis, including the possibility of recall bias, not distinguishing between nondaily and daily e-cigarette or combustible tobacco use, and combining respiratory conditions together to achieve adequate power. The study shows an association, but the mechanism by which e-cigarettes may contribute to the development of lung disease remains under investigation.

This study was supported by grants from the National Institute on Drug Abuse; the National Cancer Institute; the FDA Center for Tobacco Products; the National Heart, Lung, and Blood Institute; and the University of California, San Francisco Helen Diller Family Comprehensive Cancer Center Global Cancer Program. Dr. Bhatta and Dr. Glantz reported no relevant conflicts of interest.

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SOURCE: Bhatta DN, Glantz SA. *Am J Prev Med*. 2019 Dec 16. doi: 10.1016/j.amepre.2019.07.028.

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PULMONOLOGY

Cannabis users struggle to quit cigarettes

BY HEIDI SPLETE

MDedge News

Cigarette smokers who also use cannabis appear to face high hurdles to quit smoking, a large national survey has found.

“Over the past decade, there has been an increase in the use of cannabis among cigarette smokers and prevalence of cigarettes and cannabis co-use, suggesting that the negative consequences of cigarette-cannabis co-use may also become more prevalent over time,” wrote Andrea H. Weinberger, PhD, of Yeshiva University, New York, and colleagues. They noted that the prevalence of cigarette smoking is nearly three times higher among persons who use cannabis and have cannabis use disorders relative to those who do not.

The 2019 National Survey of Drug Use and Health estimated that 15.9% of Americans aged 12 years or older used cannabis in the past year. This number has been rising throughout the 2000s.

In that same report, cannabis use disorder (or marijuana use disorder) was defined as when an individual experiences clinically significant impairment caused by the recurrent use of marijuana, including health problems, persistent or increasing use, and failure to meet major responsibilities at work, school, or home. The report stated that approximately 1.6% of Americans aged 12 or older in 2018 had marijuana use disorder.

In the study published in *Tobacco Control*, the researchers used the National Survey on Drug Use and Health data to analyze cigarette smoking quit ratios among U.S. adults with and without cannabis use and cannabis use disorders. “Quit ratio was calculated as the proportion of former smokers among lifetime smokers and is considered a measure of total cessation in a population,” the researchers said.

In 2016, the quit ratios for adults with a history of cannabis use or cannabis use disorders were 23% and 15%, respectively, compared with 51% and 48%, respectively, in those with no cannabis use or cannabis use disorders.

Overall, quit ratios did not change significantly from 2002 to 2016 for individuals with cannabis use

disorders after controlling for multiple demographic factors and other substance use disorders. However, during the same time period, quit ratios showed a nonlinear increase in cannabis users, nonusers, and individuals without cannabis use disorders.

The study findings were limited by several factors including the inability to generalize results to youth or individuals living outside the United States, the use of DSM-



KatarzynaBialasiewicz/Thinkstock

IV criteria to identify cannabis use disorder, the use of self-reports, and the inability to examine the timing of cannabis use as related to attempts to quit smoking, the researchers noted. However, the results highlight the need to consider offering smoking cessation treatment to individuals being treated for cannabis use disorders, and to include cannabis users in smoking cessation programs, the researchers noted.

“Based on our results, both public health and clinical efforts to improve cigarette quit outcomes may benefit from including those with any cannabis use,” they said. More research is needed to determine whether trends in the quit ratio change over time for cannabis users or those with cannabis use disorder, they added.

The study was funded by the National Institute on Drug Abuse. The researchers had no financial conflicts to disclose.

chestphysiciannews@chestnet.org

SOURCE: Weinberger AH et al. *Tob Control*. 2020;29(1):74-80. doi: 10.1136/tobaccocontrol-2018-054590.

Screen for cannabis use in cardiovascular care settings

BY JENNIFER SMITH

MDedge News

Researchers are recommending routine screening of marijuana use in cardiovascular care settings.

A review of current evidence suggests an association between marijuana use and adverse cardiovascular effects, as well as interactions between marijuana and cardiovascular medications.

Although more research is needed, the review authors suggested patients may benefit from marijuana screening and testing as well as discussions about the potential risks of marijuana use in the setting of cardiovascular disease.

Ersilia M. DeFilippis, MD, of Columbia University Irving Medical Center in New York and colleagues conducted this review, which was published in the *Journal of the American College of Cardiology*.

The authors noted that research on marijuana use and cardiovascular disease is limited. The different forms of cannabis and various routes of administration have made it difficult to draw concrete conclusions about marijuana products.

Additionally, there have been no randomized, controlled trials of marijuana products in the United States because such trials are illegal; however, there are observational studies linking marijuana use and adverse cardiovascular effects.

Snapshot of available evidence

One study showed that smoking marijuana produces many of the same cardiotoxic chemicals produced by smoking tobacco (*BMJ*. 2003 May 3;326[7396]:942-3). Another study suggested marijuana smokers may have greater exposure to harmful chemicals (*J Psychoactive Drugs*. 1988 Jan-Mar;20[1]:43-6).

More specifically, a meta-analysis suggested that smoking marijuana was one of the top three triggers of myocardial infarction (*Lancet*. 2011 Feb 26;377[9767]:732-40). And in a systematic analysis, 28 of 33 studies linked marijuana use to an increased risk of acute coronary syndromes (*Clin Toxicol [Phila]*. 2019 Oct;57[10]:831-41).

Furthermore, a study of 2.5 million marijuana users showed that 3% experienced arrhythmias (*Int J Cardiol*. 2018 Aug 1;264:91-2).

A population survey showed that people who smoked marijuana in the past year experienced a 3.3-fold higher rate of cerebrovascular events (*Aust N Z J Public Health*. 2016 Jun;40[3]:226-30).

Studies have also indicated that cannabinoids can affect cardiovascular medications, including antiarrhythmics, calcium-channel blockers, isosorbide dinitrate/mononitrate, statins, beta-blockers, warfarin, theophylline, and nonsteroidal anti-inflammatory drugs (*Medicines [Basel]*. 2018 Dec 23;6[1] pii: E3; *Curr Top Behav Neurosci*. 2017;32:249-62; *Pharmacogenet Genomics*. 2009 Jul;19[7]:559-62; *Ann Pharmacother*. 2009 Jul;43[7]:1347-53; *Pharmacol Ther*. 2019 Sep;201:25-38).

Reviewer recommendations

Cardiovascular specialists should be informed about regulations governing marijuana products, as well as “potential health consequences of marijuana and its derivatives,” according to Dr. DeFilippis and colleagues.

The authors recommend routinely screening patients for marijuana use, perhaps using the Daily Sessions, Frequency, Age of Onset,

and Quantity of Cannabis Use Inventory (PLoS One. 2017 May 26;12[5]:e0178194) or the Cannabis Abuse Screening Test (*Int J Methods Psychiatr Res*. 2018 Jun;27[2]:e1597).

The authors say urine toxicology “may be reasonable” for patients with myocardial infarction or new-onset heart failure. Such testing is required for patients undergoing a heart transplant because marijuana use may affect their candidacy.

Dr. DeFilippis and colleagues say cardiovascular specialists should inform patients about the risks associated with marijuana use. The authors recommend shared decision making for patients who use marijuana for symptom management or palliative purposes.

Three review authors disclosed relationships with many different pharmaceutical companies. One author disclosed relationships with Medscape Cardiology and WebMD, which are owned by the same parent company as MDedge.

jen smith@mdedge.com

SOURCE: DeFilippis EM et al. *J Am Coll Cardiol*. 2020 Jan 20. doi: 10.1016/j.jacc.2019.11.025.

New heart failure trial data presage guideline revisions

BY MITCHEL L. ZOLER

MDedge News

PHILADELPHIA – The definition and treatment of heart failure with reduced ejection fraction should change based on recent findings and analyses from major trials, said a key heart failure leader at the American Heart Association scientific sessions.

The people charged with writing U.S. guidelines for heart failure management already have enough evidence to change the recommended way of using sacubitril/valsartan (Entresto) in patients with heart failure with reduced ejection fraction (HFrEF), said Clyde W. Yancy, MD, professor of medicine and chief of cardiology at Northwestern University, Chicago. Accumulated evidence from studies and more than 5 years of experience in routine practice with the angiotensin receptor neprilysin inhibitor (ARNI) combination sacubitril/valsartan for treating HFrEF patients justifies striking the existing recommendation to first start patients on an ACE inhibitor or angiotensin receptor blocker and only after that switching to sacubitril/valsartan, a sequence that has rankled some clinicians as an unnecessary delay and barrier to starting patients on the ARNI regimen.

U.S. guidelines should now suggest that ARNI treatment start immediately, suggested Dr. Yan-



Dr. Clyde W. Yancy

cy, who chaired the AHA/American College of Cardiology panel that updated U.S. guidelines for heart failure management in 2013 (*Circulation*. 2013 Oct 15;128[16]:e240-327), 2016 (*J Am Coll Cardiol*. 2016 Sep;68[13]:1476-88), and 2017 (*Circulation*. 2017 Aug 8; 136[6]:e137-61).

Expanding the heart failure group for sacubitril/valsartan

Dr. Yancy also proposed a second major and immediate change to the existing heart failure guideline based on a new appreciation of a heart failure population that could benefit from ARNI

treatment: patients with “mid-range” heart failure, defined by a left ventricular ejection fraction (LVEF) of 41%-49% that places them between patients with HFrEF with an ejection fraction of 40% or less, and those with heart failure with preserved ejection fraction (HFpEF) of 50% or more. As yet unchanged in the 2013 AHA/ACC heart failure guideline is the proposition that patients with heart failure and an ejection fraction of 41%-49% have “borderline” heart failure with characteristics, treatment patterns, and outcomes “similar to patients with HFpEF.”

That premise should now go out the window, urged Dr. Yancy, based on a new analysis of data collected from both the recent PARAGON-HF trial of sacubitril/valsartan in patients with HFpEF and ejection fractions of 45% or higher (*N Engl J Med*. 2019 Oct 24;381[17]:1609-20) and the landmark PARADIGM-HF trial that established sacubitril/valsartan as a treatment for patients with HFrEF (*N Engl J Med*. 2014 Sep 11;371[11]:993-1004). A combined analysis of the more than 13,000 total patients in both studies suggested that “patients with ejection fraction lower than normal, which includes those with so-called heart failure with mid-range ejection fraction or borderline ejection fraction, would likely benefit from sacubitril/valsartan, compared with RAS inhibition,” concluded the authors of

Continued on following page

ID consult for *Candida* bloodstream infections can reduce mortality risk

BY MARK S. LESNEY

MDedge News

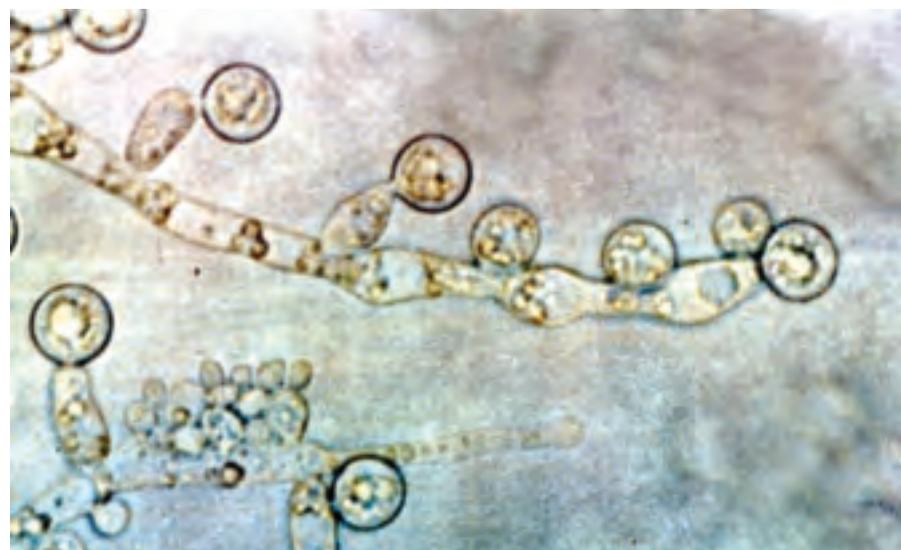
Clinicians managing patients who have *Candida* bloodstream infection should consider an infectious disease (ID) consultation, findings from a large retrospective study suggest.

Mortality attributable to *Candida* bloodstream infection ranges between 15% and 47%, and delay in initiation of appropriate treatment has been associated with increased mortality. Previous small studies showed that ID consultation has conferred benefits to patients with *Candida* bloodstream infections. Carlos Mejia-Chew, MD, and colleagues from Washington University, St. Louis, sought to explore this further by performing a retrospective, single-center cohort study of 1,691 patients aged 18 years or older with *Candida* bloodstream infection from 2002 to 2015. They analyzed demographics, comorbidities, predisposing factors, all-cause mortality, antifungal use, central-line removal, and ophthalmologic and

echocardiographic evaluation in order to compare 90-day all-cause mortality between individuals with and without an ID consultation.

They found that those patients who received an ID consult for a *Candida* bloodstream infection had a significantly lower 90-day mortality rate than did those who did not (29% vs. 51%).

With a model using inverse weighting by the propensity score, they found that ID consultation was associated with a hazard ratio of 0.81 for mortality (95% confidence interval, 0.73-0.91; *P* less than .0001). In the ID consultation group, the median duration of antifungal therapy was significantly longer (18 vs. 14 days; *P* less than .0001); central-line removal was significantly more common (76% vs. 59%; *P* less than .0001); echocardiography use was more frequent (57% vs. 33%; *P* less than .0001); and ophthalmologic examinations were performed more often (53% vs. 17%; *P* less than .0001). Importantly, fewer patients in the ID consultation group were untreated



GrahamCoim/Wikimedia Commons

(2% vs. 14%; *P* less than .0001).

