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"Having a mutation of some kind that is actionable is very common in adenocarcinoma," said Dr. Mark G. Kris, FCCP.

Lung Cancer Rx Guided By Mutation Testing

BY PATRICE WENDLING
Elsevier Global Medical News

CHICAGO – The newly minted Lung Cancer Mutation Consortium detected a driver mutation in 54% of lung adenocarcinoma tumors, allowing clinicians to use the information in real time to select erlotinib as initial therapy or to direct patients to trials targeting their specific mutation.

The collaborative effort points to the revolutionary changes taking place in the management of lung adenocarcinoma and the potential for personalized treatment in routine practice.

"While an individual mutation may be quite rare, having a mutation of some kind that is actionable is very common in adenocarcinoma," said Dr. Mark G. Kris, FCCP, who presented the findings at the annual meeting of the American Society of Clinical Oncology (ASCO).

Earlier this year, the National Comprehensive Cancer Network and ASCO recommended epidermal growth factor receptor (EGFR) mutation testing to identify patients with advanced non–small cell lung cancer (NSCLC) who may benefit from EGFR tyrosine kinase inhibitors such as erlotinib (Tarceva) and gefitinib (Iressa). Adenocarcinoma is the most common form of NSCLC, accounting for up to 50% of cases in the United States.

Dr. Kris said new mutations can be quickly added to the testing process and that they plan to maintain and expand the scope of the consortium when federal funding ends for the National Cancer Institute–sponsored initiative made up of 14 cancer centers across the country.

"I think this can serve as a model for other institutions developing similar programs in lung cancer and for other cancers," said Dr. Kris, chief of thoracic oncology at Memorial Sloan-Kettering Cancer Center in New York.

See **Lung Cancer** • *page 4*

Sleep Debt Takes Toll in Many Aspects of Life

ADHD, weight, relationships affected.

BY DIANA MAHONEY
Elsevier Global Medical News

MINNEAPOLIS – The effects of insufficient shut-eye extend across multiple domains, according to a collection of independent studies presented at this year's annual meeting of the Associated Professional Sleep Societies.

For example, sleep loss was linked to the development or exacerbation of symptoms of ADHD in early childhood, an individual's genetic risk of obesity, inhibitory response to images of high-calorie foods, and even marital discontent.

ADHD and Sleep Loss

In a study designed to tease out the complex relationship between sleep problems – particularly falling asleep and staying asleep – and the development or worsening of inattention and hyperactivity and impulsivity in children and adolescents diagnosed with ADHD, Erika Gaylor, Ph.D., of SRI International in Menlo Park, Calif., and her colleagues analyzed data from the preschool and kindergarten waves of the Early Childhood Longitudinal Study–Birth Cohort. The cohort comprises a representative sample of approximately 6,860 children and their families living the United States.

The investigators calculated total nighttime sleep duration based on parent-reported bedtime and wake time, and assessed children's behavior using brief measures of attention and task persistence, Dr. Gaylor reported. "We performed two sets of regression analyses to identify whether sleep duration in preschool-age children predicts attention and hyperactivity at kindergarten entry and [whether] attention and hyperactivity symptoms at

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INSIDE

Kids' Empyema Resolves by 6 Months

BY BRUCE JANCIN
Elsevier Global Medical News

What can you tell parents they can reasonably expect after their child with empyema gets discharged from the hospital?

Clinically important sequelae commonly persist in the first month after discharge but resolve in almost all cases by 6 months. And the rare patient who has lingering significant abnormalities on chest x-ray or spirometry 6 months after leaving the hospital can expect them to normalize by 1 year, according to a prospective Canadian study.

"Long-term [sequelae] are uncommon. This information may aid decision making for clinicians and families balancing the risks and benefits of interventions," Dr. Eyal Cohen observed.

The findings in this observational study take on added clinical relevance because the incidence of complicated pneumonia, or empyema, is increasing throughout the world, particularly in younger children.

See **Empyema** • *page 15*

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IASLC Embraces CT Screening of Heavy Smokers

BY MITCHEL L. ZOLER
Elsevier Global Medical News

AMSTERDAM – The International Association for the Study of Lung Cancer has issued a call for physicians to discuss lung cancer screening with patients who match the high-risk smoking history of the people enrolled in the landmark National Lung Screening Trial.

The National Lung Screening Trial (NLST) showed that an annual, low-dose CT chest scan can lead to significant reductions in lung cancer deaths and overall mortality in patients aged 55-74 years who smoked for at least 30 pack-years and, if former smokers, quit within the prior 15 years (N. Engl. J. Med. 2011 [doi: 364:10.1056/NEJMoa1102873]).

Based on these unprecedented findings, the International Association for the Study of Lung Cancer (IASLC)'s position-writing committee issued a call for physicians to discuss the data and its implications with such patients.

"It is appropriate for heavy smokers ages 55 to 74 to discuss relevant lung cancer screening information with their physicians to assist them in deciding whether to undergo spiral CT screening," said the statement, issued as IASLC started its world conference.

Although some committee members, including the chairman, urged caution when routinely discussing screening with the target population before the cost effectiveness of this approach is proven, two of the Americans on the 10-member position-statement writing committee endorsed immediately offering screening to fully informed people who match the study's screening profile.

"For patients with metastatic lung cancer, the cure rate is essentially zero. Finding lung cancer early is the best way to deal with this disease, and that's why this is such an extraordinary result," said Dr. Roy S. Herbst, a member of the task force and chief of medical oncology at Yale University in New Haven, Conn.

"Even with all the cautions, I think that in the United States at least you'll see screening, especially since the NLST was largely sponsored by the National Cancer Institute. Assuming that the CMS [Centers for Medicare and Medicaid Services] and insurers will pick this up, I think [screening] is something we're going to see. I think there will be great pressure in the United States for this to be covered, at a cost of about $300-$400 per scan.

"At Yale, we'll start screening people who meet the enrollment criteria for the trial, as will several other U.S. centers. We'll offer screening with all the caveats," including informing patients about the risks they will face from screening, their need to stop smoking, their need for ongoing screening, and the need to have a multidisciplinary team in place at the screening site to deal with all the possible consequences of screening, Dr. Herbst said at the World Conference on Lung Cancer.

"We know there is effectiveness from screening, but is there cost effectiveness? Is there value?" asked Dr. Richard Gralla, another member of the statement-writing committee and chief of hematology-oncology at North Shore University Medical Center and Long Island Jewish Medical Center in New Hyde Park, N.Y.

'Finding lung cancer early is the best way to deal with this disease.'

DR. HERBST

"My prediction is that screening will not only be shown to be cost effective, but it will be *very* cost effective. It will also be very expensive" to run annual screens on the millions of middle-aged smokers who meet the trial's screening profile, he added. The NLST report estimated that 7 million Americans match the age and smoking history of the people enrolled in the trial.

By thrusting medicine into a new era of routine lung cancer screening, these developments will trigger creation of a new system of quality oversight for lung cancer screening that will likely follow the model of breast cancer screening.

"There is a laundry list of requirements that will need to be established by the institutions that want to do CT screening," said Dr. Denise R. Aberle, professor of radiology at the University of California, Los Angeles, and a collaborator on the NLST. "That will likely evolve into a form of accreditation to better guarantee quality assurance, as with breast cancer screening." Dr. Aberle also noted that the NLST researchers collected cost-effectiveness data, and that they will soon release a report on their analysis of those data.

Routine lung cancer screening will also place new responsibilities on the thoracic surgeons who follow up on suspicious lung lesions found though screening, most of which will not be cancers.

"For surgeons it will be a very large challenge to offer correct treatment to patients with very small cancers," said Dr. Jesper Pedersen, a thoracic surgeon at Copenhagen University Hospital. "We're planning on writing guidelines for surgeons, because they will be at risk by operating on so many patients without lung cancer." The NLST results showed that 96% of suspicious lesions identified by CT screening were not cancers.

"There is potential for physical and psychiatric harm from cancer screening, but the results from many studies of breast cancer screening have shown that the benefits of screening outweigh its harms," said Dr. David R. Gandara, IASLC president and professor of medicine and director of the thoracic oncology program at the University of California, Davis, in Sacramento.

"We're in the early days of screening for lung cancer, and we must do everything to make sure that screening is done appropriately and that follow-up is appropriate. But our message to patients about screening is positive. We can't overemphasize that," Dr. Gandara said.

Dr. Herbst said that he has been a consultant to, on the advisory boards of, and received research grants from several pharmaceutical companies, including Genentech, Boehringer Ingelheim, Sanofi-Aventis, Pfizer, and ImClone. Dr. Gralla and Dr. Aberle had no relevant disclosures. Dr. Pedersen said that he has been on the speakers bureau for Eli Lilly and Roche and received grant support from AstraZeneca. Dr. Gandara said that he has been a consultant to or received research support from several pharmaceutical companies, including AstraZeneca, GlaxoSmithKline, Genentech, Merck, and Novartis. ■

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CHEST PHYSICIAN

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CT Lung Cancer Screening Raises Policy Questions

BY KERRI WACHTER
Elsevier Global Medical News

VITALS

Major Finding: Low-dose CT screening reduced the relative rate of death from lung cancer by 20%, compared with chest x-ray screening.

Data Source: A study of 53,454 Americans aged 55-74 years, who were current or former smokers with a smoking history of at least 30 pack-years.

Disclosures: All but two of the NLST study authors reported that they have no relevant financial relationships. Jonathan Clap reported having financial interest in Human Genome Sciences. Constantine Gatsonis is a consultant for Wilex AG, Mela Sciences, and Endocyte, has received speaker fees from Bayer Health, and payment for education development by the Radiologic Society of North America. He also has invested in the Vanguard Health Fund. Dr. Sox had no conflicts.

Final results from the National Lung Screening Trial show a significant reduction in lung cancer mortality with the use of annual low-dose CT screening, compared with standard chest x-rays, among former heavy smokers at high risk for lung cancer.

Low-dose CT screening led to a relative reduction of 20% in the rate of death from lung cancer, according to findings released online by the New England Journal of Medicine on June 29 (doi: 10.1056/NEJMoa1102873).The number needed to screen with low-dose CT to prevent one death from lung cancer was 320.

Although preliminary study results were announced in November 2010, the article by the National Lung Screening Trial (NLST) research team marks the first time that the results appear in a peer-reviewed journal. Acknowledging that the earlier announcement has led to calls for lung cancer screening, the authors urge rigorous analysis of cost-effectiveness before public policy recommendations are made.

"The reduction in lung-cancer mortality must be weighed against the harms from positive screening results and overdiagnosis, as well as the costs," they wrote.

In the study, 53,454 men and women aged 55-74 years – who were current or former smokers with a smoking history of at least 30 pack-years – were recruited at 33 U.S. medical centers. A total of 26,722 participants were randomized to receive three annual screens with low-dose helical CT; 26,732 were randomized to three annual screens using chest x-ray. The two groups were virtually identical in demographics and smoking history.

In all three screening rounds, positive screening tests were substantially more common in the low-dose CT group than in the radiography group (27.3% vs. 9.2% in the first round; 27.9% vs. 6.2% in the second; and 16.8% vs. 5% in the third). All told, 39.1% of the CT group and 16% of the radiography group had at least one positive result.

The percentage of screening tests that identified a clinically significant abnormality – other than an abnormality suspicious for lung cancer – also was more than three times as high in the low-dose CT group as in the radiography group (7.5% vs. 2.1%).

More than 90% of positive screenings in the first round of the study led to a diagnostic evaluation, though the follow-up rates were lower in the later rounds. Diagnostic evaluation most often consisted of additional imaging with invasive procedures being performed infrequently.

Across the three screenings, most of the positive results were false positives – 96.4% in the CT group and 94.5% in the radiography group. Of the total number of low-dose CT screening tests, 24.2% were classified as positive and 23.4% had false-positive results; of the total number of radiographic screening tests, 6.9% were classified as positive and 6.5% were false-positive results.

In all, 1,060 lung cancers were diagnosed in the low-dose CT group (645/100,000 person-years) vs. 941 in the radiography group (572/100,000 person-years). Of these cancers, 649 in the low-dose CT group were diagnosed after a positive screening test and 44 were diagnosed after a negative screening test. In the radiography group, 279 cancers were diagnosed after a positive screening test and 137 were diagnosed after a negative screening test.

In both groups, the remaining cases were among participants who missed screening or were diagnosed after their trial screening phase was over.

Analysis of lung cancer–specific mortality showed that in the CT group, 356 lung cancer deaths occurred after 144,103 person-years; in the radiography group, 443 lung cancer deaths occurred after 143,368 person-years. This corresponded to 247 and 309 lung cancer deaths, respectively, per 100,000 person-years in the CT and radiography groups.

There were 1,877 and 2,000 deaths from all causes in the CT and radiography groups, respectively, "representing a significant reduction with low-dose CT screening of 6.7% … in the rate of death from any cause," the investigators wrote. While lung cancer accounted for 24.1% of all the deaths in the trial, 60.3% of the excess deaths in the radiography group were due to lung cancer.

The authors concluded that "although some agencies and organizations are contemplating the establishment of lung-cancer screening recommendations on the basis of the findings of the NLST, the current NLST data alone are, in our opinion, insufficient to fully inform such important decisions."

They noted that "the observation that low-dose CT screening can reduce the rate of death from lung cancer has generated many questions." Among these they listed: Will populations with different risk profiles benefit from screening? Could less-frequent screening programs be equally effective? Would the use of different criteria for a positive screening result translate to similar benefit? For how long should people be screened?

In an editorial, Dr. Harold C. Sox, professor of medicine at the Dartmouth Institute in Hanover, N.H., agreed with the investigators' reservations. In particular, "policy makers should wait for cost-effectiveness analyses to determine the amount of overdiagnosis in the NLST and, perhaps, identification of biologic markers of cancers that do not progress."

In addition, "it may be possible to define subgroups of smokers who are at higher or lower risk for lung cancer and tailor the screening strategy accordingly," he said. "The findings of the NLST regarding lung-cancer mortality signal the beginning of the end of one era of research on lung-cancer screening and the start of another. The focus will shift to informing the difficult patient-centered and policy decisions that are yet to come."

Dr. Sox also noted that "overdiagnosis is a problem because predicting which early-stage cancers will not progress is in an early stage of development, so that everyone with screen-detected cancer receives treatment that some do not need" (N. Engl. J. Med. 2011 June 29 [doi: 10.1056/NEJME1103776]). ■

VATS, Open Lobectomy Similar for Early Lung Cancer

BY MITCHEL L. ZOLER
Elsevier Global Medical News

AMSTERDAM – Video-assisted thoracoscopic surgery worked as well as open lobectomy for 5-year survival in early-stage lung cancer, based on a secondary analysis of nonrandomized patients who underwent surgery as part of a multicenter trial.

"These data demonstrate that VATS, when properly done, can achieve long-term survival that is similar to open lobectomy," Dr. Walter J. Scott, FCCP, said at the World Conference on Lung Cancer. He stressed that the study included only patients with early-stage lung cancer that was node negative or was nonhilar N1 disease, and hence the finding is specific for only these patients. Until now, questions existed about the oncologic efficacy of VATS, noted Dr. Scott, chief of the division of thoracic surgery at Fox Chase Cancer Center in Philadelphia. But "VATS lobectomy provides comparable oncologic outcomes" for this group of patients, he said.

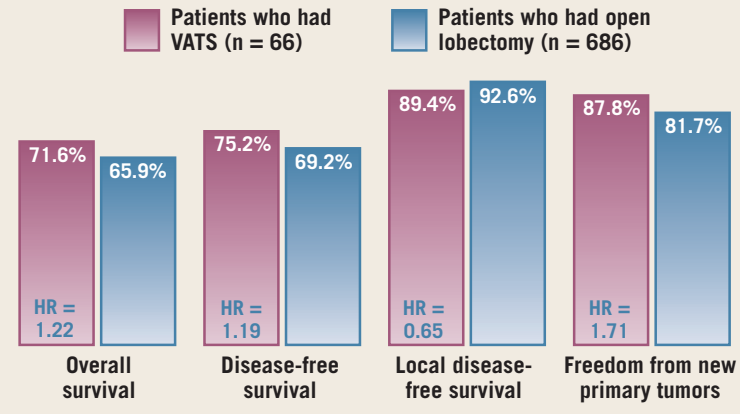
His analysis used data collected from 964 lung cancer patients who participated in a multicenter study during 1999-2004 that compared two different strategies for lymph node assessment in early-stage lung cancer (Ann. Thorac. Surg. 2006; 81:1013-20). Although most surgeons did not perform VATS during this time, a few surgeons did, and 5-year outcome results were available for 66 patients in the study underwent VATS. Five-year data also existed for 898 of the patients who underwent open lobectomy.

In order to adjust for baseline differences among the patients, Dr. Scott and his associates ran a propensity score analysis that took into account age, sex, performance status, tumor histology, location, and tumor size and invasion. The analysis excluded about a fifth of the open lobectomy patients because their propensity scores fell outside the range of the VATS patients, so the final survival comparison included 66 VATS and 686 open lobectomy patients.

With propensity adjustment, the results showed no significant differences between the VATS and open lobectomy patients in their 5-year rates of overall survival, disease-free survival, local disease-free survival, or freedom from new primary tumors (see table), Dr. Scott reported at the meeting, which was sponsored by the International Association for the Study of Lung Cancer.

Dr. Scott said that he is a shareholder in Biogen Idec, Celgene, and Johnson & Johnson. ■

VATS and Open Lobectomy Compared
(5-year risk-adjusted measures)



Notes: All patients underwent surgery for early-stage, node-negative, or nonhilar N1 lung cancer. HR = hazard ratio (VATS:open lobectomy).
Source: Dr. Scott

ELSEVIER GLOBAL MEDICAL NEWS

Trial Upholds Erlotinib Use in EGFR-Mutant Lung Cancer

The objective response rate was 58% for erlotinib vs. 15% for chemotherapy.

BY PATRICE WENDLING
Elsevier Global Medical News

CHICAGO – Data from the prospective, phase III EURTAC trial cement the need for personalized treatment of lung cancer patients but also leave clinicians in uncharted waters in terms of treatment options.

First-line erlotinib (Tarceva) improved the primary end point of progression-free survival from 5.2 months with standard platinum-based chemotherapy to 9.4 months in white patients who had advanced non–small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutations, in an interim analysis.

Study cochair Dr. Rafael Rosell, president of the Spanish Lung Cancer Group, reported a significant 63% reduction in the risk of progression (hazard ratio, 0.37; log-rank *P* less than .0001) in an updated analysis presented at the annual meeting of the American Society of Clinical Oncology.

'IS THERE A DIFFERENCE IN TERMS OF THE EFFECTIVENESS BETWEEN THE [TYROSINE KINASE INHIBITORS] IN PATIENTS WITH EGFR MUTATIONS?'

Based on positive results in the earlier interim analysis, Genentech and partner OSI Pharmaceuticals announced in January that the trial had been halted and they were set to pursue a broader indication for erlotinib as first-line treatment in NSCLC with EGFR mutations.

Erlotinib, a tyrosine kinase inhibitor (TKI), is approved in the United States and Europe as a maintenance and second-line treatment for advanced or metastatic NSCLC with and without EGFR-activating mutations. Genentech's parent company, Roche, submitted a bid to the European Medicines Agency in June 2010 to expand the drug's label.

Even though the proverbial cat had already been let out of the bag by the drug makers, EURTAC caused a stir at ASCO, where the full data were formally presented and the study was chosen as one of the Best of ASCO 2011.

Invited discussant Dr. Tony Mok of the Chinese University of Hong Kong called the data trustworthy and a true reflection of erlotinib's efficacy in patients with EGFR mutations. He drew parallels between EURTAC and the OPTIMAL trial in which erlotinib proved potent among Asians with this genetically distinct form of lung cancer. EGFR mutations are present in about 10% of patients in the West and about 30% of Asians, and they are associated with an increased response to erlotinib and the TKI gefitinib (Iressa).

Dr. Mok said that there's a good chance erlotinib will be approved as first-line therapy. The EURTAC data are on par with the IPASS trial that helped gain approval for gefitinib as first-line therapy for patients with EGFR mutations in more than 70 countries, except the United States, where gefitinib use is restricted, and AstraZeneca has said it will not seek a new indication for the drug.

"Now we have two drugs," said Dr. Mok, principal investigator of IPASS. "What are we going to do when faced with an EGFR mutation? Is there a difference in terms of the effectiveness between the TKIs in patients with EGFR mutations? That is the million-dollar question or the billion-dollar question."

Dr. Mok pointed out that three other TKIs are in the pipeline for patients with EGFR mutations, including icotinib (Zhejang BetaPharma); afatinib (Boehringer Ingelheim), which binds EGFR and inhibits HER2; and the oral, once-daily PF-299804 (Pfizer). A poster presented at ASCO on the phase III ICOGEN trial reported that icotinib provides similar overall efficacy and better tolerability than gefitinib in patients with NSCLC who progressed after one to two lines of chemotherapy; it also improved efficacy in a subset of EGFR-mutant patients.

VITALS

Major Finding: Erlotinib resulted in a significant 63% reduction in the risk of progression, compared with standard chemotherapy (HR 0.37).

Data Source: Phase III, prospective randomized EURTAC trial in 174 white patients with advanced non–small cell lung cancer and EGFR mutations.

Disclosures: The Spanish Lung Cancer Group sponsored the trial. Dr. Rosell disclosed a consultant/advisory role with Roche. Two of his coauthors reported a similar role, with one also providing expert testimony for Roche. Dr. Mok disclosed relationships with several drug companies, including AstraZeneca, Roche, Boehringer Ingelheim, and Pfizer.

