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FRANCES CORREA/IMNG MEDICAL MEDIA

Demonstrators both for and against the Affordable Care Act flocked to the Supreme Court steps before the decision.

ACA Can Move Ahead, Supreme Court Says

BY ALICIA AULT
IMNG Medical News

The Supreme Court's decision to largely uphold the Affordable Care Act in essence preserved the status quo for the health system and took away some uncertainty – but only in the short term. The congressional and presidential elections in November could bring further changes to the law.

For now, though, the nation's physicians are pondering the Court's ruling and how it will affect their practices. While concerns remain regarding some aspects of the law – and there is uncertainty on what the justices' Medicaid decision means – most physician organizations praised the Court's opinions, noting that keeping the law in place would increase health care coverage and maintain the ACA's enhanced preventive care benefits.

"We are pleased that this decision means millions of Americans can look forward to the coverage they need to get healthy and stay healthy," said Dr. Jeremy Lazarus, president of the American Medical Association, in a statement. "This decision protects important improvements, such as ending coverage denials due to preexisting conditions and lifetime caps on insurance and allowing the 2.5 million young adults up to age 26 who gained coverage under the law to stay on their parents' health insurance policies."

Because the law basically remains the same – for now – the 2.3% excise tax on medical devices will still go into effect on Jan. 1, 2013. AdvaMed, an industry lobbying group, said it will continue to try to overturn that tax, which could end up driving up the cost of devices such as pacemakers. AdvaMed president and CEO Stephen J. Ubl said in a statement that "the House has already voted to repeal the device tax, and we are heartened by the

See **ACA** • *page 2*

FDG-PET Performs Poorly in Lung Cancer Diagnosis

Results generalizable to clinical practice.

BY PATRICE WENDLING
IMNG Medical News

CHICAGO – The diagnostic accuracy of FDG-PET in lung cancer performed below previous reports and varied widely among U.S. centers in a secondary analysis of a large phase III clinical trial.

"FDG-PET performed poorly for diagnosing non–small cell lung cancer in a national sample of clinical stage 1 patients," Dr. Eric L. Grogan, FCCP, said at the annual meeting of the American Society of Clinical Oncology.

The current National Comprehensive Cancer Network guidelines recommend fluorodeoxyglucose positron-emission tomography (FDG-PET) for the diagnosis of NSCLC based on studies showing a high degree of accuracy for this diagnostic tool, notably a sensitivity of 94% and a median specificity of 83% in a meta-analysis of 40 studies (JAMA 2001;285:914-24).

Others have reported, however, that FDG-PET performs poorly at single institutions in regions of endemic fungal lung diseases (Ann. Thor. Surg. 2011;92:428-32 and Lung Cancer 2002;36:297-301), observed Dr. Grogan, of Vanderbilt-Ingram Cancer Center in Nashville, Tenn.

Among 682 patients in the American College of Surgeons Oncology Group (ACOSOG) Z4031 trial, the overall accuracy of FDG-PET was 73%, the sensitivity 82%, and the specificity only 31%. The series is the largest to date evaluating the accuracy of FDG-PET in patients with known or suspected clinical stage 1 NSCLC. In addition, it is generalizable to clinical practice because multiple FDG-PET scanners were used

See **FDG-PET** • *page 17*

INSIDE

Select Carefully for Segmentectomy

BY DAMIAN McNAMARA
IMNG Medical News

SAN FRANCISCO – Thoracic surgeons should not shy away from segmentectomy in select patients with non–small cell lung cancer, an expert advises, because the technique confers specific advantages.

In addition, it is as feasible as lobectomy. "If you can do a lobectomy, you can do a segmentectomy. There is no doubt about it," Dr. Matthew J. Schuchert said at the annual meeting of the American Association for Thoracic Surgery.

He shared patient selection criteria and technique tips based on experience with the more than 800 segmentectomies performed at the University of Pittsburgh Medical Center/UPMC Cancer Institute, where he is a general and thoracic surgeon.

Anatomic segmentectomy accomplishes the fundamental surgical tenets achieved by lobectomy, including R0 resection, adequate margins, and an opportunity for systematic

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IPAB Still a Sticking Point

ACA • *from page 1*

number of Senators who have said they oppose the tax. We will continue to work with policy makers on both sides of the aisle to achieve this goal."

The largely positive statements from organized medicine did not hide the fact that many individual physicians are still fearful of the law's effect on their practice.

In a survey of 644 primary care physicians conducted on the day that the Supreme Court ruled, 66% of respondents said that they did not believe the law could achieve health care coverage for all Americans. The poll was conducted by MDLinx, a Web-based information provider for doctors. "The survey showed a surprisingly high level of skepticism among primary care physicians," said Stephen Smith, chief marketing officer for MDLinx, in a statement. The poll also found that only 21% said that increased patient volume would have an "extremely positive" impact on their medical practice. Almost half said it would have an "extremely negative" impact.

And most physician organizations indicated their continuing dissatisfaction with some parts of the law, including the Independent Payment Advisory Board (IPAB) and the lack of any concrete malpractice reform.

Looking Ahead

With the Supreme Court's efforts in the rear-view mirror, Republicans renewed their vow to repeal all or part of the ACA; however, that's unlikely to happen as long as Democrats maintain control of the Senate and the White House.

If Republicans win a majority in the Senate in November, and if Mitt Romney wins the presidential election, there could be major change.

In the meantime, most physician groups said they would work to fix the parts of the law that they found most objectionable. ■

Whither Medicaid?

In its opinions, the Supreme Court essentially ruled that states could choose whether to expand Medicaid eligibility criteria to cover more of their low-income residents. As passed by Congress, the ACA would have directed states to expand eligibility across the board to 133% of the federal poverty level beginning in 2014. Any state that refused would have lost not just the federal government's 100% subsidy for those new enrollees, but also all existing federal Medicaid matching funds.

Now, under the court's majority opinion, states can choose whether they want to expand eligibility; if they don't, they won't face the penalty of losing existing funding. If all the states expanded their programs, some 15 million more Americans would be covered under Medicaid, according to an analysis by Avalere Health.

In the states that don't accept the subsidy, people below the poverty line won't be eligible for subsidies to join the health exchanges and they won't be eligible for Medicaid, according to the Center on Budget and Policy Priorities. That will likely lead to more uninsured in those states.

More people could become uninsured if the Republicans are successful in repealing the ACA's maintenance of effort provision, which requires states to do everything possible to keep Medicaid and Children's Health Insurance Plan recipients enrolled.

IN THIS ISSUE

CHEST PHYSICIAN Is Online

CHEST PHYSICIAN is available on the Web at www.chestnet.org/accp/chest-physician.

Dr. W. Michael Alberts, FCCP, is Medical Editor in Chief of CHEST PHYSICIAN.

COMMENTARY

Dr. Stuart M. Garay, FCCP, comments: The Supreme Court's decision to uphold the Affordable Care Act is the most monumental decison regarding health care in decades. The Court validated the ACA's most controversial provision that all Americans must obtain health insurance by 2014 or pay a penalty. Most physician organizations applauded the Court's decision, citing increased health care coverage and enhanced benefits for preventive care. Health care organizations, health care delivery systems, and industry noted an "end to the uncertainty" surrounding the ACA and are making plans to move forward to deal with the individual provisons. The fate of Medicaid expansion remains uncertain, since the Court ruled against a key provision, leaving the states to decide upon extended coverage without facing a penalty. Finally, individual physicians – the foot soldiers in health care – remain skeptical, divided, and confused regarding the Court's decision: 1) Who is going to care for the additional 30 million patients? 2) Significant malpractice reform has not been addressed; 3) Antagonistic interactions between insurance companies, patients, and physicians remain a problem. Furthermore, physicians are not pleased with the Medicare Independent Payment Advisory Board, which would recommend spending cuts when the program exceeds certain growth targets. If the ACA remains in effect after the November election, physicians have a lot of work to do. In the end, the devil will be in the details of the 2,700-page report. Physicians must work to fix parts of the law that they find objectionable and lead in the creation of the new systems that have been mandated. Otherwise, we will be left behind.

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CHEST PHYSICIAN, the newspaper of the American College of Chest Physicians, provides cutting-edge reports from clinical meetings, FDA coverage, clinical trial results, expert commentary, and reporting on the business and politics of chest medicine. Each issue also provides material exclusive to the members of the American College of Chest Physicians. Content for **CHEST PHYSICIAN** is provided by International Medical News Group, an Elsevier company. Content for NEWS FROM THE COLLEGE is provided by the American College of Chest Physicians.

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For PAH (WHO Group 1) patients on oral monotherapy

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Short treatment sessions: just 2 to 3 minutes each[2]

ONLY inhaled prostacyclin analogue approved as an add-on to oral PAH monotherapy[1]

- 52% of patients improved 6MWD by greater than 20 m[3]
- Improvement in 6MWD at peak (20 m) and trough (14 m) exposure[3]

Dosing regimen fits into patients' schedules

- Short treatment sessions: just 2 to 3 minutes, 4x daily[2]
- Set up once daily[1,2]
  - —One plastic ampule per day—no need to replace ampule for each treatment session[1]
  - —About 5 minutes a day for device preparation—once in the morning, and the device is ready to go all day[2]
- Treatment timing can be adjusted for planned activities[1]

Adverse events

- The most common adverse events seen with Tyvaso in ≥4% of PAH patients and more than 3% greater than placebo in the placebo-controlled clinical study were cough, headache, throat irritation/pharyngolaryngeal pain, nausea, flushing, and syncope[1]

STUDY DESIGN: TRIUMPH I was a 12-week, randomized, double-blind, placebo-controlled, multicenter study of patients (N=235) with PAH who were receiving a stable dose of bosentan or sildenafil for 3 months before study initiation. Patients were administered either placebo or Tyvaso in 4 daily treatment sessions with a target dose of 9 breaths (54 mcg) per session over the course of the 12-week study. Primary endpoint was change in 6MWD at 12 weeks. Secondary endpoints included time to clinical worsening, Borg dyspnea score, NYHA functional class, trough 6MWD at week 12 (obtained at least 4 hours after study drug administration), peak 6MWD at 6 weeks, quality of life as measured by the MLWHF questionnaire, and PAH signs and symptoms.[3]

INDICATION

Tyvaso is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).

The effects diminish over the minimum recommended dosing interval of 4 hours; treatment timing can be adjusted for planned activities.

While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase type 5 inhibitor). The controlled clinical experience was limited to 12 weeks in duration.

IMPORTANT SAFETY INFORMATION

- Tyvaso is intended for oral inhalation only. Tyvaso is approved for use only with the Tyvaso Inhalation System
- The safety and efficacy of Tyvaso have not been established in patients with significant underlying lung disease (such as asthma or chronic obstructive pulmonary disease) and in patients under 18 years of age. Patients with acute pulmonary infections should be carefully monitored to detect any worsening of lung disease and loss of drug effect
- Tyvaso may increase the risk of bleeding, particularly in patients receiving anticoagulants
- In patients with low systemic arterial pressure, Tyvaso may cause symptomatic hypotension. The concomitant use of Tyvaso with diuretics, antihypertensives, or other vasodilators may increase the risk of symptomatic hypotension
- Hepatic or renal insufficiency may increase exposure to Tyvaso and decrease tolerability. Tyvaso dosage adjustments may be necessary if inhibitors of CYP2C8 such as gemfibrozil or inducers such as rifampin are added or withdrawn
- The most common adverse events seen with Tyvaso in ≥4% of PAH patients and more than 3% greater than placebo in the placebo-controlled clinical study were cough (54% vs 29%), headache (41% vs 23%), throat irritation/pharyngolaryngeal pain (25% vs 14%), nausea (19% vs 11%), flushing (15% vs <1%), and syncope (6% vs <1%)
- Tyvaso should be used in pregnancy only if clearly needed. Caution should be exercised when Tyvaso is administered to nursing women

Please see brief summary of Full Prescribing Information on following page. For more information, please see Full Prescribing Information, Patient Package Insert, and the Tyvaso Inhalation System Instructions for Use manual. These items are available at www.tyvaso.com.

6MWD=6-minute walk distance. MLWHF=Minnesota Living With Heart Failure. NYHA=New York Heart Association. WHO=World Health Organization.

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PROSTACYCLIN MADE PRACTICAL

BY MICHAEL J. MORRIS, M.D., COL (RET), MC, FCCP

COMMENTARY

Department of Defense Research Studies on Deployment-Related Respiratory Symptoms

The opinions in this manuscript do not constitute endorsement by Brooke Army Medical Center, the U.S. Army Medical Department, the U.S. Army Office of the Surgeon General, the Department of the Army, the Department of Defense, or the U.S. Government.

The Department of Defense (DoD) is very concerned about potential adverse health impacts from military deployment to Southwest Asia, including impacts on respiratory health. Respiratory hazards in the deployed environment include suspended geologic dusts, burn pits, vehicle exhaust emissions, industrial air pollution, and exposure incidents.[1] The DoD has been actively evaluating epidemiologic associations and clinical implications of these exposures. The DoD takes the health of military personnel seriously, and remains in the best position to evaluate military members for pulmonary complaints.

In 2005, the Assistant Secretary of Defense for Health Affairs chartered the Joint Particulate Matter Working Group to investigate potential health effects of particulate matter (PM) exposure. A roundtable meeting of staff from the DoD and the Department of Veterans Affairs (VA) and academic researchers and physicians was convened at National Jewish Health in Denver in 2010 to begin discussions on deployment-related respiratory health and to outline general strategies.[2]

A separate DoD Pulmonary Working Group assembled later in 2010 and again in 2011 to review current research and map the strategy for future work.

THERE WAS NO EVIDENCE OF INCREASED RISK FOR RESPIRATORY DISEASES ASSOCIATED WITH EXPOSURE TO BURN PIT EMISSIONS.

Numerous studies have been developed from the working group to evaluate associations between deployment and lung disease.

Published studies of noninfectious respiratory disease in military personnel are largely retrospective, rely on survey data, and typically lack detailed exposure assessments. Several reports have documented increases in nonspecific respiratory symptoms such as cough and dyspnea during and following deployment. In a study of redeploying military from Iraq and Afghanistan, 69.1% reported experiencing respiratory illnesses, of which 17% required medical care.[3] The Millennium Cohort Study is a longitudinal cohort study conducted by the Naval Health Research Center designed to evaluate the long-term health effects of military service. Surveys of deployed personnel found that they have higher rates of newly reported respiratory symptoms, compared with nondeployed personnel (14% vs. 10%), although similar rates of chronic bronchitis/emphysema (1% vs. 1%) and asthma (1% vs. 1%) were observed.[4]

Despite observed respiratory symptoms, short-term respiratory health effects have not been identified. The U.S. Army Public Health Command augmented environmental sampling efforts with enhanced PM surveillance at 15 locations throughout Southwest Asia.[5] A study using these data found no association with acute cardiorespiratory events that required medical encounters.[6]

Continued on following page

Continued from previous page

The 2010 DoD report on potential health impacts of burn pits concluded that there was no evidence of increased risk for respiratory diseases associated with exposure to burn pit emissions.[7] A 2011 Institute of Medicine report came to a similar conclusion.[8] Long-term respiratory effects of PM exposure remain a concern, and data on chronic lung diseases are scarce.