In an accompanying commentary, Katrien Lagrou, MD, and Eric Van Wijngaerden, MD, of the department of microbiology, immunology and transplantation, University Hospitals Leuven (Belgium) stated: “We think that the high proportion of patients (14%) with a *Candida* bloodstream infection who did not receive any antifungal treatment and did not have an infectious disease consultation is a particularly alarming finding. ... Ninety-day mortality in these untreated patients was high (67%).”

“We believe every hospital should have an expert management strategy addressing all individual cases of candidaemia. The need for such expert management should be incorporated in all future candidaemia

management guidelines,” they concluded.

The study was funded by the Astellas Global Development Pharma, the Washington University Institute of Clinical and Translational Sciences, and the Agency for Healthcare Research and Quality. Several of the authors had financial connections to Astellas Global Development or other pharmaceutical companies. Dr. Lagrou and Dr. Van Wijngaerden both reported receiving personal fees and nonfinancial support from a number of pharmaceutical companies, but all outside the scope of the study.

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SOURCE: Mejia-Chew C et al. Lancet Infect Dis. 2019;19:1336-44.

Continued from previous page

the new analysis (Circulation. 2019 Nov 17. doi: 10.1161/CIRCULATIONAHA.119.044586).

Dr. Yancy argued that, based on this new analysis, a further revision to the 2013 guideline should say that patients with heart failure with a LVEF of 41%-49% have characteristics, treatment responses, and outcomes that “appear similar to

those of patient with HF_{rEF},” a sharp departure from the existing text that lumps these patients with the HF_{pEF} subgroup. “There appears to be a signal that extends the benefit of ARNI to patients with ejection fractions above the current threshold for HF_{rEF} but below what is typically HF_{pEF},” he said.

Bringing SGLT2 inhibitors into heart failure management

Dr. Yancy also cited recently reported data from another landmark trial, DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure), as an impetus for both another immediate change to the guideline and for a potential second change pending a report of confirmatory evidence that may arrive in 2020.

The DAPA-HF results showed that the sodium-glucose cotransporter 2 (SGLT2) inhibitor dapagliflozin (Farxiga) was just as effective for preventing all-cause death and heart failure hospitalizations and urgent visits in patients without type 2 diabetes as it is in patients with type 2 diabetes (N Engl J Med. 2019 Nov 21;381[21]:1995-2008), a remarkable finding for an agent that came onto the U.S. market as a diabetes drug specifically aimed at reducing levels of glycosylated hemoglobin.

Dr. Yancy proposed an immediate guideline change to acknowledge the proven protection

against incident heart failure that treatment with a SGLT2 inhibitor gives patients with type 2 diabetes. There is now “a strong opportunity to use an SGLT2 inhibitor in patients with type 2 diabetes to reduce the incidence of heart failure,” he said.

And he added that, if results from EMPEROR REDUCED (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction), studying the SGLT2 inhibitor empagliflozin (Jardiance) in HF_{rEF} patients with and without type 2 diabetes, can confirm the efficacy of a second drug from this class in preventing heart failure events in patients with HF_{rEF} but without diabetes, then the time will have arrived for another guideline change to establish the SGLT2 inhibitors as a new “foundational” drug for the management of all HF_{rEF} patients, regardless of their level of glycemic control.

The SGLT2 inhibitors are a particularly attractive additional drug because they are taken once daily orally with no need for dosage adjustment, so far they have shown excellent safety in patients without diabetes with no episodes of hypoglycemia or ketoacidosis, and they have even shown evidence for heart failure benefit in patients older than 75 years, Dr. Yancy noted.

Dr. Yancy had no relevant disclosures.

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VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments:

Management of patients with heart failure and reduced ejection fraction is a challenge for the clinicians. The clinical evidence on the use of ARNI as the first-choice therapy in HF_{rEF} and the DAPA-HF trial data confirming the positive impact of SGLT2 inhibitor dapagliflozin on reducing mortality and hospitalization and urgent visits due to heart failure in patients with and without type 2 diabetes are important findings which will lead to changes in guidelines for treating this group of patients.



PCVs don't always protect children with asthma

BY MICHELE G. SULLIVAN
MDedge News

Even on-time pneumococcal vaccines don't completely protect children with asthma from developing invasive pneumococcal disease, a meta-analysis has determined.

Despite receiving pneumococcal valent 7, 10, or 13, children with asthma were still almost twice as likely to develop the disease as were children without asthma, Jose A. Castro-Rodriguez, MD, PhD, and colleagues reported in *Pediatrics* (2020 Jan. doi: 10.1542/peds.2019-1200). None of the studies included rates for those who received the pneumococcal polysaccharide vaccine (PPSV23).

"For the first time, this meta-analysis reveals 90% increased odds of invasive pneumococcal disease (IPD) among [vaccinated] children with asthma," said Dr. Castro-Rodriguez, of Pontificia Universidad Católica de Chile, Santiago, and colleagues. "If confirmed, these findings will bear clinical and public health importance," they noted, because guidelines now recommend PPSV23 after age 2 in children with asthma only if they're treated with prolonged high-dose oral corticosteroids.

However, because the analysis comprised only four studies, the authors cautioned that the results aren't enough to justify changes to practice recommendations.

Asthma treatment with inhaled corticosteroids (ICS) may be driving the increased risk, Dr. Castro-Rodriguez and his coauthors suggested. ICS deposition in the oropharynx could boost oropharyngeal candidiasis risk by weakening the mucosal immune response, the researchers noted. And that same process may be at work with *Streptococcus pneumoniae*.

A prior study found that children with asthma who received ICS for at least 1 month were almost four times more likely to have oropharyngeal colonization by *S. pneumoniae* as were those who didn't get the drugs. Thus, a higher carrier rate of *S. pneumoniae* in the oropharynx, along with asthma's impaired airway clearance, might increase the risk of pneumococcal diseases, the investigators explained.

Dr. Castro-Rodriguez and colleagues analyzed four studies with more than 4,000 cases and controls,

and about 26 million person-years of follow-up.

Rates and risks of IPD in the four studies were as follows:

- Among those with IPD, 27% had asthma, compared with 18% of

those without, an adjusted odds ratio of 1.8.

- In a European study of patients who received at least 3 doses of PCV7, IPD rates per 100,000 person-years for 5-year-olds were

11.6 for children with asthma and 7.3 for those without. For 5- to 17-year-olds with and without asthma, the rates were 2.3 and 1.6, respectively.

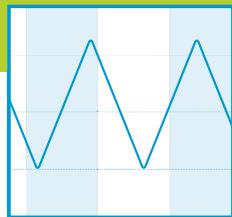
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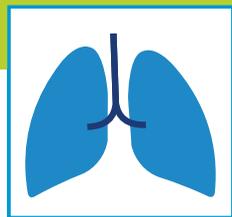


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1. Milla CE, Hansen LG, Weber A, Warwick WJ. High frequency chest compression: effect of the third generation waveform. *Biomed Instrum Technol* 2004; 38:322-328. Note: 8 CF comparing triangular waveform vs. sine waveform technology.
2. Milla CE, Hansen LG, Warwick WJ. Different frequencies should be prescribed different high frequency chest compression machines. *Biomed Instrum Technol* 2006;40:319-324. Note: 100 CF patient study comparing triangular vs. sine waveform technology.
3. RespirTech's bronchiectasis patient outcomes program consists of follow-up calls at periodic intervals for up to two years to encourage HFCWO adherence and ensure the device is properly set for individual needs.
4. Methodology: As of 6/30/19, self-reported data from over 16,000 bronchiectasis patients.

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President's report

BY STEPHANIE M. LEVINE,
MD, FCCP
CHEST President

After an outstanding annual meeting in New Orleans, with the greatest number of attendees and a number of other firsts, and with the holidays rapidly approaching, you might think there would be a lull in activity, but your CHEST leadership and staff have been busy. Let's start with a CHEST 2019 recap.

This year's meeting had a total of 5,960 medical professionals and 8,593 total attendees. All were the highest in CHEST history! In addition, there were more international attendees, and CHEST 2019 saw the largest number of fellows-in-training and the largest number of advanced practice providers attending.

Since CHEST 2019, we have held five live learning sessions at headquarters in Glenview, with a total of 281 attendees, including: Extracorporeal Support for Respiratory and Cardiac Failure in Adults; Critical Care Ultrasound: Integration Into Clinical Practice; Comprehensive Pleural Procedures; Ultrasonography: Essentials in Critical Care; and the Advanced Critical Care Echocardiography Board Review Exam Course. In case you missed those opportunities, in the near future, CHEST will be holding the following 2020 courses: Comprehensive Bronchoscopy With Endobronchial Ultrasound February 20 - 22, Mechanical Ventilation: Advanced Critical Care Management February 27 - 29, Ultrasonography: Essentials in Critical Care March 5 - 7, Bronchoscopy and Chest Tubes in the ICU March 20 - 21, Advanced Clinical Training in Pulmonary Function Testing March 27 - 28, Critical Skills for Critical Care: A State-of-the-Art Update, and Procedures for ICU Providers April 30 - May 2. For additional information, check out the events at chestnet.org.

Internationally, the program for the Italian CHEST Congress, to be held with the Italian CHEST Chapter in Bologna in June (June 25-27), is finished. This meeting will be designed on a smaller scale of that of the annual CHEST meeting, with plenty of educational opportunities in the areas of pulmonary, critical care, and sleep medicine, and will also feature faculty from around the world. Come experience all the education, as well as the beauty of Italy in June! CHEST has continued other international activities with leadership attendance and lectures at the Asian Pacific Society of Respiratory (APSR), where we engaged with multiple societies as CHEST continues to grow our international strategy to educate those who request further education in our fields. CHEST also sent selected young investigators to the APSR meeting.

Plans are well under way to hold another successful annual meeting in Chicago - CHEST 2020. The call for topics has ended, and proposal grading is ongoing. The call for abstracts has gone out and will close March 31. We encourage all, including our learners in training, to submit high quality abstracts and case reports, and we will offer suggestions for those needing editorial assistance. This is one of the many ways to get CHEST-involved. In addition to the innovations and experiences we offered last year, there will be continued social media presence and new exciting offerings at this year's annual meeting. Save the dates - October 17-21, in our home town of Chicago!

One of my goals for this year is to evaluate ways to increase engagement and leadership opportunities within the organization, with our CHEST NetWorks being one example. The work of the NetWorks task force is ongoing. Expect to see pilots of twitter handles, infographics, and e-bytes coming from some Net-



Dr. Stephanie M. Levine

Works in the near future.

The editorial board for the next volume of SEEK Critical Care has been selected, and work is under way for delivery of the next print edition and library update at the summer Board Review Courses in August in Washington DC. Your CHEST journal editorial board has also been busy. The redesigned issue with the new content structure has hit mailboxes, and you can expect to see updated guidelines for "Managing Chronic Cough as a Symptom in Children and Management Algorithms: CHEST Guideline and Expert Panel Report" and "Chronic Cough Due to Stable Chronic Bronchitis: CHEST Expert Panel Report" out soon. Also, look for publications that CHEST has endorsed to include the College of American Pathologists' supplement "Collection and Handling of Thoracic Small Biopsy and Cytology Specimens for Ancillary Studies" and the Society of Critical Care Medicine's algorithm and bundle for the "Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children." CHEST had representatives to both of these writing groups. In addition, more podcasts will soon be on the horizon.

The CHEST Foundation gala, The

Golden Era of EP (Erin Popovich) was held in early December at the AT & T center in San Antonio, with over 500 people in attendance, including many from the San Antonio community, current and former Spurs players and coaches, in addition to our leadership and staff. The Erin Popovich (EP) endowment is dedicated to empowerment and access for patients with interstitial lung disease, as well as research in this area. Over 3 million dollars have been raised to date to directly support this endowment. One of the early products from this endowment is the soon to be available Oxygen Access Toolkit, developed for use by provider offices, clinicians, DME suppliers, patients, and caregivers to answer some of the basic facts about access to oxygen that so many of our patients with ILD and other lung diseases need. Other resources will include the ILD Tree, Get a Second Opinion, You're Not Alone Patient Journey, Mnemonic for ILD Patients, the Patients' Bill of Rights, and a co-morbidities one-page information sheet.

After the next quarterly Board Meeting in January, I will update you on decisions regarding future strategy that emerge from that meeting. The agenda will include many of the topics mentioned above, in addition to a strategic discussion regarding CHEST's increased role in advocacy, which has been requested by many members.

Of course, all these events and activities could not be accomplished without the incredible effort by your CHEST staff and volunteer leadership. I look forward to many updates in my next report. As always, please reach out to me with any comments, questions, or suggestions, and if I am unable to respond, I will address it with the appropriate staff person. Thank you all for being the most important reason that CHEST exists. Have a great 2020!

Continued from previous page

- In 2001, a Korean study found an aOR of 2.08 for IPD in children with asthma, compared with those without. In 2010, the aOR was 3.26. No vaccine types were reported in the study.
- Rates of IPD were 3.7 per 100,000 person-years for children with asthma, compared with 2.5 for healthy controls - an adjusted relative risk of 1.5.

The pooled estimate of the four studies revealed an aOR of 1.9 for IPD among children with asthma, compared with those without, Dr.