The EURTAC trial randomly assigned 174 chemo-naive, stage IIIB/IV NSCLC patients with exon 19 deletions or L858R mutations to receive erlotinib 150 mg/day or platinum-based doublet chemotherapy every 3 weeks for four cycles. The doublet could include cisplatin 75 mg/m^2 on day 1 plus docetaxel 75 mg/m^2 on day 1; cisplatin 75 mg/m^2 on day 1 plus gemcitabine 1,250 mg/m^2 on days 1 and 8; carboplatin area under the curve (AUC) 6 on day 1 plus docetaxel 75 mg/m^2 on day 1 or carboplatin AUC 5 on day 1 plus gemcitabine 1,000 mg/m^2 on days 1 and 8.

The objective response rate was 58% for erlotinib vs. 15% for chemotherapy in the updated analysis, said Dr. Rosell, head of medical oncology at the Catalan Institute of Oncology in Barcelona. At the time of the interim analysis, two patients had a complete response to erlotinib and 40 had partial responses, with 8 additional partial responses reported in the updated analysis. No patient had a complete response with chemotherapy, eight patients had partial responses early on, and five more reported partial responses in the updated analysis.

The disease control rate in the interim analysis was 79% for erlotinib vs. 66% in the updated analysis.

Median overall survival was 18.8 months with chemotherapy and 22.9 months in the interim analysis (hazard ratio, 0.80; log rank $P = .42$). As of the Jan. 26, 2011, cutoff date for the updated analysis, 94 patients remain in overall survival follow-up, with a high level of known crossover, Dr. Rosell said. A subgroup analysis suggested that progression-free survival was better in patients with a performance status of 0, never-smokers, and those with an exon 19 deletion.

The majority of patients who relapsed on erlotinib were switched to chemotherapy. The tolerability of erlotinib was consistent with previous studies, he noted. ■

Testing Directed Therapy

Lung Cancer • *from page 1*

A total of 1,234 patients with stage IV lung adenocarcinoma agreed to undergo testing for 10 known mutations using standard multiplexed assays and fluorescence in situ hybridization. Inadequate tissue in 170 patients (14%) resulted in a study group of 1,064 patients. Mutations were identified in 280 (54%) of 516 tumor specimens tested to date (95% confidence interval 50%-59%).

As suspected, the most common mutations were KRAS (22%), EGFR (17%), and EML4-ALK rearrangement (7%), Dr. Kris said. Other mutations were BRAF (2%), PIK3CA, HER2, MET amplification, MEK1, NRAS, and AKT1.

The vast majority (97%) of mutations were mutually exclusive. Of the 14 double-mutant tumors, the two molecular lesions most commonly seen together were MET amplification and PIK3CA, he said.

Four sites had testing available prior to the study, with seven additional sites now able to provide multiplex mutation testing. Preliminary data from 121 patients enrolled at a single site show that driver mutations were found in 60 (59%) of 102 patients in whom testing was completed. That information was used to direct therapy in 35 patients – 19 to receive erlotinib up front and 16 to go on a trial of an agent targeting their specific mutation.

"In truth, we used it for every patient because when we did not find an EGFR mutation, we did not give them erlotinib," Dr. Kris said.

The turnaround time for mutational testing varied by site, but generally took only a few days. The great majority of time is in specimen acquisition, preparation, and submission to the molecular lab.

"Those are formidable obstacles that we all have to face," Dr. Kris said. "But I think with programs like this, we'll get over those."

Invited discussant Dr. Ramaswamy Govindan, a professor of medicine at Washington University in St. Louis, said EGFR mutation testing is ready for routine clinical use and that EML4 ALK fusion testing will soon be ready. He pointed out that there are more than 15,000 NSCLC mutations alone in the Catalog of Somatic Mutations in Cancer database and that many questions remain, including the cost-effectiveness of mutational testing.

"It's important to remember that not all mutations are created equal," he said.

Dr. Govindan described the most important aspect of the presentation as the linking of the consortium to targeted clinical trials. Last year he was coauthor of a review that found only 8% of nearly 500 ongoing clinical trials in NSCLC used biomarkers for patient selection (J. Thorac. Oncol. 2010;5:1116-9). He contrasted that study with the observation that no fewer than 112 drugs were discussed at this year's Targeted Therapies in Lung Cancer meeting.

'IN TRUTH, WE USED [TEST RESULTS] FOR EVERY PATIENT BECAUSE WHEN WE DID NOT FIND AN EGFR MUTATION, WE DID NOT GIVE THEM ERLOTINIB.'

Some of the agents being evaluated in trials linked to the consortium include crizotinib for EML4-ALK rearrangements, tivantinib plus erlotinib for KRAS mutations, erlotinib plus the investigational agents OSI 906 or MM 121 for EFGR mutations, and an afatinib trial targeting HER2 led by Dr. Kris. Full information on ongoing clinical trials can be found at the consortium's website at www.golcmc.com.

The Lung Cancer Mutation Consortium was funded by an American Recovery and Relief grant. Dr. Kris reported consulting for ArQule, Boehringer Ingelheim, Chugai Pharma, and Pfizer. Dr. Govindan reported consulting for Taiho and receiving honoraria from AstraZeneca, Boehringer Ingelheim, and GlaxoSmithKline. ■

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INDICATIONS AND USAGE

- TEFLARO is indicated for the treatment of **community-acquired bacterial pneumonia (CABP)** caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Streptococcus pneumoniae* (including cases with concurrent bacteremia), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Escherichia coli*.
- TEFLARO is also indicated for the treatment of **acute bacterial skin and skin structure infections (ABSSSI)** caused by susceptible isolates the following Gram-positive and Gram-negative microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and -resistar isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*.
- To reduce the development of drug-resistant bacteria and maintain the effectiveness of TEFLARO and other antibacterial drugs, TEFLARO should be used to treat only ABSSSI or CABP that are proven or strongly suspected to be caused by susceptible bacteria.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Hypersensitivity Reactions

- Serious and occasionally fatal hypersensitivity (anaphylactic) reactions and serious skin reactions have been reported with beta-lactam antibacterials. Before therapy with TEFLARO is instituted, careful inquiry about previous hypersensitivity reactions to other cephalosporin penicillins, or carbapenems should be made. If this product is to be given to a penicillin- or other beta-lactam-allergic patient, caution should be exercised because cross sensitivity among beta-lactam antibacterial agents has been clearly established.
- If an allergic reaction to TEFLARO occurs, the drug should be discontinued. Serious acute hypersensitivity (anaphylactic) reactions require emergency treatment with epinephrine and other emergency measures that may include airway management, oxygen, intravenous fluids, antihistamines, corticosteroids, and vasopressors as clinically indicated.

Clostridium difficile-associated Diarrhea

- *Clostridium difficile*-associated diarrhea (CDAD) has been reported for nearly all systemic antibacterial agents, including TEFLARO, and ma range in severity from mild diarrhea to fatal colitis. Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents. If CDAD is suspected or confirmed, antibacterials not directed against *C. difficile* should be discontinued, if possible.

Broad-spectrum coverage for treating CABP and ABSSSI

Bactericidal Activity Against a Broad Spectrum of Gram-positive and Gram-negative Pathogens, Including *S. pneumoniae* in CABP and MRSA in ABSSSI[1]

Proven efficacy in 2 common infections
in patients admitted to the hospital[1,2]

CABP | **ABSSSI**

- **Convenient q12h dosing in CABP and ABSSSI[1]**
  - **600 mg intravenous over 1 hour**
  - **Treatment duration**
    - **5-7 days for CABP**
    - **5-14 days for ABSSSI**

IMPORTANT SAFETY INFORMATION

Direct Coombs' Test Seroconversion

- Seroconversion from a negative to a positive direct Coombs' test result occurred in 120/1114 (10.8%) of patients receiving TEFLARO and 49/1116 (4.4%) of patients receiving comparator drugs in the four pooled Phase 3 trials. No adverse reactions representing hemolytic anemia were reported in any treatment group. If anemia develops during or after treatment with TEFLARO, drug-induced hemolytic anemia should be considered. If drug-induced hemolytic anemia is suspected, discontinuation of TEFLARO should be considered and supportive care should be administered to the patient if clinically indicated.

Development of Drug-Resistant Bacteria

- Prescribing TEFLARO in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Please see additional Important Safety Information throughout and brief summary of Prescribing Information on last page of this advertisement.

Teflaro®
(ceftaroline fosamil) for injection
600 mg • 400 mg

Demonstrated efficacy in CABP

TEFLARO CABP Study Designs[1,3]

Type of trial: Two randomized, multicenter, multinational, double-blind, noninferiority trials

Study population: 1231 adults with a diagnosis of CABP

Comparative agents: TEFLARO – 600 mg administered IV over 1 hour every 12 hours for 5-7 days;
Ceftriaxone – 1 g ceftriaxone administered IV over 30 minutes every 24 hours for 5-7 days

Adjunctive therapy: CABP Trial 1, two doses on Day 1 of oral clarithromycin 500 mg every 12 hours;
CABP Trial 2, no adjunctive macrolide therapy

TEFLARO Study Populations

Day 4 Population (mITT)*		A microbiological intent-to-treat population (mITT population) containing only subjects with a confirmed bacterial pathogen at baseline.
Test of Cure (TOC) Populations†		
MITT	Modified Intent-to-treat	All randomized subjects who received any amount of study drug.
MITTE	Modified Intent-to-treat Efficacy	All subjects in the MITT population who were in PORT Risk Class III or IV at baseline.
CE	Clinically Evaluable	All subjects in the MITTE population who demonstrated sufficient adherence to the protocol. Sufficient adherence is defined as patients who met the minimal disease criteria for CABP and for whom sufficient information regarding the CABP was available to determine the patient's outcome.
ME	Microbiologically Evaluable	All subjects in the CE population who had at least one typical bacterial pathogen identified at baseline from an appropriate microbiological specimen (eg, blood, sputum, or pleural fluid).

* To evaluate the treatment effect of ceftaroline, an analysis was conducted in CABP patients for whom the treatment effect of antibacterials may be supported by historical evidence. This analysis endpoint required subjects to meet sign and symptom criteria at Day 4 of therapy: a responder had to both (a) be in stable condition according to consensus treatment guidelines, and (b) show improvement from baseline on at least one symptom of cough, dyspnea, pleuritic chest pain, or sputum production, while not worsening on any of these four symptoms.

†The protocol-specified analyses included clinical cure rates at the TOC (8 to 15 days after the end of therapy) in the coprimary MITTE and CE populations and clinical cure rates at TOC by pathogen in the ME population.

INDICATION AND USAGE

- TEFLARO is indicated for the treatment of **community-acquired bacterial pneumonia (CABP)** caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Streptococcus pneumoniae* (including cases with concurrent bacteremia), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Escherichia coli*.
- To reduce the development of drug-resistant bacteria and maintain the effectiveness of TEFLARO and other antibacterial drugs, TEFLARO should be used to treat only CABP that is proven or strongly suspected to be caused by susceptible bacteria.

IMPORTANT SAFETY INFORMATION

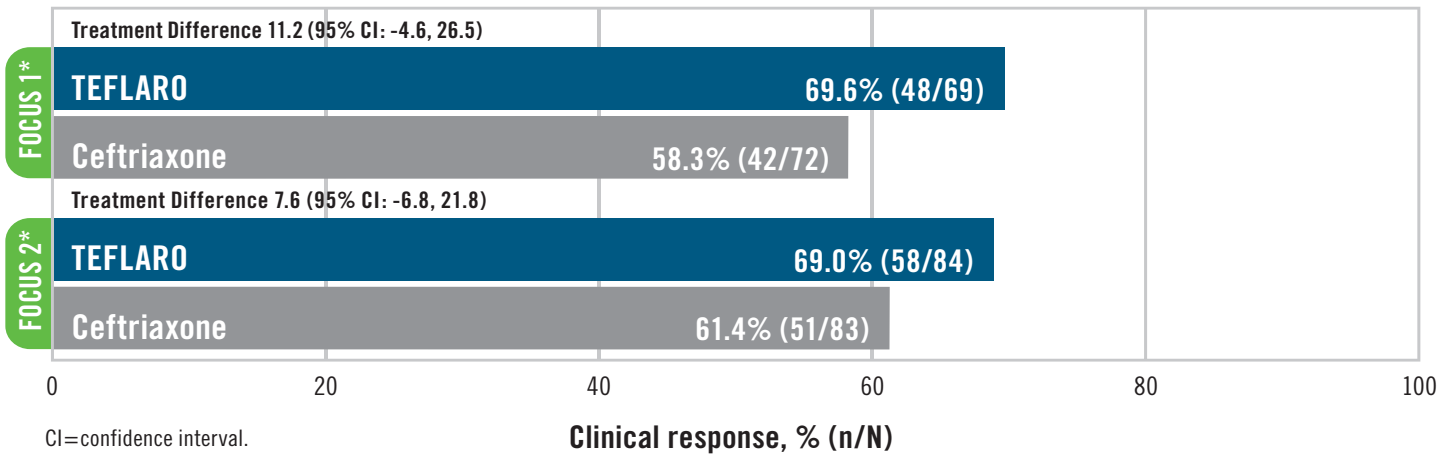
Adverse Reactions

- In the four pooled Phase 3 clinical trials, serious adverse events occurred in 98/1300 (7.5%) of patients receiving TEFLARO and 100/1297 (7.7%) of patients receiving comparator drugs. Treatment discontinuation due to adverse events occurred in 35/1300 (2.7%) of patients receiving TEFLARO and 48/1297 (3.7%) of patients receiving comparator drugs with the most common adverse events leading to discontinuation being hypersensitivity for both treatment groups at a rate of 0.3% in the TEFLARO group and 0.5% in the comparator group.
- No adverse reactions occurred in greater than 5% of patients receiving TEFLARO. The most common adverse reactions occurring in >2% of patients receiving TEFLARO in the pooled Phase 3 clinical trials were diarrhea, nausea, and rash.

Please see additional Important Safety Information throughout and brief summary of Prescribing Information on last page of this advertisement.

CABP

TEFLARO Demonstrated Clinical Response at Day 4 (mITT) in Community-Acquired Bacterial Pneumonia[1]

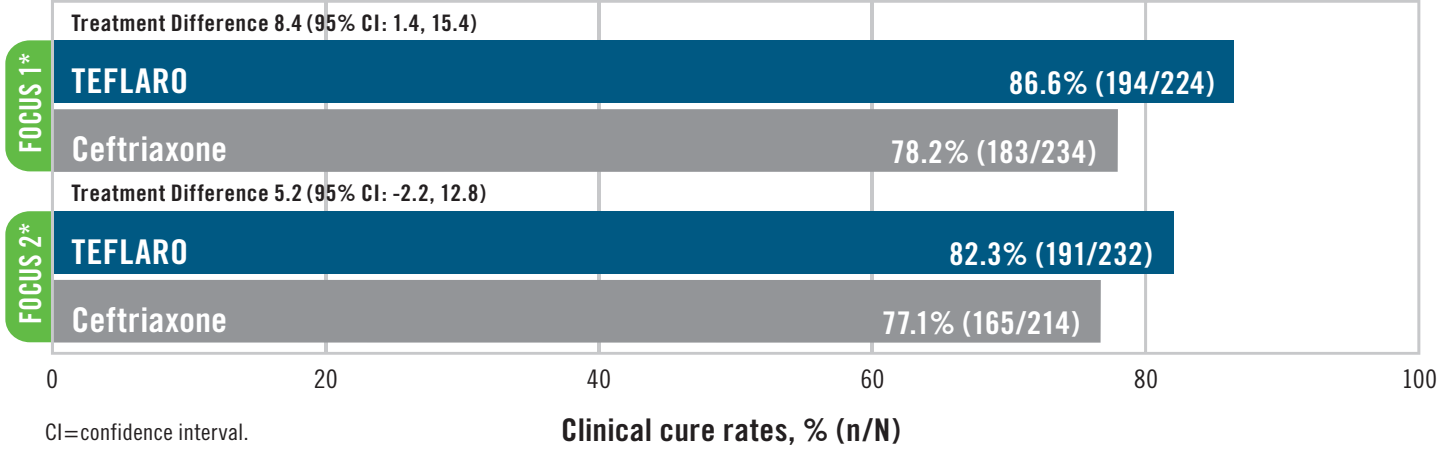


CI=confidence interval.

Neither trial established that TEFLARO was statistically superior to ceftriaxone in terms of clinical response rates.

CABP

TEFLARO Demonstrated Efficacy at TOC† (CE) in Community-Acquired Bacterial Pneumonia[1]



CI=confidence interval.

Neither trial established that TEFLARO was statistically superior to ceftriaxone in terms of clinical response rates.

Patients with known or suspected MRSA were excluded from both trials.

*FOCUS=Ce**f**tar**o**line **C**ommunity-Acquired Pne**u**monia Trial v**s** Ceftriaxone in Hospital Patients. FOCUS 1=CABP Trial 1, FOCUS 2=CABP Trial 2.

†There are insufficient historical data to establish the magnitude of drug effect for antibacterial drugs compared with placebo at a TOC time point. Therefore, comparisons of TEFLARO to ceftriaxone based on clinical response rates at TOC cannot be utilized to establish noninferiority.

IMPORTANT SAFETY INFORMATION

Drug Interactions

- No clinical drug-drug interaction studies have been conducted with TEFLARO. There is minimal potential for drug-drug interactions between TEFLARO and CYP450 substrates, inhibitors, or inducers; drugs known to undergo active renal secretion; and drugs that may alter renal blood flow.

Teflaro®
(ceftaroline fosamil) for injection
600 mg • 400 mg

Demonstrated efficacy in ABSSSI

TEFLARO ABSSSI Study Design[1,3]

Type of trial: Two identical, randomized, multicenter, multinational, double-blind, noninferiority trials

Study population: 1396 adults with clinically documented complicated skin and skin structure infection

Comparative agents: TEFLARO – 600 mg administered IV over 1 hour every 12 hours for 5-14 days;
Vancomycin plus aztreonam – 1 g vancomycin administered IV over 1 hour followed by 1 g aztreonam administered IV over 1 hour every 12 hours for 5-14 days

Treatment duration: Treatment duration was 5 to 14 days. A switch to oral therapy was not allowed

TEFLARO Study Populations

Day 3 Population*		The analysis evaluated patients with lesion size ≥75 cm^2 and having one of the following infection types: – Major abscess with ≥5 cm of surrounding erythema – Wound infection – Deep/extensive cellulitis
Test of Cure (TOC) Populations†		
MITT	Modified Intent-to-treat	All randomized subjects who received any amount of study drug.
CE	Clinically Evaluable	Patients in the MITT population who demonstrated sufficient adherence to the protocol. Sufficient adherence is defined as patients who met the minimal clinical disease criteria for cSSSI and all evaluability criteria, including subjects who received at least the pre-specified minimal amount of the intended dose and duration of study drug therapy, for which sufficient information regarding the cSSSI site is available to determine the subject's outcome, and for which there were no confounding factors that interfered with the assessment of that outcome.
ME	Microbiologically Evaluable	This population consists of a subset of subjects from the CE population who had at least one bacterial pathogen identified from a blood culture or culture of an adequate microbiological sample obtained from the cSSSI site at baseline and who had susceptibility testing performed on at least one of the isolated baseline pathogens.

* To evaluate the treatment effect of ceftaroline, an analysis was conducted in 797 patients with ABSSSI (such as deep/extensive cellulitis or a wound infection [surgical or traumatic]) for whom the treatment effect of antibacterials may be supported by historical evidence. This analysis evaluated responder rates based on achieving both cessation of lesion spread and absence of fever on Trial Day 3.

† The protocol-specified analyses included clinical cure rates at the TOC (8 to 15 days after the end of therapy) in the coprimary CE and MITT populations and clinical cure rates at TOC by pathogen in the ME population.

INDICATION AND USAGE

- TEFLARO is indicated for the treatment of **acute bacterial skin and skin structure infections (ABSSSI)** caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*.
- To reduce the development of drug-resistant bacteria and maintain the effectiveness of TEFLARO and other antibacterial drugs, TEFLARO should be used to treat only ABSSSI that is proven or strongly suspected to be caused by susceptible bacteria.

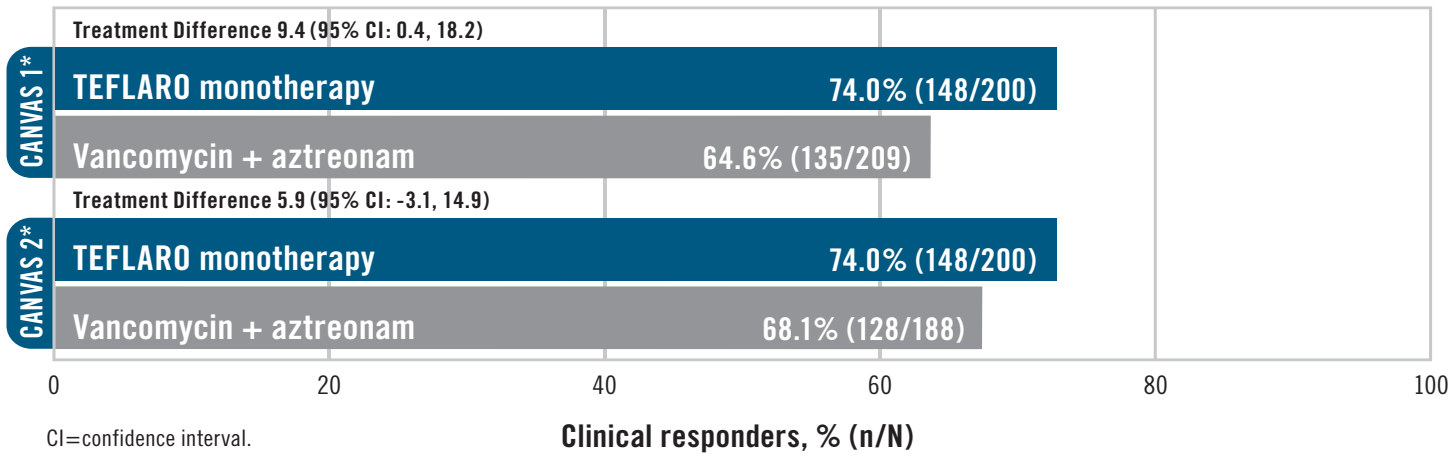
IMPORTANT SAFETY INFORMATION

Use in Specific Populations

- TEFLARO has not been studied in pregnant women. Therefore, TEFLARO should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.
- It is not known whether ceftaroline is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TEFLARO is administered to a nursing woman.
- Safety and effectiveness in pediatric patients have not been established.
- Because elderly patients, those ≥65 years of age, are more likely to have decreased renal function and ceftaroline is excreted primarily by the kidney, care should be taken in dose selection in this age group and it may be useful to monitor renal function. Dosage adjustment for elderly patients should therefore be based on renal function.
- Dosage adjustment is required in patients with moderate (CrCl >30 to ≤50 mL/min) or severe (CrCl ≥15 to ≤30 mL/min) renal impairment and in patients with end-stage renal disease (CrCl <15 mL/min).
- The pharmacokinetics of ceftaroline in patients with hepatic impairment have not been established.