Increased tobacco use in the military during deployment is a complicating factor in evaluating impacts of deployment-related environmental exposures. Soldiers deployed to Iraq reported that 58.3% of males and 52.1% of females were using tobacco during deployment and that 25.4% of males and 48% of females increased tobacco use during deployment.[9]

Laboratory work conducted with PM sampled from Camp Buehring by the Navy Environmental Health Effects Laboratory showed no long-term toxicity in exposed rats.[10] Two-week inhalational exposures of rats to filtered Camp Victory surface soil also conducted by the Navy did not induce notable adverse responses in the animals. These findings are consistent with independent rat studies conducted by the U.S. Army Center for Environmental Health Research using intratracheally instilled PM from Camp Victory, which caused acute inflammation after instillation with minimal pulmonary effects at 150 days.

The evidence for chronic pulmonary disease is limited. Despite accession restrictions for individuals with asthma, it remains a significant problem in military personnel that is similar to the general population. Nearly half of their active duty military with exertional dyspnea had either asthma or exercise-induced bronchospasm.[11] The extreme climate conditions and high PM levels in Southwest Asia could potentially contribute to poor asthma control and increased exacerbations. A survey by Roop et al. demonstrated that 5% of troops deployed to Southwest Asia reported having a previous diagnosis of asthma.[12]

Both asthmatics and nonasthmatics reported significantly increased respiratory symptoms during deployment, compared with symptoms before deployment. Data from a VA review of ICD-9 diagnostic codes for asthma in deployed military suggested a higher prevalence of new-onset asthma in deployed personnel (6.6% vs. 4.3%).[13] However, an ongoing DoD review of medical records for active duty personnel undergoing physical evaluation boards for asthma found that 54% never deployed, 22% deployed with an existing diagnosis, and 24% were diagnosed post deployment.[14]

King et al. also reported on a case series of constrictive bronchiolitis among formerly deployed military personnel.[15] Most of the patients had symptoms with high levels of activity, had normal PFTs and HRCT, did not undergo a comprehensive evaluation to rule out etiologies such as asthma or vocal cord dysfunction, and were nevertheless subjected to an open lung biopsy. The patients comprising the case series had varied deployment exposures; fewer than half had exposure to sulfur dioxide. An epidemiologic comparison demonstrated no increase in postdeployment medical encounters among personnel exposed to the 2003 Mishraq sulfur fire, compared with unexposed personnel.[16]

Performing an open lung biopsy in the absence of supporting clinical data is controversial, as is the diagnosis of constrictive bronchiolitis.

EXTREME CLIMATE AND HIGH PARTICULATE MATTER LEVELS IN SOUTHWEST ASIA COULD CONTRIBUTE TO POOR ASTHMA CONTROL AND EXACERBATIONS.

DoD pulmonologists do not concur with the evaluation process due to lack of definitive clinical data. Supported by DoD funding, blinded review of the biopsy samples from the Vanderbilt study is currently being undertaken to validate the pathologic findings.

Clinical studies are being conducted at San Antonio Military Medical Center. A comprehensive review of all pulmonary cases in the DoD is ongoing and specifically evaluating the relationship between deployment and common pulmonary conditions.

The Army also maintains a registry for military personnel with pulmonary conditions potentially related to deployment.

The prospective Study of Active Duty Military for Pulmonary Disease related to Environmental Dust Exposure (STAMPEDE) evaluated redeploying soldiers with new respiratory complaints and found minimal evidence for chronic lung disease based on imaging, PFTs and bronchoalveolar lavage.[17]

Additional studies that have recently been initiated include pre- and postdeployment spirometry in soldiers from Fort Hood, the utility of screening spirometry in new military recruits, and a comprehensive evaluation of postdeployment dyspnea. This active clinical research program is being jointly conducted with the VA to evaluate pulmonary disease in the DoD population and to further evaluate links to deployment-related exposures.

It is very evident that the DoD is committed to continue ongoing investigations into the respiratory symptoms of redeploying military, to provide comprehensive evaluations for those with chronic symptoms, and to acquire additional laboratory and clinical data on the relationship between deployment and lung disease. ■

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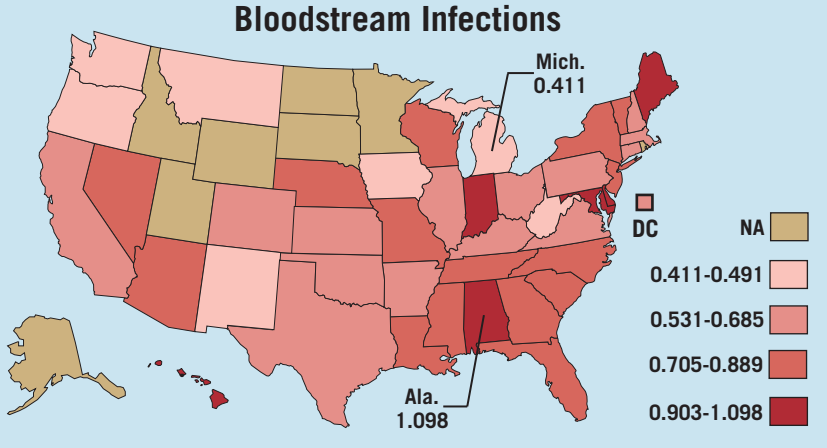
DR. MORRIS *served in Operations Desert Shield/Storm with the First Infantry Division. He completed a fellowship in Pulmonary Disease/Critical Care Medicine at Brooke Army Medical Center, Fort Sam Houston, Tex., in 1995. After serving 21 years in the Army Medical Corps, he returned to Brooke Army Medical Center to serve as the Associate Program Director for the SAUSHEC Internal Medicine Residency and a staff physician for the Pulmonary/Critical Care Service. He is a nationally recognized expert in evaluation of the active duty patient with dyspnea, asthma, exercise-induced bronchospasm, and vocal cord dysfunction. He has a current faculty appointment with the Uniformed Services University, is a member of the Board of Medical Advisors for the AARC, and has been appointed to the ACCP Airways Disorders NetWork.*

DATA WATCH

Standardized Infection Ratios for Central Line–Associated Bloodstream Infections



Notes: The standardized infection ratio (SIR) compares the actual number of health care–associated infections with the predicted number, adjusted for risk factors most associated with differences in infection rates. A lower SIR indicates fewer infections.
Source: Centers for Disease Control and Prevention

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INDICATION

BROVANA is indicated for the long term, twice daily (morning and evening) maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. BROVANA is for use by nebulization only.

IMPORTANT SAFETY INFORMATION

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another long-acting beta$_2$-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including arformoterol, the active ingredient in BROVANA (see WARNINGS). The safety and efficacy of BROVANA in patients with asthma have not been established. All LABA, including BROVANA, are contraindicated in patients with asthma without use of a long-term asthma control medication (see CONTRAINDICATIONS).

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

Please visit **www.brovana.com** for full Prescribing Information.

References: 1. Baumgartner RA, Hanania NA, Calhoun WJ, Sahn SA, Sciarappa K, Hanrahan JP. Nebulized arformoterol in patients with COPD: a 12-week, multicenter, randomized, double-blind, double-dummy, placebo- and active-controlled trial. *Clin Ther*. 2007;29(2):261-278. **2.** BROVANA [prescribing information]. Marlborough, MA: Sunovion Pharmaceuticals Inc; 2012.

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BRIEF SUMMARY

WARNING: ASTHMA RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another long-acting beta$_2$-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including arformoterol, the active ingredient in BROVANA (see WARNINGS). The safety and efficacy of BROVANA in patients with asthma have not been established. All LABA, including BROVANA, are contraindicated in patients with asthma without use of a long-term asthma control medication (see CONTRAINDICATIONS).

INDICATIONS AND USAGE

BROVANA (arformoterol tartrate) Inhalation Solution is indicated for the long-term, twice daily (morning and evening) maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. BROVANA is for use by nebulization only.

CONTRAINDICATIONS

BROVANA (arformoterol tartrate) Inhalation Solution is contraindicated in patients with a history of hypersensitivity to arformoterol, racemic formoterol or to any other components of this product.

All LABA, including BROVANA, are contraindicated in patients with asthma without use of a long-term asthma control medication. (see **WARNINGS**).

WARNINGS

- **ASTHMA RELATED DEATH**
  Long-acting beta$_2$-adrenergic agonists may increase the risk of asthma-related death. The safety and efficacy of BROVANA in patients with asthma have not been established. All LABA, including BROVANA, are contraindicated in patients with asthma without use of a long-term asthma control medication (see CONTRAINDICATIONS).
  – A 28-week, placebo-controlled US study comparing the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13/13, 176 in patients treated with salmeterol vs. 3/13, 179 in patients treated with placebo; RR 4.37, 95% CI 1.25, 15.34). The increased risk of asthma-related death may represent a class effect of the long-acting beta$_2$-adrenergic agonists, including BROVANA. No study adequate to determine whether the rate of asthma related death is increased in patients treated with BROVANA has been conducted.
  – Clinical studies with racemic formoterol (Foradil® Aerolizer™) suggested a higher incidence of serious asthma exacerbations in patients who received racemic formoterol than in those who received placebo. The sizes of these studies were not adequate to precisely quantify the differences in serious asthma exacerbation rates between treatment groups.
- **The studies described above enrolled patients with asthma. Data are not available to determine whether the rate of death in patients with COPD is increased by long-acting beta$_2$-adrenergic agonists.**
- **BROVANA is indicated for the long term, twice daily (morning and evening) maintenance treatment for bronchoconstriction in chronic obstructive pulmonary disease (COPD), and is not indicated for the treatment of acute episodes of bronchospasm, i.e., rescue therapy.**
- **BROVANA should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. The use of BROVANA in this setting is inappropriate.**
- **BROVANA should not be used in children as the safety and efficacy of BROVANA have not been established in pediatric patients.**
- **BROVANA should not be used in conjunction with other inhaled, long-acting beta$_2$-agonists. BROVANA should not be used with other medications containing long-acting beta$_2$-agonists.**
- **When beginning treatment with BROVANA, patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms.**
- **See PRECAUTIONS and Information for Patients.**

Paradoxical Bronchospasm

As with other inhaled beta$_2$-agonists, BROVANA can produce paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, BROVANA should be discontinued immediately and alternative therapy instituted.

Deterioration of Disease

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If BROVANA no longer controls the symptoms of bronchoconstriction, or the patient's inhaled, short-acting beta$_2$-agonist becomes less effective or the patient needs more inhalation of short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting, a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dosage of BROVANA beyond the recommended 15 mcg twice daily dose is not appropriate in this situation.

Cardiovascular Effects

BROVANA, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of BROVANA at the recommended dose, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QT_c interval, and ST segment depression. The clinical significance of these findings is unknown. BROVANA, as with other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension (see **PRECAUTIONS, General**).

Immediate Hypersensitivity Reactions

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

Do Not Exceed Recommended Dose

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. As with other inhaled beta$_2$-adrenergic drugs, BROVANA should not be used more often, at higher doses than recommended, or with other long-acting beta-agonists.

PRECAUTIONS

General

BROVANA (arformoterol tartrate) Inhalation Solution should not be used to treat acute symptoms of COPD. BROVANA has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. When prescribing BROVANA, the physician should also provide the patient with an inhaled, short-acting beta$_2$-agonist for treatment of COPD symptoms that occur acutely, despite regular twice-daily (morning and evening) use of BROVANA. Patients should also be cautioned that increasing inhaled beta$_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated (see **Information for Patients**).

BROVANA, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and/or diastolic blood pressure, pulse rate and electrocardiograms have been seen infrequently in individual patients in controlled clinical studies with arformoterol tartrate. Doses of the related beta$_2$-agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

Beta-agonist medications may produce significant hypokalemia in some patients, possibly though intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.

Clinically significant changes in blood glucose and/or serum potassium were infrequent during clinical studies with long-term administration of BROVANA at the recommended dose.

Information for Patients

Patients should be instructed to read the accompanying Medication Guide with each new prescription and refill. Patients should be given the following information:

1. Patients should be informed that long-acting beta$_2$-adrenergic agonists, such as BROVANA, increase the risk of asthma-related death. All LABA, including BROVANA, are contraindicated in patients with asthma without use of a long-term asthma control medication (see **CONTRAINDICATIONS**).
2. BROVANA is not indicated to relieve acute respiratory symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting, beta$_2$-agonist (the health-care provider should prescribe the patient with such medication and instruct the patient in how it should be used). Patients should be instructed to seek medical attention if their symptoms worsen, if BROVANA treatment becomes less effective, or if they need more inhalations of a short-acting beta$_2$-agonist than usual. Patients should not inhale more than one dose at any one time. The daily dosage of BROVANA should not exceed one ready-to-use vial (15 mcg) by inhalation twice daily (30 mcg total daily dose).
3. Patients should be informed that treatment with beta$_2$-agonists may lead to adverse events which include palpitations, chest pain, rapid heart rate, tremor, or nervousness.
4. Patients should be instructed to use BROVANA by nebulizer only and not to inject or swallow this inhalation solution.
5. Patients should protect BROVANA ready-to-use vials from light and excessive heat. The protective foil pouches should be stored under refrigeration between 2ºC and 8ºC (36º–46ºF). They should not be used after the expiration date stamped on the container. After opening the pouch, unused ready-to-use vials should be returned to, and stored in, the pouch. An opened ready-to-use vial should be used right away. Discard any ready-to-use vial if the solution is not colorless.
6. The drug compatibility (physical and chemical), efficacy and safety of BROVANA when mixed with other drugs in a nebulizer have not been established.
7. Women should be advised to contact their physician if they become pregnant or if they are nursing.
8. It is important that patients understand how to use BROVANA appropriately and how it should be used in relation to other medications to treat COPD they are taking.

Drug Interactions

If additional adrenergic drugs are to be administered by any route, they should be used with caution because the pharmacologically predictable sympathetic effects of BROVANA may be potentiated.

When paroxetine, a potent inhibitor of CYP2D6, was co-administered with BROVANA at steady-state, exposure to either drug was not altered. Dosage adjustments of BROVANA are not necessary when the drug is given concomitantly with potent CYP2D6 inhibitors.