Castro-Rodriguez and his team concluded.

None of the studies reported hospital admissions, mortality, length of hospital stay, intensive care admission, invasive respiratory support, or additional medication use.

One, however, did find asthma severity was significantly associated with increasing IPD treatment costs per 100,000 person-years: \$72,581 for healthy controls, compared with \$100,020 for children with mild asthma, \$172,002 for moderate asthma, and \$638,452 for severe asthma.

In addition, treating all-cause pneumonia was

more expensive in children with asthma. For all-cause pneumonia, the researchers found that estimated costs per 100,000 person-years for mild, moderate, and severe asthma were \$7.5 million, \$14.6 million, and \$46.8 million, respectively, compared with \$1.7 million for healthy controls.

The authors had no relevant financial disclosures.

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SOURCE: Castro-Rodriguez JA et al. *Pediatrics*. 2020 Jan. doi: 10.1542/peds.2019-1200.

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Streptococcus pyogenes

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CHEST NETWORKS

Beta-blockers. Interstitial lung disease. Vaping. GL-ILD.

Clinical research

Nintedanib in progressive fibrosing interstitial lung diseases: Does one size really fit all?

Interstitial lung diseases (ILDs) include a variety of lung disorders, such as idiopathic interstitial pneumonias (IIPs), autoimmune diseases, granulomatous lung disease, and environmental diseases. They all have one thing in common—a progressive fibrosing phenotype that is almost universally fatal. It has been suggested that such diseases have a shared pathophysiologic mechanism irrespective of the cause and, hence, could respond to similar therapy. Nintedanib acts intracellularly by inhibiting multiple tyrosine kinases. Previous clinical trials have suggested that nintedanib inhibits the progression of lung fibrosis in patients with idiopathic pulmonary



Dr. Ijaz

fibrosis (Richeldi, et al. *N Engl J Med.* 2014;370[22]:2071) and systemic sclerosis-associated ILD (Distler, et al. *N Engl J Med.* 2019;380[26]:2518). The INBUILD trial was conducted to study the efficacy and safety of nintedanib in patients with fibrosing interstitial lung diseases (Flaherty, et al. *N Engl J Med.* 2019;381[18]:1718).

Patients with a wide spectrum of progressive fibrosing ILD were enrolled in the INBUILD trial. This gave the phenotypic approach needed to study the effects of nintedanib in fibrosing ILDs. The authors reported an absolute difference of 107 mL in the annual rate of decline in forced vital capacity in the overall population, 128.2 mL (95% CI 65.4 to 148.5; *P* less than .001) in patients with UIP-like fibrotic pattern and 75.3 mL in patients with other fibrotic patterns, between patients who received nintedanib and those who received placebo. Earlier studies have shown similar results in patients with IPF. The most frequent adverse event was diarrhea (66.9% in the nintedanib group and 23.9%

in placebo group). Liver enzymes derangement was more common in the nintedanib group. Nausea, vomiting, abdominal pain, decreased appetite, and weight decrease were also more frequent in the nintedanib group than in those in the placebo group. In conclusion, this study not only explored the effects of nintedanib on progressive fibrosing ILDs but also helped to enhance the understanding of their natural history, suggesting a final common pathway toward lung fibrosis.

Mohsin Ijaz, MD, FCCP
Steering Committee Member

Airway disorders

Beta-blockers in COPD: A settled debate?

Beta-blockers are the cornerstone in the management of patients with heart failure and myocardial infarction where they have shown to improve morbidity and mortality. Cardiovascular disease is common in patients with COPD. A 2014 meta-analysis of retrospective studies involving patients with COPD using a



Dr. Adrish

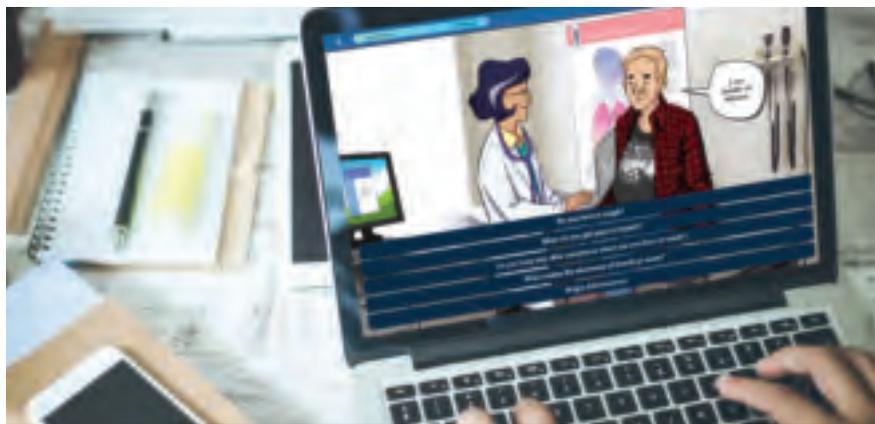


Dr. Ramesh

beta-blocker has shown lower death and lower exacerbation rate (Du Q, et al. *PLoS One.* 2014;9[11]:e113048). More recent studies continue to note underutilization of beta-blockers in patients with COPD due to concerns for adverse effects on pulmonary function (Lipworth B, et al. *Heart.* 2016;102[23]:1909).

To further study these concerns, Dransfield and colleagues conducted a randomized controlled trial (BLOCK COPD) of 532 randomly assigned patients to receive either metoprolol or placebo (Dransfield, et al. *N Engl J Med.* 2019;381[24]:2304).

Primary outcome was time to first COPD exacerbation whereas



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secondary outcomes included rate of exacerbation, mortality, hospitalization, symptoms, and spirometry data. Median time to exacerbation was similar between the two groups; however, metoprolol was associated with higher incidence of severe exacerbation requiring hospitalization (HR 1.91, 95% CI 1.29-2.83).

There was nonstatistical increase in deaths in metoprolol group, mainly contributed by fatal COPD events (seven in metoprolol vs one in placebo). The study results validated some of the concerns of worsening pulmonary function with beta-blocker use; however, in order to better understand the study results, we must pay attention to the study cohort.

In summary, patients did not have significant cardiac disease and, therefore, did not have an overt indication for beta-blocker use. Patients with COPD in this study were sicker than average patients. Lastly, there were more patients in the metoprolol group who had COPD exacerbations requiring ED visit or hospitalization in 12 months prior to study enrollment. For the above-mentioned reasons, the conclusion of this study should not discourage the use of beta-blockers in patients with COPD when underlying cardiac disease warrants their use, after careful consideration of benefits and risks.

Muhammad Adrish, MD, FCCP
Steering Committee Member
Navitha Ramesh, MD, FCCP
Steering Committee Member

Home-based mechanical ventilation and neuromuscular disease

Keeping up with the times: incorporating home mechanical ventilation education into pulmonary and critical care fellowship and clinical practice

Home mechanical ventilation (HMV) utilization for patients with chronic respiratory conditions is rapidly increasing in both pediatric and adult populations. By 2016, the estimated prevalence of HMV was 2.9-12.9/100,000 (3.1-18% via tracheotomy) (Rose, et al. *Respir Care*. 2015;60[5]:695; Valko, et al. *BMC Pulm Med*. 2018;18[1]:190). In 2012, limited regional US data were extrapolated to approximate a prevalence of 4.7-6.4/100,000 children utilizing HMV (King, A. *Respir Care*. 2012;57[6]:921), but there is currently no comprehensive registry of HMV use in the United States. A US Department of Health and Human Services report in 2016 described an 85-fold increase in Medicare claims for home ventilators in

2015 compared with 2009 (OEI-12-15-00370; 9/22/2016).

With increasing demand, educating clinicians responsible for providing and managing HMV is paramount. Education specific to longitudinal management of the HMV is noticeably overlooked. The ACGME core competencies for PCCM fellowships include principles inherent to HMV, including modes/principles of ventilation, modalities/principles of oxygen supplementation, tracheostomy tube management, as well as the use of “masks for delivery of supplemental oxygen, humidifiers, nebulizers, and incentive spirometry” (ACGME Common Program Requirements



Dr. Lussier

7/1/2019). However, training programs are not required to provide skills essential in HMV management, including: (1) appropriate patient selection for long-term HMV, (2) selection of well-matched home ventilators suited to patients' chronic conditions, (3) assessment/timing of transition to invasive ventilation, or (4) adjustments necessary to maintain optimal ventilator support. Life-sustaining ventilators used in ICUs differ from life-supporting HMV systems in modes, interface, cost, algorithms, circuitry, and available adjuncts.

There is an opportunity (and responsibility) to improve current training guidelines to meet growing needs of the population and anticipate needs of trainees as they enter unsupervised practice. Although simulation initiatives at national CHEST meetings attempt to bridge education gaps, it is incumbent upon fellowship training programs to prepare pulmonologists with skills to manage HMV in order to maintain high standards of care in a safe, financially responsible, and evidence-based manner.

Bethany L. Lussier, MD, FCCP
NetWork Member
Won Y. Lee, MD, FCCP
Steering Committee Member

Critical care

Vaping-related acute lung injury: Where there's smoke, there's fire

E-cigarette or vaping product use-associated lung injury (EVALI) is a burgeoning public health problem in the United States. There have been more than 2,506 hospitalizations and 54 deaths from EVALI (cdc.gov). Unfortunately, the diagnosis is one of exclusion at present.

The CDC defines EVALI as lung disease associated with e-cigarette or vaping exposure within 90 days, infiltrates, and absence of other causes (Layden, et al. *N Engl J Med*.



Dr. Ouellette

2019 Sep 6. doi: 10.1056/NEJMoa1911614). As critical care providers, we are uniquely poised to detect and treat this illness, given that roughly one in three patients with EVALI require mechanical ventilation. Moreover, one-quarter of rehospitalizations and deaths occur 2 days after discharge from initial hospitalization (Mikosz, et al. *MMWR* 2020;68[5152]:1183).

To better identify EVALI, the Centers for Disease Control and Prevention (CDC) recommends that health-care providers ask e-cigarette or vaping product users about respiratory, gastrointestinal, and constitutional symptoms, obtain chest imaging in those suspected of EVALI, consider outpatient management of stable patients, test for influenza, and use caution when prescribing steroids in the outpatient setting. Emphasizing cessation and advocating for annual influenza vaccination is also recommended (Update: Interim Guidance for Health Care Providers for Managing Patients with Suspected E-cigarette, or Vaping, Product Use-Associated Lung Injury. *MMWR*. 2019;68[46]:1081).

So how can critical care providers assist in the understanding and treatment of EVALI? Critical care physicians treating patients with EVALI face unique challenges moving forward. We need to develop a better understanding of the triggers and pathophysiology of EVALI and learn to improve our recognition of the disease. We should study interventions that may improve outcomes such as corticosteroids. We know little about the long-term outcomes and sequelae of EVALI.

The best treatment for EVALI is prevention. Critical care physicians are experts at identifying and treating life-threatening conditions but as a community have less experience in the public health arena. If as physicians we are called upon to advocate for our patients, then perhaps there is a role for critical care physicians to advocate for a ban on vaping.

Matthew K. Hensley, MD, MPH
Fellow-in-Training Member
Daniel R. Ouellette, MD, MS, FCCP
NetWork Vice-Chair

Interstitial and diffuse lung disease

Granulomatous lymphocytic interstitial lung disease (GL-ILD)

Among the granulomatous lung diseases, GL-ILD is hardly a new discovery, but for many reasons, it often goes undiagnosed for years. The relative rareness of the disease itself and, hence, the lack of awareness makes it an uncommon differential for granulomatous ILD. Patients with GL-ILD are often misdiagnosed with sarcoidosis, unspecified ILD, or lymphoid interstitial pneumonia, etc, before receiving a diagnosis of GL-ILD.

GL-ILD is seen in 5% to 22% of patients with common variable immunoglobulin deficiency (CVID). There are instances where



Dr. Wynn

patients are diagnosed with CVID based on a radiologic or histologic diagnosis of GL-ILD. Although GL-ILD suggests a pulmonary process, it actually encompasses a multisystemic granulomatous inflammatory disease that may affect the liver, spleen, bowels, lymphoid tissue, and conceivably any other organ system (Hartono, et al. *Ann Allergy Asthma Immunol*. 2017;118[5]:614. Pathogenesis of GL-ILD in CVID includes dysfunctional antigen handling (due to impaired T cell function) and aberrant immune response to viruses (Hurst, et al. *J Allergy Clin Immunol Pract*. 2017;5[4]:938).

Patients with GL-ILD often present with progressive shortness of breath, restrictive lung functions with a background of CVID. Imaging findings are 5-30 mm lower lobe-predominant, nodules, ground glass opacities, and splenomegaly. Histopathology varies with predominant granulomas vs lymphocytic infiltrates. The process can be treated and often reversed with use of high dose immunoglobulin replacement, immunomodulatory therapy with agents like azathioprine, and rituximab. However, steroids are not helpful. Due to the lymphocytic dysregulation in GL-ILD, patients are at high risk of death from lymphoma. Part of the management is surveillance for malignancy and involvement of other organ systems.

A. Thanushi Wynn, MD
Fellow-in-Training Member

MODERATE

SEVERE

EOSINOPHILIC

ELEVATED EOS +/- IgE

OCS DEPENDENT

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

DUPIXENT

A PATH TO ASTHMA CONTROL



A NOVEL BIOLOGIC THAT INHIBITS IL-4 AND IL-13 SIGNALING,
TWO OF THE SOURCES OF INFLAMMATION IN ASTHMA^{1,a}

^aThe mechanism of dupilumab action in asthma has not been established.