ABSSSI

TEFLARO Demonstrated Clinical Response at Day 3 in Acute Bacterial Skin and Skin Structure Infections[1]

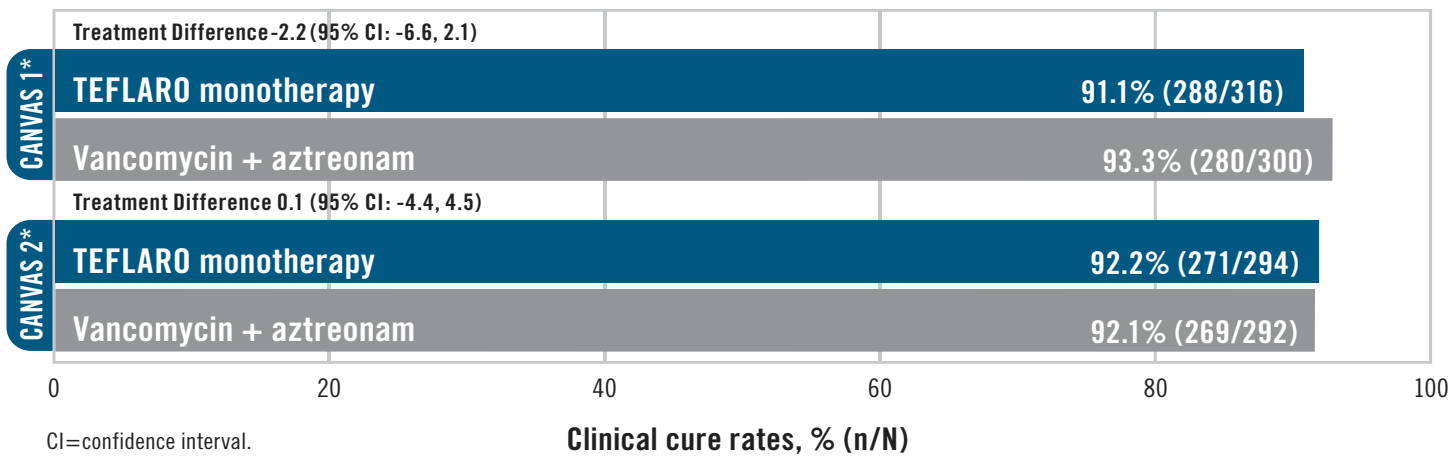


CI=confidence interval.

Neither trial established that TEFLARO was statistically superior to vancomycin plus aztreonam in terms of clinical response rates.

ABSSSI

TEFLARO Demonstrated Efficacy at TOC† (CE) in Acute Bacterial Skin and Skin Structure Infections[1]



CI=confidence interval.

Neither trial established that TEFLARO was statistically superior to vancomycin plus aztreonam in terms of clinical response rates.

*CANVAS=**C**eft**a**roli**n**e **v**s **Va**ncomycin in **S**kin and Skin Structure Infection. CANVAS 1=ABSSSI Trial 1, CANVAS 2=ABSSSI Trial 2.

† There are insufficient historical data to establish the magnitude of drug effect for antibacterial drugs compared with placebo at a TOC time point. Therefore, comparisons of TEFLARO to vancomycin plus aztreonam based on clinical response rates at TOC cannot be utilized to establish noninferiority.

References: 1. TEFLARO (ceftaroline fosamil) [prescribing information]. St Louis, MO: Forest Pharmaceuticals, Inc; 2011. **2.** Elixhauser A, Owens P. *Reasons for being admitted to the hospital through the emergency department, 2003.* Healthcare Cost and Utilization Project Statistical Brief #2. February 2006. Agency for Healthcare Research and Quality, Rockville, MD. www.hcup-us.ahrq.gov/reports/statbriefs/sb2.pdf. Accessed February 10, 2011. **3.** Data on file. Forest Laboratories, Inc.

Please see brief summary of Prescribing Information on following page.
Please also see full Prescribing Information at www.TEFLARO.com.

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Crizotinib Boosts Overall Survival in ALK+ NSCLC

'ALK-positive patients … live a lot longer if you give them this targeted therapy, crizotinib.'

BY MITCHEL L. ZOLER
Elsevier Global Medical News

AMSTERDAM – Crizotinib treatment boosted overall survival of selected patients with advanced non–small cell lung cancer by about a year compared with patients on standard chemotherapy in a historical control analysis, adding to the growing body of evidence for the efficacy of this novel targeted therapy.

"Crizotinib may prolong overall survival and fundamentally alter the natural history" of NSCLC that features alterations in the anaplastic lymphoma kinase (ALK) gene, Dr. Alice T. Shaw said at the World Conference on Lung Cancer. Results from several recent studies indicated that about 7% of patients with advanced NSCLC have ALK-positive tumors in which the gene is rearranged.

Results from Dr. Shaw's new analysis also indicated that the overall survival of patients with ALK-positive NSCLC closely tracked the survival rate of patients with normal ALK genes and advanced NSCLC, suggesting that the presence of ALK mutation does not change prognosis.

"ALK-positive patients do not intrinsically do better on their own, but you can make them live a lot longer if you give them this targeted therapy, crizotinib," said Dr. Shaw, an oncologist at Harvard Medical School and Massachusetts General Hospital, both in Boston.

In May, the Food and Drug Administration began a priority review of crizotinib, an ALK inhibitor, for an indication to treat patients with advanced, ALK-positive NSCLC.

VITALS

Major Finding: Selected patients with ALK-positive, advanced NSCLC treated with crizotinib had a 1-year overall survival rate of 74% and a 2-year rate of 54%, compared with rates of 44% and 12%, respectively, in matched patients who did not receive crizotinib. The hazard ratio for survival among the patients not on crizotinib was 0.36, compared with those who got the drug ($P = .004$).

Data Source: The 18-month median follow-up data from a phase I study of crizotinib-treated patients, and follow-up on matched ALK-positive patients who had been evaluated for possible treatment in this trial but who never received crizotinib.

Disclosures: The crizotinib study that provided much of the data used in this analysis was funded by Pfizer, the company developing the drug. Dr. Shaw said that she has been a consultant to Pfizer, Ariad, Chugai, and Millennium. She has received research support from Novartis and AstraZeneca.

"For regulatory approval, people look at overall survival, but you'll never get [overall survival] from the large randomized studies because it would be unethical not to let patients [who were initially randomized to not receive crizotinib] cross over. That's why this analysis is important, even with its flaws, because it shows – or at least strongly suggests – that this drug improves overall survival, that we are really making a difference for these patients," Dr. Shaw said in an interview. Prior reports from crizotinib studies in ALK-positive patients documented a response rate of 50%-60%, and a median progression-free survival of 10 months.

Dr. Shaw and her associates used data on patients who were treated with crizotinib from the first, phase I study of the drug, because those patients have had the longest follow-up on the drug, a median of 18 months for those who remained alive (N. Engl. J. Med. 2010; 363:1693-703).

The phase I crizotinib study included 82 ALK-positive patients who received the drug. To better match these patients with a control group of ALK-positive patients who never got crizotinib, the researchers focused on the 56 patients who came from study centers

Continued on following page

Proton Therapy May Lead to Fewer Side Effects

BY SARA FREEMAN
Elsevier Global Medical News

VITALS

Major Finding: PBT resulted in significantly lower rates of grade 2 or higher esophagitis (*P* less than .0001), pneumonitis (*P* less than .002), hematologic toxicities (*P* less than .0001 for neutrophil toxicity and *P* less than .001 for hemoglobin and white blood cell toxicities), and fatigue (*P* less than .0001) than IMRT.

Data Source: Two retrospective studies: one involving 135 patients with NSCLC treated with concurrent chemoradiation (PBT, IMRT) and one involving 678 patients with NSCLC treated with concurrent chemoradiation between 1999 and 2008.

Disclosures: Dr. Komaki and Dr. Gomez said they had no financial conflicts of interest.

LONDON – Proton beam therapy for non–small cell lung cancer is associated with fewer radiation-induced side effects than are conventional radiotherapy methods when combined with chemotherapy, according to preliminary data from two retrospective studies conducted at the University of Texas M.D. Anderson Cancer Center in Houston.

Significantly less esophagitis, pneumonitis, and bone marrow toxicity were observed with proton beam therapy (PBT) than with intensity-modulated radiotherapy (IMRT), Dr. Ritsuko Komaki reported at the European Society for Therapeutic Radiation Oncology Anniversary Conference.

Proton beam therapy also significantly reduced the incidence of esophagitis when compared with IMRT and three-dimensional conformal radiotherapy (3D-CRT). A mean esophageal dose of 40 Gy or higher was identified as the cut-off point for high-grade esophagitis occurring with any method.

"Radiation dose escalation improves local control but increases toxicity, especially when combined with concurrent chemotherapy for non–small cell lung cancer [NSCLC] or even small cell lung cancer," said Dr. Komaki, a professor of radiation oncology at M.D. Anderson, which opened its 94,000-square-foot Proton Therapy Center in 2006. As such, "radiation chemotherapy is a double-edged sword. It will kill cancer cells, but it also kills normal tissues, and more targeted treatment is needed," she said.

"One of the most important benefits of PBT is that there is no exit dose," Dr. Komaki said in an interview. "The protons stop after penetrating the tumor, and there is no dose of radiation beyond it."

This has the potential to spare surrounding cells and organs from damage, she observed. Normal tissues that might be affected by radiation therapy for NSCLC include the lungs, esophagus, heart, and bone marrow, which cannot always be avoided by the use of 3D-CRT or even IMRT.

An expensive new technology that delivers highly targeted radiation with electrically charged particles, PBT is promising but unproven, according to a 2009 review commissioned by the Agency for Healthcare Research and Quality. The authors found few comparative studies to establish effectiveness or safety for the technology, which is housed in a small but growing number of proton beam centers that can cost $100 million to $225 million to build (Ann. Intern. Med. 2009;151:556-65).

Dr. Komaki and her associates are recruiting patients into the first prospective randomized trial to directly compare proton beam therapy with IMRT in unresectable stage II and III NSCLC. The phase II trial is supported by a grant from the National Cancer Institute, and involves treatment with 74-Gy PBT or IMRT with concurrent carboplatin and paclitaxel. To date, 107 of the planned 168 patients have been enrolled in the study at the Texas institution and at Massachusetts General Hospital in Boston, the other participating center, she said.

A recent report from M.D. Anderson showed that higher doses of proton radiation could be delivered to lung tumors with a lower risk of esophagitis and pneumonitis than either IMRT or 3D-CRT (Cancer 2011;117:3004-13).

The new data presented by Dr. Komaki showed significantly reduced rates of grade 2 or higher esophagitis (*P* less than .0001), pneumonitis (*P* less than .002), hematologic toxicities (*P* less than .0001 for neutrophil toxicity and *P* less than .001 for hemoglobin and white blood cell toxicities), and fatigue (*P* less than .0001) in 60 patients treated with proton beam therapy compared with 75 patients treated with IMRT (Radiother. Oncol. 2011;99:S89-90).

Other research from the M.D. Anderson team focused on esophagitis, and examined dosimetric and clinical factors that could lead to this side effect following proton beam therapy, IMRT, or 3D-CRT for definitive NSCLC treatment (Radiother. Oncol. 2011;99[Suppl.1]:S210).

Dr. Daniel Gomez, a radiation oncologist at M.D. Anderson, presented data on 678 patients treated at the institution between 1999 and 2008. Dr. Gomez explained that the type of radiation therapy received had altered over the years, with 463 patients treated with 3D-CRT between 1999 and 2005, 122 with IMRT between 2005 and 2007, and 94 patients treated with proton beam therapy between 2006 and 2008.

"Esophagitis is a common toxicity in the treatment of NSCLC with definitive radiation," Dr. Gomez said. Although studies have looked at what factors might predict this life-limiting side effect, there have been conflicting results.

'One of the most important benefits of [proton beam therapy] is that there is no exit dose.'

DR. KOMAKI

Data show, for example, that the presence of acute toxicity is a predictor of late toxicity (Int. J. Radiat. Oncol. Biol. Phys. 2005;61:335-47), but a variety of dosimetric parameters have been noted and there does not appear to be a single threshold for toxic effects (Int. J. Radiat. Oncol. Biol. Phys. 2010;76:S86-93).

Data presented by Dr. Gomez, however, suggest that a mean delivered esophageal dose of above 40 Gy may be predictive of high-grade inflammation regardless of whether proton beams, IMRT, or 3D-CRT is used. This research might eventually help develop dosing guides for clinicians to use in routine practice, he suggested.

"Patients receiving IMRT had a higher rate of esophagitis in all grades, including grade 3," Dr. Gomez said. In contrast, "patients receiving proton therapy had lower rates of esophagitis at all grades." The incidence of grade 3 or higher esophagitis was 14% (n = 65) for 3D-CRT, 27% (n = 33) for IMRT, and 6% (n = 6) for proton beam therapy.

Dr. Gomez also reported that grade 3 or higher esophagitis was more likely in patients who received concurrent chemotherapy than in those who did not (18.4% vs. 7.4%, *P* less than .001). However, the mean esophageal dose of radiation delivered to patients given concurrent chemotherapy also was significantly higher (32.2 Gy vs. 15.8 Gy, *P* less than 001).

The M.D. Anderson investigators said they have just finished recruiting patients into a phase III trial (Radiation Therapy Oncology Group [RTOG] 0617) that will compare conventional (60 Gy in 6 weeks) vs. high dose (74 Gy in 7.5 weeks) radiation therapy in combination with paclitaxel and carboplatin, with or without the addition of cetuximab (Erbitux) in 500 patients with NSCLC.

Although the trial is not directly comparing the type of radiation treatment used, it should still be possible to retrospectively analyze the results to determine the individual effects of the radiation modalities used at each participating center, Dr. Komaki noted.

"When we started this trial, it was not acquiring patients because some of the radiation and medical oncologists said that it was obvious that patients given 60 Gy would do worse compared to 74 Gy," she added in the interview. "When we included cetuximab based on the results of the RTOG 0324 trial, however, recruitment started to rocket." The RTOG 0324 trial showed the feasibility of combining cetuximab with chemoradiation in NSCLC (J. Clin. Oncol. 2011;29:2312-8).

Discussing the downsides of PBT vs. IMRT, Dr. Komaki conceded that the newer method involved a lot more sophisticated planning and was more expensive. There is also concern that the sharp drop-off of radiation received with PBT might mean that important areas of the tumor are missed.

As relatively few proton beam facilities are in operation, large cooperative trials are difficult to perform. The prospective phase II trial of PBT and IMRT now being conducted at M.D. Anderson and Massachusetts General Hospital will be the proof that such trials are possible. ■

Continued from previous page

in the United States and Australia, and specifically on the 30 patients within this subgroup who received crizotinib as their second or third chemotherapy agent.

They compared overall survival of these 30 patients with 21 ALK-positive patients from the United States or Australia who had been assessed for potential enrollment in the phase I study but never received crizotinib. In addition, during follow-up all of these control patients remained on second-line chemotherapy.

'Crizotinib may significantly improve survival outcomes in patients with advanced ALK-positive NSCLC.'

DR. SHAW

The new analysis showed that the 30 crizotinib-treated patients had an overall 1-year survival rate of 74%, and a 2-year rate of 54%, with median survival not yet reached during the median 18-month follow-up. The 21 matched control patients had a 1-year survival rate of 44% and a 2-year rate of 12%, and median survival duration of 6 months.

Calculations showed a hazard ratio for overall survival of 0.36 for the patients who did not get crizotinib compared with those who did ($P = .004$).

"These results suggest that crizotinib may significantly improve survival outcomes in patients with advanced ALK-positive NSCLC," Dr. Shaw said.

To confirm that ALK positivity itself played no role in overall survival, Dr. Shaw and her associates compared overall survival in the 21 control patients who never received crizotinib vs. 48 patients who had advanced NSCLC without any ALK mutations, who never received crizotinib, and who had been treated with standard, second-line chemotherapy. In addition, all 48 control patients and all 21 ALK-positive patients had tumors with adenocarcinoma histology, and they all had a history of being never or light smokers. The two groups had virtually identical overall survival rates, Dr. Shaw reported at the meeting, which was sponsored by the International Association for the Study of Lung Cancer. ■

Gene Test Helps Assess Stage I and II Lung Cancer

BY MITCHEL L. ZOLER
Elsevier Global Medical News

AMSTERDAM – A commercially available gene-expression test significantly improved discrimination between low- and high-risk stage I and IIa lung cancer patients in a pair of validation tests, leading investigators to propose routine use of the test to identify early-stage patients who should get adjuvant chemotherapy.

"The multigene assay can outperform conventional risk factors and staging, and may lead to personalized therapies for patients with early-stage nonsquamous non–small cell lung cancer," Dr. Johannes Kratz said at the World Conference on Lung Cancer.

Dr. Kratz conceded that no prospective, randomized study has yet tested whether identification of high-risk stage I patients singled out a subgroup that would definitely benefit from adjuvant chemotherapy. But the prognostic information that the genetic test already provides justifies its routine use in stage I and II patients, said Dr. Kratz, a surgeon who performed this study while at the University of California, San Francisco (UCSF), but who is now at Massachusetts General Hospital in Boston.

"I think [the test] is certainly ready for prognosis, to give patients information," he said in an interview. "We'll start using it routinely for prognosis at UCSF. We believe the strength of the results show it's ready for prime time. Whether it should also be used to guide treatment, especially for stage I patients, is up to each health care provider, but it opens an interesting possibility before anything is proven in a randomized, controlled trial. The hope is that by identifying high-risk patients, you'll improve their survival by giving them adjuvant chemotherapy. And in some of the low-risk stage II patients, you can avoid some of the toxicities of adjuvant chemotherapy."

VITALS

Major Finding: Adding a commercially available genetic test to standard TNM staging significantly refined the prognosis of stage I and IIa patients. Patients identified as being at high risk for mortality by the genetic test had a statistically significant, 90% increased risk ($P = .010$) in a multivariate analysis in one validation cohort, and a threefold increased mortality risk (P less than .001) in the second validation cohort.

Data Source: Validation cohorts of 433 nonsquamous non–small cell lung cancer patients collected by Kaiser Permanente of Northern California and 1,006 similar lung cancer patients collected by the Chinese Clinical Trials Consortium, and a training cohort of 361 similar lung cancer patients collected at UCSF.

Disclosures: Dr. Kratz said that he has been a consultant to and has an equity interest in Pinpoint Genomics, the company that developed the genetic test used in the study.

Although several different genetic tests for stage I lung cancer have been studied over the past decade, none have wound up as marketed tests. Dr. Kratz and his associates set out to develop a practical and commercially viable test. They worked in collaboration with Pinpoint Genomics, the company that has now begun marketing the test.

The test they developed uses polymerase chain reaction–based gene expression assays for 11 different genes, based on results from prior studies that identified genes critical to key causal pathways leading to lung cancer. "We took a truly blinded, one-shot approach" in putting together the genetic test panel, without any tinkering during the validation phase to boost the prognostic strength of the test, he explained at the conference sponsored by the International Association for the Study of Lung Cancer. They also focused on tests that use paraffin-embedded specimens.

"I don't think a prospective validation study is needed" before routine prognostic use of the test begins, he said. The validation studies "were done retrospectively, but in a very controlled way that was equivalent to prospective validation. I think we have powerful evidence that these markers provide additional prognostic information. We're not saying to abandon traditional staging, but this adds useful prognostic information."

The initial test development cohort consisted of 361 stage I, II, and III patients treated and followed at UCSF. Validation used two independent cohorts, 433 stage I patients treated by physicians from Kaiser Permanente of Northern California, and a second cohort of 1,006 patients with stage I, II, or II disease treated at hospitals affiliated with the China Clinical Trials Consortium. Median follow-up in the three cohorts ranged from just over 3 years to just short of 6 years. Five-year mortality was about 42% in each of the three cohorts. About 80% of the nonsquamous non–small cell lung cancer patients in the three cohorts had adenocarcinomas.

Using the genetic test to discriminate among three risk levels in the UCSF cohort identified a low-risk group with a calculated 5-year survival of 78%, an intermediate group with a 5-year survival of 60%, and a high-risk group with a survival rate of 30%. Between-group differences were statistically significant ($P = .00005$). The U.S. and Chinese validation cohorts each led to identification of three very similar prognostic subgroups, "suggesting that the assay was based on principles of lung cancer biology that are fundamental to the disease and remain constant despite the diverse genetic backgrounds of the populations studied," Dr. Kratz said.

In a multivariate analysis that controlled for age, sex, tumor size, and smoking history, high-risk identification using the genetic test led to a near doubling of the mortality risk in the Kaiser cohort (hazard ratio = 1.93, $P = .010$) and a more than tripling of the mortality risk in the Chinese cohort, compared with the low-risk tertile (HR = 3.25, P less than .001).

Based on their findings, Dr. Kratz and his associates proposed a new variation on the conventional tumor size, lymph node status, metastases (TNM) staging system that they called TNMM; the second M stands for multigene assay.