Concomitant treatment with methylxanthines (aminophylline, theophylline), steroids, or diuretics may potentiate any hypokalemic effect of adrenergic agonists.

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

BROVANA, as with other beta$_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QT_c interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QT_c interval have an increased risk of ventricular arrhythmias. The concurrent use of intravenously or orally administered methylxanthines (e.g., aminophylline, theophylline) by patients receiving BROVANA has not been completely evaluated. In two combined 12-week placebo controlled trials that included BROVANA doses of 15 mcg twice daily, 25 mcg twice daily, and 50 mcg once daily, 54 of 873 BROVANA-treated subjects received concomitant theophylline at study entry. In a 12-month controlled trial that included a 50 mcg once daily BROVANA dose, 30 of the 528 BROVANA-treated subjects received concomitant theophylline at study entry. In these trials, heart rate and systolic blood pressure were approximately 2-3 bpm and 6-8 mm Hg higher, respectively, in subjects on concomitant theophylline compared with the overall population.

Beta-adrenergic receptor antagonists (beta-blockers) and BROVANA may interfere with the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of beta-agonists, but may produce severe bronchospasm in COPD patients. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies were conducted in mice using oral administration and rats using inhalation administration to evaluate the carcinogenic potential of arformoterol.

In a 24-month carcinogenicity study in CD-1 mice, arformoterol caused a dose-related increase in the incidence of uterine and cervical endometrial stromal polyps and stromal cell sarcoma in female mice at oral doses of 1 mg/kg and above (AUC exposure approximately 70 times adult exposure at the maximum recommended daily inhalation dose).

In a 24-month carcinogenicity study in Sprague-Dawley rats, arformoterol caused a statistically significant increase in the incidence of thyroid gland c-cell adenoma and carcinoma in female rats at an inhalation dose of 200 mcg/kg (AUC exposure approximately 130 times adult exposure at the maximum recommended daily inhalation dose). There were no tumor findings with an inhalation dose of 40 mcg/kg (AUC exposure approximately 55 times adult exposure at the maximum recommended daily inhalation dose).

Arformoterol was not mutagenic or clastogenic in the following tests: mutagenicity tests in bacteria, chromosome aberration analyses in mammalian cells, and micronucleus test in mice.

Arformoterol had no effects on fertility and reproductive performance in rats at oral doses up to 10 mg/kg (approximately 2700 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis).

Pregnancy: Teratogenic Effects

Pregnancy Category C

Arformoterol has been shown to be teratogenic in rats based upon findings of omphalocele (umbilical hernia), a malformation, at oral doses of 1 mg/kg and above (AUC exposure approximately 370 times adult exposure at the maximum recommended daily inhalation dose). Increased pup loss at birth and during lactation and decreased pup weights were observed in rats at oral doses of 5 mg/kg and above (AUC exposure approximately 1100 times adult exposure at the maximum recommended daily inhalation dose). Delays in development were evident with an oral dose of 10 mg/kg (AUC exposure approximately 2400 times adult exposure at the maximum recommended daily inhalation dose).

Arformoterol has been shown to be teratogenic in rabbits based upon findings of malpositioned right kidney, a malformation, at oral doses of 20 mg/kg and above (AUC exposure approximately 8400 times adult exposure at the maximum recommended daily inhalation dose). Malformations including brachydactyly, bulbous aorta, and liver cysts were observed at doses of 40 mg/kg and above (approximately 22,000 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women. BROVANA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Labor and Delivery

There are no human studies that have investigated the effects of BROVANA on preterm labor or labor at term. Because beta-agonists may potentially interfere with uterine contractility, BROVANA should be used during labor and delivery only if the potential benefit justifies the potential risk.

Nursing Mothers

In reproductive studies in rats, arformoterol was excreted in the milk. It is not known whether arformoterol is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BROVANA is administered to a nursing woman.

Pediatric

BROVANA is approved for use in the long term maintenance treatment of bronchoconstriction associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema. This disease does not occur in children. The safety and effectiveness of BROVANA in pediatric patients have not been established.

Geriatric

Of the 873 patients who received BROVANA in two placebo-controlled clinical studies in adults with COPD, 391 (45%) were 65 years of age or older while 96 (11%) were 75 years of age or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Among subjects age 65 years and older, 129 (33%) received BROVANA at the recommended dose of 15 mcg twice daily, while the remainder received higher doses. ECG alerts for ventricular ectopy in patients 65 to ≤75 years of age were comparable among patients receiving 15 mcg twice daily, 25 mcg twice daily, and placebo (3.9%, 5.2%, and 7.1%, respectively).

A higher frequency (12.4%) was observed when BROVANA was dosed at 50 mcg once daily. The clinical significance of this finding is not known. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Experience in Adult Patients with COPD

Of the 1,456 COPD patients in the two 12-week, placebo-controlled trials, 288 were treated with BROVANA (arformoterol tartrate) Inhalation Solution 15 mcg twice daily and 293 were treated with placebo. Doses of 25 mcg twice daily and 50 mcg once daily were also evaluated. The numbers and percent of patients who reported adverse events were comparable in the 15 mcg twice daily and placebo groups.

The following table shows adverse events where the frequency was greater than or equal to 2% in the BROVANA 15 mcg twice daily group and where the rates of adverse events in the BROVANA 15 mcg twice daily group exceeded placebo. Ten adverse events demonstrated a dose relationship: asthenia, fever, bronchitis, COPD, headache, vomiting, hyperkalemia, leukocytosis, nervousness, and tremor.

Patient Selection Is Paramount

Segmentectomy • *from page 1*

nodal staging in early lung cancer, Dr. Schuchert said.

Lung preservation is another potential benefit of segmentectomy. In addition, the procedure is particularly useful for tumors with low malignancy potential where you may not have to take out an entire lobe to gain oncologic control, he said.

"This is an excellent tool that can be both diagnostic and therapeutic for a solitary pulmonary nodule" as well, he noted. "It's also a great procedure when you're dealing with possible metastasis. Is it a lung cancer or a metastasis? You do a segment and you are pretty much done either way."

Equivalent survival to lobectomy has been demonstrated for stage 1A disease, Dr. Schuchert said, especially for lesions smaller than 2 cm.

In addition, compared with lobectomy, segmentectomy may result in "decreased morbidity and mortality risk, especially among the elderly, a population we are going to be seeing more and more of."

Patient selection is paramount. In addition to the elderly, segmentectomy is particularly suitable for patients with marginal pulmonary function; those with "ground glass opacity" that may have low nodal positivity rates; and those who had prior lobectomy seeking parenchymal preservation.

"If you are contemplating the use of segmentectomy, it all really comes down to evaluation of the case," he said. Preoperative imaging ideally reveals a small tumor (less than 2 cm) in the outer third of the lung. In addition, tumors should be confined to a discrete segmental boundary. "That's critical. That's the ticket for success," he said.

Surgeons can use the same anatomic approach they employ for lobectomy, only direct it at one segment. It is important to know segmental vascular and segmental bronchial anatomy, Dr. Schuchert noted.

"All of the same anatomic concerns, exposure concerns, and dissection concerns and techniques really apply." Segmentectomy can be performed through video-assisted thoracic surgery (VATS) or an open approach; the majority of cases at the University of Pittsburgh are VATS.

He described his customary surgical setup: "We typically position the camera at about the seventh interspace in the midaxillary line. Along the same interspace, a little more posteriorly, we will utilize a 10-mm incision for retraction and stapling. The access incision is pretty much the same as it is for a VATS lobectomy, usually somewhere along the line of the inframammary crease, and we place it right over the anterior hilum." This incision is usually around the level of the minor fissure on the right and slightly above the major fissure on the left, he added.

Next a 5-mm incision is made for retraction; it can also be particularly useful during node dissection, Dr. Schuchert said.

'If you can do a lobectomy, you can do a segmentectomy.'

DR. SCHUCHERT

"In general, we take vein first, then artery, then bronchus," he said. "Exceptions include superior and posterior segments, where we are forced in some cases to work in the fissure and start with the arteries, then do the bronchus, and then do the vein."

Preservation of the remaining lung is always a goal. "If you devitalize the remaining lung or impinge upon the bronchial supply, that patient is going to be doomed to have some perioperative issues." Remember that segmentectomy is a functional operation as well, he pointed out. "We are not just taking things out; what we leave behind still has to work."

Segmental dissection assisted by use of energy is a more recent development in their technique. "We have now utilized energy in well over 100 patients undergoing both segmentectomy and lobectomy," Dr. Schuchert said.

Another essential goal of segmentectomy is to achieve a margin-to-tumor ratio greater than the size of the tumor itself, he said.

As an example, he cited the case of a 71-year-old man with a history of diverticulitis with a pulmonary nodule picked up on an abdominal CT scan. The nodule was 1.7 cm, well confined in the outer third of the lung, and well centered within the basilar segment. Fine-needle aspiration of the nodule revealed adenocarcinoma.

"He was considered to be an excellent candidate for segmentectomy. In this case, the margin was about 5 cm for a 1.7-cm tumor."

Dr. Schuchert and his colleagues published additional details of the segmentectomies they performed between 2002 and 2010 at UPMC in a retrospective study (Ann. Thorac. Surg. 2012:93:1780-7).

Dr. Schuchert said he had no relevant financial disclosures. ■

Some Antidepressants Increased Risk of Death in ICU

BY SHERRY BOSCHERT
IMNG Medical News

SAN FRANCISCO – Patients on selective serotonin reuptake inhibitors or serotonin norepinephrine reuptake inhibitors when they were admitted to an intensive care unit were 73% more likely to die in the hospital, compared with ICU patients who were not on these antidepressants, a retrospective study found.

VITALS

Major Finding: ICU mortality rates were 10% in patients on fluoxetine, 13% with paroxetine, and 15% with sertraline, compared with 7% of control patients.

Data Source: Findings are from a retrospective analysis of data on 1,876 patients on an SSRI or SNRI and 8,692 patients not taking these drugs who were admitted to four ICUs.

Disclosures: Dr. Berg reported having no financial disclosures.

Dr. Katherine M. Berg and her associates analyzed electronic records from admissions to four ICUs in 2001-2008 to compare outcomes for 1,876 patients who were on an SSRI or SNRI and 8,692 control patients who were not taking an SSRI or SNRI before admission.

The mortality risk remained elevated at 1,000 days after ICU admission, she reported at an international conference of the American Thoracic Society.

Certain subgroups were at even greater risk of dying in the hospital if they were on an SSRI or SNRI when admitted to the ICU. Patients who had acute coronary syndrome or had undergone cardiac surgery were more than twice as likely to die if they were on an SSRI/SNRI upon admission to the ICU, compared with controls, said Dr. Berg, a pulmonary/critical care fellow at Massachusetts General Hospital and Harvard University, Boston.

The increased mortality risk appeared to be associated mainly with medications with higher degrees of serotonin reuptake inhibition. "Citalopram, which is a lower-potency drug, by itself did not incur a higher mortality risk, but sertraline, which is one of the more potent drugs, did. Even comparing the two drugs to each other, if you were on sertraline, your mortality risk was higher" than if you were on citalopram, Dr. Berg said in an interview.

Fluoxetine, paroxetine, and sertraline were associated with significantly higher mortality, but no significant mortality differences were seen between patients on citalopram or escitalopram and control patients.

Of the 8,692 control patients, 7% died in the hospital, compared with in-hospital death rates of 10% in 286 patients on fluoxetine, 13% in 320 patients on paroxetine, and 15% in 426 patients on sertraline at the time of ICU admission. The remaining 844 patients were on other antidepressants.

The study adjusted for the effects of each patient's age, Simplified Acute Physiology Score, and combined Elixhauser comorbidity score on in-hospital mortality risk.

The mortality risk remained elevated at 1,000 days after ICU admission.

DR. BERG

Slight but statistically significant differences in the characteristics of the two groups included a greater proportion of the women in the SSRI/SNRI group, compared with controls (57% vs. 40%), and a higher prevalence of diabetes (21% vs. 17%) or chronic obstructive pulmonary disease (11% vs. 7%) in patients on an SSRI/SNRI, compared with controls. Patients in the SSRI/SNRI group were more likely to have an infection than were controls (11% vs. 8%), but less likely to have acute coronary syndrome (8% vs. 10%) or cardiovascular disease (67% vs. 70%).

Further studies are needed to ascertain if this is a causal relationship or just an association between SSRI/SNRI use and mortality in ICU patients, she said. The findings are limited by the retrospective nature of the study, which also was unable to control for the effects of potentially important confounders such as smoking status or the presence of depression.

The data came from the Multiparameter Intelligent Monitoring in Intensive Care II database, a public collection of data with patient identifiers removed.

Antidepressants were the most commonly prescribed medication class in the United States in 2011, and SSRIs were the most common type of antidepressant, she said. SSRI use has been associated with increased risk of bleeding, falls, bradycardia, and stroke in previous studies, which also suggest a possible protective effect of SSRIs in patients with coronary artery disease. ■

COMMENTARY

Dr. Steven Q. Simpson, FCCP, comments: SSRIs and SSNIs are among the best-selling drugs in history. This is an important analysis, pointing out a previously occult association of prehospitalization use of these agents with mortality. Clearly, we need more evidence and possibly prospective evidence, as this report gives us no inkling of the cause of death or of how deaths in these patients may be either surveilled for or curtailed. I agree with the authors that causation will need to be established by further study, but the widespread use of SSRIs/SSNIs makes such study an important undertaking.

VTE Risk Heightened in Rheumatoid Arthritis

BY BRUCE JANCIN
IMNG Medical News

BERLIN – Rheumatoid arthritis patients face a moderately elevated risk of venous thromboembolism that continues unabated for many years, according to findings from two large studies that were presented at the European Congress of Rheumatology.

Dr. Seoyoung C. Kim offered a retrospective cohort study involving 22,143 patients with rheumatoid arthritis (RA) and 88,572 age- and sex-matched controls. None of the subjects had a baseline history of malignancy or venous thromboembolism (VTE). The data came from a large U.S. commercial insurance plan.

During a mean follow-up of 2 years (starting when the RA patients received their first prescription for a disease-modifying antirheumatic drug), deep vein thrombosis or pulmonary embolism occurred in 1.2% of RA patients and 0.5% of controls. The incidence among RA patients was 6.1 cases per 1,000 person-years, a rate 2.4-fold greater than in controls. The pulmonary embolism rate was 2.7 times higher than in controls, whereas the deep vein thrombosis rate was 2.2-fold higher, according to Dr. Kim of Brigham and Women's Hospital, Boston, where she is a rheumatologist.