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 (EGPA), 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 were reported in adult patients who participated in the asthma development program and cases of vasculitis consistent with EGPA have been reported with DUPIXENT in adult patients who participated in the asthma development program as well as in adult patients with co-morbid asthma in the chronic rhinosinusitis with nasal polyposis 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](https://www.dupilumab.com)

TRIAL 1: BASELINE EOS \geq 300 CELLS/ μ L



UP TO
81%

REDUCTION IN ANNUALIZED RATE OF SEVERE EXACERBATIONS through Week 24^{1,b}

- **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 \geq 300 CELLS/ μ L



UP TO
430 mL

IMPROVEMENT IN PRE-BRONCHODILATOR FEV₁ from baseline at Week 12¹

- **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 (\geq 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^c + SOC (n=150), DUPIXENT 300 mg Q2W^d + 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 FEV₁ in patients with baseline eosinophils \geq 300 cells/ μ L. **Other endpoint:** Annualized rate of severe exacerbation events during the 24-week treatment period.^e **Selected baseline demographics:** Mean duration of asthma: 22 years; mean exacerbations in previous year: 2.2; high-dose ICS use: 50%; pre-dose FEV₁ at baseline: 1.84 L; mean FeNO: 39 ppb; mean total IgE: 435 IU/mL; and mean baseline blood eosinophil count: 350 cells/ μ L.

^b 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.

^c With 400 mg loading dose.

^d With 600 mg loading dose.

^e Results were evaluated in the overall population and subgroups based on baseline blood eosinophil count.

EOS, eosinophils; FeNO, fractional exhaled nitric oxide; FEV₁, 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

RAPID AND SUSTAINED IMPROVEMENT IN LUNG FUNCTION WITH DUPIXENT¹

TRIAL 1: BASELINE EOS \geq 300 CELLS/ μ L

 **430** mL

IMPROVEMENT IN PRE-BRONCHODILATOR FEV₁ from baseline at Week 12

with DUPIXENT 200 mg + SOC (n=65) vs **180 mL** with placebo + SOC (n=68) (LSM difference: 260 mL [95% CI: 110, 400 mL]) and sustained through 24 weeks (380 mL vs 220 mL)

TRIAL 1: BASELINE EOS \geq 300 CELLS/ μ L

 **390** mL

IMPROVEMENT IN PRE-BRONCHODILATOR FEV₁ from baseline at Week 12

with DUPIXENT 300 mg + SOC (n=64) vs **180 mL** with placebo + SOC (n=68) (LSM difference: 210 mL [95% CI: 60, 360 mL]) and sustained through 24 weeks (380 mL vs 220 mL)



~68% OF THE TOTAL IMPROVEMENT IN FEV₁ SEEN AT WEEK 2 WITH DUPIXENT 200 mg + SOC (Trial 1 \geq 300 cells/ μ L)²

IMPORTANT SAFETY INFORMATION

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

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

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.

DUPIXENT[®] 
(dupilumab) Injection
200mg • 300mg

MORE PATIENTS STOPPED USING OCS WITH DUPIXENT WHILE IMPROVING ASTHMA CONTROL^{1,3}

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 FEV₁ 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])

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. **Additional secondary endpoints:** Annualized rate of severe exacerbation events during the 24-week treatment period; and mean change from baseline to Week 24 in FEV₁. **Selected baseline demographics:** Mean duration of asthma: 20 years; mean exacerbations in previous year: 2.1; high-dose ICS use: 89%; pre-dose FEV₁ at baseline: 1.58 L; mean FeNO: 38 ppb; mean total IgE: 431 IU/mL; and mean baseline blood eosinophil count: 350 cells/ μ L.

^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.

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

References: **1.** DUPIXENT Prescribing Information. **2.** Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet*. 2016;388(10039):31-44. **3.** 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.

SANOFI GENZYME 

REGENERON

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

1 INDICATIONS AND USAGE

1.1 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 DUXIPENT 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 DUXIPENT [see *Adverse Reactions* (6.1, 6.2)].

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 were reported in adult patients who participated in the asthma development program and cases of vasculitis consistent with eosinophilic granulomatosis with polyangiitis have been reported with DUXIPENT in adult patients who participated in the asthma development program, as well as in adult patients with comorbid asthma in the CRSwNP development program. A causal association between DUXIPENT and these conditions has not been established.

5.4 Acute Asthma Symptoms or Deteriorating Disease

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

5.5 Reduction of Corticosteroid Dosage

Do not discontinue systemic, topical, or inhaled corticosteroids abruptly upon initiation of therapy with DUXIPENT. 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.

5.7 Parasitic (Helminth) Infections

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

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.

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. DUXIPENT 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 DUXIPENT 200 mg Q2W group, and 6% of the DUXIPENT 300 mg Q2W group.

Table 3 summarizes the adverse reactions that occurred at a rate of at least 1% in subjects treated with DUXIPENT and at a higher rate than in their respective comparator groups in Asthma Trials 1 and 2.

Table 3: Adverse Reactions Occurring in ≥1% of the DUXIPENT 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 DUXIPENT through Week 52 was generally consistent with the safety profile observed at Week 24.

Specific Adverse Reactions:

Hypersensitivity Reactions

Hypersensitivity reactions were reported in <1% of DUXIPENT-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

DUXIPENT-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 DUXIPENT and placebo groups. Treatment-emergent eosinophilia (≥5,000 cells/mcL) was reported in <2% of DUXIPENT-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, nonfatal myocardial infarctions [MI], and nonfatal strokes) were reported in 1 (0.2%) of the DUXIPENT 200 mg Q2W group, 4 (0.6%) of the DUXIPENT 300 mg Q2W group, and 2 (0.3%) of the placebo 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 that follow, with the incidence of antibodies in other studies or to other products, may be misleading. Approximately 5% of subjects with atopic dermatitis, asthma, or CRSwNP who received DUXIPENT 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 DUXIPENT 200 mg Q2W for 52 weeks developed antibodies to dupilumab; ~4% exhibited persistent ADA responses, and ~4% had neutralizing antibodies.

Approximately 4% of subjects in the placebo groups in the 52-week studies were positive for antibodies to DUXIPENT; approximately 2% exhibited persistent ADA responses, and approximately 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 call 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-4R α) 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-4R α 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 embryo-fetal 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

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 FEV₁ (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 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).

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)*].

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)*].

PULMONARY PERSPECTIVES®

Resurgence of black lung among U.S. coal miners

BY CARA N. HALLDIN, PHD, MPH; AND A. SCOTT LANEY, PHD, MPH

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention.

Advances in technology over the last century, as well as the exportation of many high exposure jobs, nearly eliminated lung diseases caused by occupational exposure to respirable dust (the pneumoconioses) in the United States. One such example of this near elimination is black lung, or coal workers' pneumoconiosis (CWP), following the 1969 Federal Coal Mine Health and Safety Act.

The Act established permissible exposure limits to respirable dust, designed to prevent the most severe forms of CWP from occurring, and a national respiratory health screen-

ing program for underground coal miners. Between 1970 and the mid-1990s, disease prevalence plummeted from nearly 35% to less than 5% prevalence among longer tenured miners, and from 3% to less than 1% in miners with less than 10 years of mining tenure (Hall NB, et al. *Curr Environ Health Rep.* 2019;6[3]:137).

Many assumed that this was the last we'd hear of black lung – that the cases of disease existing in the 1990s were likely caused by exposures that occurred prior to the 1969 Act, and within a few years, no further cases would be detected.

This appeared to be an entirely reasonable assumption in the 1990s given the 30 years of declining prevalence and the continuous technological advances designed to continue reductions in dust exposures. In fact, the precipitous decline in black lung was briefly viewed as a public health triumph, as the most severe forms appeared to be near eradication in the

United States just 2 decades ago (Attfield MD, et al. *Am J Public Health.* 1992;82[7]:971; Attfield MD, et al. *Am J Public Health.* 1992;82[7]:964).

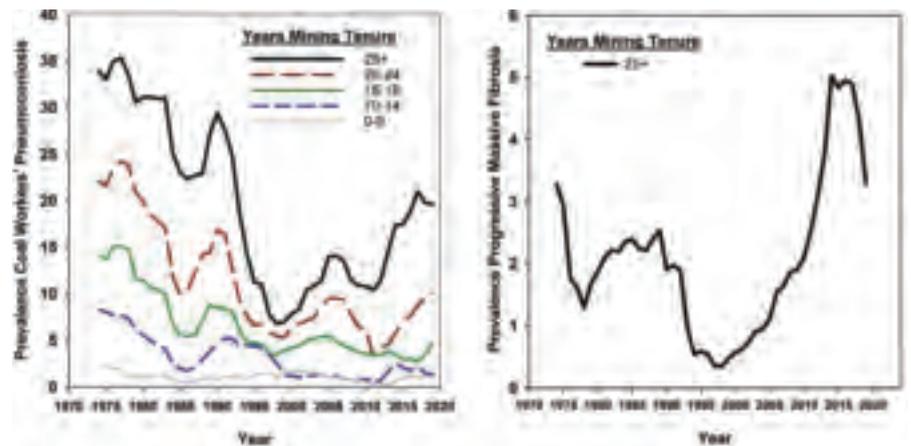


Figure 1. Prevalence of coal workers' pneumoconiosis and progressive massive fibrosis among working underground coal miners participating in the NIOSH Coal Workers' Health Surveillance Program, in Kentucky, Virginia, and West Virginia 1974-2019. Data are presented as the 5-year moving average percentage; surveillance is conducted on a 5-year national cycle (Data from NIOSH CWHSP [Coal Workers' Health Surveillance Program CWHSP Data Query System accessible: <http://webappa.cdc.gov/ords/cwhsp-database.html>]).

However, what has since been observed is a strong and ongoing resurgence of the potentially deadly fibrotic interstitial disease starting in the early 2000s (Figure 1), with the most striking increase observed in the Central Appalachian states of Kentucky, Virginia, and West Virginia (Blackley DJ, et al. *Am J Respir Crit Care Med.* 2014;190[6]:708; Blackley DJ, et al. *Am J Public Health.* 2018;108[9]:1220).

Of great concern is the resurgence of complicated Black Lung (progressive massive fibrosis [PMF]), which is completely disabling and leads to premature mortality. The prevalence of PMF is higher today than when NIOSH started formally tracking the disease in the 1970s, especially among specific populations. Since the mid-2000s, NIOSH and others have described the following (Hall NB, et al. *Curr Environ Health Rep.* 2019;6[3]:137):

- Increasing prevalence and severity of CWP both nationwide and specifically in Central Appalachia.
- Rapid progression of CWP.
- Increases in the frequency of lung transplantation for CWP.
- Severe disease among surface coal miners with no underground mining tenure.
- Increased severity of disease among former and retired miners.
- Hundreds of cases of PMF among

coal miners seeking care at clinics in eastern Kentucky and southwestern Virginia.

- Increasing numbers of miners with PMF filing for federal black lung compensation.
- Radiologic and pathologic indications of increased respirable silica exposure among coal miners.
- Premature mortality in miners diagnosed with CWP.
- Underutilization of a secondary prevention worker removal program designed to reduce the exposure of miners with disease.
- Former miners with severe disease describing extreme pressure to operate outside of applicable protective federal standards in order to increase productivity.

In our surveillance work, we have talked to many miners who, after having months or years' worth of extensive workups for pneumonia, sarcoidosis, lung cancer, and/or diseases other than the pneumoconioses, have eventually learned that they actually had dust-induced lung disease attributable to their work. Additionally, through our evaluation of the transplantation data, it has become clear that dust-related lung disease is likely underreported or underrecognized among those receiving lung transplants.

Finally, through analysis of mortality data, it is apparent that CWP is also underreported as a cause of death among miners with black lung. We mention these points to emphasize how important it is to document



Dr. Halldin



Dr. Laney

This month in the journal CHEST®

Editor's Picks

BY PETER J. MAZZONE, MD, MPH, FCCP

Editor in Chief

CHEST Reviews

Critically ill patients with the HIV: 30 years later.

By Dr. E. Azoulay, et al.

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By Drs. A. Zinchuk and H. K. Yaggi.

Basic primer for finances in academic adult and pediatric pulmonary divisions.

By Dr. L. Schnapp, et al.



Original Research

Eligibility for lung volume reduction surgery in chronic obstructive pulmonary disease patients identified in a UK primary care setting.

By Dr. H. Whittaker, et al.

Early life exposure to oral antibiotics and lung function into early adulthood.

By Dr. K. dos Santos, et al.

a full occupational history for proper diagnoses, early intervention, and improved public health information to inform primary and secondary disease prevention efforts.

Resources for clinicians

CWP is most commonly identified using plain posterior-anterior chest radiography and presence/severity of fibrotic change is described using an international standard established by the International Labour Office (International Labour Office. Guidelines for the use of the ILO international classification of radiographs of pneumoconioses. Geneva: International Labour Office; 2011).

In the United States, NIOSH operates the B Reader Training and Certification Program, which offers a free self-study syllabus, <https://www.cdc.gov/niosh/topics/chest-radiography/breader.html>, and in-person training courses on occasion, to assist physicians in learning and demonstrating continuous competency in classifying chest radiographs of dust-exposed workers according to the ILO Standards (Halldin CN, et al. *J Occup Environ Med.* 2019;61[12]:1045).

The B Reader Program and ILO Standards are currently undergoing a decade-long revision process where both will feature digitally acquired chest radiograph images. This process should be fully complete in the following months.