The researchers also found that adding the gene test led to statistically significant increases in the area under the curve for prognostic accuracy. ■

COMMENTARY

Dr. W. Michael Alberts, FCCP, comments: A reliable and accurate way to identify high-risk patients would be a very welcome addition to management protocols for stage I and IIa lung cancer. Validation studies of any proposed gene-expression test to be used in this manner are crucial. As a result, the statement that "I don't think a prospective validation study is needed" before routine prognostic use of the test begins gives me some pause. While I hope that it works, I'd prefer that it was proven prospectively.

Dysplasia Could Be Marker for Lung Ca Chemoprevention

BY SHARON WORCESTER
Elsevier Global Medical News

ORLANDO – Endobronchial dysplasia appears useful as a biomarker for measuring the success of lung cancer chemoprevention, investigators reported at the annual meeting of the American Association for Cancer Research.

Bronchoscopies, along with biopsies of standard endobronchial sites and any other abnormal-appearing areas, were performed at baseline and at 6 months after randomization to treatment with iloprost or placebo in a phase II chemoprevention trial involving 152 former or current smokers with at least a 20 pack-year history.

Former smokers who received iloprost, an oral prostacyclin analog approved for treatment of primary pulmonary hypertension, had significant improvements on several measures of endobronchial dysplasia, while current smokers had no improvement, Dr. Paul Bunn reported.

Former smokers who got iloprost had significant improvements on measures of endobronchial dysplasia.

DR. BUNN

The findings show that iloprost, which has been shown to prevent the development of lung cancer in various murine models involving cigarette-smoke exposure, also might have the same effect in humans and thus deserves further study for this purpose, Dr. Bunn and his coauthors concluded.

The results also show that endobronchial dysplasia could serve as a biomarker for effectiveness of chemopreventive treatment – much as cholesterol does in patients being treated with statins to prevent cardiovascular disease, according to Dr. Bunn, executive director of the International Association for the Study of Lung Cancer and professor of lung cancer research at the University of Colorado, Aurora.

In the current study, baseline histology was significantly worse in current smokers than in former smokers (average biopsy scores of 3.0 vs. 2.1, respectively, with a score of 4 indicating mild dysplasia). Former smokers experienced a 0.41-point improvement in average biopsy score ($P = .010$), a 1.10-point improvement in their worst baseline biopsy score ($P = .002$), and a 12.5% improvement in dysplasia index ($P = .006$), which was the percentage of biopsies with a score of at least 4, said Dr. Bunn.

"The histologic improvement in the treated patients who were former smokers was larger than the magnitude of the difference between current and former smokers," he said.

For example, the baseline dysplasia index in current and former smokers was 46% and 31%, respectively, but the pre- and post-treatment dysplasia index in former smokers was 43% and 19.6%, respectively.

Study participants had an average 30 pack-year history of smoking, and at least mild cytologic atypia on sputum cytology, but no previous history of cancer. The treatment and placebo groups were well-matched for age, tobacco exposure and baseline histology, and there was no difference in dropout rate or serious adverse events between the treatment and placebo groups, Dr. Bunn noted.

People who quit smoking remain at greater risk of lung cancer than are never smokers, and it is important to find effective chemopreventive measures for these individuals, he said.

Dr. Bunn discussed an off-label use of iloprost; he had no other disclosures. ■

No Negative Eye Effects Found With Long-Term ICS

BY SHERRY BOSCHERT
Elsevier Global Medical News

SAN FRANCISCO – Using inhaled budesonide daily for chronic asthma for a mean of 16 years from childhood into adulthood didn't cause more cataracts or significantly change intraocular pressure or vision in a prospective, longitudinal, placebo-controlled study.

'This is a very strong finding' of safety with long-term inhaled budesonide.

DR. PEDERSEN

Among 300 Danish patients taking inhaled budesonide for chronic asthma, 148 underwent eye examinations 15-20 years after the start of the study, as did 53 of 163 healthy siblings in the control group. The exams detected two posterior subcapsular cataracts that were outside the central 3-mm zone, but both were in the control group and none in the budesonide group, Dr. Søren Pedersen and his associates reported at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

Nineteen cataracts in the budesonide group would have been needed to demonstrate a statistically significant 5% increased risk for cataracts, a poststudy power analysis found.

Average vision measurements were identical between groups (1.04 in each eye), said Dr. Pedersen of the University of Southern Denmark, Kolding. Intraocular pressures did not differ significantly between groups, with average measurements of 13.8 mm Hg in each eye of the asthma patients, and averages of 14.5 mm Hg in the right eyes and 14.2 mm Hg in the left eyes of the control group.

"This is a very strong finding" of safety with long-term inhaled budesonide, he said in an interview.

Patients took a mean daily dose of 385 mcg of budesonide and accumulated a mean dose of 2.3 g. Increased intraocular pressures (higher than 21 mm Hg) were seen in five patients (3.4%) and in one sibling in the control group (1.9%), a nonsignificant difference between groups. The accumulated dose of budesonide was not significantly associated with intraocular pressure, Dr. Pedersen said.

The study is part of a larger study that began with 270 children, including 62 with asthma who did not use inhaled corticosteroids, all of whom were evaluated for cataracts, bruises, growth, bone mineral density, and clinical effects of inhaled budesonide 4-6 years after treatment started, with no adverse effects found. At that point, 32 children in the control group dropped out, the other 30 shifted to the budesonide group, and 163 healthy siblings became the new control group. Patients were evaluated every 1-2 years.

The mean age of those who had eye exams 15-20 years into the study was 26 years for patients and 28 years for siblings. A total of 68% of patients and 47% of controls were male. Treatment duration ranged from 3 to 22 years. Daily budesonide dose ranged from 50 to 1,220 mcg. The accumulated budesonide dose ranged from less than 1 g to 8.8 g.

Previous studies of the risk of posterior subcapsular cataracts from oral or inhaled steroids were cross-sectional studies with little or no information on the dose of inhaled corticosteroid used, he said. ■

VITALS

Major Finding: Children with chronic asthma who used daily inhaled budesonide for an average of 16 years showed no increased risk of cataracts, intraocular pressure, or vision problems.
Data Source: Prospective longitudinal study of 300 treated children with chronic asthma and 163 healthy sibling controls.
Disclosures: AstraZeneca, which markets budesonide, funded the study. Dr. Pedersen said he had no other relevant financial disclosures.

Nitric Oxide Not Useful for Congenital Diaphragmatic Hernia

BY DOUG BRUNK
Elsevier Global Medical News

PALM DESERT, CALIF. – Nitric oxide use in neonates with diaphragmatic hernia remains widespread even though its efficacy remains to be proven, results from a large national analysis demonstrated.

"Nitric oxide has been studied extensively in newborns with hypoxemic respiratory failure," Dr. Brendan T. Campbell said at the annual meeting of the American Pediatric Surgical Association. "There have been 14 randomized, controlled trials done in term newborns with respiratory failure, and two of these studies enrolled significant numbers of patients with congenital diaphragmatic hernia. Both studies demonstrated conclusively that treatment with nitric oxide does not improve outcomes in newborns with congenital diaphragmatic hernia."

The first of these studies, he said, found that patients treated with nitric oxide were actually 30% more likely to require extracorporeal membrane oxygenation than were those who did not receive nitric oxide (Pediatrics 1997;99:838-45).

In an effort to describe national trends, interhospital variability in use, and costs associated with nitric oxide use in neonates with congenital diaphragmatic hernia (CDH), a health services research team led by Dr. Campbell analyzed records in the Pediatric Health Information System (PHIS) database. For the years 2003-2010, they identified all patients with a diagnostic code of CDH and a procedural code for CDH repair at 40 children's hospitals that contribute data to the PHIS. Patients with congenital cardiac anomalies and inaccurate nitric oxide discharge data were excluded from analysis, said Dr. Campbell, a pediatric surgeon at Connecticut Children's Medical Center, Hartford, and an assistant professor of surgery and pediatrics at the University of Connecticut.

The analysis identified a total of 3,651 infants with CDH; 514 infants with cardiac anomalies and missing or inaccurate data were excluded. The overall mortality rate was 15%, but the mortality rate for the 761 patients treated with nitric oxide was 47%, compared with roughly 5% for the 2,376 patients who were not treated with nitric oxide.

Patients treated with nitric oxide had a significantly longer median length of stay, compared with their counterparts (a median of 31 days vs. 6 days, respectively) and significantly higher median total charges billed (a median of $456,473 vs. $36,270).

Dr. Campbell estimated that the 761 patients treated with nitric oxide generated nearly $34 million in unnecessary hospital charges. "Reducing nitric oxide use in these patients would significantly lower costs without adversely affecting outcomes," he said.

Wide variation in the use of nitric oxide in neonates with CDH existed among the 40 PHIS hospitals. At one hospital, for example, more than 50% were treated with nitric oxide, while the rate was 10% or less at two other PHIS hospitals.

Limitations of the study included its retrospective design and the potential for coding errors and missing data.

Dr. Campbell said that he had no relevant financial conflicts to disclose.

The meeting was supported by a grant from Elsevier, which owns this news organization. ■

COMMENTARY

Dr. Burt Lesnick, FCCP, comments: The overwhelming evidence from clinical trials suggests that we should not be using inhaled nitric oxide for infants who have congenital diaphragmatic hernia. Strategies need to be implemented to enhance clinicians' ability to adopt this change in practice.

Long-Term Issues Rare

Empyema • *from page 1*

Proposed explanations include pneumococcal serotype replacement and/or evolving antimicrobial resistance patterns, said Dr. Cohen of the Hospital for Sick Children, Toronto.

He recently reported on 82 children with empyema – as defined by ultrasound evidence of pleural effusions with loculations – at the annual meeting of the Pediatric Academic Societies. The children were seen at 1 and 6 months post discharge, when they underwent clinical examination, a chest x-ray, quality-of-life assessment using the Peds-QL, and spirometry if they were at least 5 years old.

The median age of the subjects was 3.6 years; 27% of them had an organism isolated, most commonly *Streptococcus pneumoniae*. Of note, methicillin-resistant *Staphylococcus aureus* was the causative organism in only one child. A chest drain was used in 51 children, and 40 of those also received fibrinolytics. The remaining patients were treated only with antibiotics. Video-assisted thoracopic surgery was not employed.

The average hospital stay was 10 days. Eight children went to the pediatric ICU.

At discharge, 21% of patients still had fever, which lasted up to 1 further week; 7% of children were readmitted within 1 month.

At the 1-month follow-up, 18% of the patients had fever, 23% cough, and 2% failure to thrive; 59% of the school-age children had missed a median of 5 classroom days. By 6 months, however, only 16% of children were still coughing, and 30% of school-age children had missed an average of 2 days of school since the 1-month evaluation. None were experiencing fever or failure to thrive at late follow-up.

At 1 month post discharge, 7 of 20 children had abnormal spirometry, defined as an FEV_1 that was 80% or less of predicted. Of the 82 children, 24 had persistent abnormalities on chest x-ray, mostly effusion, pneumatocele, or abscess. Twelve of 68 parents rated their child's health-related quality of life as abnormal based on a Peds-QL score more than 1 standard deviation below the normal population.

By 6 months, only one child had abnormal spirometry and three had persistent chest x-ray abnormalities. At 1 year, these abnormalities had resolved in three patients, while the fourth was lost to follow-up.

Moreover, at 6 months, parents rated their child's quality of life on the Peds-QL as similar to that in 8,430 healthy historical controls and significantly better than were the scores for 157 children with asthma, Dr. Cohen said.

He declared having no financial conflicts of interest. ■

Important safety information

Because of the risks of liver injury and birth defects, Tracleer may be prescribed and dispensed only through the Tracleer Access Program (T.A.P.), a restricted distribution program, by calling 1-866-228-3546. Only prescribers and pharmacies registered with T.A.P. may prescribe and distribute Tracleer. Tracleer may be dispensed only to patients who are enrolled in and meet all conditions of T.A.P.

Liver injury

Elevations of liver aminotransferases (ALT, AST) and liver failure have been reported with Tracleer. In a setting of close monitoring, rare cases of liver failure and unexplained hepatic cirrhosis were observed after prolonged treatment. In general, avoid using Tracleer in patients with elevated aminotransferases (>3 × ULN). Measure liver aminotransferases prior to initiation of treatment and then monthly. Discontinue Tracleer if aminotransferase elevations are accompanied by signs or symptoms of liver dysfunction or injury or increases in bilirubin ≥2 × ULN.

Teratogenicity

Based on animal data, Tracleer is likely to cause major birth defects if used during pregnancy. Exclude pregnancy before and during treatment. To prevent pregnancy, females of childbearing potential must use 2 reliable forms of contraception during treatment and for 1 month after stopping Tracleer unless the patient has a tubal sterilization or Copper T 380A IUD or LNg-20 IUS inserted, in which case no other contraception is needed. Monthly pregnancy tests should be obtained.

Contraindications

Tracleer is contraindicated with cyclosporine A, glyburide, in females who are or may become pregnant, or in patients who are hypersensitive to bosentan or any component of Tracleer.

Warnings and precautions

In clinical trials, Tracleer caused ALT/AST elevations (>3 × ULN) in 11% of patients accompanied by elevated bilirubin in a few cases. The combination of hepatocellular injury (increases in aminotransferases of >3 × ULN) and increases in total bilirubin (≥3 × ULN) is a marker for potential serious liver injury. Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. Avoid using Tracleer in patients with moderate or severe liver impairment or elevated ALT/AST >3 × ULN.

If clinically significant fluid retention develops, with or without associated weight gain, the cause, such as Tracleer or underlying heart failure, must be determined. Patients may require treatment or Tracleer therapy may need to be discontinued.

Preclinical data and an open-label safety study (N=25) showed a decline in sperm count of ≥50% in 25% of Tracleer-treated patients after 3 or 6 months. After 6 months, sperm count remained in normal range, with no changes in sperm morphology or motility, or hormone levels. Endothelin receptor antagonists such as Tracleer may adversely affect spermatogenesis.

Treatment with Tracleer can cause a dose-related decrease in hemoglobin (Hgb) and hematocrit. Hgb should be checked after 1 and 3 months, and then every 3 months. Upon marked decrease in Hgb, determine the cause and need for specific treatment.

If signs of pulmonary edema occur, the possibility of associated pulmonary veno-occlusive disease should be considered. Tracleer should be discontinued.

Adverse events

In Tracleer pivotal trials, the most common adverse events occurring more often in Tracleer-treated patients than in patients taking placebo (≥2%) were respiratory tract infection, edema, hypotension, sinusitis, arthralgia, liver function test abnormal, palpitations, and anemia.

CELEBRATING 10 YEARS OF PUTTING PATIENTS FIRST

Introducing the Tracleer Patient Coupon Program—patients pay no more than $10 per month for Tracleer.

NOVEMBER '11

Since bringing the first ERA to market 10 years ago, we have been continually inspired by patients and the dedication of the medical community.

Ten years and 82,000 patients later, we at Actelion are celebrating this decade of commitment by helping to ensure that patients pay no more than $10 monthly for therapy. Actelion will contribute up to $10,000 annually per patient.*

Indication

Tracleer is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital systemic-to-pulmonary shunts (18%). Patients with WHO class II symptoms showed reduction in the rate of clinical deterioration and a trend for improvement in walk distance. Physicians should consider whether these benefits are sufficient to offset the risk of liver injury in WHO class II patients, which may preclude future use as their disease progresses.

Please see accompanying brief summary of prescribing information, including ***BOXED WARNING*** *about liver injury and pregnancy, on following pages.*

*Patients ineligible for the Tracleer Patient Coupon Program include any patients whose prescriptions are paid for by the government, Medicare, Medicaid, VA/DOD (Tricare), or Indian Health Service, patients in Massachusetts and Puerto Rico, or where prohibited by law.

ACTELION

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Tracleer® BOSENTAN TABLETS

WARNING: RISKS OF LIVER INJURY and TERATOGENICITY

Because of the risk of liver injury and birth defects, Tracleer is available only through a special restricted distribution program called the Tracleer Access Program (T.A.P.), by calling 1 866 228 3546. Only prescribers and pharmacies registered with T.A.P. may prescribe and distribute Tracleer. In addition, Tracleer may be dispensed only to patients who are enrolled in and meet all conditions of T.A.P. [see **Warnings and Precautions**].

Liver Injury

In clinical studies, Tracleer caused at least 3-fold upper limit of normal (ULN) elevation of liver aminotransferases (ALT and AST) in about 11% of patients, accompanied by elevated bilirubin in a small number of cases. Because these changes are a marker for potential serious liver injury, serum aminotransferase levels must be measured prior to initiation of treatment and then monthly [see **Dosage and Administration, Warnings and Precautions**]. In the postmarketing period, in the setting of close monitoring, rare cases of unexplained hepatic cirrhosis were reported after prolonged (> 12 months) therapy with Tracleer in patients with multiple co-morbidities and drug therapies. There have also been reports of liver failure. The contribution of Tracleer in these cases could not be excluded.

In at least one case, the initial presentation (after > 20 months of treatment) included pronounced elevations in aminotransferases and bilirubin levels accompanied by non-specific symptoms, all of which resolved slowly over time after discontinuation of Tracleer. This case reinforces the importance of strict adherence to the monthly monitoring schedule for the duration of treatment and the treatment algorithm, which includes stopping Tracleer with a rise of aminotransferases accompanied by signs or symptoms of liver dysfunction [see **Dosage and Administration**].

Elevations in aminotransferases require close attention [see **Dosage and Administration**]. Tracleer should generally be avoided in patients with elevated aminotransferases (> 3 x ULN) at baseline because monitoring liver injury may be more difficult. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥ 2 x ULN, treatment with Tracleer should be stopped. There is no experience with the re-introduction of Tracleer in these circumstances.

Teratogenicity

Tracleer is likely to cause major birth defects if used by pregnant females based on animal data [see **Contraindications**]. Therefore, pregnancy must be excluded before the start of treatment with Tracleer. Throughout treatment and for one month after stopping Tracleer, females of childbearing potential must use two reliable methods of contraception unless the patient has a tubal sterilization or Copper T 380A IUD or LNg 20 IUS inserted, in which case no other contraception is needed. Hormonal contraceptives, including oral, injectable, transdermal, and implantable contraceptives should not be used as the sole means of contraception because these may not be effective in patients receiving Tracleer [see **Drug Interactions**]. Monthly pregnancy tests should be obtained.

INDICATIONS AND USAGE

Pulmonary Arterial Hypertension

Tracleer® is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominately patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital systemic-to-pulmonary shunts (18%).

Considerations for use

Patients with WHO Class II symptoms showed reduction in the rate of clinical deterioration and a trend for improvement in walk distance. Physicians should consider whether these benefits are sufficient to offset the risk of liver injury in WHO Class II patients, which may preclude future use as their disease progresses.

DOSAGE AND ADMINISTRATION

Recommended Dosing

Tracleer treatment should be initiated at a dose of 62.5 mg twice daily for 4 weeks and then increased to the maintenance dose of 125 mg twice daily. Doses above 125 mg twice daily did not appear to confer additional benefit sufficient to offset the increased risk of liver injury.

Tablets should be administered morning and evening with or without food.

Required Monitoring

Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. If elevated aminotransferase levels are seen, changes in monitoring and treatment must be initiated.

Dosage Adjustments for Patients Developing Aminotransferase Elevations

The table below summarizes the dosage adjustment and monitoring recommendations for patients who develop aminotransferase elevations >3 X ULN during therapy with Tracleer. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥ 2 x ULN, treatment with Tracleer should be stopped. There is no experience with the re-introduction of Tracleer in these circumstances.

Table 1: Dosage Adjustment and Monitoring in Patients Developing Aminotransferase Elevations >3 x ULN

ALT/AST levels	Treatment and monitoring recommendations
> 3 and ≤ 5 x ULN	Confirm by another aminotransferase test; if confirmed, reduce the daily dose to 62.5 mg twice daily or interrupt treatment, and monitor aminotransferase levels at least every 2 weeks. If the aminotransferase levels return to pre-treatment values, continue or re-introduce the treatment as appropriate (see below).
> 5 and ≤ 8 x ULN	Confirm by another aminotransferase test; if confirmed, stop treatment and monitor aminotransferase levels at least every 2 weeks. Once the aminotransferase levels return to pre-treatment values, consider re-introduction of the treatment (see below).
> 8 x ULN	Treatment should be stopped and re-introduction of Tracleer should not be considered. There is no experience with re-introduction of Tracleer in these circumstances.

If Tracleer is re-introduced it should be at the starting dose; aminotransferase levels should be checked within 3 days and thereafter according to the recommendations above.

Use in Females of Childbearing Potential

Initiate treatment in females of child-bearing potential only after a negative pregnancy test and only in females who are using two reliable methods of contraception. Females who have had a tubal sterilization or a Copper T 380A IUD or LNg 20 IUS inserted do not require other forms of contraception. Effective contraception must be practiced throughout treatment and for one month after stopping Tracleer. Females should seek contraceptive advice as needed from a gynecologist or similar expert. Urine or serum pregnancy tests should be obtained monthly in females of childbearing potential taking Tracleer [see **Boxed Warning, Contraindications, Drug Interactions**].

Use in Patients with Pre-existing Hepatic Impairment

Tracleer should generally be avoided in patients with moderate or severe liver impairment. There are no specific data to guide dosing in hepatically impaired patients; caution should be exercised in patients with mildly impaired liver function [see **Warnings and Precautions**].

Patients with Low Body Weight

In patients with a body weight below 40 kg but who are over 12 years of age the recommended initial and maintenance dose is 62.5 mg twice daily. There is limited information about the safety and efficacy of Tracleer in children between the ages of 12 and 18 years.

Use with Ritonavir

Co-administration of Tracleer in Patients on Ritonavir

In patients who have been receiving ritonavir for at least 10 days, start Tracleer at 62.5 mg once daily or every other day based upon individual tolerability [see **Drug Interactions**].