VITALS

Major Finding: The risk of venous thromboembolism was 40% greater in RA patients than controls in one 2-year study, whereas a second study found the risk of pulmonary embolism to be 80%-100% higher in RA patients than controls who were followed for as long as 15 years.

Data Source: The U.S. retrospective cohort study included more than 22,000 RA patients, whereas the Swedish prospective cohort study involved 8,077.

Disclosures: Neither study had commercial sponsorship. Dr. Holmqvist and Dr. Kim reported having no financial conflicts.

After adjustment for known risk factors for VTE, including surgery, hospitalization, and cardiovascular disease, the VTE risk associated with having RA remained moderately elevated, with a 40% increase compared with controls.

The mechanism underlying this increased risk is believed to hinge upon the systemic inflammation that is a central feature of RA. This inflammation is thought to predispose to thrombus formation, up-regulation of procoagulants, down-regulation of anticoagulants, and suppression of fibrinolysis, Dr. Kim noted.

Dr. Marie Holmqvist presented a prospective population-based cohort study including 8,077 patients who were newly diagnosed with RA during 1997-2009, as well as 203,329 controls.

In all, 84 RA patients were diagnosed with a pulmonary embolism during 43,178 person-years of prospective follow-up. That translated to an incidence of 1.9 cases per 1,000 person-years, compared with 1.1 cases per 1,000 person-years among controls.

The increased risk of pulmonary embolism was evident 1 year after diagnosis of RA and remained unchanged thereafter. In the period 1-4 years after diagnosis of RA, the RA group had a 1.8-fold greater risk of pulmonary embolism than did controls drawn from the general population. During years 5-9, the risk was increased 2.0-fold, and in years 10-15 the risk of pulmonary embolism in RA patients was 1.9-fold greater than in controls, although only a small number of subjects were followed that long.

Control subjects who were hospitalized for any reason had a 5.4-fold increased risk of pulmonary embolism for the next year, compared with nonhospitalized controls. The risk of pulmonary embolism in hospitalized RA patients was elevated for the next year to the same extent as in hospitalized controls. In other words, having RA didn't pile on additional risk beyond hospitalization itself, according to Dr. Holmqvist of the Karolinska Institute, Stockholm. ■

COMMENTARY

Dr. Jun Chiong, FCCP, comments: Rheumatoid arthritis is not generally considered to be a risk factor for VTE, although abnormalities of coagulation factors have been found in patients with RA. These studies suggest that RA patients may have higher rates of VTE and raise our awareness of the risks to lower the threshold for VTE prophylaxis as well as evaluation of patients suspected for possible VTE or PE.

Adaptive Servoventilation Bests CPAP Over Time

BY DIANA MAHONEY
IMNG Medical News

BOSTON – Adaptive servoventilation is more reliably effective than continuous positive airway pressure is for the prolonged treatment of complex sleep apnea, a study has shown.

Prior studies have shown that the adaptive ventilatory support method, which continuously monitors and analyzes a patient's breathing pattern and adds variable amounts of inspiratory pressure support to low levels of background expiratory positive airway pressure as needed, is initially more effective than is continuous positive airway pressure (CPAP) in complex sleep apnea patients. But sustained efficacy over time has not been established, according to Dr. Timothy I. Morgenthaler, FCCP, of the Center for Sleep Medicine at the Mayo Clinic in Rochester, Minn.

"The concern is that residual central breathing events may resolve over time with CPAP therapy, which is less expensive than adaptive servoventilation [ASV] and therefore may be a better option," he said at the annual meeting of the Associated Professional Sleep Societies.

To evaluate the longer-term efficacy of ASV relative to CPAP in individuals with complex sleep apnea syndrome (CSAS), Dr. Morgenthaler and his colleagues conducted a multicenter, prospective trial of 66 patients with CSAS, defined as those meeting the criteria for obstructive sleep apnea on diagnostic polysomnography who also had a central apnea index (CAI) score of 10 or higher while on optimal CPAP. The participants were randomized to treatment with either CPAP (N = 33) or ASV (N = 33), both titrated to optimal settings. Clinical and polysomnographic measures were collected at baseline and after 90 days of therapy, he said.

VITALS

Major Finding: The apnea-hypopnea index scores of adults who underwent adaptive servoventilation for the treatment of complex sleep apnea decreased to 4.4 at 3 months from a baseline mean of 37.7, while the AHI score of those who underwent continuous positive airway pressure treatment decreased to 9.9. A successful outcome, defined as AHI of less than 10, was observed in 89.7% of the ASV patients, compared with 64.5% of the CPAP patients.

Data Source: Results were taken from a multicenter, prospective, randomized study designed to compare the efficacy of ASV and CPAP in 66 adults with complex sleep apnea.

Disclosures: Dr. Morgenthaler disclosed that this study was supported by a grant from ResMed, the manufacturer of the ASV device used in the investigation.

In addition to having a diagnosis of CSAS, eligible patients were older than 18 years and were naive to positive airway pressure treatment. The mean age of the study participants was 59.2 years, and the mean body mass index was 35.0 kg/m^2, with no between-group differences. Additionally, about 9% of the patients had congestive heart failure and 13.6% reported chronic opiate use, Dr. Morgenthaler reported.

At baseline, the mean apnea-hypopnea index (AHI) and CAI scores were 37.7 and 3.2, respectively. After second-night treatment titration, the AHI scores were 4.7 in the ASV group vs. 14.1 in the CPAP group, and the respective CAI scores were 1.1 and 8.8, said Dr. Morgenthaler. At 90 days, the AHI for the ASV group was 4.4, compared with 9.9 for CPAP, and the respective CAI scores were 0.7 and 4.8, he said.

"In the intention-to-treat analysis, treatment was successful [defined as an AHI of less than 10] in 89.7% of the adaptive servoventilation group," while only 64.5% of the CPAP patients attained similar success, Dr. Morgenthaler stated, noting that there were no significant differences between the groups with respect to compliance, Epworth Sleepiness Scale (ESS) changes, or sleep apnea quality of life index (SAQLI) scores.

Although significantly more ASV patients showed evidence of treatment efficacy based on polysomnographic measures than did CPAP patients, "there were no similar symptomatic differences between the groups," Dr. Morgenthaler acknowledged. It is possible, but yet to be determined, that ASV-induced improvements on polysomnography will translate into other positive health outcomes, such as maximal suppression of Cheyne-Stokes respiration and central sleep apnea (CSR-CSA), as well as improvement in brain natriuretic peptide, in patients with heart failure, he said. ■

COMMENTARY

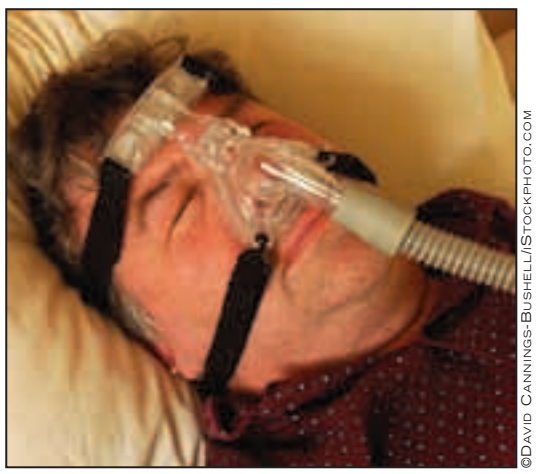
Dr. Paul A. Selecky, FCCP, comments: Before the advent of ASV for the treatment of complex sleep apnea, our approach to obstructive sleep apnea patients who develop central apneas on exposure to positive airway pressure (PAP) was to continue the PAP treatment with the hope that the central apneas would resolve over time. That debate continues, so it is reassuring to now learn of the benefits of ASV over PAP in these patients.

CPAP Linked to Improved Mood in Sleep Apnea

BY DIANA MAHONEY
IMNG Medical News

BOSTON – Treatment with continuous positive airway pressure does double duty in patients with obstructive sleep apnea by improving their mood while promoting restful sleep, Dr. Charles Bae reported at the annual meeting of the Associated Professional Sleep Societies.

In a retrospective study of 769 adults with OSA, the Cleveland Clinic neurologist and his colleagues observed a significant decrease in depressive symptoms as measured by the Patient Health Questionnaire 9 (PHQ-9) among patients who used a CPAP device.



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CPAP-adherent sleep apnea patients had a signficant decrease in depressive symptoms.

"A number of studies have confirmed an association between obstructive sleep apnea and depressive symptoms, but until now none have looked specifically at the link between CPAP and symptom severity as measured by PHQ-9," Dr. Bae said in an interview. "Our goal was to assess the impact of CPAP therapy on patient mood by measuring the change in depressive symptoms following treatment."

Toward this end, the investigators reviewed data for all of the adult patients (18 years or older) with OSA seen at the Cleveland Clinic Sleep Disorders Center from January 2008 to July 2011. Patients who met study criteria had been treated with CPAP and had at least two outpatient visits (one before and one within 30 days after initiating CPAP), had completed the PHQ-9 questionnaire, and had a pre-CPAP score on the questionnaire of at least 5, Dr. Bae said.

Of the 769 study patients (mean age, 51.8 years), 654 were characterized as adherent to CPAP therapy based on self-reported use of the device 4 or more hours per night; the remaining 115 used the device either inconsistently or for fewer than 4 hours per night and were considered nonadherent. The baseline PHQ-9 scores for patients in the adherent and nonadherent groups were similar, at 11.2 and 11.8, respectively. Significant decreases from baseline in PHQ-9 scores were observed in both groups, but the difference was "significantly more robust" in the adherent group at 3.8, compared with 2.0 in the nonadherent group, Dr. Bae reported.

VITALS

Major Finding: In treatment-adherent OSA patients, scores on the Patient Health Questionnaire 9 improved 3.8 points from baseline, compared with 2.0 points in the nonadherent group.

Data Source: The retrospective study examined post-treatment mood changes in 769 adults with OSA.

Disclosures: Dr. Bae reported no relevant conflicts of interest.

The results were even more robust among patients who had reported sleepiness at baseline, according to Dr. Bae. Specifically, in the patients who had a minimum score of 10 on the Epworth Sleepiness Scale prior to CPAP, ESS scores decreased by 4.0 in the adherent group vs. 2.8 in the nonadherent group, he said. In the CPAP-adherent group, there was a significant difference between sleepy vs. nonsleepy patients in their average decrease in PHQ-9 score. "The PHQ-9 score dropped 4.3 points among patients whose [ESS] score was at least 10 at baseline, compared with 3.1 points among those whose score was less than 10," he said.

Marital status was also examined as a covariate in the multiple regression model and appeared to have an effect. The mean PHQ-9 score decrease among the 475 married patients after CPAP was 4.0, compared with 3.0 among single patients and 2.3 among divorced patients, Dr. Bae said, noting that the difference between married and divorced patients was significant.

While the specific mechanisms contributing to the mood improvements associated with CPAP treatment in OSA patients can't be ascertained from a retrospective study, the findings are fairly intuitive, according to Dr. Bae. When people sleep better, "a lot of things look better," he said. ■

COMMENTARY

Dr. Paul A. Selecky, FCCP, comments: We know that depression is closely associated with poor-quality sleep. It therefore seems intuitive that better-quality sleep, such as in successfully treated sleep apnea patients, can result in helping decrease symptoms of depression. This study confirms that.

Treating Kids' Sleep Apnea Can Improve Brain Function

BY DIANA MAHONEY
IMNG Medical News

BOSTON – Neuronal abnormalities in the brains of children with obstructive sleep apnea are reversible with treatment, a prospective study has shown.

The findings are the first to show that the altered brain metabolites of the frontal cortex – the neuronal network responsible for attention and executive function – normalize with treatment of pediatric obstructive sleep apnea, Dr. Ann C. Halbower reported at the annual meeting of the Associated Professional Sleep Societies.

Previous studies have demonstrated an association between obstructive sleep apnea (OSA) and deficits in attention, cognition, and executive function, "but ours is the first to look at the effect of [OSA] treatment on the neuronal brain injury and to show a relationship between treatment and improvements in attention and verbal memory in these patients," said Dr. Halbower of the Children's Hospital Colorado Sleep Center and the University of Colorado at Denver. The study included 28 children aged 8-11 years; 17 had moderate or severe OSA and 11 were healthy controls matched by age, sex, race, and socioeconomic status. At study baseline, all participants underwent neuropsychological testing, and 22 of the children (15 with OSA and 7 healthy controls) also underwent magnetic resonance spectroscopy imaging. Six months post treatment, 11 of the OSA patients underwent repeat brain imaging and neuropsychological testing, Dr. Halbower said. Treatment for OSA consisted of adenotonsillectomy followed by monitored continuous positive airway pressure (CPAP) for children whose apnea-hypopnea index (AHI) score was higher than 3, or nasal treatments for those with an AHI score of 2-3, she explained.

Among the OSA patients, the mean AHI score at baseline was 13.6, compared with 0.3 for the healthy controls – a discrepancy mirrored by differences observed in both the brain imaging and the function tests. Specifically, Dr. Halbower reported, "the *N*-acetyl aspartate to choline (NAA/Cho) ratios in the left hippocampus and left frontal cortex were significantly decreased in [OSA] patients, compared with healthy controls, and the [OSA] patients had significant decreases in the executive function of working memory, attention, and verbal memory."

After treatment, "the neuronal metabolites of the right and left frontal cortex normalized, and the hippocampal metabolites improved with a medium effect size," Dr. Halbower said. The follow-up neuropsychological testing showed significant improvements in verbal memory and attention, "which correlated with the normalization of the [NAA/Cho] ratios in the frontal lobes," she said. A further analysis of the data linked improvement on the AHI with a more comprehensive reversal of the hippocampal abnormalities in children with mild OSA, she said, noting, however, that this finding "is very preliminary."

Based on the study results, "we speculate that early diagnosis and treatment of obstructive sleep apnea in children could have profound effects on the trajectory of their development," Dr. Halbower said. ■

VITALS

Major Finding: Ratios of *N*-acetyl aspartate to choline in the frontal cortex of children with obstructive sleep apnea normalized after treatment, correlating to improvements in verbal memory and attention.

Data Source: The prospective study compared the pre- and posttreatment neuroimaging and neuropsychological test results of children with OSA to those of matched controls.

Disclosures: Dr. Halbower said she had no relevant financial disclosures.

COMMENTARY

Dr. Susan Millard, FCCP, comments: Dr. Ann C. Halbower's research gives us the exciting insight that neurodevelopment can be adversely affected by pediatric obstructive sleep apnea.

Low-Risk Kids With Asthma May Not Need Daily ICS

Older children (those aged 12-18 years) did not benefit from daily ICS.

BY M. ALEXANDER OTTO
IMNG Medical News

SAN FRANCISCO – Children aged 12 years and older may be less likely to have asthma exacerbations than are younger children, according a 44-week trial in 288 children with mild, persistent asthma.