To educate miners, mine operators, and others about the risks of respirable dust, NIOSH produced an educational video, “Faces of Black Lung,” in 2008 that featured two miners in their 50s and 60s who had complicated Black Lung. Because of the resurgence of disease and particularly severe cases being identified among much younger miners, NIOSH recently released an updated version of the video, “Faces of Black Lung II,” where three Kentucky underground miners, ages 39, 42, and 48, describe the incredible disability and quality of life lost due to a disease caused by gross overexposure of respirable coal mine dust.

Unfortunately, the 42-year-old miner died from complications stemming from Black Lung less than a year after filming his part in the video, and the other two miners have been advised to be evaluated for lung transplantation.

Access the video here: <https://www.cdc.gov/niosh/docs/video/2020-109d/default.html>. We hope

that these men’s stories will help younger miners relate to the risks of respirable coal mine dust and help others understand the severity of disease as all three of these men struggled to breathe just describing their day to day tasks.

Parting message

No one should ever have to consider a lung transplant at the age of 40 because they went to work attempting to provide for their family. No one should ever be faced with end-of-life planning

while their kids are in grade school because of a disease they acquired at work. Respirable coal mine dust is the only cause of black lung, and the coal mining industry has the necessary tech-

Continued on following page

NOW APPROVED
to slow the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD)¹

FACE SSc-ILD
HEAD ON

OFEV (nintedanib) is proven to reduce lung function decline in patients with SSc-ILD^{1,2}

OFEV[®]
(nintedanib)
capsules 150mg

INDICATION

OFEV is indicated to slow the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD).

IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS

Hepatic Impairment: OFEV is not recommended in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment. Patients with mild hepatic impairment (Child Pugh A) can be treated with a reduced dosage (100 mg twice daily). Consider treatment interruption or discontinuation for management of adverse reactions.

Please see additional Important Safety Information on the following pages and accompanying Brief Summary of Prescribing Information.

Continued from previous page

nology and tools to prevent harmful exposures to respirable dust, and, together with miners, must successfully and consistently implement dust suppression controls. There is no cure for black lung; it's

irreversible and can be first recognized and continue to progress even after a miner has left exposure. However, early identification and appropriate intervention can prevent progression to the most disabling manifestations.

The role of the clinician is to be part of the early identification of black lung through including CWP in the differential diagnosis for unusual or unexpected respiratory illness in otherwise healthy primarily working aged miners. The public

health community must continue to monitor disease prevalence in working populations and implement policies and recommendations to support the efforts of those on the frontline – the miners, industry, and health-care workers.

NOW APPROVED



Studied in the largest phase 3 trial in SSc-ILD to date

580 patients with SSc-ILD were randomized in a double-blind, placebo-controlled, 52-week trial. The primary endpoint was the annual rate of decline in FVC over 52 weeks¹⁻³



Proven to reduce lung function decline in patients with SSc-ILD

OFEV reduced the annual rate of FVC decline by 41 mL/year (44% relative reduction) compared with placebo ($P=.04$; 95% CI=3, 79)^{1,2}

FDA, Food and Drug Administration; FVC, forced vital capacity.

*Diarrhea was reported in 76% of patients receiving OFEV vs 32% on placebo.¹

IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS (CONT'D)

Elevated Liver Enzymes and Drug-Induced Liver Injury

- Cases of drug-induced liver injury (DILI) have been observed with OFEV treatment. In the clinical trials and post-marketing period, non-serious and serious cases of DILI were reported. Cases of severe liver injury with fatal outcome have been reported in the post-marketing period. The majority of hepatic events occur within the first three months of treatment. OFEV was associated with elevations of liver enzymes (ALT, AST, ALKP, and GGT) and bilirubin. Liver enzyme and bilirubin increases were reversible with dose modification or interruption in the majority of cases. In the SSc-ILD study, a maximum ALT and/or AST greater than or equal to 3 times ULN was observed in 4.9% of patients treated with OFEV.
- Patients with low body weight (less than 65 kg), patients who are Asian, and female patients may have a higher risk of elevations in liver enzymes. Nintedanib exposure increased with patient age, which may result in increased liver enzymes.
- Conduct liver function tests prior to initiation of treatment, at regular intervals during the first three months of treatment, and periodically thereafter or as clinically indicated. Measure liver function tests

promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. Dosage modifications, interruption, or discontinuation may be necessary for liver enzyme elevations.

Gastrointestinal Disorders Diarrhea

- In the SSc-ILD study, diarrhea was the most frequent gastrointestinal event reported in 76% versus 32% of patients treated with OFEV and placebo, respectively. Events were primarily mild to moderate in intensity and occurred within the first 3 months. Diarrhea led to permanent dose reduction in 22% and discontinuation in 7% of OFEV patients versus 1% and 0.3% in placebo patients, respectively.
- Dosage modifications or treatment interruptions may be necessary in patients with diarrhea. Treat diarrhea at first signs with adequate hydration and antidiarrheal medication (e.g., loperamide), and consider treatment interruption if diarrhea continues. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If severe diarrhea persists, discontinue treatment.

The Energy Information Agency projects that coal will continue to be a substantial source of U.S. energy production and consumption well into the mid- to late-century. Unfortunately, Black Lung has made a resurgence and is killing miners,

and each of us has a role to play in eliminating it once and for all.

We will continue to carry out our mandate to screen working coal miners for respiratory disease; however, given the continued contraction of the coal mining industry,

it's much more likely for cases of disease to be recognized in the clinic setting. Therefore, we reiterate our previous plea to clinicians: when identifying an individual with interstitial fibrosis consider their full occupational history.

Dr. Halldin and Dr. Laney are from the Surveillance Branch, Respiratory Health Division, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Morgantown, WV.

OFEV is the **FIRST AND ONLY** FDA-approved therapy to slow the rate of decline in pulmonary function in patients with SSc-ILD^{1,3}



Demonstrated safety and tolerability profile

The most common adverse reactions were gastrointestinal in nature and generally of mild or moderate intensity^{1*}



One capsule, twice daily with food¹

See Brief Summary of Prescribing Information for complete dosing recommendations

[Learn more at OFEVhcp.com](https://www.ofevhcp.com)

IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS (CONT'D)

Gastrointestinal Disorders (cont'd) Nausea and Vomiting

- In the SSc-ILD study, nausea was reported in 32% versus 14% and vomiting was reported in 25% versus 10% of patients treated with OFEV and placebo, respectively. Events were primarily of mild to moderate intensity. Nausea and vomiting led to discontinuation of OFEV in 2% and 1% of patients, respectively.
- If nausea or vomiting persists despite appropriate supportive care including anti-emetic therapy, consider dose reduction or treatment interruption. OFEV treatment may be resumed at full dosage or at reduced dosage, which subsequently may be increased to full dosage. If severe nausea or vomiting does not resolve, discontinue treatment.

Embryofetal Toxicity: OFEV can cause fetal harm when administered to a pregnant woman and patients should be advised of the potential risk to a fetus. Women should be advised to avoid becoming pregnant while receiving OFEV and to use highly effective contraception during treatment and at least 3 months after the last dose of OFEV. As the impact of nintedanib on the effectiveness of hormonal contraception is unknown, advise women using hormonal contraceptives to add a barrier method. Verify pregnancy status prior to starting OFEV and during treatment as appropriate.

Arterial Thromboembolic Events: In the SSc-ILD study, arterial thromboembolic events were reported in 0.7% of patients in both the OFEV-treated and placebo-treated patients. There were 0 cases of myocardial infarction in OFEV-treated patients compared to 0.7% of placebo-treated patients. Use caution when treating patients at higher cardiovascular risk, including known coronary artery disease. Consider treatment interruption in patients who develop signs or symptoms of acute myocardial ischemia.

Risk of Bleeding: OFEV may increase the risk of bleeding. In the SSc-ILD study, bleeding events were reported in 11% of OFEV versus 8% of placebo patients. Use OFEV in patients with known risk of bleeding only if the anticipated benefit outweighs the potential risk. There have been post-marketing reports of non-serious and serious bleeding events, some of which were fatal.

Please see additional Important Safety Information on the following page and accompanying Brief Summary of Prescribing Information.



OFEV[®]
(nintedanib)
capsules 150mg

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Bologna, Italy, will set a perfect backdrop for CHEST Congress 2020, hosted by CHEST and the CHEST Italian Delegates. This premier education event in

pulmonary, critical care, and sleep medicine will give attendees access to world-renowned faculty from regional and international centers of excellence.

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and evidence-based medicine to shine through. We will be featuring innovative and diverse education opportunities incorporating the best of CHEST Annual Meeting, including lectures, recent advancements in clinical practice and science, guided poster presentations, and hands-on

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FAX THE PRESCRIPTION FORM TO ONE OF THE SPECIALTY PHARMACIES

IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS (CONT'D)

Gastrointestinal Perforation: OFEV (nintedanib) may increase the risk of gastrointestinal perforation. In the SSc-ILD study, no cases of gastrointestinal perforation were reported in either OFEV or placebo-treated patients. In the post-marketing period, cases of gastrointestinal perforations have been reported, some of which were fatal. Use caution when treating patients who have had recent abdominal surgery, have a previous history of diverticular disease, or who are receiving concomitant corticosteroids or NSAIDs. Discontinue therapy with OFEV in patients who develop gastrointestinal perforation. Only use OFEV in patients with known risk of gastrointestinal perforation if the anticipated benefit outweighs the potential risk.

ADVERSE REACTIONS

- Adverse reactions reported in the SSc-ILD study in greater than or equal to 5% of OFEV patients, and more than placebo, included diarrhea, nausea, vomiting, skin ulcer, abdominal pain, liver enzyme elevation, weight decreased, fatigue, decreased appetite, headache, pyrexia, back pain, dizziness and hypertension.
- In the SSc-ILD study, the most frequent serious adverse events reported in patients treated with OFEV, more than placebo, were interstitial lung disease (2.4% vs. 1.7%) and pneumonia (2.8% vs. 0.3%). Within 52 weeks, 5 patients treated with OFEV (1.7%) and 4 patients treated with placebo (1.4%) died. There was no pattern among adverse events leading to death in either treatment arm.

DRUG INTERACTIONS

- **P-glycoprotein (P-gp) and CYP3A4 Inhibitors and Inducers:** Coadministration with oral doses of a P-gp and CYP3A4 inhibitor, ketoconazole, increased

exposure to nintedanib by 60%. Concomitant use of potent P-gp and CYP3A4 inhibitors (e.g., erythromycin) with OFEV may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of OFEV. Management of adverse reactions may require interruption, dose reduction, or discontinuation of therapy with OFEV. Coadministration with oral doses of a P-gp and CYP3A4 inducer, rifampicin, decreased exposure to nintedanib by 50%. Concomitant use of P-gp and CYP3A4 inducers (e.g., carbamazepine, phenytoin, and St. John's wort) with OFEV should be avoided as these drugs may decrease exposure to nintedanib.

- **Anticoagulants:** Nintedanib may increase the risk of bleeding. Monitor patients on full anticoagulation therapy closely for bleeding and adjust anticoagulation treatment as necessary.

USE IN SPECIFIC POPULATIONS

- **Nursing Mothers:** Because of the potential for serious adverse reactions in nursing infants from OFEV, advise women that breastfeeding is not recommended during treatment.
- **Reproductive Potential:** OFEV may reduce fertility in females of reproductive potential.
- **Smokers:** Smoking was associated with decreased exposure to OFEV, which may affect the efficacy of OFEV. Encourage patients to stop smoking prior to and during treatment.

CL-OF-100021 09.06.19

Please see accompanying Brief Summary of Prescribing Information on the following pages.

References: 1. OFEV[®] (nintedanib) Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2019. 2. Distler O et al. *N Engl J Med.* 2019;380(26):2518-2528. 3. Distler O et al. *Clin Exp Rheumatol.* 2017;35 Suppl 106(4):75-81.



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simulation opportunities.

Additionally, look for CHEST Challenge to come to Italy! This international meeting will connect the best minds in chest medicine from Europe, the United States, and other countries around the world to help you and your team

learn the latest and greatest in chest medicine. Italy attracts hundreds of thou-

sands of people from all over the world each year, and it is easy to see why; Italy, a European country

with a long Mediterranean coastline, has left a powerful mark on Western culture and cuisine. Bologna is the lively, historic capital of the Emilia-Romagna region in northern Italy. Piazza Maggiore is a sprawling plaza lined with arched colonnades;

Continued on following page

OFEV® (nintedanib) capsules, for oral use **BRIEF SUMMARY OF PRESCRIBING INFORMATION.**

Please see package insert for full Prescribing Information, including Patient Information

1 INDICATIONS AND USAGE: 1.1 Idiopathic Pulmonary Fibrosis: OFEV is indicated for the treatment of idiopathic pulmonary fibrosis (IPF). **1.2 Systemic Sclerosis-Associated Interstitial Lung Disease:** OFEV is indicated to slow the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD).

2 DOSAGE AND ADMINISTRATION: 2.1 Testing Prior to OFEV Administration: Conduct liver function tests in all patients and a pregnancy test in females of reproductive potential prior to initiating treatment with OFEV [see *Warnings and Precautions*]. **2.2 Recommended Dosage:** The recommended dosage of OFEV is 150 mg twice daily administered approximately 12 hours apart. OFEV capsules should be taken with food and swallowed whole with liquid. OFEV capsules should not be chewed or crushed because of a bitter taste. The effect of chewing or crushing of the capsule on the pharmacokinetics of nintedanib is not known. If a dose of OFEV is missed, the next dose should be taken at the next scheduled time. Advise the patient to not make up for a missed dose. Do not exceed the recommended maximum daily dosage of 300 mg. In patients with mild hepatic impairment (Child Pugh A), the recommended dosage of OFEV is 100 mg twice daily approximately 12 hours apart taken with food.