Co-administration of Ritonavir in Patients on Tracleer

Discontinue use of Tracleer at least 36 hours prior to initiation of ritonavir. After at least 10 days following the initiation of ritonavir, resume Tracleer at 62.5 mg once daily or every other day based upon individual tolerability [see **Dosage and Administration** and **Drug Interactions**].

Treatment Discontinuation

There is limited experience with abrupt discontinuation of Tracleer. No evidence for acute rebound has been observed. Nevertheless, to avoid the potential for clinical deterioration, gradual dose reduction (62.5 mg twice daily for 3 to 7 days) should be considered.

DOSAGE FORMS AND STRENGTHS

Tracleer is available as 62.5 mg and 125 mg film-coated, unscored tablets for oral administration.

62.5 mg tablets: film-coated, round, biconvex, orange-white tablets, embossed with identification marking "62,5"

125 mg tablets: film-coated, oval, biconvex, orange-white tablets, embossed with identification marking "125"

CONTRAINDICATIONS

Pregnancy Category X *[see BOXED WARNING]*

Use of Tracleer is contraindicated in females who are or may become pregnant. While there are no adequate and well controlled studies in pregnant females, animal studies show that Tracleer is likely to cause major birth defects when administered during pregnancy. In animal studies, bosentan caused teratogenic effects including malformations of the head, mouth, face, and large blood vessels. Therefore, pregnancy must be excluded before the start of treatment with Tracleer. Throughout treatment and for one month after stopping Tracleer, females of child bearing potential must use two reliable methods of contraception unless the patient has a tubal sterilization or Copper T 380A IUD or LNg 20 IUS inserted, in which case no other contraception is needed. Monthly pregnancy tests should also be obtained. If this drug is used during pregnancy or if a patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. [see **Use in Specific Populations**].

Use with Cyclosporine A

Co-administration of cyclosporine A and bosentan resulted in markedly increased plasma concentrations of bosentan. Therefore, concomitant use of Tracleer and cyclosporine A is contraindicated [see **Drug Interactions**].

Use with Glyburide

An increased risk of liver enzyme elevations was observed in patients receiving glyburide concomitantly with bosentan. Therefore co-administration of glyburide and Tracleer is contraindicated [see **Drug Interactions**].

Hypersensitivity

Tracleer is contraindicated in patients who are hypersensitive to bosentan or any component of the product. Observed reactions include rash and angioedema [see **Adverse Reactions**].

WARNINGS AND PRECAUTIONS

Potential Liver Injury

Elevations in ALT or AST by more than 3 x ULN were observed in 11% of bosentan-treated patients (N = 658) compared to 2% of placebo-treated patients (N = 280). Three-fold increases were seen in 12% of 95 pulmonary arterial hypertension (PAH) patients on 125 mg twice daily and 14% of 70 PAH patients on 250 mg twice daily. Eight-fold increases were seen in 2% of PAH patients on 125 mg twice daily and 7% of PAH patients on 250 mg twice daily. Bilirubin increases to ≥3 x ULN were associated with aminotransferase increases in 2 of 658 (0.3%) of patients treated with bosentan. The combination of hepatocellular injury (increases in aminotransferases of > 3 x ULN) and increases in total bilirubin (≥ 3 x ULN) is a marker for potential serious liver injury.

Elevations of AST and/or ALT associated with bosentan are dose-dependent, occur both early and late in treatment, usually progress slowly, are typically asymptomatic, and usually have been reversible after treatment interruption or cessation. Aminotransferase elevations also may reverse spontaneously while continuing treatment with Tracleer.

Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. If elevated aminotransferase levels are seen, changes in monitoring and treatment must be initiated. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥ 2 x ULN, treatment should be stopped. There is no experience with the re-introduction of Tracleer in these circumstances [see **Dosage and Administration**].

Patients with Pre-existing Hepatic Impairment

Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. Tracleer should generally be avoided in patients with moderate or severe liver impairment [see **Dosage and Administration**]. In addition, Tracleer should generally be avoided in patients with elevated aminotransferases (> 3 x ULN) because monitoring liver injury in these patients may be more difficult [see **Boxed Warning**].

Fluid Retention

Peripheral edema is a known clinical consequence of PAH and worsening PAH and is also a known effect of other endothelin receptor antagonists. In PAH clinical trials with Tracleer, combined adverse events of fluid retention or edema were reported in 1.7 percent (placebo-corrected) of patients [see **Clinical Studies**].

In addition, there have been numerous post-marketing reports of fluid retention in patients with pulmonary hypertension occurring within weeks after starting Tracleer. Patients required intervention with a diuretic, fluid management, or hospitalization for decompensating heart failure.

If clinically significant fluid retention develops, with or without associated weight gain, further evaluation should be undertaken to determine the cause, such as Tracleer or underlying heart failure, and the possible need for treatment or discontinuation of Tracleer therapy.

Decreased Sperm Counts

An open-label, single arm, multicenter, safety study evaluated the effect on testicular function of Tracleer 62.5 mg twice daily for 4 weeks, followed by 125 mg twice daily for 5 months. Twenty-five male patients with WHO functional class III and IV PAH and normal baseline sperm count were enrolled. Twenty-three completed the study and 2 discontinued due to adverse events not related to testicular function. There was a decline in sperm count of at least 50% in 25% of the patients after 3 or 6 months of treatment with Tracleer. Sperm count remained within the normal range in all 22 patients with data after 6 months and no changes in sperm morphology, sperm motility, or hormone levels were observed. One patient developed marked oligospermia at 3 months and the sperm count remained low with 2 follow-up measurements over the subsequent 6 weeks. Tracleer was discontinued and after two months the sperm count had returned to baseline levels. Based on these findings and preclinical data from endothelin receptor antagonists, it cannot be excluded that endothelin receptor antagonists such as Tracleer have an adverse effect on spermatogenesis.

Decreases in Hemoglobin and Hematocrit

Treatment with Tracleer can cause a dose-related decrease in hemoglobin and hematocrit. It is recommended that hemoglobin concentrations be checked after 1 and 3 months, and every 3 months thereafter. If a marked decrease in hemoglobin concentration occurs, further evaluation should be undertaken to determine the cause and need for specific treatment.

The overall mean decrease in hemoglobin concentration for bosentan-treated patients was 0.9 g/dL (change to end of treatment). Most of this decrease of hemoglobin concentration was detected during the first few weeks of bosentan treatment and hemoglobin levels stabilized by 4–12 weeks of bosentan treatment. In placebo-controlled studies of all uses of bosentan, marked decreases in hemoglobin (> 15% decrease from baseline resulting in values < 11 g/dL) were observed in 6% of bosentan-treated patients and 3% of placebo-treated patients. In patients with PAH treated with doses of 125 and 250 mg twice daily, marked decreases in hemoglobin occurred in 3% compared to 1% in placebo-treated patients.

A decrease in hemoglobin concentration by at least 1 g/dL was observed in 57% of bosentan-treated patients as compared to 29% of placebo-treated patients. In 80% of those patients whose hemoglobin decreased by at least 1 g/dL, the decrease occurred during the first 6 weeks of bosentan treatment.

During the course of treatment the hemoglobin concentration remained within normal limits in 68% of bosentan-treated patients compared to 76% of placebo patients. The explanation for the change in hemoglobin is not known, but it does not appear to be hemorrhage or hemolysis.

Pulmonary Veno-Occlusive Disease

Should signs of pulmonary edema occur when Tracleer is administered, the possibility of associated pulmonary veno-occlusive disease should be considered and Tracleer should be discontinued.

Prescribing and Distribution Program for Tracleer

Because of the risks of liver injury and birth defects, Tracleer is available only through a special restricted distribution program called the Tracleer Access Program (T.A.P.). Only prescribers and pharmacies registered with T.A.P. may prescribe and distribute Tracleer. In addition, Tracleer may be dispensed only to patients who are enrolled in and meet all conditions of T.A.P. Information about Tracleer and T.A.P. can be obtained by calling 1-866-228-3546.

To enroll in T.A.P., prescribers must complete the T.A.P. Tracleer (bosentan) Enrollment and Renewal Form (see T.A.P. Tracleer (bosentan) Enrollment and Renewal Form for full prescribing physician agreement) indicating agreement to:

- Read and understand the communication and educational materials for prescribers regarding the risks of Tracleer.
- Review and discuss the Tracleer Medication Guide and the risks of bosentan (including the risks of teratogenicity and hepatotoxicity) with every patient prior to prescribing Tracleer.
- Review pretreatment liver function tests (ALT/AST/bilirubin) and, for females of childbearing potential, confirm that the patient is not pregnant.
- Agree to order and monitor monthly liver function tests and, for females of childbearing potential, pregnancy tests.
- Enroll all patients in T.A.P. and renew patients' enrollment annually thereafter.
- Educate and counsel females of childbearing potential to use reliable contraception, as defined on the Tracleer Enrollment and Renewal Form, during treatment with Tracleer and for one month after treatment discontinuation.
- Counsel patients who fail to comply with the program requirements.
- Notify Actelion Pharmaceuticals US, Inc. of any adverse events, including liver injury, and report any pregnancy during Tracleer treatment.

Throughout treatment and for one month after stopping Tracleer, females of childbearing potential must use two reliable methods of contraception unless the patient has a tubal sterilization or Copper T 380A IUD or LNg 20 IUS inserted, in which case no other contraception is needed. Hormonal contraceptives, including oral, injectable, transdermal, and implantable contraceptives should not be used as the sole means of contraception because these may not be effective in patients receiving Tracleer.

ADVERSE REACTIONS

The following important adverse reactions are described elsewhere in the labeling:

Potential liver injury [see **Boxed Warning, Warnings and Precautions**]

Fluid retention [see **Warnings and Precautions**]

Clinical Studies Experience

Safety data on bosentan were obtained from 13 clinical studies (9 placebo-controlled and 4 open-label) in 870 patients with pulmonary arterial hypertension and other diseases. Doses up to 8 times the currently recommended clinical dose (125 mg twice daily) were administered for a variety of durations. The exposure to bosentan in these trials ranged from 1 day to 4.1 years (N=94 for 1 year; N=61 for 1.5 years and N=39 for more than 2 years). Exposure of pulmonary arterial hypertension patients (N=328) to bosentan ranged from 1 day to 1.7 years (N=174 more than 6 months and N=28 more than 12 months).

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.

Treatment discontinuations due to adverse events other than those related to pulmonary hypertension during the clinical trials in patients with pulmonary arterial hypertension were more frequent on bosentan (6%; 15/258 patients) than on placebo (3%; 5/172 patients). In this database the only cause of discontinuations > 1% and occurring more often on bosentan was abnormal liver function.

The adverse drug events that occurred in ≥3% of the bosentan-treated patients and were more common on bosentan in placebo-

controlled trials in pulmonary arterial hypertension at doses of 125 or 250 mg twice daily are shown in Table 2:

Adverse events* occurring in ≥3% of patients treated with bosentan 125-250 mg twice daily and more common on bosentan in placebo-controlled studies in pulmonary arterial hypertension

Adverse Event	Bosentan N=258		Placebo N=172	
	No.	%	No.	%
Respiratory Tract Infection	56	22%	30	17%
Headache	39	15%	25	14%
Edema	28	11%	16	9%
Chest Pain	13	5%	8	5%
Syncope	12	5%	7	4%
Flushing	10	4%	5	3%
Hypotension	10	4%	3	2%
Sinusitis	9	4%	4	2%
Arthralgia	9	4%	3	2%
Liver Function Test Abnormal	9	4%	3	2%
Palpitations	9	4%	3	2%
Anemia	8	3%	–	

*Note: only AEs with onset from start of treatment to 1 calendar day after end of treatment are included. All reported events (at least 3%) are included except those too general to be informative, and those not reasonably associated with the use of the drug because they were associated with the condition being treated or are very common in the treated population.

Combined data from Study-351, BREATHE-1 and EARLY

Postmarketing Experience

There have been several post-marketing reports of angioedema associated with the use of bosentan. The onset of the reported cases occurred within a range of 8 hours to 21 days after starting therapy. Some patients were treated with an antihistamine and their signs of angioedema resolved without discontinuing Tracleer.

The following additional adverse reactions have been reported during the post approval use of Tracleer. Because these adverse reactions are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to Tracleer exposure:

- Unexplained hepatic cirrhosis [see **Boxed Warning**]
- Liver failure [see **Boxed Warning**]
- Hypersensitivity [see **Contraindications**]
- Thrombocytopenia
- Rash
- Jaundice
- Anemia requiring transfusion
- Neutropenia and leukopenia

DRUG INTERACTIONS

Cytochrome P450 Summary

Bosentan is metabolized by CYP2C9 and CYP3A. Inhibition of these enzymes may increase the plasma concentration of bosentan (see ketoconazole). Concomitant administration of both a CYP2C9 inhibitor (such as fluconazole or amiodarone) and a strong CYP3A inhibitor (e.g., ketoconazole, itraconazole) or a moderate CYP3A inhibitor (e.g., amprenavir, erythromycin, fluconazole, diltiazem) with bosentan will likely lead to large increases in plasma concentrations of bosentan. Co-administration of such combinations of a CYP2C9 inhibitor plus a strong or moderate CYP3A inhibitor with Tracleer is not recommended.

Bosentan is an inducer of CYP3A and CYP2C9. Consequently plasma concentrations of drugs metabolized by these two isozymes will be decreased when Tracleer is co-administered. Bosentan had no relevant inhibitory effect on any CYP isozyme in vitro (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A). Consequently, Tracleer is not expected to increase the plasma concentrations of drugs metabolized by these enzymes.

Hormonal Contraceptives

Hormonal contraceptives, including oral, injectable, transdermal, and implantable forms, may not be reliable when Tracleer is co-administered. Females should practice additional methods of contraception and not rely on hormonal contraception alone when taking Tracleer [see **Boxed Warning, Contraindications**].

An interaction study demonstrated that co-administration of bosentan and a combination oral hormonal contraceptive produced average decreases of norethindrone and ethinyl estradiol levels of 14% and 31%, respectively. However, decreases in exposure were as much as 56% and 66%, respectively, in individual subjects.

Cyclosporine A

The concomitant administration of bosentan and cyclosporine A is contraindicated [see **Contraindications**].

During the first day of concomitant administration, trough concentrations of bosentan were increased by about 30-fold. The mechanism of this interaction is most likely inhibition of transport protein-mediated uptake of bosentan into hepatocytes by cyclosporine. Steady-state bosentan plasma concentrations were 3- to 4-fold higher than in the absence of cyclosporine A. Co-administration of bosentan decreased the plasma concentrations of cyclosporine A (a CYP3A substrate) by approximately 50%.

Glyburide

An increased risk of elevated liver aminotransferases was observed in patients receiving concomitant therapy with glyburide. Therefore, the concomitant administration of Tracleer and glyburide is contraindicated, and alternative hypoglycemic agents should be considered [see **Contraindications**].

Co-administration of bosentan decreased the plasma concentrations of glyburide by approximately 40%. The plasma concentrations of bosentan were also decreased by approximately 30%. Bosentan is also expected to reduce plasma concentrations of other oral hypoglycemic agents that are predominantly metabolized by CYP2C9 or CYP3A. The possibility of worsened glucose control in patients using these agents should be considered.

Lopinavir/Ritonavir or Other Ritonavir-containing HIV Regimens

In vitro data indicate that bosentan is a substrate of the Organic Anion Transport Protein (OATP), CYP3A and CYP2C9. Ritonavir inhibits OATP and inhibits and induces CYP3A. However, the impact of ritonavir on the pharmacokinetics of bosentan may largely result from its effect on OATP.

In normal volunteers, co-administration of Tracleer 125 mg twice daily and lopinavir/ritonavir 400/100 mg twice daily increased the trough concentrations of bosentan on Days 4 and 10 approximately 48-fold and 5-fold, respectively, compared with those measured after Tracleer administered alone. Therefore, adjust the dose of Tracleer when initiating lopinavir/ritonavir [see **Dosage and Administration**].

Co-administration of Tracleer 125 mg twice daily had no substantial impact on the pharmacokinetics of lopinavir/ritonavir 400/100 mg twice daily.

Simvastatin and Other Statins

Co-administration of bosentan decreased the plasma concentrations of simvastatin (a CYP3A substrate), and its active β-hydroxy acid metabolite, by approximately 50%. The plasma concentrations of bosentan were not affected. Bosentan is also expected to reduce plasma concentrations of other statins that are significantly metabolized by CYP3A, such as lovastatin and atorvastatin. The possibility of reduced statin efficacy should be considered. Patients using CYP3A-metabolized statins should have cholesterol levels monitored after Tracleer is initiated to see whether the statin dose needs adjustment.

Rifampin

Co-administration of bosentan and rifampin in normal volunteers resulted in a mean 6-fold increase in bosentan trough levels after the first concomitant dose (likely due to inhibition of OATP by rifampin), but about a 60% decrease in bosentan levels at steady-state. The effect of bosentan on rifampin levels has not been assessed. When consideration of the potential benefits and known and unknown risks leads to concomitant use, measure liver function weekly for the first 4 weeks before reverting to normal monitoring.

Tacrolimus

Co-administration of tacrolimus and bosentan has not been studied in humans. Co-administration of tacrolimus and bosentan resulted in markedly increased plasma concentrations of bosentan in animals. Caution should be exercised if tacrolimus and bosentan are used together.

Ketoconazole

Co-administration of bosentan 125 mg twice daily and ketoconazole, a potent CYP3A inhibitor, increased the plasma concentrations of bosentan by approximately 2-fold in normal volunteers. No dose adjustment of bosentan is necessary, but increased effects of bosentan should be considered.

Warfarin

Co-administration of bosentan 500 mg twice daily for 6 days in normal volunteers, decreased the plasma concentrations of both S-warfarin (a CYP2C9 substrate) and R-warfarin (a CYP3A substrate) by 29 and 38%, respectively. Clinical experience with concomitant administration of bosentan and warfarin in patients with pulmonary arterial hypertension did not show clinically relevant changes in INR or warfarin dose (baseline vs. end of the clinical studies), and the need to change the warfarin dose during the trials due to changes in INR or due to adverse events was similar among bosentan- and placebo-treated patients.

Digoxin, Nimodipine, and Losartan

Bosentan has no significant pharmacokinetic interactions with digoxin and nimodipine, and losartan has no significant effect on plasma levels of bosentan.

Sildenafil

In normal volunteers, co-administration of multiple doses of 125 mg twice daily bosentan and 80 mg three times daily sildenafil resulted in a reduction of sildenafil plasma concentrations by 63% and increased bosentan plasma concentrations by 50%. The changes in plasma concentrations were not considered clinically relevant and dose adjustments are not necessary. This recommendation holds true when sildenafil is used for the treatment of pulmonary arterial hypertension or erectile dysfunction.

Iloprost

In a small, randomized, double-blind, placebo-controlled study, 34 patients treated with bosentan 125 mg twice daily for at least 16 weeks tolerated the addition of inhaled iloprost (up to 5 mcg 6 to 9 times per day during waking hours). The mean daily inhaled dose was 27 mcg and the mean number of inhalations per day was 5.6.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category X: Teratogenic Effects [see Contraindications]

Use of Tracleer is contraindicated in females who are or may become pregnant. While there are no adequate and well controlled studies in pregnant females, animal studies show that Tracleer is likely to cause major birth defects when administered during pregnancy. Bosentan caused teratogenic effects in animals including malformations of the head, mouth, face, and large blood vessels. If this drug is used during pregnancy or if a patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Females of childbearing potential should have a negative pregnancy test before starting treatment with Tracleer. The prescriber should not dispense a prescription for Tracleer without documenting a negative urine or serum pregnancy test performed during the first 5 days of a normal menstrual period and at least 11 days after the last unprotected act of sexual intercourse. Follow-up urine or serum pregnancy tests should be obtained monthly in females of childbearing potential taking Tracleer. The patient should contact her physician immediately for pregnancy testing if onset of menses is delayed or pregnancy is suspected. If the pregnancy test is positive, the physician and patient must discuss the risks to her, the pregnancy, and the fetus.

Drug interaction studies show that Tracleer reduces serum levels of the estrogen and progestin in oral contraceptives. Based on these findings, hormonal contraceptives (including oral, injectable, transdermal, and implantable contraceptives) may be less effective for preventing pregnancy in patients using Tracleer and should not be used as a patient's only contraceptive method [see **Drug Interactions**]. Females of childbearing potential using Tracleer must use two reliable forms of contraception unless she has a tubal sterilization or has a Copper T 380A IUD or LNg 20 IUS. In these cases, no additional contraception is needed. Contraception should be continued until one month after completing Tracleer therapy. Females of childbearing potential using Tracleer should seek contraception counseling from a gynecologist or other expert as needed.

Bosentan was teratogenic in rats given oral doses two times the maximum recommended human dose [MRHD] (on a mg/ m^2 basis). In an embryo-fetal toxicity study in rats, bosentan showed dose-dependent teratogenic effects, including malformations of the head, mouth, face and large blood vessels. Bosentan increased stillbirths and pup mortality at oral doses 2 and 10 times the MRHD (on a mg/m^2 basis). Although birth defects were not observed in rabbits given oral doses of up to the equivalent of 10.5 g/day in a 70 kg person, plasma concentrations of bosentan in rabbits were lower than those reached in the rat. The similarity of malformations induced by bosentan and those observed in endothelin-1 knockout mice and in animals treated with other endothelin receptor antagonists indicates that teratogenicity is a class effect of these drugs [see **Nonclinical Toxicology**].

Nursing mothers

It is not known whether Tracleer is excreted into human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from Tracleer, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric use

Safety and efficacy in pediatric patients have not been established.

Geriatric use

Clinical studies of Tracleer did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. Clinical experience has not identified differences in responses between elderly and younger patients. In general, caution should be exercised in dose selection for elderly patients given the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this age group.