Girls also may be less likely to have asthma exacerbations than are boys. The lower risk in girls and older children means that these patients probably don't need inhaled corticosteroids (ICS) daily, but only for symptoms or rescue, said Dr. Joseph Gerald of the University of Arizona, Tucson.

THE INVESTIGATORS WERE UNABLE TO SHOW A SIGNIFICANT BENEFIT FOR ANY ICS STRATEGY IN GIRLS.

"It's a reasonable" approach that limits impaired growth and other potential ICS side effects when "the benefit to be gained from daily inhaled steroids is not that great," he said at an international conference of the American Thoracic Society.

VITALS

Major Finding: Over 44 weeks, almost 30% of boys but only 15% of girls with mild, persistent asthma had more than two exacerbations requiring oral corticosteroids.

Data Source: This was a randomized, placebo-controlled trial of 288 children with mild, persistent asthma.

Disclosures: The investigators said they have no relevant disclosures.

The researchers randomized 72 children to daily ICS, 71 to rescue ICS only, 71 to combined treatment with ICS and inhaled albuterol, and 74 to placebo. The daily ICS regimen consisted of one 40-mcg puff of beclomethasone twice daily; combined treatment consisted of one 40-mcg puff of beclomethasone with each albuterol puff used for symptom relief. Dummy inhalers were used as needed to maintain blinding. The participants were 6-18 years old.

Compared with placebo, all three ICS regimens reduced treatment failures (defined as more than two exacerbations requiring oral corticosteroids) in boys, in children 6-11 years old, and in children with allergic forms of the disease as indicated by eczema, positive skin tests, methacholine PC_{20} (a provocative concentration of methacholine causing a 20% fall in forced expiratory volume in 1 second) at or below 12.5 mg/dL, and IgE levels at or above 185 kU/L. For instance, 29.3% of boys (12 of 41) in the placebo group failed treatment, but only 2.4% of boys (1 of 42) in the daily ICS group did so.

The investigators were unable to show a statistically significant benefit for any ICS strategy in girls, in children 12-18 years old, and in those with higher methacholine PC_{20} levels, lower IgE levels, negative skin tests, and no eczema.

That's probably not because inhaled steroids work better in boys and other responders, but rather because nonresponders had lower exacerbation rates in general, making it harder to detect a benefit, Dr. Gerald said.

For example, although almost 30% of boys in the placebo group failed treatment, only 15.2% of girls (5 of 33) in the placebo group failed. Similarly, 26% of children aged 6-11 years (13 of 50) failed treatment in the placebo arm, but only 16.7% of children aged 12-18 years (4 of 24) did so.

"We think the baseline [exacerbation] risk is what we are detecting here. [Nonresponders] started from a lower risk and just didn't benefit as much," Dr. Gerald said. The study did not determine the best ICS regimen among responders. ■

COMMENTARY

Dr. Burt Lesnick, FCCP, comments: At CHEST 2012, on Oct. 23 at 4:30 p.m., a pro/con session is dedicated to this topic. Dr. Leonard Bacharier will present the "pro" position in favor of using intermittent ICS in mild asthma. Dr. Craig Schramm will present the "con" position. We encourage those interested to attend what should be a lively discussion.

NEWS FROM THE FDA

Twice-Daily Inhaled Anticholinergic Approved for COPD

Aclidinium bromide, a long-acting anticholinergic bronchodilator, has been approved as a treatment for chronic obstructive pulmonary disease, for the long-term maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema, the Food and Drug Administration announced on July 3.

The product, a dry powder inhaler used twice a day, will be marketed as Tudorza Pressair by Forest Pharmaceuticals, a subsidiary of Forest Laboratories. A statement released by Forest Laboratories said that the product was expected to become available to wholesalers in the fourth quarter of 2012. The inhaler delivers 60 doses of aclidinium bromide powder for inhalation, the statement said.

Approval was based on three randomized, placebo-controlled, confirmatory clinical trials, which included 1,276 patients aged 40 years and older diagnosed with COPD. At a meeting in February 2012, the majority of the FDA's Pulmonary-Allergy Drugs Advisory Committee agreed that the data in clinical trials provided evidence that this dose had a clinically meaningful benefit in patients, citing the significant increases in trough forced expiratory volume in 1 second (FEV_1) from baseline (the primary efficacy end point) among those treated with 400 mcg twice a day, compared with those on placebo after 12 weeks of treatment in clinical studies.

The most common side effects reported by patients treated with aclidinium bromide included headache, nasopharyngitis, and cough. Serious adverse effects associated with treatment include paradoxical bronchospasm, new or worsened acute narrow-angle glaucoma, or new or worsened urinary retention, according to the FDA statement.

Forest Laboratories licensed the U.S. rights for aclidinium from Almirall, a pharmaceutical company based in Spain. In May, the Committee for Medicinal Products for Human Use of the European Medicines Agency has issued a positive opinion for approval of aclidinium for treating COPD in the E.U.

Test IDs Bloodstream Bacteria in Under 3 Hours

A diagnostic test that can identify in just hours 12 different bacteria that cause bloodstream infections has received marketing approval from the FDA.

The Verigene GP Blood Culture Nucleic Acid Test (BC-GP) simultaneously discerns the bacterial types and three associated resistance genes rapidly after the first sign of bacterial growth. Results can be available within 2½ hours, according to test manufacturer Nanosphere. Traditional methods require 2-4 days to identify bacteria and possible resistance.

The test can identify different types of *Staphylococcus* – including methicillin-resistant *S. aureus* – *Streptococcus*, *Enterococcus* (including vancomycin-resistant *Enterococci*), and *Listeria*.

The agency's decision was based on a study of 1,642 patient blood samples obtained from incubated blood culture bottles that contained gram-positive bacteria. The study included a comparison of BC-GP and traditional blood culture laboratory methods. The BC-GP results were consistent with traditional blood culture methods in 93%-100% of the comparisons, according to the FDA.

Rivaroxaban Goes Back to Janssen For ACS Indication

The FDA has declined to approve the oral anticoagulant rivaroxaban as a treatment for patients with acute coronary syndrome, according to a statement issued by Johnson & Johnson.

The FDA has issued a complete response letter regarding the supplemental indication for rivaroxaban for use in reducing the risk of secondary cardiovascular events in patients with ACS that has been under review at the agency, the statement said.

The FDA issues complete response letters for a drug when there are outstanding issues that need to be resolved before approval; the FDA does not make these letters public, and the company statement did not provide any details about the issues raised in the letter.

Rivaroxaban, an oral factor Xa inhibitor marketed as Xarelto by Janssen Pharmaceuticals, a Johnson & Johnson subsidiary, was initially approved in July 2011 for the prophylaxis of deep vein thrombosis in patients undergoing knee or hip replacement surgery; and in November 2011 for reducing the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

In December of last year, Janssen submitted the ACS application for rivaroxaban at a dose of 2.5 mg twice a day, to "reduce the risk of thrombotic cardiovascular events in patients with ACS [ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), or unstable angina (UA)] in combination with aspirin alone or with aspirin plus clopidogrel or ticlopidine."

But at a meeting in May, the majority of the FDA's Cardiovascular and Renal Drugs Advisory Committee recommended against approval of this indication, with those voting no citing a large amount of missing data in ATLAS ACS, the pivotal study, as well as safety concerns, among the reasons for their votes (6-4 with 1 abstention). Warfarin and three P2Y12 inhibitors – ticagrelor (Brilinta), prasugrel (Effient), and ticlopidine (Ticlid) – are approved for reducing the risk of thrombotic CV events in patients with ACS.

FDA Wants to See More ARISTOTLE Data on Apixaban

More information from a large clinical trial of apixaban is needed before the FDA can move forward in reviewing the oral anticoagulant for preventing stroke and systemic embolism for approval in patients with nonvalvular atrial fibrillation, according to a statement issued by Bristol-Myers Squibb on June 25.

Apixaban, a factor Xa inhibitor, is being reviewed by the FDA for this indication, but the agency has issued a complete response letter requesting "additional information on data management and verification from the ARISTOTLE trial," one of the two large studies submitted to the FDA for the approval of this indication, the statement said. No other details were provided.

The FDA has not asked for any new studies, and Bristol-Myers Squibb and Pfizer, which are collaborating to develop and commercialize apixaban in the United States and internationally, plan to work closely with the FDA on the next steps for the application, the statement said.

The statement adds that the companies plan to conduct studies of almost 60,000 patients worldwide for different indications and patient populations, including nine phase III studies that have either been completed or are still underway. It is being studied as a treatment for VTE in the phase III studies.

Panel Rejects New Heparin for VTE Prevention in Cancer

A new molecular weight heparin for preventing deep vein thromboses and pulmonary emboli in select cancer patients on chemotherapy failed to pass muster with an FDA panel.

The FDA's Oncologic Drugs Advisory Committee voted 14-1, with 1 abstention, that semuloparin sodium lacked a favorable risk-benefit profile when used to prevent venous thromboembolic events (VTEs) in patients receiving chemotherapy for locally advanced or metastatic lung or pancreatic cancer, or for patients receiving chemotherapy for locally advanced or metastatic solid tumors who are determined to be at a high risk of VTEs – the indication proposed for approval by the drug's manufacturer, Sanofi-Aventis U.S.

Semuloparin sodium, administered subcutaneously once a day, has not been approved anywhere, and if approved for this indication, it would be the first low-molecular-weight heparin (LMWH) – and the first anticoagulant – approved for preventing VTEs in cancer patients. One of the FDA reviewers pointed out that approval of the drug would "set a new standard of care" that would affect a large proportion of patients with cancer in the United States.

Current guidelines from the American Society of Clinical Oncology recommend anticoagulants for the treatment and prevention of recurrent VTE. The routine use of VTE prophylaxis is not advised for patients with cancer, except for those who are hospitalized, scheduled for major oncologic surgery, or receiving thalidomide or lenalidomide-based treatment.

Members of the panel pointed out that there were many unresolved issues, including the need for more information about the types of patients who would benefit, uncertainty over how long patients should be treated, problems with the single clinical trial that did not have robust results, and the lack of a clear benefit and toxic effects of the treatment.

Several panelists noted that there was a need for such a treatment, and encouraged the company to continue studying the drug and determine the types of cancer patients who could benefit.

FDA Warns of QT Prolongation With Ondansetron Dose

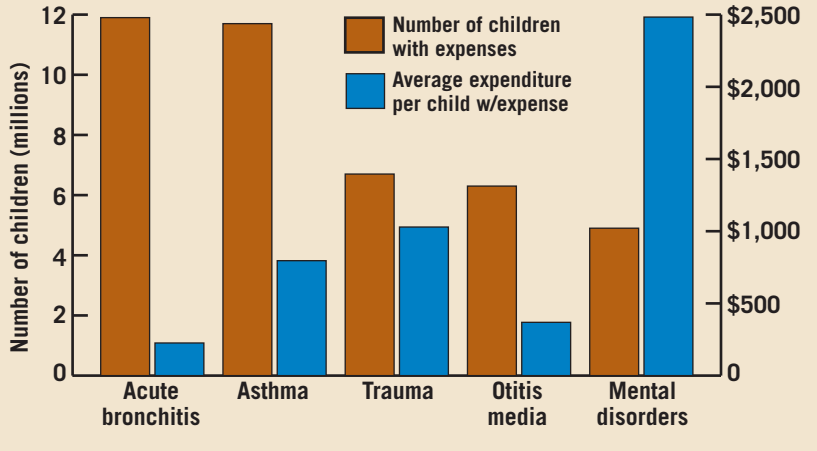
Preliminary data indicate that a single 32-mg intravenous dose of ondansetron should be avoided because it may increase the risk of QT prolongation, along with the potentially fatal arrhythmia torsades de pointes, the FDA announced.

GlaxoSmithKline, which manufactures ondansetron (Zofran), is removing the 32-mg single IV dose from the antinausea and vomiting drug's label, according to an FDA statement.

The updated label will say that ondansetron, a 5-HT_3 receptor antagonist, can continue to be used to treat adults and children with chemotherapy-induced nausea and vomiting at the dose of 0.15 mg/kg administered every 4 hours for three doses. "However, no single intravenous dose of ondansetron should exceed 16 mg due to the risk of QT prolongation," the FDA said. ■

DATA WATCH

Bronchitis and Asthma the Two Most Common Conditions in Children



Note: Based on data from the Medical Expenditure Panel Survey, 2008.
Source: Agency for Healthcare Resarch and Quality

Varenicline Plus Counseling Elevates Quit Rate

BY M. ALEXANDER OTTO
IMNG Medical News

SAN FRANCISCO – Almost a third of 196 patients (61) were smoke free a year after starting 12 weeks of varenicline therapy and having smoking-cessation counseling in a randomized Australian trial. Only 21% (42) of 196 patients given counseling alone stopped smoking.

The varenicline-plus-counseling results are impressive because the study included people who were on antidepressants and those with depression histories, both of whom had been excluded from several earlier studies of varenicline (Chantix), said lead investigator Dr. Brian Smith of the respiratory medicine unit at the Queen Elizabeth Hospital in Woodville, Australia.

But the most important take-home message of the study was its setup, he said at an international conference of the American Thoracic Society.

The participants had been hospitalized for at least 1 day for cardiac, respiratory, neurologic, or vascular smoking-related complications. Instead of handing them a quit-smoking hotline card as they walked out the door – the general practice in many hospitals – the investigators had them make their initial counseling service call from the bedside table while they were still in the hospital, Dr. Smith said. "Only about 6% of patients will make that call" from home. "[We took] the opportunity while they were still inpatients – a captive audience, if you like – to use the bedside phone to make the call. Instead of a 6% success rate, [we had a] 100% success rate," he said.

Patients found a friendly counselor on the other end of the line who emphasized the benefits of quitting instead of the dangers of continuing to smoke. Patients could arrange calls for days when they knew they would be particularly stressed. Counselors would call then to "pull them through," Dr. Smith said.

The mean number of phone calls in the varenicline-plus-counseling arm was 3.8, and in the counseling-only arm it was 4.1.

"The novel thing of our study is [that we] grabbed the opportunity while these patients were in hospital to get them to make the phone call that otherwise [they] would have been reluctant to make," Dr. Smith said. ■

VITALS

Major Finding: Varenicline (Chantix) plus counseling was more effective than was counseling alone in getting patients to quit smoking. Patients made the first quit-line call while they were in the hospital.

Data Source: Data were taken from a randomized Australian study of 392 smokers hospitalized for smoking complications.

Disclosures: Dr. Smith said he had no disclosures. Pfizer, the maker of Chantix, did not fund and was not involved in the trial, he said. Patients covered at least part of the cost of the drug themselves.