2.3 Dosage Modification due to Adverse Reactions: In addition to symptomatic treatment, if applicable, the management of adverse reactions of OFEV may require dose reduction or temporary interruption until the specific adverse reaction resolves to levels that allow continuation of therapy. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If a patient does not tolerate 100 mg twice daily, discontinue treatment with OFEV [see *Warnings and Precautions and Adverse Reactions*]. Dose modifications or interruptions may be necessary for liver enzyme elevations. Conduct liver function tests (aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin) prior to initiation of treatment with OFEV, at regular intervals during the first three months of treatment, and periodically thereafter or as clinically indicated. Measure liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. Discontinue OFEV in patients with AST or ALT greater than 3 times the upper limit of normal (ULN) with signs or symptoms of liver injury and for AST or ALT elevations greater than 5 times the upper limit of normal. For AST or ALT greater than 3 times to less than 5 times the ULN without signs of liver damage, interrupt treatment or reduce OFEV to 100 mg twice daily. Once liver enzymes have returned to baseline values, treatment with OFEV may be reintroduced at a reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage (150 mg twice daily) [see *Warnings and Precautions and Adverse Reactions*]. In patients with mild hepatic impairment (Child Pugh A), consider treatment interruption, or discontinuation for management of adverse reactions.

4 CONTRAINDICATIONS: None

5 WARNINGS AND PRECAUTIONS: 5.1 Hepatic Impairment: Treatment with OFEV is not recommended in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment [see *Use in Specific Populations*]. Patients with mild hepatic impairment (Child Pugh A) can be treated with a reduced dose of OFEV [see *Dosage and Administration*]. **5.2 Elevated Liver Enzymes and Drug-Induced Liver Injury:** Cases of drug-induced liver injury (DILI) have been observed with OFEV treatment. In the clinical trials and postmarketing period, non-serious and serious cases of DILI were reported. Cases of severe liver injury with fatal outcome have been reported in the postmarketing period. The majority of hepatic events occur within the first three months of treatment. In clinical trials, administration of OFEV was associated with elevations of liver enzymes (ALT, AST, ALKP, GGT) and bilirubin. Liver enzyme and bilirubin increases were reversible with dose modification or interruption in the majority of cases. In IPF studies (Studies 1, 2, and 3), the majority (94%) of patients with ALT and/or AST elevations had elevations less than 5 times ULN and the majority (95%) of patients with bilirubin elevations had elevations less than 2 times ULN. In

the SSc-ILD study (Study 4), a maximum ALT and/or AST greater than or equal to 3 times ULN was observed for 4.9% of patients in the OFEV group and for 0.7% of patients in the placebo group [see *Use in Specific Populations*]. Patients with a low body weight (less than 65 kg), Asian, and female patients may have a higher risk of elevations in liver enzymes. Nintedanib exposure increased with patient age, which may also result in a higher risk of increased liver enzymes. Conduct liver function tests (ALT, AST, and bilirubin) prior to initiation of treatment with OFEV, at regular intervals during the first three months of treatment, and periodically thereafter or as clinically indicated. Measure liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. Dosage modifications or interruption may be necessary for liver enzyme elevations. [see *Dosage and Administration*]. **5.3 Gastrointestinal Disorders: Diarrhea:** In clinical trials, diarrhea was the most frequent gastrointestinal event reported. In most patients, the event was of mild to moderate intensity and occurred within the first 3 months of treatment. In IPF studies (Studies 1, 2, and 3), diarrhea was reported in 62% versus 18% of patients treated with OFEV and placebo, respectively [see *Adverse Reactions*]. Diarrhea led to permanent dose reduction in 11% of patients treated with OFEV compared to 0 placebo-treated patients. Diarrhea led to discontinuation of OFEV in 5% of the patients compared to less than 1% of placebo-treated patients. In the SSc-ILD study (Study 4), diarrhea was reported in 76% versus 32% of patients treated with OFEV and placebo, respectively [see *Adverse Reactions*].

Diarrhea led to permanent dose reduction in 22% of patients treated with OFEV compared to 1% of placebo-treated patients. Diarrhea led to discontinuation of OFEV in 7% of the patients compared to 0.3% of placebo-treated patients. Dosage modifications or treatment interruptions may be necessary in patients with adverse reactions of diarrhea. Treat diarrhea at first signs with adequate hydration and antidiarrheal medication (e.g., loperamide), and consider treatment interruption if diarrhea continues [see *Dosage and Administration*]. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If severe diarrhea persists despite symptomatic treatment, discontinue treatment with OFEV. **5.4 Nausea and Vomiting:** In IPF studies (Studies 1, 2, and 3), nausea was reported in 24% versus 7% and vomiting was reported in 12% versus 3% of patients treated with OFEV and placebo, respectively. In the SSc-ILD study (Study 4), nausea was reported in 32% versus 14% and vomiting was reported in 25% versus 10% of patients treated with OFEV and placebo, respectively [see *Adverse Reactions*]. In most patients, these events were of mild to moderate intensity. In IPF studies (Studies 1, 2, and 3), nausea led to discontinuation of OFEV in 2% of patients and vomiting led to discontinuation of OFEV in 1% of the patients. In the SSc-ILD study (Study 4), nausea led to discontinuation of OFEV in 2% of patients and vomiting led to discontinuation of OFEV in 1% of the patients. For nausea or vomiting that persists despite appropriate supportive care including anti-emetic therapy, dose reduction or treatment interruption may be required [see *Dosage and Administration*]. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If severe nausea or vomiting does not resolve, discontinue treatment with OFEV. **5.5 Embryo-Fetal Toxicity:** Based on findings from animal studies and its mechanism of action, OFEV can cause fetal harm when administered to a pregnant woman. Nintedanib caused embryo-fetal deaths and structural abnormalities in rats and rabbits when administered during organogenesis at less than (rats) and approximately 5 times (rabbits) the maximum recommended human dose (MRHD) in adults. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to avoid becoming pregnant while receiving treatment with OFEV and to use highly effective contraception during treatment and at least 3 months after the last dose of OFEV. It is currently unknown whether nintedanib may reduce the effectiveness of hormonal contraceptives, therefore advise women using hormonal contraceptives to add a barrier method. Verify pregnancy status prior to treatment with OFEV and during treatment as appropriate [see *Use in Specific Populations*]. **5.6 Arterial Thromboembolic Events:** Arterial thromboembolic events have been reported in patients taking OFEV. In IPF studies (Studies 1, 2, and 3), arterial thromboembolic

events were reported in 2.5% of patients treated with OFEV and 0.8% of placebo-treated patients. Myocardial infarction was the most common adverse reaction under arterial thromboembolic events, occurring in 1.5% of OFEV-treated patients compared to 0.4% of placebo-treated patients. In the SSc-ILD study (Study 4), arterial thromboembolic events were reported in 0.7% of patients in both treatment arms. There were 0 cases of myocardial infarction in OFEV-treated patients compared to 0.7% of placebo-treated patients. Use caution when treating patients at higher cardiovascular risk including known coronary artery disease. Consider treatment interruption in patients who develop signs or symptoms of acute myocardial ischemia. **5.6 Risk of Bleeding:** Based on the mechanism of action (VEGFR inhibition), OFEV may increase the risk of bleeding. In IPF studies (Studies 1, 2, and 3), bleeding events were reported in 10% of patients treated with OFEV and in 7% of patients treated with placebo. In the SSc-ILD study (Study 4), bleeding events were reported in 11% of patients treated with OFEV and in 8% of patients treated with placebo. In the postmarketing period non-serious and serious bleeding events, some of which were fatal, have been observed. Use OFEV in patients with known risk of bleeding only if the anticipated benefit outweighs the potential risk. **5.7 Gastrointestinal Perforation:** Based on the mechanism of action, OFEV may increase the risk of gastrointestinal perforation. In IPF studies (Studies 1, 2, and 3), gastrointestinal perforation was reported in 0.3% of patients treated with OFEV, compared to 0 cases in the placebo-treated patients. In the SSc-ILD study (Study 4), no cases of gastrointestinal perforation were reported in patients treated with OFEV or in placebo-treated patients. In the postmarketing period, cases of gastrointestinal perforations have been reported, some of which were fatal. Use caution when treating patients who have had recent abdominal surgery, previous history of diverticular disease or receiving concomitant corticosteroids or NSAIDs. Discontinue therapy with OFEV in patients who develop gastrointestinal perforation. Only use OFEV in patients with known risk of gastrointestinal perforation if the anticipated benefit outweighs the potential risk.

6 ADVERSE REACTIONS: The following adverse reactions are discussed in greater detail in other sections of the labeling: Elevated Liver Enzymes and Drug-Induced Liver Injury [see *Warnings and Precautions*]; Gastrointestinal Disorders [see *Warnings and Precautions*]; Embryo-Fetal Toxicity [see *Warnings and Precautions*]; Arterial Thromboembolic Events [see *Warnings and Precautions*]; Risk of Bleeding [see *Warnings and Precautions*]; Gastrointestinal Perforation [see *Warnings and Precautions*]. **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. The safety of OFEV was evaluated in over 1000 IPF patients and over 280 patients with SSc-ILD. Over 200 IPF patients were exposed to OFEV for more than 2 years in clinical trials. **Idiopathic Pulmonary Fibrosis:** OFEV was studied in three randomized, double-blind, placebo-controlled, 52-week trials. In the phase 2 (Study 1) and phase 3 (Studies 2 and 3) trials, 723 patients with IPF received OFEV 150 mg twice daily and 508 patients received placebo. The median duration of exposure was 10 months for patients treated with OFEV and 11 months for patients treated with placebo. Subjects ranged in age from 42 to 89 years (median age of 67 years). Most patients were male (79%) and Caucasian (60%). The most frequent serious adverse reactions reported in patients treated with OFEV, more than placebo, were bronchitis (1.2% vs. 0.8%) and myocardial infarction (1.5% vs. 0.4%). The most common adverse events leading to death in patients treated with OFEV, more than placebo, were pneumonia (0.7% vs. 0.6%), lung neoplasm malignant (0.3% vs. 0%), and myocardial infarction (0.3% vs. 0.2%). In the predefined category of major adverse cardiovascular events (MACE) including MI, fatal events were reported in 0.6% of OFEV-treated patients and 1.8% of placebo-treated patients. Adverse reactions leading to permanent dose reductions were reported in 16% of OFEV-treated patients and 1% of placebo-treated patients. The most frequent adverse reaction that led to permanent dose reduction in the patients treated with OFEV was diarrhea (11%). Adverse reactions leading to discontinuation were reported in 21% of OFEV-treated patients and 15% of placebo-treated patients. The most frequent adverse reactions that led to discontinuation in OFEV-treated patients were diarrhea (5%), nausea (2%), and decreased appetite (2%). The most common adverse

Continued from previous page

cafes; and medieval and Renaissance structures such as City Hall, the Fountain of Neptune, and the Basilica di San Petronio. Italy has easy rail transportation between cities, so plan to extend your stay and

visit any number of the great Italian cities, including Rome: home of the Vatican, landmark art, and ancient ruins.

Make your plans soon for CHEST Congress 2020 in Bologna – June 25-27.



The Piazza Maggiore in Bologna, Italy

treeffe/Getty Images

reactions with an incidence of greater than or equal to 5% and more frequent in the OFEV than placebo treatment group are listed in Table 1.

Table 1 Adverse Reactions Occurring in ≥5% of OFEV-treated Patients and More Commonly Than Placebo in Studies 1, 2, and 3

Adverse Reaction	OFEV, 150 mg n=723	Placebo n=508
Gastrointestinal disorders		
Diarrhea	62%	18%
Nausea	24%	7%
Abdominal pain ^a	15%	6%
Vomiting	12%	3%
Hepatobiliary disorders		
Liver enzyme elevation ^b	14%	3%
Metabolism and nutrition disorders		
Decreased appetite	11%	5%
Nervous system disorders		
Headache	8%	5%
Investigations		
Weight decreased	10%	3%
Vascular disorders		
Hypertension ^c	5%	4%

^a Includes abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain and abdominal tenderness.

^b Includes gamma-glutamyltransferase increased, hepatic enzyme increased, alanine aminotransferase increased, aspartate aminotransferase increased, hepatic function abnormal, liver function test abnormal, transaminase increased, blood alkaline phosphatase-increased, alanine aminotransferase abnormal, aspartate aminotransferase abnormal, and gamma-glutamyltransferase abnormal.

^c Includes hypertension, blood pressure increased, hypertensive crisis, and hypertensive cardiomyopathy.

In addition, hypothyroidism was reported in patients treated with OFEV, more than placebo (1.1% vs. 0.6%).