Hepatic Impairment

Because there is *in vitro* and *in vivo* evidence that the main route of excretion of bosentan is biliary, liver impairment could be expected to increase exposure (C_{max} and AUC) of bosentan. Mild liver impairment was shown not to impact the pharmacokinetics of bosentan. The influence of moderate or severe liver impairment on the pharmacokinetics of Tracleer has not been evaluated. There are no specific data to guide dosing in hepatically impaired patients; caution should be exercised in patients with mildly impaired liver function. Tracleer should generally be avoided in patients with moderate or severe liver impairment [see **Dosage and Administration, Warnings and Precautions**].

Renal Impairment

The effect of renal impairment on the pharmacokinetics of bosentan is small and does not require dosing adjustment.

Patients with Low Body Weight [See Dosage and Administration].

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carinogenesis and Mutagenesis

Two years of dietary administration of bosentan to mice produced an increased incidence of hepatocellular adenomas and carcinomas in males at doses as low as 450 mg/kg/day (about 8 times the maximum recommended human dose [MRHD] of 125 mg twice daily, on a mg/m^2 basis). In the same study, doses greater than 2000 mg/kg/day (about 32 times the MRHD) were associated with an increased incidence of colon adenomas in both males and females. In rats, dietary administration of bosentan for two years was associated with an increased incidence of brain astrocytomas in males at doses as low as 500 mg/kg/day (about 16 times the MRHD). In a comprehensive battery of *in vitro* tests (the microbial mutagenesis assay, the unscheduled DNA synthesis assay, the V-79 mammalian cell mutagenesis assay, and human lymphocyte assay) and an *in vivo* mouse micronucleus assay, there was no evidence for any mutagenic or clastogenic activity of bosentan.

Reproductive and Developmental Toxicology

Bosentan was teratogenic in rats given oral doses ≥60 mg/kg/day. In an embryo-fetal toxicity study in rats, bosentan showed dose-dependent teratogenic effects, including malformations of the head, mouth, face and large blood vessels. Bosentan increased stillbirths and pup mortality at oral doses of 60 and 300 mg/kg/day. Although birth defects were not observed in rabbits given oral doses of up to 1500 mg/kg/day, plasma concentrations of bosentan in rabbits were lower than those reached in the rat. The similarity of malformations induced by bosentan and those observed in endothelin-1 knockout mice and in animals treated with other endothelin receptor antagonists indicates that teratogenicity is a class effect of these drugs.

Impairment of Fertility/Testicular Function

The development of testicular tubular atrophy and impaired fertility has been linked with the chronic administration of certain endothelin receptor antagonists in rodents.

Treatment with bosentan at oral doses of up to 1500 mg/kg/day (50 times the MRHD on a mg/m^2 basis) or intravenous doses up to 40 mg/kg/day had no effects on sperm count, sperm motility, mating performance or fertility in male and female rats. An increased incidence of testicular tubular atrophy was observed in rats given bosentan orally at doses as low as 125 mg/kg/day (about 4 times the MRHD and the lowest doses tested) for two years but not at doses as high as 1500 mg/kg/day (about 50 times the MRHD) for 6 months. Effects on sperm count and motility were evaluated only in the much shorter duration fertility studies in which males had been exposed to the drug for 4-6 weeks. An increased incidence of tubular atrophy was not observed in mice treated for 2 years at doses up to 4500 mg/kg/day (about 75 times the MRHD) or in dogs treated up to 12 months at doses up to 500 mg/kg/day (about 50 times the MRHD).

PATIENT COUNSELING INFORMATION

Advise patients to consult the Medication Guide on the safe use of Tracleer.

Important Information

- Monthly monitoring of serum aminotransferases

The physician should discuss with the patient the importance of monthly monitoring of serum aminotransferases.

- Pregnancy testing and avoidance of pregnancy

Patients should be advised that Tracleer is likely to cause birth defects based on animal studies. Tracleer treatment should only be initiated in females of childbearing potential following a negative pregnancy test. Females of childbearing potential must have monthly pregnancy tests and need to use two different forms of contraception while taking Tracleer and for one month after discontinuing Tracleer. Females who have a tubal ligation or a Copper T 380A IUD or LNg 20 IUS can use these contraceptive methods alone. Patients should be instructed to immediately contact their physician if they suspect they may be pregnant and should seek contraceptive advice from a gynecologist or similar expert as needed.

- Drug Interactions

The physician should discuss with the patient possible drug interactions with Tracleer, and which medications should not be taken with Tracleer. The physician should discuss the importance of disclosing all concomitant or new medications.

Manufactured for: Actelion Pharmaceuticals US, Inc. South San Francisco, CA 94080, USA
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References for previous pages: 1. Data on file, Actelion Pharmaceuticals.

ACTELION

Sleep Apnea Tied to Diabetic Retinopathy, Neuropathy

BY SHERRY BOSCHERT
Elsevier Global Medical News

SAN DIEGO – Obstructive sleep apnea in patients with type 2 diabetes predicted a three- to fourfold higher risk for diabetic peripheral neuropathy or sight-threatening retinopathy, separate analyses found.

The results suggest that OSA may play a role in the development of peripheral neuropathy and sight-threatening retinopathy in people with diabetes, Dr. Abd Tahrani and his associates reported at the meeting the annual scientific sessions of the American Diabetes Association. Ongoing studies are exploring the possible mechanisms involved.

Further research also is warranted on the possibility that treating OSA might affect the development or progression of retinopathy or neuropathy, added Dr. Tahrani of the University of Birmingham (England), where he is a research fellow for the U.K. National Institute for Health Research.

The prospective studies recruited random patients from a hospital-based, outpatient diabetes clinic in the United Kingdom. Individuals were excluded if they had a known respiratory disorder, including OSA. Patients had a mean age of 59 years and a mean 11-year history of diabetes, and 48% were white.

Participants underwent one night of home-based multichannel respiratory monitoring, and were considered to have OSA if they had an apnea-hypopnea index of at least 5 events per hour.

In 224 patients who also were assessed for sight-threatening retinopathy, 63% had OSA and 38% had sight-threatening retinopathy. Patients with OSA were significantly more likely to have sight-threatening retinopathy (48%) than were patients without OSA (20%).

The study defined sight-threatening retinopathy as the presence of preproliferative or proliferative retinopathy, maculopathy, or the need for laser treatment.

After adjustment for a wide range of possible confounders, patients with OSA were 3.6 times more likely to have sight-threatening retinopathy, 5 times more likely to have advanced diabetic retinopathy, and 4.4 times more likely to have maculopathy than were patients without obstructive sleep apnea.

In a separate study by the same investigators involving 231 patients who were assessed for both OSA and peripheral neuropathy, 65% had OSA and 45% had diabetic peripheral neuropathy. Patients with OSA reported more neuropathic symptoms.

Among patients with OSA, 60% had diabetic peripheral neuropathy, compared with 27% of patients without sleep apnea.

OSA conferred a significant threefold higher risk for peripheral neuropathy after adjustment for a wide variety of potentially confounding variables, Dr. Tahrani reported. The severity of peripheral neuropathy correlated with the severity of sleep apnea.

OSA was prevalent in 75% and 52% of white and South Asian patients, respectively. Likewise, diabetic peripheral neuropathy was more prevalent in whites (56% vs. 40%). Both differences were significant.

The lower prevalence of OSA in the South Asian patients might be one reason for the lower prevalence of diabetic peripheral neuropathy, the investigators suggested.

Dr. Tahrani reported having no conflicts of interest. ■

COMMENTARY

Dr. Paul Selecky, FCCP, comments: The link between OSA and diabetes is well established, including studies that show an improvement in diabetes management when the patient is successfully treated with continuous positive airway pressure. These studies demonstrate that the link is even tighter, demonstrated by the increased incidence of retinopathy and neuropathy in OSA patients not yet on treatment. It will be exciting to learn if CPAP can have a beneficial effect and if it is worth further study.

Sleep Deficit Costly

Toll • *from page 1*

preschool predict sleep duration at kindergarten," she explained.

Controlling for the outcome of interest at the preschool time point, sex, ethnicity, and family income, researchers found that less sleep at preschool significantly predicted worse scores on parent-reported hyperactivity and attention at kindergarten, whereas parent-reported hyperactivity and attention at preschool did not predict sleep duration at kindergarten, Dr. Gaylor stated. "These findings suggest that some children who are not getting adequate sleep may be at risk for developing behavioral problems manifested by hyperactivity, impulsivity, and problems sitting still and paying attention," she said. The results extend those of a previous study in which she and her colleagues determined that having a consistent bedtime was the most reliable predictor of positive developmental outcomes by age 4 years, she noted.

The Obesity Link

In a twin study designed to look more closely at the previously reported link between short sleep duration and elevated body mass index, Dr. Nathaniel Watson of the University of Washington in Seattle and his colleagues determined that short sleep may potentiate an underlying genetic mechanism for obesity.

The investigators examined whether sleep duration modified genetic and environmental influences on BMI in 1,811 pairs of twins drawn from the population-based University of Washington Twin Registry. The mean age of the study participants was 36.6 years. The participants provided self-reported information on height and weight, which was used to calculate BMI, as well as on habitual sleep duration, Dr. Watson said. The mean BMI of the group was 25.4 kg/m^2, and the mean sleep duration was 7.18 hours, he said.

Using behavioral genetic interaction models, the investigators found significant relationships between habitual sleep duration and genetic and shared environmental influences on BMI. Specifically, longer sleep duration was associated with decreased BMI, Dr. Watson reported. "When sleep duration was 7 hours, the heritability of BMI was more than double [70%] that observed when sleep duration was 9 hours [33%]," he said, noting that "there appears to be something about short sleep that creates a permissive environment for expression of obesity-related genes." Similarly, he added, longer sleep duration may suppress genetic influences on body weight.

The findings are an important addition to the existing body of research on the relationship between sleep duration and BMI, Dr. Watson said. "Studies attempting to identify specific genotypes for BMI may benefit from considering the moderating role of sleep duration."

A connection between sleepiness and lack of self-control with respect to dietary choices may also contribute to the sleep loss/obesity equation, according to a study presented by William Killgore, Ph.D., of Harvard Medical School in Boston.

To test their hypothesis that greater daytime sleepiness correlates with reduced prefrontal cortex response during passive viewing of images of high-calorie foods, Dr. Killgore and his colleagues analyzed the functional magnetic resonance imaging (fMRI) scans of 12 healthy adults obtained while they were shown pictures of high-calorie foods, low-calorie foods, and control images of plants and rocks. Using a second-level regression model, the researchers correlated the fMRI findings with subjects' self-reported daytime sleepiness, assessed via the Epworth Sleepiness Scale (ESS).

"Greater ESS scores correlated with reduced activation in the dorsolateral prefrontal cortex when high-calorie vs. low-calorie food images were perceived," Dr. Killgore reported, noting that this region is typically implicated in attention and inhibitory processing. Similarly, greater daytime sleepiness was also associated with increased activation in the right parietal and inferior temporal cortex, he said.

The findings suggest the possibility that sleepiness may affect an individual's inhibitory control when he or she is exposed to highly appetizing, high-calorie foods, according to Dr. Killgore, although it's uncertain as of yet whether the observed patterns relate to actual food consumption, he said.

COMMENTARY

Dr. Paul Selecky, FCCP, comments: As science pulls back the curtain on the effects of acute and chronic sleep deprivation, we continue to learn more about the important effects of sleep on our health. These three studies can be added to a growing list of benefits of sleep and detriments of its loss, including memory, school grades, athletic performance, diabetes risk, hypertension, driving safety, growth hormone, immunity, creativity, and more. As the old adage says, "There is nothing better than a good night's sleep."

Marital Discord

Although most sleep research focuses on the individual, the fact that sleep problems and relationship trouble often co-occur led Wendy M. Troxel, Ph.D., of the University of Pittsburgh, and her colleagues to consider the dyadic nature of sleep in a recent study. The investigators examined the bidirectional links between nightly sleep and daily marital interactions among 35 healthy married couples (mean age, 32 years) by correlating the actigraph results for sleep latency, wakefulness after sleep onset, and total sleep time of each partner over 10 nights, with daily self-reported positive and negative marital interactions assessed via electronic diaries during the same period.

"We found stronger evidence linking sleep to the next day's marital interactions, rather than the reverse direction," reported Dr. Troxel. Specifically, wives' prolonged sleep latency significantly predicted their own and their husbands' reports of more negative and less positive interactions the next day, even after adjustment for depressive symptoms, whereas the quality of marital interactions did not appear to predict sleep measures in women, she said. The sleep quality of husbands did not appear to affect their own or their wives' reports of next-day marital interactions; however, for men, a higher level of positive marital interactions predicted shorter total sleep duration the next night.

The findings suggest, perhaps, that "men are more likely to repress their feelings or not be as aware" of mood changes, whereas women are more likely to express their emotional concerns and to "drive the emotional climate of the relationship," Dr. Troxel said. The results highlight the potential interpersonal consequences of sleep disorders, and as such may have important clinical implications, she said.

The presenters reported no financial conflicts relevant to their respective presentations. ■

Jaw Surgery Limits Severe Sleep Apnea in Soldiers

BY DIANA MAHONEY
Elsevier Global Medical News

MINNEAPOLIS – Maxillomandibular advancement may be a reasonable option for patients who have severe sleep apnea and are unable to tolerate continuous positive airway pressure therapy, according to a study by the Department of Veterans Affairs.

In maxillomandibular advancement (MMA), the upper and lower jaws are moved forward to optimize the airway and minimize soft-tissue blockages. Dr. Vincent Mysliwiec, FCCP, and his colleagues in the Critical Care Medicine and Sleep Medicine Service at Madigan Healthcare System, Joint Base Lewis-McChord, Tacoma, Wash., evaluated outcomes in an active-duty population.

"Obstructive sleep apnea is an increasingly common diagnosis in soldiers, and those soldiers with more severe cases are not deployable without going through an extensive waiver process," Dr. Mysliwiec said at the annual meeting of the Associated Professional Sleep Societies. "We wanted to assess whether [MMA] represents a surgical cure that can potentially remove the requirement for CPAP in these individuals and, in so doing, increase the number of soldiers who are fully deployable."

The researchers reviewed all of the MMA procedures performed for obstructive sleep apnea at their institution in 2006-2009 and identified 37 soldiers who had severe disease – defined as an apnea-hypopnea index (AHI) of more than 30 events/hr – and underwent the surgery as well as pre- and postoperative polysomnography. The primary study outcomes were comparisons of the pre- and postoperative AHI and minimum nocturnal oxyhemoglobin saturation. Surgical cure was defined as an AHI reduction of at least 50%, compared with preoperative AHI, and a postoperative AHI of less than 15.

The mean body mass index of the study cohort was 29 kg/m^2, and the mean preoperative AHI was 50.5, Dr. Mysliwiec reported. Following the procedure, "the mean postoperative [AHI] dropped significantly to 13.8," he said. "Twenty-two of the soldiers – nearly 60% of the group – reduced their [AHI] by at least half, which met the criteria for surgical cure." Further, he said, 16 of the soldiers had a postoperative AHI of less than 5, "meaning they had no residual disease at all following the procedure." One study patient did not experience a clinically significant reduction in AHI following the surgery. The mean minimum nocturnal oxyhemoglobin saturation increased postoperatively from 85% to 86%, a non-significant change ($P = .21$; standard deviation for both measures, 7%).

"Maxillomandibular advancement significantly reduced the severity of sleep apnea for our patients and improved the quality of their sleep," Dr. Mysliwiec said. "These findings could improve the standard of care for civilians and active-duty service members with severe obstructive sleep apnea who can't tolerate CPAP or have failed other soft-tissue procedures." ■

VITALS

Major Finding: After maxillomandibular advancement surgery, the severity of obstructive sleep apnea was reduced by at least 50% in 22 patients, of whom 16 had no residual disease.

Data Source: A VA retrospective review of 37 active-duty service personnel.

Disclosures: Dr. Mysliwiec reported having no financial conflicts of interest.

COMMENTARY

Dr. Paul Selecky, FCCP, comments: Jaw surgery has its place in the treatment of obstructive sleep apnea (OSA) and has been limited largely to patients who have severe OSA and cannot tolerate treatment with the usually successful continuous positive airway pressure (CPAP), and who have an upper airway anatomy that is conducive to surgery. This study group is a unique population of active-duty personnel with OSA who would not be able to be deployed, as duty would exclude the availability of CPAP treatment. The impact of MMA treatment on the general population of OSA patients is less evident.

FROM THE CEO

Make No Little Plans

"Make no little plans. They have no magic to stir men's blood and probably themselves will not be realized. Make big plans; aim high in hope and work, remembering that a noble, logical diagram once recorded will never die, but long after we are gone will be a living thing, asserting itself with ever-growing insistency. .... Think big."
—Daniel Burnham, architect and urban planner, 1846-1912

BY PAUL A. MARKOWSKI, CAE

With Burnham's words in mind, the Board of Regents approved the ACCP Strategic Plan 2011-2012 in June. However, the process that led to this blueprint for the future of the College originated last year. At that time, ACCP leaders and staff "thought big" by identifying and acknowledging our core competency—providing the best clinical education in chest medicine—and updated our mission and vision statements accordingly. We developed the first-of-its-kind ACCP strategic plan, which set ambitious goals that looked several years ahead and outlined specific strategies and metrics for measuring our success.

How did we do?

For starters, the College ended the fiscal year in a strong financial position, with a $2.26 million positive bottom line. We surpassed the 18,000 membership mark; the *CHEST* journal received the highest impact factor and ranking in its 75-year history; the largest number of international registrants attended CHEST 2010; and The CHEST Foundation launched its new branding campaign, Web site, and public-facing program, OneBreath™: Make The Most Of It.

Most recently, the American Board of Internal Medicine approved our performance improvement module on VTE prevention for MOC credit. We took our first train-the-trainer program for simulation education to Saudi Arabia. We launched the *CHEST* journal podcast series. The Foundation also had the highest number of assets in the last 5 years—$9 million—closing FY 2011 with an $822,000 gain.

In short, the ACCP met or exceeded the demanding metrics that we delineated in our strategic plan.

ACCP Strategic Plan 2011-2012

The *ACCP Strategic Plan 2011-2012* builds on our strategic plan from last year in several key ways. First, an updated vision statement reflects our commitment to eliminating disparities in health care. Second, this streamlined plan focuses on a few critical goals for the ACCP as a whole; and, third, for the first time, the College articulates its core values—the foundation for how we achieve our mission and vision. The *ACCP Strategic Plan 2011-2012* also includes ambitious and forward-looking strategies to achieve identified goals, along with metrics to rigorously track progress along the way. The Foundation plays a prominent role, as well, by, for example, increasing public awareness through its OneBreath™ campaign.

Following are highlights from the *ACCP Strategic Plan 2011-2012*.

▶ ***Our Mission and Vision: Why the ACCP exists and what the College aspires to be.***

Mission: To promote the prevention, diagnosis, and treatment of chest diseases through education, communication, and research.

Vision: As the global leader in providing education in cardiopulmonary, critical care, and sleep medicine, the ACCP will promote diversity to optimize health, advance patient care, and support research while fostering health equity.

▶ ***Our Goals: How the ACCP will realize its vision.***

Goal 1: Continue to implement a new association management system (AMS). Improving our technology infrastructure, including integrating and implementing a new AMS, is key to moving the College forward in all areas.

Goal 2: Maintain a strong and diverse financial base. Sound financial planning, along with identifying and securing alternative revenue sources, is integral to supporting ACCP efforts.

Goal 3: Maintain and diversify our successful programs (eg, AQuIRE, simulation, development of education products). Providing the best clinical education in chest medicine necessitates expanding and diversifying existing ACCP programs, such as AQuIRE, simulation, and the development of education products.

Goal 4: Grow ACCP membership in various ways, such as expanding categories for international, fellows-in-training, nonphysician providers, and others. Targeting key segments for membership growth, as well as implementing alternative membership models and policies, enhances the inclusiveness, efficiency, and financial position of the ACCP.

Goal 5: Increase public awareness/branding of the ACCP.

The ACCP strengthens its impact by forging new partnerships with healthcare and other societies, as well as by reaching out to the public through the OneBreath™ campaign.

Goal 6: Ensure that the ACCP leadership structure is strategically aligned to advance College priorities. Exceptional goals demand exceptional leadership. The College will continuously develop its current and future leaders to meet identified organizational needs.

▶ ***Our Core Values: The foundation for how the ACCP achieves its mission and vision; the organizational culture that we aspire to and how we treat one another and our constituents.***

Collegiality: We foster collegiality between and among members and staff in all ACCP activities.

Innovation: We cultivate innovation through an atmosphere of creativity, optimism, and empowerment.

Transparency: We promote transparency by ensuring access to appropriate and accurate information for members, staff, other stakeholders, and interested members of the public.

Diversity: We promote diversity of background, expertise, and other needed resources at all levels of the ACCP.

Excellence: We strive for the highest standards in everything that we do.

Integrity: We treat members, staff, and other stakeholders with integrity by accepting responsibility for our actions, being truthful, and following through with commitments.

Results-Oriented: We are results-oriented. We measure our progress toward the ACCP mission and vision, as well as evaluate the performance of our programs and services.

We thank our leaders and staff, who thoughtfully considered what it meant to take the ACCP to the next level and how to get there. Those deliberations from an environmental snapshot and March 2011 planning session formed the basis for the *ACCP Strategic Plan 2011-2012*. While we are proud of the work presented here, the current plan is by no means a finished product. Leaders and staff will implement identified strategies and ensure that programs and activities are aligned with the plan. The Board of Regents also will make certain that the College is on course to achieve its goals and modify the plan, as necessary. Indeed, our strategic plan will become a way of life at the ACCP, guiding decision making at all levels.