COMMENTARY

Dr. Jeana O'Brien, FCCP, comments: Findings at 1-year follow-up favored the combination of medication and counseling and showed a fairly impressive quit rate of nearly a third of the target group. The investigators' unique approach in having patients call the quitline counselor before leaving the hospital likely contributed to the good results. Perhaps this should be an addendum to discharge instructions and medication reviews for hospitalized patients with tobacco abuse.

Smokers Less Likely to Respond to Biologic Therapy for RA

BY SARA FREEMAN
IMNG Medical News

GLASGOW, SCOTLAND – Patients who smoke are substantially less likely to respond to biologic treatment for rheumatoid arthritis than are those who have never smoked.

The percentage of current smokers who responded to treatment with anti–tumor necrosis factor-alpha (anti-TNF-alpha) drugs at 6 months was just 27%, compared with 90% of never smokers and 63% of ex-smokers in a retrospective study of 359 patients.

Similarly poor response to rituximab was seen in patients who were current smokers, with respective response rates for current, ex-, and never smokers of 20%, 68%, and 98%.

A response was defined as a mean change in 28-joint disease activity score (DAS28) of 1.2 or greater, according to the U.K. National Institute for Health and Clinical Excellence (NICE) definition.

This begs the controversial question of whether current smokers should be given treatment with biologic agents, said Dr. Abdul Khan, a rheumatology specialist trainee at St. George's Hospital in London, speaking at the annual meeting of the British Society for Rheumatology.

Working with Dr. David L. Scott, Dr. Khan assessed whether two biomarkers – rheumatoid factor (RF) and smoking status – could help predict response to biologic therapy for RA (Rheumatology 2012;51:iii41-2, abstract O40). They studied 209 patients treated with anti-TNFs and 150 treated with rituximab. The mean age of patients was 56 years for the anti-TNF patients and 61 years for the rituximab group. Mean disease duration was 8 years and 13 years, respectively, and 61% and 53% were RF positive.

Primary outcome assessments included the 6-month change in DAS28 and calculation of NICE responders (DAS28 change greater than or equal to 1.2). Smoking status was assessed as current, previous, or never. Dr. Khan observed that a more detailed evaluation of smoking history might be warranted in future investigations, such as the calculation of pack-years. RF status was determined, and anticitrullinated protein autoantibody (ACPA) positivity was determined for patients on rituximab.

The mean change in DAS28 scores after 6 months' anti-TNF therapy for never smokers was 2.6. For current smokers, the mean change was just 0.9 and for ex-smokers, it was 1.39. Corresponding figures for rituximab patients were 2.92, 0.63, and 1.49.

RF status predicted responses to rituximab but not to anti-TNFs, with a mean change of 2.14 for RF-positive patients and 0.98 for RF-negative patients treated with rituximab after 6 months.

Combining RF and ACPA status showed significant effects with regards to response to rituximab – 80% of never but only 22% of current smokers responded to treatment at 6 months if they were positive for both RF and ACPA.

In a statement, Dr. Scott, professor of rheumatology at King's College in London, said that "these findings show what a dramatic effect modifying your lifestyle, such as giving up smoking, can have on treatment outcomes." ■

VITALS

Major Finding: Response rates to 6 months of anti-TNF therapy were 27% for current, 63% for previous, and 90% for never smokers. Corresponding data for rituximab were 20%, 68%, and 98%.

Data Source: This was a retrospective study of 359 RA patients treated with anti-TNF agents or rituximab.

Disclosures: Dr. Khan and Dr. Scott had no financial disclosures.

Bronchiectasis Responds Well to Erythromycin

BY M. ALEXANDER OTTO
IMNG Medical News

SAN FRANCISCO – Long-term, low-dose erythromycin reduces pulmonary exacerbations, sputum production, and breathing problems in patients with non–cystic fibrosis bronchiectasis, according to a randomized, placebo-controlled Australian study.

Low-dose erythromycin also may be less likely to induce antibiotic resistance than is azithromycin, the usual choice for prophylaxis. For these reasons, erythromycin should be considered for non-CF bronchiectasis, said lead investigator Dr. David Serisier at an international conference of the American Thoracic Society.

A total of 59 nonsmoking adults with the disease were randomized to erythromycin ethylsuccinate 400 mg twice daily and 58 to placebo, for 48 weeks. (The dosage of the better-tolerated salt is the equivalent of 250 mg of erythromycin b.i.d.) All patients had at least two infective exacerbations in the preceding year, said Dr. Serisier, a chest physician and associate professor of medicine at the University of Queensland in Brisbane.

VITALS

Major Finding: Non-CF bronchiectasis patients have almost 40% fewer exacerbations when treated with low-dose erythromycin, compared with placebo.

Data Source: Data are from a randomized, double-blind, placebo-controlled 48-week trial in 117 patients with non-CF bronchiectasis.

Disclosures: Dr. Serisier said he had no relevant disclosures.

The erythromycin group had almost 40% fewer exacerbations (odds ratio, 0.64; 95% confidence interval [CI], 0.48-0.86; $P = .02$), corresponding to a mean reduction of 0.7 exacerbations per patient per year. About a third of the erythromycin patients (19) and more than half (30) of the placebo patients had two or more exacerbations during the trial ($P = .039$). One erythromycin patient was withdrawn for possible QTc prolongation.

FEV_1 declined slightly in both groups, but more so in the placebo arm, with a treatment effect of 2.02% (95% CI, 0.04-4.2; $P = .046$) in favor of erythromycin. Erythromycin patients also produced about 6 g less of sputum per day.

By study's end, about 36% of oropharyngeal streptococci isolates in the erythromycin group were resistant vs. about 5% in the placebo group (P less than .0001). "Erythromycin resulted in a very substantial increase in the proportion of macrolide-resistant streptococci," Dr. Serisier said.

Azithromycin, however, appears to be a more potent inducer of resistance, according to a randomized Belgian trial that found a 53.4% increase (P less than .0001) in macrolide-resistant oral streptococci after just 3 days of treatment (Lancet 2007;369:482-90).

"We are not exactly comparing apples with apples, but there's a suggestion that this effect is less with erythromycin," even after an entire year of therapy, Dr. Serisier said.

Even so, erythromycin "should be reserved for subjects who have evidence of more severe airway infection. I don't think it's something we should be throwing at all non-CF bronchiectasis patients, and not those who just have a mild, troublesome cough. I want this drug to be used in patients who really need it," he said. ■

COMMENTARY

Dr. Marcos I. Restrepo, FCCP, comments: This study provides more evidence suggesting that macrolides (e.g., erythromycin) used as immunomodulators improved outcomes in non-CF bronchiectasis. Erythromycin reduced the number and frequency of exacerbations and resulted in less decline in FEV_1 and less sputum production, compared with placebo. However, despite no differences in QT prolongation, the higher rate of erythromcyin-resistant pathogens in the erythromycin-treated group is cause for concern. Clinicians should be cautious in generalizing this information and assessing the clinical benefit with the risk of adverse events and antimicrobial resistance.

Sarcoidosis Doubles Mortality in Black Women

BY SHERRY BOSCHERT
IMNG Medical News

SAN FRANCISCO – Black women with a history of sarcoidosis have a mortality rate twice that of women without sarcoidosis, according to an analysis of data from approximately 59,000 women in the Black Women's Health Study during 1995-2009.

The age-adjusted mortality rate was 17/10,000 person-years in black women with a history of sarcoidosis and 8/10,000 person-years in those without a history of sarcoidosis, Dr. Melissa H. Tukey reported.

A total of 686 women had a diagnosis of sarcoidosis at the start of the Black Women's Health Study in 1995, and 506 women developed sarcoidosis during follow-up; of these, 121 died. Among the remaining women without sarcoidosis, 2,813 died. Cumulative mortality rates were 10% in those with sarcoidosis and 5% in those without sarcoidosis, Dr. Tukey and her associates reported at an international conference of the American Thoracic Society.

Sarcoidosis was the leading cause of death in women with the disease who died. Of deaths among women with a history of sarcoidosis, 24% were directly attributable to the disease, and 47% of these deaths were caused by respiratory failure, an analysis of National Death Index data showed. Another 6% died from pulmonary fibrosis or pulmonary hypertension.

The current analysis is the largest epidemiologic study specifically focused on mortality in black women with sarcoidosis, said Dr. Tukey of Boston University.

VITALS

Major Finding: Black women with a history of sarcoidosis had an age-adjusted mortality rate of 17/10,000 person-years, compared with a rate of 8/10,000 person-years in those with no sarcoidosis history.

Data Source: Data are from approximately 59,000 participants in the Black Women's Health Study during 1995-2009 and the National Death Index.

Disclosures: Dr. Tukey reported having no financial disclosures.

Previous data suggesting that African American women are disproportionately affected by sarcoidosis and have a higher mortality from the disease come primarily from single-site studies, she added.

In each age category at the end of the follow-up period, the all-cause mortality rate among women with a history of sarcoidosis was higher than for women with no history of sarcoidosis.

For most black women with sarcoidosis, "it's primarily a benign disease," Dr. Tukey said. "But there is this cohort of patients that just have a more progressive and severe course, and often end up dying of their disease. Now we're finally able to really quantify what that actual risk is."

A clinician who has a female black patient with sarcoidosis who starts to develop pulmonary fibrosis or signs of severe disease should discuss the option of more aggressive treatment with the patient, she suggested.

The Black Women's Health Study is not a random sample, so results may not be generalizable to the entire population. ■

Whooping Cough Epidemic: Vaccination Is Key

Pertussis cases have increased 1,300% from the same time period last year.

BY ELIZABETH MECHCATIE
IMNG Medical News

The current pertussis epidemic in Washington state and increased rates being seen nationwide underline the critical importance of pertussis vaccination in pregnant women and other adults who are in contact with babies, Dr. Anne Schuchat said during a Centers for Disease Control and Prevention telebriefing.

Reports of pertussis have been increasing in infants, as well as among children aged 10, 13, and 14 years in Washington and nationwide, making the recommended Tdap booster vaccine essential for children, said Dr. Schuchat, director of the National Center for Immunization and Respiratory Diseases at the CDC in Atlanta.

Pertussis vaccination "remains the single most effective approach to preventing infection," she said, noting that unvaccinated children are at an eightfold greater risk of getting pertussis than are those who have been fully vaccinated with DTaP. And vaccinated children who do contract pertussis typically have milder cases.

In 2010, only 8% of adults had any history of having ever received a Tdap booster, she said.

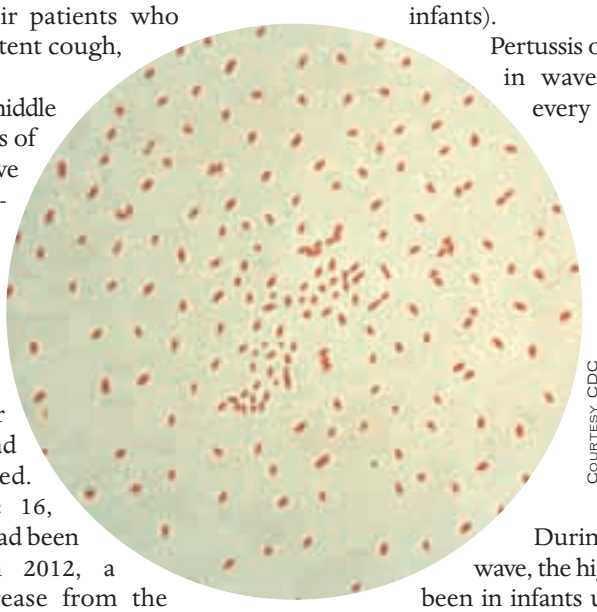
In addition to encouraging patients to get vaccinated, clinicians are being urged to consider pertussis as a possible diagnosis in their patients who have a persistent cough, she said.

Since the middle of 2011, cases of pertussis have been increasing in Washington state, and in April 2012, a pertussis epidemic was declared after 640 cases had been reported. As of June 16, 2,520 cases had been reported in 2012, a 1,300% increase from the same time period the year before, and the highest number of cases reported since the early 1940s (MMWR 2012; 61:517-22).

To date, nine babies in the United States have died of whooping cough (one more than reported in the MMWR), Dr. Schuchat reported.

A higher-than-expected number of cases also have been reported in other states, with similar trends in the age groups affected, "and there may be many more coming," Dr. Schuchat said. In 2010, more than 27,000 cases were reported nationally, with 27 deaths (25 in infants).

Pertussis outbreaks occur in waves, with peaks every 3-5 years.



COURTESY CDC

The number of pertussis cases is the highest since the early 1940s (gram-stained photomicrograph at left depicts the Bordetella pertussis bacteria, the etiologic pathogen for pertussis).

During this current wave, the highest rates have been in infants under 1 year of age, with over half in babies under 3 months. These children are too young to be protected by the vaccine that is first administered at age 2 months, so they are dependent on the immunity of people around them. This gap in immunity is why pregnant women and adults who are around babies are being urged to get vaccinated, she said.

The rates of pertussis have started to increase after late childhood, with a higher rate in 10-year-olds. Although the rate decreases in 11- to 12-year-olds, it subsequently increases again among 13-year-olds, Dr. Schuchat said. These trends also point to the importance of the recommended Tdap booster vaccine in those aged 11 and 12 years.

The increase in pertussis cases reported in adolescents aged 13-14 in Washington state and nationally is a concern, and possible causes are being studied further. A contributing factor could be the switch from the whole cell to the acellular vaccine, which may have an effect on how long immunity persists. "Waning of protection over time may be part of the story," she said. However, she pointed out that unvaccinated people are not thought to be driving this current wave of infection.

Dr. Schuchat said that the increase in pertussis cases goes beyond Washington state.

"We really think the disease is spreading around the country. …We're in for a tough year and a tough couple of years," she said. ■

CPFE Syndrome Common in Smokers, Former Smokers

BY SHARON WORCESTER
IMNG Medical News

DESTIN, FLA. – A 2010 study by Dr. Anna-Luise A. Katzenstein, FCCP, and her colleagues was the first to show that interstitial fibrosis is remarkably common and often severe in cigarette smokers, including those with no clinical evidence of interstitial lung disease.

Pathologic specimens showed that interstitial fibrosis occurred in 12 of 20 smokers (60%) but in none of 3 nonsmokers; 3 of the smokers with fibrosis had well-defined smoking-related disorders such as respiratory bronchiolitis–interstitial lung disease (RB-ILD), while 9 had pathology showing more than 10% fibrosis on their lung biopsies (Hum. Pathol. 2010;41:316-25). They were considered to have smoking-related interstitial lung disease, Dr. David Moller said at the Congress of Clinical Rheumatology.