Combination with Pirfenidone: Concomitant treatment with nintedanib and pirfenidone was investigated in an exploratory open-label, randomized (1:1) trial of nintedanib 150 mg twice daily with add-on pirfenidone (titrated to 801 mg three times a day) compared to nintedanib 150 mg twice daily alone in 105 randomized patients for 12 weeks. The primary endpoint was the percentage of patients with gastrointestinal adverse events from baseline to Week 12. Gastrointestinal adverse events were in line with the established safety profile of each component and were experienced in 37 (70%) patients treated with pirfenidone added to nintedanib versus 27 (53%) patients treated with nintedanib alone. Diarrhea, nausea, vomiting, and abdominal pain (includes upper abdominal pain, abdominal discomfort, and abdominal pain) were the most frequent adverse events reported in 20 (38%) versus 16 (31%), in 22 (42%) versus 6 (12%), in 15 (28%) versus 6 (12%) patients, and in 15 (28%) versus 7 (14%) treated with pirfenidone added to nintedanib versus nintedanib alone, respectively. More subjects reported AST or ALT elevations (greater than or equal to 3x the upper limit of normal) when using pirfenidone in combination with nintedanib (n=3 (6%)) compared to nintedanib alone (n=0) [see *Warnings and Precautions*]. **Systemic Sclerosis-Associated Interstitial Lung Disease:** OFEV was studied in a phase 3, randomized, double-blind, placebo-controlled trial (Study 4) in which 576 patients with SSC-ILD received OFEV 150 mg twice daily (n=288) or placebo (n=288). Patients were to receive treatment for at least 52 weeks; individual patients were treated for up to 100 weeks. The median duration of exposure was 15 months for patients treated with OFEV and 16 months for patients treated with placebo. Subjects ranged in age from 20 to 79 years (median age of 55 years). Most patients were female (75%). Patients were mostly Caucasian (67%), Asian (25%), or Black (6%). At baseline, 49% of patients were on stable therapy with mycophenolate. The most frequent serious adverse events reported in patients treated with OFEV, more than placebo, were interstitial lung disease (2.4% nintedanib vs 1.7% placebo) and pneumonia (2.8% nintedanib vs 0.3% placebo). Within 52 weeks, 5 patients treated with OFEV (1.7%) and 4 patients treated with placebo (1.4%) died. There was no pattern among adverse events leading to death in either treatment arm. Adverse reactions leading to permanent dose reductions were reported in 34% of OFEV-treated patients and 4% of placebo-treated patients. The most frequent adverse reac-

tion that led to permanent dose reduction in the patients treated with OFEV was diarrhea (22%). Adverse reactions leading to discontinuation were reported in 16% of OFEV-treated patients and 9% of placebo-treated patients. The most frequent adverse reactions that led to discontinuation in OFEV-treated patients were diarrhea (7%), nausea (2%), vomiting (1%), abdominal pain (1%), and interstitial lung disease (1%). The safety profile in patients with or without mycophenolate at baseline was comparable. The most common adverse reactions with an incidence of greater than or equal to 5% in OFEV-treated patients and more commonly than in placebo are listed in Table 2.

Table 2 Adverse Reactions Occurring in ≥5% of OFEV-treated Patients and More Commonly Than Placebo in Study 4

Adverse Reaction	OFEV, 150 mg n=288	Placebo n=288
Diarrhea	76%	32%
Nausea	32%	14%
Vomiting	25%	10%
Skin ulcer	18%	17%
Abdominal pain ^a	18%	11%
Liver enzyme elevation ^b	13%	3%
Weight decreased	12%	4%
Fatigue	11%	7%
Decreased appetite	9%	4%
Headache	9%	8%
Pyrexia	6%	5%
Back pain	6%	4%
Dizziness	6%	4%
Hypertension ^c	5%	2%

^a Includes abdominal pain, abdominal pain upper, abdominal pain lower, and esophageal pain.

^b Includes alanine aminotransferase increased, gamma-glutamyltransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, blood alkaline phosphatase increased, transaminase increased, and hepatic function abnormal.

^c Includes hypertension, blood pressure increased, and hypertensive crisis.

6.2 Postmarketing Experience: The following adverse reactions have been identified during postapproval use of OFEV. 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. The following adverse reactions have been identified during postapproval use of OFEV: drug-induced liver injury [see *Warnings and Precautions*], non-serious and serious bleeding events, some of which were fatal [see *Warnings and Precautions*], pancreatitis, thrombocytopenia, rash, pruritus.

7 DRUG INTERACTIONS: 7.1 P-glycoprotein (P-gp) and CYP3A4 Inhibitors and Inducers: Nintedanib is a substrate of P-gp and, to a minor extent, CYP3A4. Coadministration with oral doses of a P-gp and CYP3A4 inhibitor, ketoconazole, increased exposure to nintedanib by 60%. Concomitant use of P-gp and CYP3A4 inhibitors (e.g., erythromycin) with OFEV may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of OFEV. Management of adverse reactions may require interruption, dose reduction, or discontinuation of therapy with OFEV [see *Dosage and Administration*]. Coadministration with oral doses of a P-gp and CYP3A4 inducer, rifampicin, decreased exposure to nintedanib by 50%. Concomitant use of P-gp and CYP3A4 inducers (e.g., carbamazepine, phenytoin, and St. John's wort) with OFEV should be avoided as these drugs may decrease exposure to nintedanib. **7.2 Anticoagulants:** Nintedanib is a VEGFR inhibitor and may increase the risk of bleeding. Monitor patients on full anticoagulation therapy closely for bleeding and adjust anticoagulation treatment as necessary [see *Warnings and Precautions*]. **7.3 Pirfenidone:** In a multiple-dose study conducted to assess the pharmacokinetic effects of concomitant treatment with nintedanib and pirfenidone, the coadministration of nintedanib with pirfenidone did not alter the exposure of either agent. Therefore, no dose adjustment is necessary during concomitant administration of nintedanib with pirfenidone. **7.4 Bosentan:** Coadministration of nintedanib with bosentan did not alter the pharmacokinetics of nintedanib.

8 USE IN SPECIFIC POPULATIONS: 8.1 Pregnancy: Risk Summary: Based on findings from animal studies and its mechanism of action, OFEV can cause fetal harm when

administered to a pregnant woman. There are no data on the use of OFEV during pregnancy. In animal studies of pregnant rats and rabbits treated during organogenesis, nintedanib caused embryo-fetal deaths and structural abnormalities at less than (rats) and approximately 5 times (rabbits) the maximum recommended human dose [see *Data*]. Advise pregnant women of the potential risk to a fetus. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects is 2% to 4% and miscarriage in clinically recognized pregnancies is 15% to 20%. **Data: Animal Data:** In animal reproduction toxicity studies, nintedanib caused embryo-fetal deaths and structural abnormalities in rats and rabbits at less than and approximately 5 times the maximum recommended human dose (MRHD) in adults (on a plasma AUC basis at maternal oral doses of 2.5 and 15 mg/kg/day in rats and rabbits, respectively). Malformations included abnormalities in the vasculature, urogenital, and skeletal systems. Vasculature anomalies included missing or additional major blood vessels. Skeletal anomalies included abnormalities in the thoracic, lumbar, and caudal vertebrae (e.g., hemivertebra, missing, or asymmetrically ossified), ribs (bifid or fused), and sternbrae (fused, split, or unilaterally ossified). In some fetuses, organs in the urogenital system were missing. In rabbits, a significant change in sex ratio was observed in fetuses (female:male ratio of approximately 71%:29%) at approximately 15 times the MRHD in adults (on an AUC basis at a maternal oral dose of 60 mg/kg/day). Nintedanib decreased post-natal viability of rat pups during the first 4 post-natal days when dams were exposed to less than the MRHD (on an AUC basis at a maternal oral dose of 10 mg/kg/day). **8.2 Lactation: Risk Summary:** There is no information on the presence of nintedanib in human milk, the effects on the breast-fed infant or the effects on milk production. Nintedanib and/or its metabolites are present in the milk of lactating rats [see *Data*]. Because of the potential for serious adverse reactions in nursing infants from OFEV, advise women that breastfeeding is not recommended during treatment with OFEV. **Data:** Milk and plasma of lactating rats have similar concentrations of nintedanib and its metabolites. **8.3 Females and Males of Reproductive Potential:** Based on findings from animal studies and its mechanism of action, OFEV can cause fetal harm when administered to a pregnant woman and may reduce fertility in females of reproductive potential [see *Use in Specific Populations*]. Counsel patients on pregnancy prevention and planning. **Pregnancy Testing:** Verify the pregnancy status of females of reproductive potential prior to treatment with OFEV and during treatment as appropriate. [see *Dosage and Administration, Warnings and Precautions and Use in Specific Populations*]. **Contraception:** OFEV can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to avoid becoming pregnant while receiving treatment with OFEV. Advise females of reproductive potential to use highly effective contraception during treatment, and for at least 3 months after taking the last dose of OFEV. It is currently unknown whether nintedanib may reduce the effectiveness of hormonal contraceptives, therefore advise women using hormonal contraceptives to add a barrier method. **Fertility:** Based on animal data, OFEV may reduce fertility in females of reproductive potential. **8.4 Pediatric Use:** Safety and effectiveness in pediatric patients have not been established. **8.5 Geriatric Use:** Of the total number of subjects in phase 2 and 3 clinical studies of OFEV in IPF, 60.8% were 65 and over, while 16.3% were 75 and over. In SSC-ILD, 21.4% were 65 and over, while 1.9% were 75 and older. In phase 3 studies, no overall differences in effectiveness were observed between subjects who were 65 and over and younger subjects; no overall differences in safety were observed between subjects who were 65 and over or 75 and over and younger subjects, but greater sensitivity of some older individuals cannot be ruled out. **8.6 Hepatic Impairment:** Nintedanib is predominantly eliminated via biliary/fecal excretion (greater than 90%). In a PK study performed in patients with hepatic impairment (Child Pugh A, Child Pugh B), exposure to nintedanib was increased. In patients with mild hepatic impairment (Child Pugh A), the recommended dosage of OFEV is 100 mg twice daily [see *Dosage and Administration*]. Monitor for adverse reactions and consider treatment interruption, or discontinuation for management of adverse reactions in these patients [see *Dosage and Administration*]. Treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with OFEV

is not recommended [see *Warnings and Precautions*].

8.7 Renal Impairment: Based on a single-dose study, less than 1% of the total dose of nintedanib is excreted via the kidney. Adjustment of the starting dose in patients with mild to moderate renal impairment is not required. The safety, efficacy, and pharmacokinetics of nintedanib have not been studied in patients with severe renal impairment (less than 30 mL/min CrCl) and end-stage renal disease.

8.8 Smokers: Smoking was associated with decreased exposure to OFEV, which may alter the efficacy profile of OFEV. Encourage patients to stop smoking prior to treatment with OFEV and to avoid smoking when using OFEV.

10 OVERDOSAGE: In IPF trials, one patient was inadvertently exposed to a dose of 600 mg daily for a total of 21 days. A non-serious adverse event (nasopharyngitis) occurred and resolved during the period of incorrect dosing, with no onset of other reported events. Overdose was also reported in two patients in oncology studies who were exposed to a maximum of 600 mg twice daily for up to 8 days. Adverse events reported were consistent with the existing safety profile of OFEV. Both patients recovered. In case of overdose, interrupt treatment and initiate general supportive measures as appropriate.

17 PATIENT COUNSELING INFORMATION: Advise the patient to read the FDA-approved patient labeling (*Patient Information*). **Elevated Liver Enzymes and Drug-Induced Liver Injury:** Advise patients that they will need to undergo liver function testing periodically. Advise patients to immediately report any symptoms of a liver problem (e.g., skin or the whites of eyes turn yellow, urine turns dark or brown [tea colored], pain on the right side of stomach, bleed or bruise more easily than normal, lethargy, loss of appetite) [see *Warnings and Precautions*]. **Gastrointestinal Disorders:** Inform patients that gastrointestinal disorders such as diarrhea, nausea, and vomiting were the most commonly reported gastrointestinal events occurring in patients who received OFEV. Advise patients that their healthcare provider may recommend hydration, antidiarrheal medications (e.g., loperamide), or anti-emetic medications to treat these side effects. Temporary dosage reductions or discontinuations may be required. Instruct patients to contact their healthcare provider at the first signs of diarrhea or for any severe or persistent diarrhea, nausea, or vomiting [see *Warnings and Precautions and Adverse Reactions*]. **Embryo-Fetal Toxicity:** Counsel patients on pregnancy prevention and planning. Advise females of reproductive potential of the potential risk to a fetus and to avoid becoming pregnant while receiving treatment with OFEV. Advise females of reproductive potential to use highly effective contraception during treatment, and for at least 3 months after taking the last dose of OFEV. Advise women using hormonal contraceptives to add a barrier method. Advise female patients to notify their doctor if they become pregnant or suspect they are pregnant during therapy with OFEV [see *Warnings and Precautions and Use in Specific Populations*]. **Arterial Thromboembolic Events:** Advise patients about the signs and symptoms of acute myocardial ischemia and other arterial thromboembolic events and the urgency to seek immediate medical care for these conditions [see *Warnings and Precautions*]. **Risk of Bleeding:** Bleeding events have been reported. Advise patients to report unusual bleeding [see *Warnings and Precautions*]. **Gastrointestinal Perforation:** Serious gastrointestinal perforation events have been reported. Advise patients to report signs and symptoms of gastrointestinal perforation [see *Warnings and Precautions*]. **Lactation:** Advise patients that breastfeeding is not recommended while taking OFEV [see *Use in Specific Populations*]. **Smokers:** Encourage patients to stop smoking prior to treatment with OFEV and to avoid smoking when using OFEV. **Administration:** Instruct patients to swallow OFEV capsules whole with liquid and not to chew or crush the capsules due to the bitter taste. Advise patients to not make up for a missed dose [see *Dosage and Administration*].