The ACCP creates its future though effective strategic planning. We are excited about this propitious future and trust that you will be, as well. We welcome your comments regarding your *ACCP Strategic Plan 2011-2012* and look forward to rolling up our sleeves with you—as College leaders, members, and other supporters—to realize this "big plan." As Burnham led the development of major cities like Chicago and Washington, DC, so too will the ACCP move forward as the global leader in clinical education for chest medicine. ■

Critical Care Commentary

Integrative Oncology and the Memorial Sloan-Kettering Cancer Center Critical Care Experience

"Integrative Oncology" is a synthesis of mainstream treatment and complementary therapies in cancer care. Complementary therapies are noninvasive and nonpharmacologic adjuncts to mainstream cancer treatment. These therapies do not directly affect or treat disease but help to relieve pain and distress by controlling physical and emotional symptoms.

In the late 1990s, the Memorial Sloan-Kettering Cancer Center (MSKCC) Board of Overseers acted on its consensus that optimal patient care requires more than expert cancer management and mandated a broader emphasis on an integrative approach to better manage patients' physical and emotional needs. The author was recruited to actualize this concept, and MSKCC has since developed an Integrative Medicine Service (IMS) within the Department of Medicine that can serve as a prototype for other centers around the world. The IMS provides clinical care, as well as research and training in collaboration with clinicians, researchers, and others throughout the institution. The service has also created a Web site to provide physicians and the public with "solid" information about herbal remedies, vitamins, and other dietary supplements (www.MSKCC.org/AboutHerbs).

A primary focus of the IMS is to study and deploy evidence-based, rational, complementary therapies to patients, their families, and staff. These approaches may be perceived as extensions of the supportive care previously associated with oncology for decades. Simultaneously, the IMS works diligently to curtail the use of "alternative," unproven therapies promoted for use in lieu of mainstream cancer treatments, also known as quackery.

The ICU staff requests integrative medicine consultations to reduce patient agitation, relieve pain, or reduce levels of narcotics needed to maintain comfort. These interventions are cost-effective and produce no negative side effects. Complementary therapies help normalize and humanize the high-tech ICU environment. Such consultations are also used by the ICU team to assist in navigating challenging interactions with patients and family members who insist on using "alternative" therapies (ie, magnet and light therapies, herbs, and supplements).

Integrative therapies available to IMS patients include massage therapy, mind-body techniques, music therapy, acupuncture, and herbs and supplements, as well as the provision of information about some herbal compounds and other dietary supplements. Each of these has a role in critical care.

DR. NEIL HALPERN, FCCP
Section Editor,
Critical Care Commentary

Massage Therapy

The main goal of massage therapy in the ICU is to reduce physical pain, induce relaxation, and provide comfort. Touch therapies, such as foot massage, also offer the benefits of a caring interaction and the human touch. The type of massage intervention is determined by the patient's clinical status and preference. In the hands of licensed massage therapists trained to work with cancer patients, this is a very safe and therapeutic intervention.

MSKCC has offered massage therapy in the ICU for many years. A 3-year study conducted at MSKCC of 1,290 study patients showed that massage therapy brought sustained relief from pain, fatigue, nausea, and other symptoms. Symptom scores were reduced by approximately 50%, even in patients who reported high baseline scores. Importantly, the benefits persisted for many patients throughout a 48-h follow-up period (Cassileth et al. *J Pain Symptom Manage*. 2004; 28[3]:244).

Mind-Body Techniques

Mind-body interventions, including meditation, self-hypnosis, yoga, qigong, and tai chi use the mind's capacity to influence bodily function and symptoms.

Multiple studies demonstrate that meditation decreases pain, anxiety, stress, and insomnia in cancer patients. A 2007 study assessed the value of presurgical hypnosis for decreasing the need for intraoperative anesthesia and analgesics, as well as lowering the side effects associated with breast cancer surgery. Subjects in the hypnosis group required less propofol and lidocaine as compared with the control group. They also reported less pain intensity and unpleasantness (Montgomery et al. *J Natl Cancer Inst*. 2007; 99[17]: 1304). Both meditation and self-hypnosis, a deeper form of meditation, can easily be learned by patients and family members and applied, when needed, to relax and reduce stress. These stress reduction approaches are tools with which patients can help themselves, and a dose-response relationship exists, where better results are seen with more meditation practice.

Music Therapy

Music therapists, musicians with graduate training in music therapy, use music to reach patients. Music therapy is felt to encourage healing and promote well-being. Benefits from music therapy may be derived passively (patient listens) or interactively (patient participates). The music can be tailored to the patient's preference in terms of the music selected and the instruments used. Typically, we bring portable instruments to the ICU, ie, guitar, keyboard, and harp (Figure). Percussion instruments are available for the patient to play as appropriate. Music therapy also permits caregiver and family member participation.

Music therapy is valuable for patients in the ICU, especially for those who are noncommunicative or withdrawn. It reduces the sense of isolation often experienced. Music therapy also offers gentle stimulation for patients who are being weaned off sedatives and helps patients relax during procedures, such as extubation. In a serendipitous result of a music therapy study designed for patients, the attendant physicians and nurses unexpectedly experienced helpful emotional, cognitive, and team effects (O'Callaghan and Magill. *Palliat Support Care*. 2009;7[2]:219).

Courtesy Barrie R. Cassileth, PhD

Portable instruments, such as guitar, keyboard, and harp, can be brought into the ICU.

Acupuncture

Acupuncture is a 3,000-year-old component of traditional Chinese medicine. It involves stimulating one or more predetermined points on the body with sterile, filiform needles, which are approximately the width of human hair. The needles target specific acupuncture points on the body that are dense with sensory receptors. These acupoints have lower electrical resistance and are closer to superficial nerve junctions (Ma. *J Altern Complement Med*. 2003;9[2]:207).

Acupuncture reduces many symptoms experienced by cancer patients in all stages of treatment, including dyspnea, fatigue, hot flashes, sexual dysfunction, urinary problems, osteoarthritis, neuropathy, xerostomia, and more. Most relevant to patients in the ICU, acupuncture can relieve anxiety, depression, stress, and pain, and it can reduce the amount of opioids required to maintain patient comfort. Randomized clinical trials show that relief offered by acupuncture is not a placebo effect. A phase III MSKCC trial reported that acupuncture reduced pain and dysfunction in cancer patients with a history of neck dissection. In addition, acupuncture relieved xerostomia in this population (Pfister et al. *J Clin Oncol*. 2010;28[15]:2565). A companion functional MRI (fMRI) study illustrated that true vs sham acupuncture produced neuronal activation associated with increased saliva production. Signal changes on neuroimaging were correlated with changes in the appropriate cortical areas (Deng et al. *BMC Complement Altern Med*. 2008; 8:37).

Herbs and Supplements

Many cancer patients turn to herbs in the misperception that, because the products are "natural," they are safe. Herbal and most other dietary supplements are not recommended for cancer patients undergoing treatment or for people receiving prescription medications. In fact, MSKCC recommends that no herbs, high-dose vitamins, or antioxidants be taken during cancer treatment. This prohibition stems from the fact that herbal remedies, which are biologically active, may interact negatively with mainstream oncologic treatments or induce toxicities. Moreover, most dietary supplements are not standardized, many are contaminated, and there are often major discrepancies between ingredients listed on the label and the supplement's actual components.

Problems caused by herbs include:

- Garlic, gingko, ginseng, vitamin E: interfere with blood coagulation
- Ephedra: lowers blood sugar
- St. John's Wort, valerian: may affect blood levels of chemotherapy
- Kava: can cause kidney failure

Herb-drug interactions represent an important problem. The MSKCC AboutHerbs Web site (www.mskcc.org/AboutHerbs) offers routinely updated and comprehensive, evidence-based data on more than 250 herbs, botanicals, antioxidants, vitamins, bogus therapies, and more, at no charge. Portals are available for patients and physicians. In conclusion, integrative oncology can benefit patients, family members, and staff in the ICU by relieving symptoms of physical pain and emotional distress and maximizing the serenity of critically ill patients throughout their ICU stay. ■

Barrie R. Cassileth, PhD
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Memorial Sloan-Kettering Cancer Center
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NETWORKS

Neuromuscular Respiratory Medicine, Women's Lung Cancer, EGFR Mutational Analysis

Pediatric Chest Medicine

Embrace the Spirit of Aloha Suggestions

This October, pulmonary experts from around the world will gather in Honolulu to promote respiratory health for children. The itinerary includes a variety of modalities, each designed to engage learners and stimulate discussion. It will include simulation laboratories, clinical workshops, and pulmonary puzzlers, to name a few. Hawaii is an especially appropriate venue for this meeting, since aloha is more than just a greeting. It encompasses a spirit of living—a joyful sharing of life. Take this time, not only to learn, but to refresh your spirit with new ideas and an enthusiasm for our profession.

With the rapid advances in technology, we have begun to see more technology-dependent children joining pediatric practices. With these machines requiring specific training and expertise, both in a home and hospital setting, it is important that pediatricians be proficient in these processes. Therefore, this year, the Subcommittee on Pulmonary Care of Patients With Neuromuscular Disease will offer a postgraduate course on Neuromuscular Respiratory Medicine, including pediatric and adult patients. It will be hosted by experts in the respiratory care of children with neuromuscular disease and will highlight evidence- and consensus-based guidelines. Overall, the number of pediatric topics has increased this year and will include controversies in pediatric lung transplantation, asthma in unusual environments, respiratory complications of sickle cell disease, and more. Access www.accpmeeting.org for details.

Dr. Dean Edell, FCCP
Steering Committee Member

Women's Health

Current Epidemic of Lung Cancer in Women

Lung cancer is now the number one killer of women, claiming the lives of more women each year than breast cancer, colon cancer, and cervical cancer combined. This shifting paradigm in lung cancer follows the smoking trend and tobacco advertisements targeted to women. The death rate from lung cancer in US women rose 600% from 1930 to 1997 due to increases in smoking (A Report of the Surgeon General; 2001). The incidence of lung cancer among women continues to grow by 0.5% per year. Although smoking is the major cause of lung cancer, nonsmoking women are found to be at greater risk for developing lung cancer than nonsmoking men.

Molecular and genetic marker studies identify lung cancer as a collection of genetically distinct diseases. The National Comprehensive Cancer Network (NCCN) guidelines, issued by the American Society of Clinical Oncology (ASCO) for clinical management of lung cancer, recommend treating patients with drugs that target the molecular drivers of their specific tumors. Therefore, molecular and mutation analysis of diagnostic tumor tissue, such as epidermal growth factor receptor (EGFR), is critically important in lung cancer management.

Women, in particular, appear to have more frequent mutations in the EGFR as compared with men. The NCCN guidelines include EGFR mutational analysis as a category 1 recommendation in the evaluation of non-small cell lung cancer. Multiple trials focused on patients with known EGFR activating mutations have demonstrated a better response and progression-free survival for patients receiving an EGFR-tyrosine kinase inhibitor (TKIs), such as erlotinib or gefitinib compared with chemotherapy as first-line therapy. These studies have been shown to identify erlotinib sensitivity in the 88% of patients with wild-type EGFR. In addition, a set of a novel, five-gene expression signatures appeared to predict disease control with erlotinib in refractory non-small cell lung cancer irrespective of EGFR mutation. Disease control at 8 weeks was seen in 83% of patients with one gene signature vs 0% in those without it, and 64% vs 10% in a similar analysis of patients with and without the second signature (*Cancer Discovery.* 2011;1[1]:OF42). Women survive longer than men, regardless of the stage at diagnosis or treatment, but the overall survival with this disease remains abysmal. We have much work to do. The importance of performing molecular tests at this time, in particular EGFR mutation analysis, with more on the horizon (EML4-ALK), cannot be overemphasized.

Dr. Daya Upadhyay, Steering Committee Member; Dr. Heather Wakelee; and Dr. Diane Stover, FCCP

Occupational and Environmental Health

Analysis of Exhaled Breath Condensate in Environmental and Occupational Lung Diseases

A noninvasive method of exhaled breath testing is becoming increasingly important in health and diseases; however, exhaled breath analysis has not yet been widely used in occupational lung diseases. Although, study of fractional exhaled nitric oxide in exhaled breath condensate has evolved from a research tool into a clinical measurement, useful for diagnosing and monitoring asthma, very little is known about its use in occupational asthma. Despite significant molecular and biological advances, newer methods have not been frequently used in conjunction with noninvasive tests in occupational lung diseases.

Current new technologies, such as infrared, electrochemical, chemiluminescence, very sensitive modern mass spectrometry, gas chromatography, and gas chromatography mass spectrometry, can now identify thousands of unique substances in exhaled breath. These substances include elemental gases like nitric oxide and carbon monoxide and a multitude of volatile organic compounds. Furthermore, exhaled breath contains aerosolized droplets collected as exhaled breath condensate (EBC), which is composed of airway lining fluid mainly formed by water vapor and aerosol particles. EBC contains several biomolecules, including leukotrienes, 8-isoprostane, prostaglandins, nitric oxide-derived products, a wide range of metabolic end products, proteins, and a variety of cytokines and chemokines. This test is also suitable for longitudinal studies that can be used to monitor the disease progression or a response to therapy. EBC is a noninvasive, inexpensive, and easy to repeat test that can provide rapid analysis of biomarker levels in the setting of occupational and environmental exposure.

Specific gene expression profiling has tremendously influenced our understanding of the pathogenesis of several diseases. EBC can be used to identify gene expression profiles of target inflammatory mediators in asthma, such as IL-4, IL-17, RANTES, macrophage inflammatory protein (MIP)-1alpha, MIP-1beta, IL-8, IFN-gamma-inducible protein (IP)-10, TNF-alpha, TGF-beta, and eotaxin-1.

Since occupational and environmental agents induce airway sensitization causing robust inflammatory responses, application of advanced investigative technologies could be useful in environmental and occupational lung diseases. We used polymerase chain reaction (PCR) array analysis in conjunction with noninvasive EBC tests to examine the effects of ozone on human airways. PCR array performs gene expression analysis with real-time PCR sensitivity and the multi-gene profiling capability of a microarray. Unlike conventional microarray, PCR array analysis is pathway-focused and profiles the expression of a panel of genes relevant to a pathway or disease state. In our analysis, the expressions of multiple cytokine and chemokine genes, including IL-12, IL-13, CCL-5, CCL-11, and IL-13RA, were found to be highly unregulated in EBC on exposure to high ozone levels in humans. These findings suggest that EBC can be used to study gene expression profiles induced by environmental and occupational lung diseases. Integration of newer molecular and biological technologies with noninvasive exhaled breath analysis can be used to advance investigational approaches in environmental and occupational lung diseases.

Dr. Daya Upadhyay
Steering Committee Member

Product of the Month

Board Review on Demand

Review the lectures and slides presented at the 2010 board review courses whenever you want with Board Review on Demand. Course presentations are recorded and synced with slides, so you can refer back to content anytime. The Board Review on Demand is available for pulmonary, critical care, and sleep medicine in multiple media formats from Digital Conference Providers at www.dcprovidersonline.com/accp. View the content online, or download mp3 or mp4 files for use on your computer, iPhone®, iPad®, or an iPod touch®. ■

CHEST Journal Continues to Rise

The just-released 2010 Journal Citation Reports® (Thomson Reuters, 2011) data show that *CHEST* now has an impact factor of 6.519, another increase over the previous year's citation ranking. *CHEST* is the third-ranked journal out of 46 respiratory journals—unique among the top tier for its clinical focus—and is only 0.006 points behind the second-ranked journal. In addition to publishing innovative, high-impact research, *CHEST* is leading the charge: the *CHEST* journal app for Apple been downloaded over 22,000 times, and the iPad® version is in the top 100 of all medical apps in iTunes®. Recent reviews of the *CHEST* and ACCP-SEEK apps from the physicians at iMedicalApps applauded both apps for their ease of use and functionality. ■

CHEST 2011 Aloha Dress

Shopping opportunities abound in Honolulu. Pick up a Hawaiian shirt to keep cool during the meeting, and don't forget to bring home some souvenirs.

Courtesy Wikimedia Commons/Jmcstrav/Public Domain

CHEST 2011 is designed to allow you to take in the Hawaiian experience. Programs and sessions will start earlier and end by mid-afternoon, giving you time to enjoy the tropical setting. And, so you feel comfortable and relaxed in the Hawaiian setting, you are invited to dress "aloha style."

For men, the norm is slacks and an "aloha shirt," short sleeved dress shirt, or golf shirt. For women, slacks and skirts with a blouse is appropriate. Suits and ties are rarely worn, but a light jacket or sweater may be needed at night. Casual dress clothes or resort wear are appropriate for Hawaii's restaurants and nightlife.

To give your outfit an authentic flair, you may want to buy a Hawaiian shirt and flip-flops (or "slippers," as the locals call them) once you arrive. Your ACCP colleagues who live in Hawaii have shared their favorite places to shop, so you can dress aloha style.

Best Places to Shop for a Hawaiian Shirt

- Hilo Hattie's (Ala Moana Shopping Center, Honolulu)
- Manuheali'i (930 Punahou Street, Honolulu)
- Reyn's (Ala Moana Shopping Center, Honolulu)
- Tori Richards (Ala Moana Shopping Center, Honolulu, and several CHEST 2011 hotels)

Hilo Hattie's carries nice, reasonably priced Hawaiian shirts. Shirts from Reyn's and Tori Richards cost a bit more but are stylish and contemporary. However, if you want the real deal, Manuheali'i is a must for authentic Hawaiian wear.

CHEST 2011

October 22 - 26
Honolulu, Hawaii

Best Places to Shop

When asked about the best place to shop, everyone gave the same response: Ala Moana Shopping Center, Honolulu. The center has a wide selection of stores and is conveniently located next to the Hawaiian Convention Center. For a different shopping experience, check out the Aloha Stadium Swap Meet & Marketplace, described as the place locals shop for the best deals in town. (Visit their Web site at www.alohastadiumswapmeet.net for more details.) A suggestion for inexpensive souvenirs is Walmart (700 Keeaumoku Street, Honolulu).

CHEST 2011 is October 22-26 in Honolulu, Hawaii. Postgraduate multipass courses and additional courses will begin Saturday, October 22, and general sessions will begin Sunday, October 23. New this year, after-CHEST postgraduate courses will be held Friday, October 28, and Saturday, October 29, so you can continue your learning momentum and take in more of Hawaii. Learn more about CHEST 2011 at www.accpmeeting.org.

Mahalo to the ACCP members who shared their favorite places to shop: Drs. John Beamis, John Chen, Sam Evans, Christine Fukui, Alvin Furuike, Don Helman, Sailaja Kolli, and Warren Tamamoto. If you see these members at CHEST 2011, be sure to say, "Mahalo," and ask for more suggestions! ■

Top Practice Management Tips You Should Consider

1. Don't be penalized—begin using an EMR.
2. Use the 6-min walk test, CPT code **94620**, to measure oxygen desaturation.
3. Remember modifier 25 on E&Ms when procedures are performed the same day.
4. Develop and maintain an active practice compliance plan.
5. Maintain ongoing education and training of physicians and staff working on coding and reimbursement issues, and conduct regular in-services.
6. Encourage coding and billing staff to obtain credentials.
7. New ICD-9-CM codes for interstitial lung disease (adult and pediatric ILD diagnosis codes) and many other codes of interest to pulmonary, critical care, and sleep medicine will be effective on October 1, 2011.
8. Identify the correct Place of Service (POS) on each claim.
9. Be familiar with both national and local coverage decisions by Medicare and other insurers.
10. Know your Medicare Administrative Contractor (MAC) Medical Director, your Durable Medical Equipment (DME) MAC Medical Director, and your ACCP pulmonary CAC representative. Consider getting involved as a CAC representative or alternate.
11. Develop a policy to appeal inappropriately denied claims and partial payments and follow it.
12. Review frequency of CPT codes billed yearly per provider to look for change.
13. Buy a copy of ACCP's *Coding for Chest Medicine 2011,* and your staff will thank you. Order your copy now from the ACCP Store at www.chestnet.org.

Questions? Contact Marla Brichta at the ACCP at mbrichta@chestnet.org.

FROM THE DESK OF THE PRACTICE MANAGEMENT COMMITTEE

ACCP Contractor Advisory Committee (CAC) Overview

BY DR. ROBERT DEMARCO, FCCP, CHAIR; AND DONNA KNAPP BYBEE, MA, FACMPE, VICE-CHAIR

The ACCP Practice Management Committee (PMC) invites your participation on the ACCP CAC. In addition to the important work of Dr. Steve Peters, FCCP, as ACCP CPT Advisor; Dr. Mike Nelson, FCCP, as ACCP CPT Alternate Advisor; Dr. Scott Manaker, PhD, FCCP, RUC Internal Medicine Rotating Seat; Dr. Burt Lesnick, FCCP, RUC Internal Medicine Rotating Seat Alternate; Dr. Kathrin Nicolacackis, FCCP, as ACCP RUC Advisor; and their American Thoracic Society colleagues, Dr. Stephen Hoffmann, FCCP, for CPT; and Dr. Alan Plummer, FCCP, for RUC, there is the work of your state CAC representatives advocating for you on Medicare reimbursement issues.

The ACCP PMC is the group of physicians and practice managers/administrators working with Dr. Alan Barker, FCCP, the current Chair of the ACCP CAC. Dr. Barker plans to work with the ACCP Governors to fill the remaining openings for pulmonary CAC representatives. He reported that general trends affecting the Medicare population are routinely reviewed at every the CAC meeting. Recent, issues include recovery audit contractors, EHR implementation, PQRS, as well as policies put forward by Medicaid.

The ACCP CAC is a formal mechanism for ACCP pulmonary, critical care, and sleep medicine providers in each state to provide ACCP membership with a forum to discuss and improve administrative policies and exchange information between providers and contractors. ACCP CAC focuses on informing about and seeking collaboration on the development of Local Coverage Determinations (LCDs).

LCDs are documents that are produced by Medicare Administrative Contractors (MACs) that outline

medical necessity for a specific procedure. In order to support MACs with developing LCDs, each state is mandated to have a CAC made up of physicians from many different specialties. Pulmonary currently has a CAC representative in almost every state. The ACCP has organized these pulmonary CAC representatives into the ACCP CAC to promote collaboration.