This has recently been described as combined pulmonary fibrosis and emphysema, or CPFE syndrome, "and it's largely with the advent of high-resolution CT scanning that it has been appreciated how common fibrosis is in association with emphysema," said Dr. Moller, professor of medicine and director of the sarcoidosis clinic at Johns Hopkins University, Baltimore.

Typically, patients with CPFE syndrome have upper-lobe emphysema and lower-lobe fibrosis, he said.

"Because of that, you can get relatively normalized lung volumes and spirometry, but what characterizes these patients is a severe reduction in diffusing capacity. This is often associated with a pulmonary hypertension, which can be a major determinant of survival," he added.

CPFE syndrome is more common in males than females, and is found in 19%-51% of smokers with emphysema on chest CT who have no defined underlying interstitial lung disease. On biopsy, a number of pathological patterns may be seen, including usual interstitial pneumonitis (UIP), nonspecific interstitial pneumonia, and RB-ILD, Dr. Moller said.

Mortality is increased in patients with this syndrome, compared with those who smoke and have chronic obstructive pulmonary disease, and survival ranges from 35% to 80% at 5 years, he added, noting that the mortality rate is unclear in patients who may have underlying idiopathic pulmonary fibrosis.

The syndrome is strongly associated with smoking but is also associated with lung cancer, asbestos and mineral dust exposures, and pulmonary hypertension. A 2011 study demonstrated that CPFE is also associated with connective tissue disease.

In that retrospective study of 34 patients with both connective tissue disease and CPFE syndrome who were followed for about 8 years, 18 had rheumatoid arthritis, 10 had systemic sclerosis, 2 had mixed connective tissues disease, 2 had overlapping connective tissue disease, 1 had Sjögren's syndrome, and 1 had polymyositis.

High-resolution CT showed emphysema of the upper lobes of the lungs and pulmonary fibrosis of the lower lobes in all patients, and all had dyspnea during exercise. Pulmonary hypertension was present in five of the systemic sclerosis patients, and four of these patients died during follow-up (Arthritis Rheum. 2011;63:295-304).

The patients in this study were significantly younger than a historical control group of patients with idiopathic CPFE syndrome, and were more frequently female than male, Dr. Moller noted.

Compared with patients with connective tissue disease and lung fibrosis without emphysema, however, the study patients with connective tissue disease and CPFE had higher lung volumes, lower diffusion capacity, and higher pulmonary pressures and were more frequently male than female.

The results also provided some suggestion that those with connective tissue disease and CPFE syndrome may have less severe outcomes than did those with idiopathic CPFE syndrome, but again, pulmonary hypertension is the key to the clinical course, Dr. Moller said.

The authors of this study concluded that CPFE syndrome should be included as a novel, distinct pulmonary manifestation within the spectrum of connective tissue disease–associated lung diseases in smokers and former smokers – particularly those with rheumatoid arthritis or systemic sclerosis.

Treatment for CPFE syndrome includes smoking cessation and treating the underlying cause when it is apparent, Dr. Moller said.

Dr. Moller reported having no financial disclosures. ■

Experimental Immunotherapy Gains Traction in NSCLC

BY PATRICE WENDLING
IMNG Medical News

CHICAGO – The experimental immunotherapeutic anti-PD-1 agent known as BMS-936558 appears active in non–small cell lung cancer, a malignancy notoriously resistant to immunotherapy.

Among 76 evaluable patients with advanced NSCLC enrolled in a multidose phase I trial, 14 patients (18%) had a response. The progression-free survival rate at 24 weeks was 26%. The responses were durable, lasting 2-21 months, Dr. Julie R. Brahmer, an oncologist at Johns Hopkins Hospital, Baltimore, reported at the annual meeting of the American Society of Clinical Oncology.

PATRICE WENDLING/IMNG MEDICAL MEDIA

Among 76 NSCLC patients, progression-free survival at 24 weeks was 26%, Dr. Julie R. Brahmer said.

BMS-936558 is a fully human IgG4 antibody that blocks the programmed death–1 (PD-1) protein. PD-1 is highly expressed by regulatory T cells and tumor-infiltrating lymphocytes in many tumor types, and plays a key role – along with one of its ligands, PD-L1 – in the ability of tumor cells to evade the host's immune system. Preliminary data suggest a relationship between PD-L1 expression on tumor cells and objective response, Dr. Brahmer noted.

When responses to BMS-936558 were evaluated by histology, the overall response rate was 33% (6 of 18) in patients with squamous histology, and 12.5% (7 of 56) in those with nonsquamous histology.

"Both of these responses are higher than the drugs we have for patients who fail chemotherapy," said discussant Dr. Giuseppe Giaccone of the Medical Oncology Branch at the National Cancer Institute. Moreover, there are no effective targeted agents for NSCLC patients with squamous cell histology.

He pointed out that tumor-infiltrating lymphocytes were associated with better survival in squamous cell carcinomas in a large retrospective analysis of patients with resected lung neoplasms (Ann. Thorac. Surg. 2009;87:365-71), suggesting that there are differences in immunogenicity and that squamous cell histology might be more immunogenic than other types.

Dr. Giaccone went on to highlight a recent phase II study reporting that first-line treatment with another immunomodulatory agent, ipilimumab (Yervoy), added in a phased fashion with paclitaxel (Taxol) and carboplatin chemotherapy, was superior to paclitaxel and carboplatin plus placebo in chemotherapy-naive patients with advanced NSCLC (J. Clin. Oncol. 2012;30:2046-54). Survival was much higher in patients with squamous cell vs. nonsquamous histology, which again suggested a difference between the types with regard to immunogenicity.

Patients in the current phase I trial with advanced NSCLC and other solid tumors that had progressed after one to five systemic therapies received intravenous BMS-936558 at varying doses until disease progression or clinical deterioration or unacceptable toxicity. Patients who responded or had stable disease, or who had progressive disease but were clinically stable, were treated until they achieved a complete response, worsening progressive disease, or unacceptable toxicity for up to 12 cycles (96 weeks).

In all, 122 patients with NSCLC were evaluable for safety and 76 for clinical activity. At baseline, 60% of the 122 patients had nonsquamous histology, 96% had an ECOG (Eastern Cooperative Oncology Group) performance status of 0-1, and 55% had received at least three prior therapies including platinum-based chemotherapy in 94%, tyrosine-kinase inhibitors in 34%, and radiotherapy in 33%.

The overall response rate was 18% in the 39 patients who were enrolled at the 10-mg/kg dose of BMS-93558, 32% in 19 patients who were given the 3-mg/kg dose, and 6% with the 1-mg/kg dose. The percentage of patients who were free of progression at 24 weeks was 24%, 41%, and 16%, respectively, Dr. Brahmer said. Three NSCLC patients had a persistent reduction in baseline target lesions in the presence of new lesions, but were not classified as responders for the overall response rate. Grade 3/4 adverse events occurred in 10 patients (8%). ■

VITALS

Major Finding: The overall response rate was 18% and the PFS rate was 26% among 76 evaluable patients with advanced non–small cell lung cancer.

Data Source: Data are from a multidose phase I study of BMS-936558 in patients with advanced solid tumors including 122 with NSCLC.

Disclosures: Bristol-Myers Squibb sponsored the study. Dr. Brahmer and Dr. Giaccone reported no relevant disclosures.

Sensitivity Varied Widely

FDG-PET • *from page 1*

and the scans were performed in community and academic centers and interpreted by multiple radiologists, Dr. Grogan said.

"Results of PET scans in this population should be interpreted cautiously, and reasons for the poor test performance should be explored in other studies," he said.

Discussant Dr. Tetsuya Mitsudomi, chief of thoracic surgery at Aichi Cancer Center Hospital in Nagoya, Japan, said FDG-PET shows reasonable sensitivity but very low specificity, compared with previous studies.

"I think this reflects the real world," he said. "So, the lung cancer diagnosis cannot be made on the basis of PET positivity alone."

Investigators at 51 sites in 39 cities enrolled 969 patients with known or clinically suspicious stage 1 lesions between 2004 and 2006 to evaluate the value of proteomic analysis in diagnosing NSCLC (the results were presented at ASCO 2010). FDG-PET scans were available for 682 patients. All underwent surgical resection. Analyses were performed for all patients and for sites with more than 25 patients.

PET avidity was determined by the radiologist's description of lesion activity or by the reported maximum standard uptake value (SUV). Avidity was classified in four categories: category 1 was no avidity/not cancer (SUV = 0), category 2 was low avidity/not likely cancer (SUV 0 to less than 2.5), category 3 was avidity/possibly cancer (SUV 2.5 to less than 5.0), and category 4 was high avidity/likely cancer (SUV 5.0 or more).

Among the 682 patients, there were 566 cancers and 116 benign cases. In all, 82% of the cancerous lesions were PET avid, and "surprisingly, 69% of the benign lesions were avid," Dr. Grogan said.

Patients with cancer were significantly older (67 vs. 61 years; *P* less than .001) and had larger lesions (26 mm vs. 20 mm; *P* less than .001).

The positive predictive value of FDG-PET was 85% and negative predictive value 26%. This translates into 80 false positives and 101 false negatives. The majority of false positives were granulomas (69%), he observed. Eleven of the false negatives were 10 mm or less.

Not surprising, FDG-PET accuracy improved with lesion size, Dr. Grogan said. The accuracy was less than 50% for lesions less than 20 mm, but greater than 80% for lesions larger than 30 mm. "Above 30 mm, the accuracy did not seem to improve," he observed.

In the eight cities with more than 25 patients, the sensitivity varied significantly, from a low of 67% in Los Angeles to a high of 91% in Durham, N.C. (*P* = .03), Dr. Grogan said, without explanation. Specificity ranged from 15% in Birmingham, Ala., to 46% in Philadelphia, but this did not reach statistical significance because of the small number of benign cases at each institution (*P* = .72).

Dr. Mitsudomi said he could not explain the reason for the heterogeneity, especially in terms of the specificity, between centers.

"It's not possible to remove all the false positives if you use FDG, but newer tracers are being developed and they may increase the specificity rate," he added.

Dr. Grogan reported no disclosures. Dr. Mitsudomi reported having a consulting/advisory role with Boehringer Ingelheim, Kyowa Hakko Kirin, Lilly, and Pfizer, and receiving honoraria from AstraZeneca, Chugai Pharma, Lilly, and Roche. ■

COMMENTARY

Dr. Lary Robinson, FCCP, comments: Although this report stems from a secondary analysis of the PET scan data obtained from an ACOSOG (Z4031) clinical trial on using proteomic profiling to diagnose lung cancer, nevertheless this analysis of PET scan results is quite useful and, frankly, its results are expected. Current FDG-PET scans have a large number of false-positives and false-negatives, especially in evaluating smaller nodules and in areas where fungal diseases are endemic. These results reinforce my own experience with PET scanning in lung cancer: 1) A PET scan is not a "cancer" scan, but rather it's a scan for metabolic activity (benign inflammatory lesions may well be strongly positive); 2) Do not assume an equivocally sized PET-positive lymph node or other distant area contains cancer unless it is histologically confirmed (low specificity rates in PET); and 3) There is a significant variability of the effectiveness of the PET scan hardware and the radiographic interpretation of scans based on frequency of use and geographic location. PET scans are a quite useful adjunct to lung cancer diagnosis and staging, but the clinician must factor in the high false-negative rate (in bronchioloalveolar carcinomas, for example) and high false-positive rate in their decision making.

PRESIDENT'S CORNER: THE MEMBERSHIP SPEAKS

Health-care Reform and Chest Physicians

The centerpiece for health-care reform is the Patient Protection and Affordable Care Act of 2010, which holds a number of implications for chest physicians. Key provisions of the Act include expanding insurance coverage to reduce the number of uninsured Americans, emphasizing preventive care, building a more robust primary care base, and placing greater value on delivery of high quality care—including more accountability for practitioners. Dr. Suhail Raoof has asked members of the College who have special expertise in critical care, sleep, and pulmonary medicine to share their ideas about what health-care reform means for chest physicians.

Critical Care

With regard to critical care medicine and its practitioners, the Act does not directly tackle key critical care issues, such as end-of-life care, disaster preparedness, and workforce shortages. However, efforts to reduce the high cost of ICU care—an estimated 1% of US GDP—are likely to play an important role in attempts to balance the health-care budget.

There has been steady growth in organized efforts and incentives to provide high quality health care in the past decade. The demonstration of successful statewide programs, such as for the near-elimination of hospital-acquired bloodstream infections in ICU patients (Pronovost et al. *N Engl J Med*. 2006;355:1725), has illustrated the clinical value and cost-savings of such programs, and there is a strong emphasis on expanding these efforts in the Act. Components that will have a direct impact on critical care include expansion of quality metrics, including support for innovative and pilot programs; increased reporting requirements on quality measures; imposition of penalties for nonreporting of quality measures (in 2015); and expansion of accountable care organizations (ACO)—voluntary organizations of providers who are accountable for quality and costs. It is clear that ICU care will be an attractive target for quality measures.

Quality care is driven by patient-focused research. Critical care specialists are leaders in performing clinical and comparative effectiveness research, such as early goal-directed therapy for severe sepsis and lung protective ventilation for ARDS. The Act emphasizes the need for and supports the funding of comparative effectiveness research, presenting an opportunity for researchers.

ICUs are at the center of the safety net for patients who experience devastating illness or injury, events that disproportionately impact the poor and uninsured. Expanding the number of Americans with health insurance is likely to influence ICU patient mix, as well as reimbursement. Similarly, elimination of preexisting condition exclusions and lifetime insurance coverage limits should promote better care for patients with serious chronic illnesses and reduce the risk for financial devastation for patients with prolonged critical illness. Greater use of preventive services and better access to care will likely reduce the use of EDs, and, thus, ICU admissions, for management of preventable progression of chronic disease to acute life-threatening illness.

While the greatest benefit will be for our critically ill patients, it is widely held that providers and institutions, including many safety-net ICUs now caring for large numbers of uninsured patients, will benefit from the Act as a result of improved payer mix. However, the anticipated reduction in Medicaid reimbursement and the uneven acceptance of the Act across the states will impact this assumption.

Sleep Medicine

In advance of implementation of the Patient Protection and Affordable Care Act, sleep medicine has already undergone substantial change. As the number of laboratory-based sleep studies and CPAP prescriptions skyrocketed in the late 1990s and the first decade of 2000, insurers started taking a hard look at their costs. In 2008, the Centers for Medicare & Medicaid Services (CMS) began to allow home sleep testing to diagnose sleep apnea. When the anticipated rush on home sleep testing did not materialize, third party payers in parts of the Northeast hired utilization management companies to "decide" if a patient referred for a sleep study could undergo home sleep testing instead. In the areas where this has been enforced, in-laboratory polysomnographies have been reduced by 50%. With increasing focus on cost-effectiveness and outcomes, this trend will likely continue to sweep across the rest of the country, probably resulting in fewer sleep laboratories and a surfeit of polysomnography technologists. Sleep centers that embrace home sleep testing may be "ahead" of the game.