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CRITICAL CARE COMMENTARY

Neuromuscular blockade for ARDS in the ICU

BY ROBERT C. HYZY, MD, FCCP

The ability to control the delivery of ventilation to patients having the acute respiratory distress syndrome (ARDS) without encountering patient respiratory effort via the administration of neuromuscular blocking drugs has been a potentially appealing therapeutic option for decades (Light RW, et al. *Anesth Analg*. 1975;54[2]:219). This practice had been common in the late 20th century in order to avoid excessive tachypnea and appearance of patient discomfort with the collateral benefit of improving oxygenation and decreasing the fraction of inspired oxygen (Fio₂) (Hansen-Flaschen JH, et al. *JAMA*. 1991;26:2870).

Following the publication by the NIH-sponsored ARDS Network of the landmark low tidal volume lung protective ventilation trial, whereupon study subjects had been allowed to breathe up to 35 times per minute (ARDS Network, *N Engl J Med*. 2000;342[18]:1301) and additional concerns that neuromuscular blockade could potentially be associated with neuromuscular weakness, this practice fell out of favor.

Although the validity of using lung protective ventilation in ARDS, with a plateau pressure of less than 30 cm H₂O via delivery of a low tidal volume, has withstood the test of time, subsequent attempts to utilize methods that would further protect the lung with additional “rescue” approaches to mechanical ventilation led to a partial renaissance of the neuromuscular blockade (NMB) approach. For example, high frequency oscillatory ventilation, with its idiosyncratic delivery of minute volumes of ventilator gas, requires NMB in order to be used. However, the publication of two negative trials, including one demonstrating an increased mortality, sidelined this approach (Ferguson ND, et al. *N Engl J Med*. 2013;368[9]:795).

More notably, the use of NMB in patients with ARDS has been advocated during conventional mechanical ventilation to avoid the generation of large tidal volumes via ventilator asynchrony occurring during patient-triggered breaths. Ostensibly, wiping out any patient effort via NMB eliminates manifestations of asynchrony, such as double triggering, which can generate areas of regional tidal hyperinflation in the injured lung and thereby worsen ventilator-induced lung injury. The utilization of NMB early in the course of ARDS (less than 48 hours) resulted in less lung inflammation (Forel JM, et al. *Crit Care Med*. 2006;34[11]:2749).

Subsequently, the ACURASYS trial found that patients with moderately severe or severe ARDS treated with NMB had a mortality benefit comparable to that seen in the original ARDS low tidal volume trial (Papazian L, et al. *N Engl J Med*. 2010;369:980).

Several criticisms of ACURASYS led to the desire for a larger confirmatory trial be undertaken. The NIH-sponsored successor to the ARDS Network, the Prevention and Early Treatment of

Acute Lung Injury (PETAL) Network, took this on straight away with its formation in 2014 (disclosure: the author is a Principal Investigator of one of the 13 PETAL Network Clinical Centers). This trial, called the Re-Evaluation of Systemic Early Neuromuscular Blockade, the ROSE



Dr. Hyzy

trial, was published last year in the *New England Journal of Medicine* and failed to confirm a mortality benefit to NMB when used early in the course of ARDS, such as had been done earlier (Moss M, et al. *N Engl J Med*. 2019;380[21]:1997).

What then, should clinicians consider the proper use of NMB in ARDS to be? There has been a recent spate of large negative trials of once-promising interventions in critical care medicine (Laffey. *Lancet Respir Med*. 2018;6[9]:659). Among these were trials related to early mobility, vitamin D administration, transpulmonary pressure titrated positive end-expiratory pressure (PEEP), and of course, high frequency oscillatory ventilation, just to name a few disappointments. Recognition of heterogeneity of treatment effect (HTE), with some subgroups being more likely to respond to an intervention than others (Iwashyna. *Am J Respir Crit Care Med*. 2015;192[9]:1045), is cold comfort to the bedside clinician and all but the most dedicated health services researcher. At least to date, personalized medicine has fallen short of prospective validation in ARDS (Constantin et al. *Lancet Respir Med*. 2019;7[10]:870).

The failure of the ROSE trial to demonstrate a mortality benefit to ARDS patients with a P/F ratio of less than 150 on at least 8 cm H₂O treated with early NMB means the routine use of this approach in all such patients isn't warranted. In a prescient nod to HTE, “a foolish consistency,” as Emerson said, “is the hobgoblin of little minds.” Importantly, there were several subtle but not necessarily irrelevant differences between ACURASYS and ROSE. ROSE used a high PEEP algorithm to titrate PEEP to Fio₂, rather than the conventional low PEEP approach used in the original ARDS Network and ACURASYS trials. Potentially, the benefits of NMB on the injured lung in ARDS may have been mitigated by using higher PEEP levels. ROSE also failed to demonstrate a decrease in barotrauma as had been reported earlier. That said, it is difficult to ascribe the lack of benefit of NMB mechanistically to less asynchrony induced regional tidal hyperinflation in the NMB group at high PEEP, especially given the lighter sedation targets employed in both the NMB and the placebo group. Meanwhile, ROSE did confirm patients were not harmed by NMB by resulting in more neuromuscular weakness upon recovery.

Among patients with Berlin severe ARDS (ie. P/F less than 100 on at least 5 cm H₂O PEEP) evaluated between publication of ACURASYS and ROSE, clinicians were far more inclined to use NMB than other rescue modalities, including prone ventilation (Duan, *Ann Am Thorac Soc*. 2017;12:1818).

It seems unlikely the publication of ROSE will alter this. As rescue modalities go, NMB is relatively inexpensive, widely available and easily performed (Co, I and Hyzy RC, *Crit Care Med*. 2019 Dec 18. doi: 10.1097/CCM.0000000000004198).

Ultimately, though the question isn't whether NMB will be used in ARDS patients with refractory hypoxemia early or even later, but whether prone ventilation should be simultaneously initiated at the time of, or even before the institution of NMB.

As in ACURASYS, patients in the landmark PROSEVA prone ventilation trial were treated with a low PEEP algorithm (Guérin C et al. *N Engl J Med*. 2013;368[23]:2159).

Prone ventilation has many salutary physiologic benefits, not the least of which is recruitment of areas of collapsed lung. Patients who are recruitable with PEEP, i.e. whose PaO₂ increases with increasing PEEP in the face of an unchanged or minimally changed plateau pressure, may also demonstrate a mortality benefit (Goligher, EC et al. *Am J Respir Crit Care Med*. 2014;190[1]:70).

It remains unknown whether prone ventilation would remain of significant benefit should a high PEEP approach be employed.

Prone ventilation clearly has its adherents (Albert, RK, *Ann Am Thorac Soc*. 2020;17[1]:24), although underutilization remains prevalent perhaps due to its somewhat cumbersome nature. While it might have been interesting had ROSE performed a simultaneous assessment of prone ventilation along with NMB via a factorial trial design, clinicians remain at the crossroads of how to escalate ventilator support in the ARDS patient with worsening, if not refractory hypoxemia. The use of NMB with a high PEEP approach often allows for recruitment and a concomitant lowering of Fio₂ to acceptable levels in advance of the utilization of prone ventilation. Although some clinicians are able to successfully utilize prone ventilation without NMB, many are not, and NMB use was widespread in PROSEVA.

With no evidence of harm, the employment of NMB in the setting of Berlin severe ARDS is entirely justifiable, whether occurring early or late in the clinical course, regardless of, or potentially with the concomitant employment of prone ventilation. These two rescue modalities remain first line and, despite evidence to the contrary (Li, et al. *Am J Respir Crit Care Med*. 2018;197[8]:991) should be employed in advance of others, most notably extracorporeal support.

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Thank you to the CHEST 2020 Scientific Program Committee

The CHEST 2020 Scientific Program Committee has been working tirelessly to select the best and most clinically relevant sessions for the upcoming meeting. CHEST would like to extend a heartfelt thank you to all who actively participated in grading, curriculum group calls, the live meeting in February, and all the homework in between. We're not done, but your work has been instrumental in making the CHEST Annual Meeting 2020 a success.



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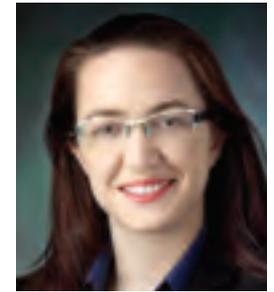
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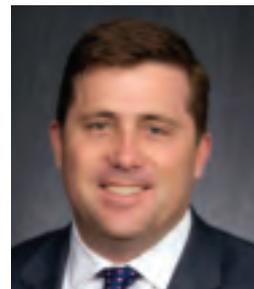
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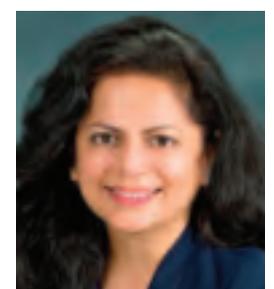
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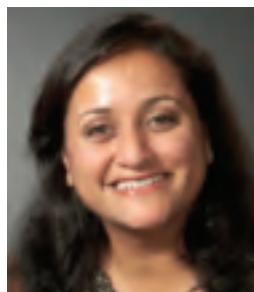
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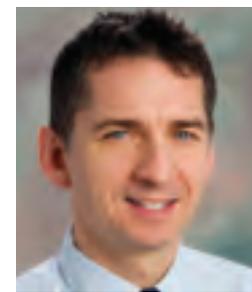
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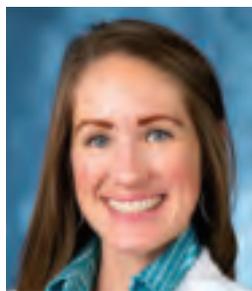
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Meet the 2019 FISH Bowl finalists

CHEST 2019 marked the inaugural FISH Bowl competition for attendees. Inspired by Shark Tank, our kinder, gentler, yet still competitive and cutting-edge FISH Bowl (Furthering Innovation and Science for Health) featured CHEST members disrupting our beliefs about how clinical care and education are performed. As health-care providers, they presented innovative ideas pertaining to education and clinical disease for pulmonary, critical care, and sleep medicine.

Six finalists were chosen from dozens of submissions, and three emerged winners! In this new Meet the FISH Bowl Finalists series, CHEST introduces you to many of them – including Education Category Finalist Dr. Bhavani.

Name: Siva Bhavani

Institution: University of Chicago

Position: Pulmonary Critical Care Fellow

Title: Quizomics

Brief summary: Quizomics is a cutting-edge mobile app that hosts

trivia competitions for medical conferences. Quizomics is unlike any medical trivia competition you have ever seen, because the Quizomics app can host 20,000 medical professionals simultaneously competing in the world's largest medical trivia competition. Physicians compete among thousands of peers in their respective specialties to prepare for boards, obtain CME, and gain recognition in their fields as they fight their way to the top of the leaderboard!

1. What inspired your innovation?

The average person checks their phone every 12 minutes, and this is no different at medical conferences. Whether you are in line for coffee, looking around at posters, or listening to a lecture - very little time passes before you are again checking your phone. The natural engagement we have with our phones can be leveraged for educational purposes by introducing gamified medical education platforms like Quizomics. I was inspired because the future of the medical confer-

ence demands digital engagement, gamified education, and large-scale social interaction. There is currently no platform that offers these services to prepare medical conferences for the digital education revolution that is coming.

2. Who do you think can benefit most from it, and why? The highest benefit is going to be to the physicians who are tired of the traditional CME options. Quizomics provides a high quality entertaining and educational platform for physicians to get CME while engaging and interacting with their peers. Further, physicians preparing for boards will find Quizomics an engaging alternative to the traditional textbooks. Finally, medical conferences will find that Quizomics can increase engagement, education, and attendance.

3. What do you see as challenges to your innovation gaining widespread acceptance? How can they be overcome? Content creation (trivia questions and explanations) is the biggest challenge to Quizom-

ics. To overcome this, we plan to partner with tech-forward medical organizations that have high quality question banks in order to provide physicians with top-notch gamified education.

4. Why was it meaningful for you to emerge as a finalist in FISH Bowl 2019? FISH Bowl was an amazing opportunity to present Quizomics to others in the pulmonary/critical care specialty. Further, it was an opportunity to get direct feedback from leading educators in the field, and much of the resulting feedback has been incorporated into Quizomics.

5. What future do you envision for your innovation beyond FISH Bowl 2019? Quizomics is launching at a national neurosurgery board review course this winter. Following this pilot launch, Quizomics is scheduled for roll-out at Chicago area internal medicine residency programs through the summer of 2020. You can expect to see Quizomics at national conferences by 2021!

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CHEST Foundation and Feldman Family Foundation Casino Night promises fun for a good cause

Keeping the momentum from our first-ever CHEST Foundation Reception and Casino Night at CHEST 2019, where champions in attendance raised more than \$35,000 for pulmonary fibrosis research, the CHEST Foundation continues their long-standing partnership with the Feldman Family Foundation and invites you to the 7th Annual Irv Feldman Texas Hold 'Em Annual Tournament & Casino Night!

Funds raised at the event support the CHEST Foundation's mission-based programming and directly impact patients living with pulmonary fibrosis by providing them with access to chest medicine experts; assistance in securing medication and portable oxygen; and empowering the patients and their clinicians to better manage their disease.

Join us at 6:00 PM on Saturday, March 7, at Chevy Chase Country Club in Wheeling, Illinois, for an exciting evening of play. The grand prize winner of the poker tournament receives a coveted seat at the World Series of Poker Main Event – allowing them to test their mettle against the world's best players. We will also be hosting a plethora of other casino games like blackjack, craps, and roulette and an ever-expanding silent auction giving everyone a chance to join in on the fun and contribute to the fight against pulmonary fibrosis.

Interested in sponsoring the event, purchasing tickets, or receiving more information about the tournament? Contact Angela Perillo, Director of Development and Foundation Operations, at aperillo@chestnet.org.

Hope to see you March 7th!

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