ACCP CAC representatives:
- Provide a formal mechanism for ACCP pulmonary, critical care, and sleep medicine physicians in each state to be informed of, and participate in, the decisions (LCD) in an advisory capacity;
- Provide a mechanism to discuss and improve administrative policies that are within contractor discretion;
- Provide ACCP members a forum for information exchange;
- Improve relations between MAC medical directors and ACCP membership;
- Distribute proposed LCDs to colleagues in their respective state and to specialty societies in order to solicit comments;
- Update state colleagues and specialty societies on Medicare program changes announced at CAC meetings;
- Provide consensus recommendations approved by the ACCP PMC and the board when appropriate; and
- Discuss inconsistent or conflicting medical review policies.

The ACCP CAC has a quarterly conference call and also meets in person annually at CHEST. An agenda is being developed for the 2011 meeting in Hawaii. Dr. Arthur Lurvey, Palmetto GBA MAC Medicare Medical Director for American Samoa, California, Guam, Hawaii, Nevada, and Northern Mariana Islands, will be attending and providing presentations at:
- The CAC meeting, Sunday, October 23, 4:30 PM
- The Practice Operations NetWork (PON) meeting, Monday, October 24, 7:15 AM

He will also be available following the PON meeting, by appointment only, with the ACCP Coding and Reimbursement Consultant, Diane Krier-Morrow, MBA, MPH, CCS-P, in Experience ACCP.

The following states currently have a vacancy for both the ACCP CAC representative and the ACCP CAC alternate: Colorado, Georgia, Idaho, Minnesota, Missouri, North Carolina, North Dakota, West Virginia, and Wyoming.

The following states (and districts) have a vacancy for the ACCP CAC alternate position only: Alabama, Alaska, Arizona, Arkansas, Connecticut, District of Columbia, Hawaii, Iowa, Kansas, Maryland, Michigan, Mississippi, Montana, Nebraska, Nevada, New Jersey, New Mexico, New York, Oklahoma, South Carolina, South Dakota, Tennessee, Texas, and Wisconsin.

If you are interested in applying for any of the ACCP CAC openings and/or interested in scheduling an appointment with Dr. Lurvey and Diane Krier-Morrow at CHEST 2011, please contact Marla Brichta, Manager, ACCP Health-care Practice and Reimbursement, at mbrichta@chestnet.org or (847) 498-8364. ■

This Month in *CHEST*: Editor's Picks

BY DR. RICHARD S. IRWIN, MASTER FCCP
Editor in Chief, CHEST

AHEAD OF THE CURVE
- **Advancing Respiratory Research.** *By Dr. J. P. Kiley.*

ORIGINAL RESEARCH
- **Survival of Chinese Patients With PAH in the Modern Treatment Era.** *By Dr. R. Zhang et al.*
- **Bronchoscopic and High-Resolution CT Scan Findings in Children With Chronic Wet Cough.** *By Dr. K. Douros et al.*
- **Physical Activity Is the Strongest Predictor of All-Cause Mortality in Patients With COPD: A Prospective Cohort Study.** *By Dr. B. Waschki et al.*
- **Reexamining the Recommended Follow-up Interval After Obtaining an In-Range INR Value: Results From the Veterans Affairs Study to Improve Anticoagulation.** *By Dr. A. J. Rose et al.*

COMMENTARY
- **Unapproved Prescription Cough, Cold, and Allergy Drug Products: Recent US FDA Regulatory Action on Unapproved Cough, Cold, and Allergy Medications.** *By C. Ostroff, PharmD, et al.*

GO WITH EDITORIAL
- **Managing Cough in the Aftermath of the Decision of the US FDA to Remove Unapproved Prescription Cough Medications From the Market.** *By Dr. R. S. Irwin, Master FCCP; and Dr. B. S. Smith.*

POINT/COUNTERPOINT EDITORIAL
- **Point: Is Pressure Assist-Control Preferred Over Volume Assist-Control Mode for Lung Protective Ventilation in Patients With ARDS?**
  Yes – Dr. J. J. Marini
  No – Dr. N. MacIntyre, FCCP

ACCP Guideline Methodology Course

March 15-16, 2012

BY SANDRA ZELMAN LEWIS, PH.D.
Manager, Evidence-Based Guidelines and Clinical Standards

It has always been the realm of the American College of Chest Physicians (ACCP) Health and Science Policy (HSP) Committee to continually elevate the rigor of the science behind evidence-based guidelines. However there has never been as great an increase as within the last few years. As the ACCP prepared to host the Guidelines International Network (G-I-N) 2010 Conference, the HSP Committee prepared a full-day course on the ACCP Guideline Methodology. Although expected to attract far fewer, 98 people from all over the world attended, and the residual acclaim and requests for additional offerings led HSP to consider offering the course again.

Several other circumstances also promoted the idea of revising and repeating the course. Within a few months of the G-I-N conference, the ACCP hired two knowledgeable methodologists to serve on the HSP staff team. Rebecca Diekemper, MPH, and Joseph Ornelas, DC, MS, MA, created a seven-module, online self-education program on how to conduct an evidence review. Although originally intended for ACCP guideline panels, the HSP Committee urged the staff to offer these modules for further orientation of future committee members. Simultaneously, one overarching theme of the Institute of Medicine (IOM) workshop on next steps for trustworthy clinical practice guidelines and systematic reviews was that most guideline developers needed mentoring and education from developers who are already meeting IOM standards.

Thus, the knowledge gaps were evident, and audience interest had been shown. Therefore, HSP plans to offer an expanded 2-day course on the ACCP Guideline Methodology with a new section on conducting evidence reviews, March 15-16, 2012. It will address the following major topics:

- Differences between guidelines and consensus statements
- Development and refinement of key questions
- Searching the literature
- Assessing study quality
- Systematic reviews and meta-analyses
- Developing evidence tables and evidence profiles
- Conflicts of interest
- Guideline development process
- Incorporating resource considerations into recommendations
- Incorporating values and preferences
- Guideline review and appraisal processes
- Dissemination/implementation
- Impact on quality improvement efforts, CME, and policy

Details on CME credits will be available soon. ■

For more information, contact Sandra Zelman Lewis, PhD, slewis@chestnet.org.

Special Opportunity for CHEST 2011 Attendees

CHEST 2011 Sessions for Purchase

- 80% of the sessions at CHEST 2011 will be recorded and available for purchase.
- Significant discount for CHEST 2011 attendees:

Attendee $35
Nonattendee $200

Watch for details, to be announced in August. ■

CHEST 2011
October 22 - 26
Honolulu, Hawaii

PCCSU Lessons for August

PCCSU
PULMONARY, CRITICAL CARE, SLEEP UPDATE

- **Building-Related Illnesses.** *By Dr. Daniel A. Gerardi, FCCP*
- **Caring for the Critically Ill Obese Patient.** *By Dr. Shyoko Honiden, MSc*

Smoking Bans, Taxes Could Save Nearly $2 Billion

BY MARY ELLEN SCHNEIDER
Elsevier Global Medical News

Enacting comprehensive state laws that ban smoking in workplaces and restaurants as well as raising the cigarette tax by $1 per pack across the country could bring in billions in revenue for cash-strapped states, while also saving nearly 2 million lives, according to new estimates from the American Cancer Society Cancer Action Network.

The ACS CAN released two reports that examined the public health benefits and economic savings from strengthening state antitobacco policies. In one report, researchers from the University of Illinois at Chicago looked at what would happen if the 27 states without comprehensive smoke-free laws were to enact such laws. In the second report, the same researchers considered the impact if all 50 states and the District of Columbia were to adopt a $1 per pack increase in the cigarette excise tax.

"The bottom line is that strong tobacco control policies are a win-win for state legislators, for the states themselves, and [for] their constituents," said John R. Seffrin, Ph.D., chief executive officer of ACS CAN.

Currently, 23 states and the District of Columbia have enacted comprehensive laws that ban smoking in all bars, restaurants, and workplaces. The remaining 27 states have either less-comprehensive laws or no laws at all in this area. But when the researchers considered the impact if these 27 states were to adopt comprehensive smoking bans, they found that more than 1 million adults would quit smoking, nearly 400,000 children would never start smoking, and smoking-related deaths would fall by 624,000.

On the economic side, those 27 states would see a savings of about $316 million from lung cancer treatment, $875 million from heart attack and stroke treatment, and $128 million from smoking-related pregnancy treatment. And the researchers estimated that Medicaid programs in those 27 states would save a collective $42 million.

The report on tobacco taxes found similar public health and financial gains if a $1 per pack tax increase were enacted around the country. Such a tax would result in 1.4 million adults quitting smoking, 1.69 million children never starting to smoke, and 1.32 million fewer people dying from smoking-related causes. States also could benefit from both decreases in Medicaid spending and increased revenue. The report estimated that the tax would cut Medicaid spending by about $146 million across the states, and would bring in $8.62 billion in new state revenue.

Dr. Seffrin said that the results are attainable. An increasing number of states are adopting smoke-free laws and nearly all the states have increased cigarette excise taxes in recent years.

But he noted the ACS CAN is concerned that the tobacco industry is working to erode current tobacco-control laws at the state level. For example, there have been efforts in several states to add exemptions to the smoke-free laws. ■

COMMENTARY

Dr. Stuart Garay, FCCP, comments: These two reports examine the health benefits and economic savings associated with more rigorous antitobacco policies. The first involves the recommendation of a more comprehensive ban of smoking in the 27 states that have less-comprehensive laws or no laws banning smoking in all bars, restaurants, and workplaces. The predicted savings in terms of preventing children from smoking and smoking-related deaths are impressive, let alone the economic savings. These bans have worked well in many big cities like New York.

The second report looks at a $1 per pack tax increase, finding that lives would be saved and states would benefit from increased revenues. While increasing taxes is not very popular, this tax is an exception. The tobacco industry is obviously opposed.

However, as pulmonologists we should work toward both recommendations.

Graphic Cigarette Packaging to Debut Next Month

BY MICHELE G. SULLIVAN
Elsevier Global Medical News

The Food and Drug Administration unveiled the final nine warning images that will appear on every package of cigarettes by 2012 – graphic photos and drawings intended to educate consumers about the dangers of smoking.

The images, set to debut in stores this September, are required by the 2009 Tobacco Control Act, according to FDA spokesman Jeffrey Ventura, who added that these are the first changes to cigarette pack warnings in 25 years. By Oct. 22, 2012, cigarette manufacturers will no longer be able to distribute cigarettes for sale in the United States unless they display these warnings.

COURTESY U.S. FOOD AND DRUG ADMINISTRATION

The law required the warnings to cover the top half of the front and back of cigarette packs and 20% of cigarette advertisements, and they must contain color graphics depicting the negative health consequences of smoking.

"This is something Congress wanted to happen and mandated that the FDA carry out," Mr. Ventura said in an interview. Based on a study of 18,000 smokers conducted for the FDA by RTI International, federal officials said they firmly believe that visually communicating smoking's harm will deter cigarette consumption over the long run.

The images include photos of tobacco-diseased lungs beside healthy lungs, a corpse in a casket, a man exhaling smoke though a tracheostomy, lip cancer, and mothers blowing smoke into infants' faces. One positive image shows a burly man exposing a T-shirt saying, "I Quit."

Mr. Ventura said the images were selected after the consumer study involving smokers aged 15-50 years. After viewing each of the images, subjects rated their emotional and cognitive responses, their ability to recall the images, and their opinions on whether the pictures could alter their beliefs about the danger of smoking and the desire to buy tobacco products and quitting tobacco.

The study concluded, however, that none of the images were significantly related to an increased likelihood of quitting smoking within the next 30 days, or the likelihood of smoking a year after viewing the images. Thus, the report noted, the campaign is more likely to exert a long-term behavioral impact than any immediate effects.

"Eliciting strong emotional and cognitive reactions to the graphic cigarette warning label enhances recall and processing of the health warning, which helps ensure that the warning is better processed, understood, and remembered," the study said. "As attitudes and beliefs change, they eventually lead to changes in intentions to quit or start smoking and then later to lower smoking initiation and successful cessation. The time scale on which this behavior change process occurs is largely unknown in the context of the impact of exposure to graphic warning labels on smoking behaviors, but the effects on behavior change are unlikely to be immediate or short-term." ■

CMS Proposes Looser E-Prescribing Rules

BY ALICIA AULT
Elsevier Global Medical News

The Centers for Medicare and Medicaid Services has proposed modifying the rules for e-prescribing so that more physicians could claim exemptions from the criteria and therefore avoid being penalized in 2012.

In a conference call with reporters, agency officials said the change in the e-prescribing program was in response to indications from providers and professional societies that many prescribers might not be able to meet the requirements of the current incentive program.

"Today's rule demonstrates that CMS is willing to work cooperatively with the medical professional community to encourage participation in electronic prescribing," Dr. Patrick Conway, chief medical officer at CMS and director of the agency's Office of Clinical Standards and Quality, said in a statement.

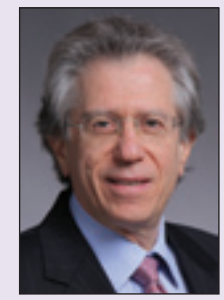
"These proposed changes will continue to encourage adoption of electronic prescribing while acknowledging circumstances that may keep health professionals from realizing the full potential of these systems right away," he said.

Under the current incentive program, which was established in the Medicare Improvements for Patients and Providers Act of 2008, eligible prescribers were due to get a 1% bonus payment for 2011 and 2012 and a 0.5% bonus in 2013. For pre-

COMMENTARY

Dr. Stuart Garay, FCCP, comments: Medicare defines an eligible professional requiring e-prescribing as meeting the following three criteria: 1) the physician has prescribing privileges as of June 30, 2011; 2) the physician has at least 100 instances of eligible patient encounters for e-prescribing, such as an office evaluation and management visit, between Jan. 1, 2011, and June 30, 2011; and 3) the physician has at least 10% of total Medicare charges associated with eligible patient encounters.

This is an important proposed revision to the Medicare e-prescribing rules. According to CMS, 100,000-200,000 physicians and other health care providers will be eligible for hardship exemptions. A special website will be available to file by Oct. 1, 2011, for one of the several exemption categories. These new rules better align the requirements of the e-prescribing and EMR programs. In addition, the exemptions will help physicians who don't prescribe enough drugs in the first place; who are barred by law from issuing enough electronic drug orders (such as prohibition on controlled drugs); or prescribe drugs only during patient encounters that don't count under the program (such as many surgeons and critical care specialists). Practices will also be able to avoid penalties if they did not e-prescribe by June 30, 2011, because they were planning instead to adopt and use an EMR in 2011 to qualify for the meaningful use bonuses.



scribers who did not meet the criteria, there would be a penalty imposed in 2012. The penalty would escalate in 2013 and 2014.

The final Medicare Physician Fee Schedule for 2011 contains exceptions to the criteria, along with two hardship exemptions. Eligible professional practices are exempt if they are in a rural area that does not have access to high-speed internet or in an area without enough available pharmacies that can accommodate electronic prescribing.

The proposed rule would modify the criteria.

For instance, prescribers who use certified electronic health records can now claim this as a "qualified" e-prescribing system.

This move was designed to more closely align the e-prescribing program with the program that offers incentives for meaningful use of EHRs.

In addition, the proposed rule would create four additional hardship exemption categories. To qualify, eligible professionals would have to demonstrate the following:

► They have registered to participate in the Medicare or Medicaid EHR incentive program and have adopted certified EHR technology.

► They are unable to electronically prescribe due to local, state, or federal law (this primarily applies to prescribing of narcotics).

► They have very limited prescribing activity.

► They have insufficient opportunities to report the electronic prescribing measure due to limitations on the measure's denominator.

Prescribers also would be granted an extension of the deadline to apply for the hardship exemption, with Oct. 1, 2011, as the extended deadline.

According to Dr. Michael Rapp, director of quality measurement at CMS, who also spoke to reporters, the final rule will not be published until this month at the earliest. ■

This Season's Flu Vaccine Is Same as Last

The vaccine for the upcoming influenza season will contain the same three strains included in this past season's vaccine, the Food and Drug Administration announced July 18.

In a statement, the FDA announced that it had approved the 2011-2012 influenza vaccine formulation, which will include the following strains: A/California/7/09 (H1N1)-like virus (pandemic [H1N1] 2009 influenza virus), A/Perth/16/2009 (H3N2)-like virus, and B/Brisbane/60/2008-like virus.

This formulation will be used by the six manufacturers that are licensed to produce and distribute the influenza vaccine in the United States.

In February, the FDA's Vaccines and Related Biological Products Advisory Committee made a preliminary recommendation that the influenza vaccine include these three strains, based on information that included the latest influenza surveillance and epidemiology data; antigenic characteristics of virus isolates; and serologic responses to current vaccines.

"There is always a possibility of a less than optimal match between the virus strains predicted to circulate and the virus strains that end up causing the most illness," according to the FDA statement. "However, even if the vaccine and the circulating strains are not an exact match, the vaccine may reduce the severity of the illness or may help prevent influenza-related complications."

Licensed vaccines include Afluria (CSL Limited); Fluarix (GlaxoSmithKline Biologicals); FluLaval (ID Biomedical); FluMist (MedImmune); Fluvirin (Novartis Vaccines and Diagnostics); and Fluzone, Fluzone High-Dose, and Fluzone Intradermal (Sanofi Pasteur).

Fluzone Intradermal was approved in May 2011; it is delivered intradermally with a very small needle and is for people aged 18-64 years, according to the FDA statement. On July 18, Sanofi Pasteur announced that the company has begun shipping the 2011-2012 Fluzone vaccine.

The Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices recommend annual influenza vaccinations for everyone aged 6 months and older.

According to the CDC, 5%-20% of the U.S. population develops influenza each year, resulting in more than 200,000 hospitalizations for influenza-related complications and 3,000-49,000 deaths.

—Elizabeth Mechcatie

TYGACIL is in the IDSA/SIS guidelines for cIAI and the SIS guidelines for cSSSI.[1,2]

Expanded broad-spectrum coverage[3]* is on your side

***TYGACIL does not cover *Pseudomonas aeruginosa*.**

TYGACIL is indicated for the treatment of adults with:

- **Complicated skin and skin structure infections** caused by *Escherichia coli, Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus agalactiae*, *Streptococcus anginosus* grp. (includes *S. anginosus, S. intermedius*, and *S. constellatus*), *Streptococcus pyogenes*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, and *Bacteroides fragilis*
- **Complicated intra-abdominal infections** caused by *Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus anginosus* grp. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *Clostridium perfringens*, and *Peptostreptococcus micros*
- **Community-acquired bacterial pneumonia** caused by *Streptococcus pneumoniae* (penicillin-susceptible isolates), including cases with concurrent bacteremia, *Haemophilus influenzae* (beta-lactamase negative isolates), and *Legionella pneumophila*

Important Safety Information

- TYGACIL is contraindicated in patients with known hypersensitivity to tigecycline
- Anaphylaxis/anaphylactoid reactions have been reported with nearly all antibacterial agents, including tigecycline, and may be life-threatening. TYGACIL should be administered with caution in patients with known hypersensitivity to tetracycline-class antibiotics
- Isolated cases of significant hepatic dysfunction and hepatic failure have been reported in patients being treated with tigecycline. Some of these patients were receiving multiple concomitant medications. Patients who develop abnormal liver function tests during tigecycline therapy should be monitored for evidence of worsening hepatic function. Adverse events may occur after the drug has been discontinued
- The safety and efficacy of TYGACIL in patients with hospital-acquired pneumonia have not been established
- **An increase in all-cause mortality has been observed across phase 3 and 4 clinical studies in TYGACIL-treated patients versus comparator-treated patients. The cause of this increase has not been established. This increase in all-cause mortality should be considered when selecting among treatment options**
- **TYGACIL may cause fetal harm when administered to a pregnant woman**
- **The use of TYGACIL during tooth development may cause permanent discoloration of the teeth.** TYGACIL should not be used during tooth development unless other drugs are not likely to be effective or are contraindicated
- Acute pancreatitis, including fatal cases, has occurred in association with tigecycline treatment. Consideration should be given to the cessation of the treatment with tigecycline in cases suspected of having developed pancreatitis
- *Clostridium difficile*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including TYGACIL, and may range in severity from mild diarrhea to fatal colitis
- Monotherapy should be used with caution in patients with clinically apparent intestinal perforation
- TYGACIL is structurally similar to tetracycline-class antibiotics and may have similar adverse effects. Such effects may include: photosensitivity, pseudotumor cerebri, and anti-anabolic action (which has led to increased BUN, azotemia, acidosis, and hyperphosphatemia). As with tetracyclines, pancreatitis has been reported with the use of TYGACIL
- To reduce the development of drug-resistant bacteria and maintain the effectiveness of TYGACIL and other antibacterial drugs, TYGACIL should be used only to treat infections proven or strongly suspected to be caused by susceptible bacteria. As with other antibacterial drugs, use of TYGACIL may result in overgrowth of non-susceptible organisms, including fungi
- The most common adverse reactions (incidence >5%) are nausea, vomiting, diarrhea, infection, headache, and abdominal pain
- Prothrombin time or other suitable anticoagulant test should be monitored if TYGACIL is administered with warfarin
- Concurrent use of antibacterial drugs with oral contraceptives may render oral contraceptives less effective
- The safety and effectiveness of TYGACIL in patients below age 18 and lactating women have not been established

Please see brief summary of Prescribing Information on adjacent page.

References: 1. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Clin Infect Dis*. 2010;50(2):133-164. **2.** May AK, Stafford RE, Bulger EM, et al. Surgical Infection Society Guidelines: Treatment of complicated skin and soft tissue infections. *Surg Infect*. 2009;10:467-499. **3.** TYGACIL® (tigecycline) Prescribing Information, Wyeth Pharmaceuticals Inc.

Pfizer

Tygacil® tigecycline IV

Expanded broad-spectrum coverage