Increasing focus on outcomes, rather than point of care, may also affect sleep laboratory accreditation. Sleep laboratory accreditation offered by the American Academy of Sleep Medicine (AASM), the Joint Commission (JC), and other entities centers on testing and treatment in a safe, controlled environment by trained staff. But the push now is to improve outcomes related to the health of patients. Recently, CMS accepted a PQRS (Physician Quality Reporting System) initiative directed at

Continued on following page

Health-care Reform: Is Anyone Listening?

With the Supreme Court ruling essentially upholding health-care reform as originally proposed, our series of articles on this topic is very germane and pertinent. This month's article is especially relevant to our members, since it covers the scope of changes expected in the fields of pulmonary, critical care, and sleep medicine. Our specialty will, most definitely, be affected in a meaningful way. In the most recent 10-year projection, the actuaries of the Centers for Medicare & Medicaid Services (CMS) project that health-care spending will nearly double to $4.4 trillion by 2018. Drs. Curt Sessler, Regent-at-Large, and Steven Simpson, Chair of the Critical Care NetWork, discuss the reporting of outcomes, following of evidence-based guidelines, and development of performance metrics that are now being instituted. They emphasize patient-focused research to define practice parameters. The practice of sleep medicine has undergone significant change in the last few years. Drs. Barbara Phillips, Regent-at-Large, and Nancy Collop, immediate past president of American Academy of Sleep Medicine, discuss these changes. They talk about the increasing thrust on home testing, the higher standards that sleep centers will be held up to, and the escalating emphasis on reporting and outcomes. Finally, the impact of Accountable Health Care Act will be felt in the practice of pulmonary medicine. Dr. Ed Diamond, ACCP Treasurer, shares his perspectives and gives advice to pulmonologists on how to trim costs of practicing medicine and to utilize non-physician health-care providers. I would like to thank Dr. Barbara Phillips for coordinating these sections and working diligently with the contributors to get the articles on time.

–Dr. Suhail Raoof, FCCP

Note: The views expressed in these articles are those of the authors and do not represent the views of the ACCP, its leadership, members, or staff.

Continued from previous page

sleep apnea (www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/PQRS/index.html?redirect=/pqrs/). This was developed by a task force working with the AMA; the ACCP was a participating partner (www.chestnet.org/accp/quality-improvement/aquire/pqri). Unfortunately, this is not yet available in a registry. In this regard, some aspects of sleep medicine that lack well-documented beneficial treatment outcomes (eg, chronic hypnotics for insomnia, pharmacologic treatment of periodic limb movements) may become not reimbursable. It is imperative for sleep medicine to develop more of these outcome measures for the other sleep disorders and to incorporate outcome measurements into sleep center accreditation standards; if not, the specialty as a whole may be left out of ACO models, and care for patients with sleep disorders may fall to the care of primary care doctors who typically get little training in sleep medicine.

Another example of such a challenge is in the patient-centered medical home. As this concept is further developed, the relationships and communication between sleep specialists and primary care providers will be critical. Sleep medicine has some unique tools including CPAP monitoring, home testing, and actigraphy that could be appealing to primary care practitioners. Trying to stay in those conversations on a local level will be key to remaining a viable specialty.

A final challenge for sleep medicine will be interfacing with the electronic health record (EHR). Sleep studies and CPAP downloads are digital and logically should interface with EHRs. But these systems typically cannot yet "talk" to each other. Interfaces will have to be developed to integrate data from these tools with the EHR.

Pulmonary Medicine

Pulmonary medicine will also be impacted by implementation of the Act. Some of the anticipated changes were reviewed in the March issue of CHEST Physician (Aranson et al. *CHEST Physician*. 2012;7[4]:)15. www.chestnet.org/downloads/LegRegChanges.pdf). They include value-based purchasing, hospital readmission reduction program, quality reporting for long-term care hospitals, inpatient rehab hospitals, and hospices, hospital-acquired conditions, medical shared-savings programs, and the use of EHRs.

Pulmonary medicine practitioners would be wise to proactively seek opportunities to decrease current costs while working creatively to reengineer care models to create greater efficiencies. The environment appears to be rapidly evolving, so complacency may result in negative consequences.

Employee salaries and benefits are typically the greatest cost items in a medical practice. Seek appropriate opportunities to utilize nonphysician providers (NPPs) in place of higher cost physicians. Downsize outpatient clinical staff when providers are out of the office, and use technology in the office to allow downsizing of clerical staff (eg, automatic phone appointment reminders, call triage).

EHR implementation will be a foundation of future practice (Diamond et al. *Chest*. 2010;138(3):716). Although some perceive that the government incentives for meaningful use might not rationalize the financial investment, it should be considered that beginning in 2015, those not demonstrating meaningful use of an EHR may be subject to payment adjustments. EHR systems will soon become interoperable, as health records will be shared among multiple providers involved in the full spectrum of care. These include physicians, hospitals, pharmacies, nursing homes, and payers.

Pulmonary practices should consider opportunities for clinical integration with hospitals and extended care facilities. Bundling of payments between hospitals and physicians for inpatient services may be enacted as soon as 2013. Clinical integration between hospitals and physician groups can take several forms, including physician employment and a professional service agreement (PSA) between a hospital and a medical practice. Hospital administrations vary regarding their preference for ownership vs relationships in which medical groups remain independent. Hospitals seeking physician ownership tend to prioritize primary care practices before addressing subspecialty practices. Pulmonary practices should focus on demonstrating their value to hospitals. Avoidance of readmissions can be supported by rapid outpatient access and by the initiation of pulmonary rehabilitation programs in extended care facilities (ECFs). The practice culture must gain the ability to shift the focus of its compensation model from productivity to cost savings and quality outcomes. Practices should implement EHR systems that facilitate mining and sharing of data across the continuum.

Ideally, health-care reform should enhance access to higher quality pulmonary, sleep, and critical care medicine for our patients while increasing our accountability and efficiency. But, there are many challenges, including the need to develop or expand infrastructure to support EHRs and ACOs. Our expects challenge us to address these changes proactively. Change is coming! ■

Dr. Nancy Collop, FCCP
[Sleep Medicine]
Professor of Medicine and Neurology
Emory University, Atlanta, Georgia

Dr. Edward Diamond, MBA, FCCP
[Pulmonary Medicine]
President, Suburban Lung Associates
Elk Grove Village, Illinois

Dr. Barbara Phillips, MSPH, FCCP
[Sleep Medicine]
Professor, Division of Pulmonary, Critical Care, and Sleep Medicine
Director, Sleep Disorders Center
University of Kentucky College of Medicine, Lexington, Kentucky

Dr. Curtis N. Sessler, FCCP
[Critical Care Medicine]
Orhan Muren Professor of Medicine
Pulmonary and Critical Care Medicine
Director, Center for Adult Critical Care
Virginia Commonwealth University Health System
Medical College of Virginia Physicians and Hospitals, Richmond, Virginia

Dr. Steven Q. Simpson, FCCP
[Critical Care Medicine]
Professor of Medicine
Director, Fellowship Training
Division of Pulmonary Diseases and Critical Care Medicine
University of Kansas
Kansas City, Kansas

This Month in *CHEST*: Editor's Picks

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

▶ **Bronchodilator Use and the Risk of Arrhythmia in COPD: Part 1: Saskatchewan Cohort Study**. *By Dr. M. Wilchesky et al.*

▶ **Bronchodilator Use and the Risk of Arrhythmia in COPD: Part 2: Reassessment in the Larger Quebec Cohort.** *By Dr. M. Wilchesky et al.*

G/W EDITORIAL

▶ **Drug Safety in COPD Revisited: What Is the Number Needed to Analyze?** *By Dr. K. F. Rabe*

▶ **Patient-Ventilator Asynchrony During Noninvasive Ventilation: A Bench and Clinical Study**. *By Dr. G. Carteaux et al.*

▶ **The Role of Conventional Bronchoscopy in the Workup of Suspicious CT Scan Screen-Detected Pulmonary Nodules.** *By Dr. S. C. van 't Westeinde et al.*

▶ **Inflammatory Biomarkers Predict Airflow Obstruction After Exposure to World Trade Center Dust.** *By Dr. A. Nolan et al.*

NETWORKS

Restless Legs Syndrome, ECMO Bridge

Women's Health

Restless Nights: Is Relief in Sight?

Restless legs syndrome (RLS) is a sleep-related movement disorder characterized by unpleasant sensations and the urge to move one's legs.

Approximately 2% to 4% of the adult US population suffers from clinically significant RLS and may require both pharmacologic and nonpharmacologic therapy (Allen et al. *Mov Disord*. 2011;26:114; Allen et al. *Arch Intern Med*. 2005;165:1286).

Nonpharmacologic therapy consists of avoidance of exacerbating substances such as alcohol, caffeine, nicotine, and certain medications. Dopaminergic agonists such as ropinirole and pramipexole are currently the mainstay of pharmacologic therapy. Though highly efficacious, their use is often limited by side effects of nausea, somnolence, hypotension, hallucinations, compulsive behaviors, or aggravation of RLS symptoms (Allen et al. *Sleep Med*. 2010;11:31).

Gabapentin also has proven benefit in treatment of RLS (Gracia-Borreguero et al. *Neurology*. 2002;59:1573). In April 2011, US Food and Drug Administration approved its pro-drug, gabapentin enacarbil, (higher bioavailability and longer duration of action). The dose is 600 mg once daily with adjustments recommended for reduced renal clearance. Data are limited in pediatric and > 65 years age groups. The drug is well tolerated, and its safety and efficacy in treating moderate-to-severe RLS symptoms has been demonstrated for up to 9 months (Bogan et al. *Mayo Clin Proc*. 2010;85:512). Side effects are transient and limited to somnolence and dizziness (Hayes et al. *Ann Pharmacother*. 2012;46:229). Although current evidence is lacking to suggest superiority to other RLS therapies, it may be an alternative for patients intolerant to dopaminergic agents.

Dr. Tilottama Majumdar, FCCP
Steering Committee Member

Transplant

Emerging Applications for ECMO as a Bridge to Lung Transplant

Although lung transplantation is now standard of care for many patients with end-stage lung disease, the persistent scarcity of donor organs leads to prolonged waiting times and unacceptably high mortality among those waiting for transplant.

Historically, extracorporeal membrane oxygenation (ECMO) was used as a rescue therapy for early postoperative graft failure, allowing time for recovery or retransplantation. However, ECMO has also been utilized pretransplant for rescue of hypoxic or hypercapneic failure in intubated patients. Recent technological innovation enabling miniaturization and streamlining of the ECMO circuit promise to mitigate both the morbidity and cost of extracorporeal support, and has renewed interest in ECMO as a primary bridging strategy for patients awaiting transplant.

Recent, provocative data by Fuehner and colleagues demonstrates that ECMO can be delivered for prolonged periods in awake patients awaiting lung transplantation, enabling patient participation in physiotherapy and rehabilitation. These applications may represent a paradigm shift in the theory and application of ECMO support that potentially avoids the sequelae of ventilator-associated lung injury, pneumonia, and progressive debilitation in this fragile patient population. Current awake extracorporeal life support (ECLS) models with dual lumen cannulas are limited by volume of flow and absence of substantial impact on pulmonary vascular resistance, which may be important in our ever-increasing population of fibrotic patients. Given the widely varying indications for initiation and management of ECLS and small numbers of patients treated, there remains no data-driven consensus regarding the most appropriate clinical applications for preoperative ECLS. Thus, while initial experience with ECMO as an alternative to mechanical ventilation preceding lung transplant is encouraging, further comparative studies are urgently needed.

Additional Reading

- Bermudez et al. *Ann Thorac Surg*. 2011;92(4):1226.
- Bittner et al. *Ann Thorac Surg*. 2012. June 27 [Epub ahead of print].
- Del Sorbo et al. *Am J Respir Crit Care Med*. 2012;1:185(7).
- Fuehner et al. *Am J Respir Crit Care Med*. 2012;185(7):763.

Dr. James Maloney, FCCP
Steering Committee Member

One Great Evening for OneBreath®

One Evening. 10 million gallons of water. 60 exhibits. 120,000 animals. 500 species. 2,000 supporters. OneBreath.

The premiere event at CHEST 2012, "The OneBreath® Evening at the Georgia Aquarium," is taking place on Sunday, October 21, and you're invited.

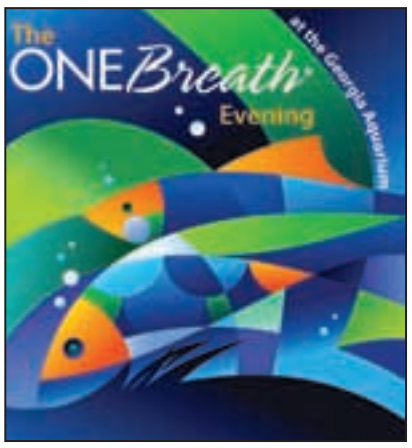
Funding from the event supports OneBreath, an initiative of The CHEST Foundation, the philanthropic arm of the American College of Chest Physicians (ACCP). Drawing from the professional expertise of the College and ACCP members who specialize in the prevention and treatment of diseases of the chest, OneBreath aims to improve lung and heart health by providing valuable prevention resources, raising public awareness, and encouraging healthy behaviors.

As the world's largest aquarium with more than 8.5 million gallons of marine and fresh water, housing more than 120,000 animals of 500 species, the Georgia Aquarium's notable specimens include whale sharks, beluga whales, bottlenose dolphins, great hammerhead sharks, and manta rays.

All event guests will feast on superb food prepared in the kitchens of Wolfgang Puck and have access to exhibits throughout the aquarium. Individuals who purchase the VIP Pass will enjoy the additional benefits of an exclusive welcome celebration, entry to the phenomenal Dolphin Tales show, and a delectable dessert reception.

VIP Passes are $300; children (ages 3-11) are $50. General Gallery Tour admission tickets are $150; children (ages 3-11) are $35.

Donors to The CHEST Foundation and OneBreath who have contributed $500 or more between January 1 and September



30, 2012, are entitled to one complimentary VIP Pass. Donors who have contributed $1,000 in this same time frame are entitled to two complimentary VIP Passes.

OneBreath is also offering chances to win an opportunity to swim with the whale sharks while visiting Atlanta during CHEST 2012. Two, four-person prize packages are available. Raffle entries are $100 each or three for $250. Only 500 entries are available, making your chances of winning quite good!

Secure your admission and raffle entries now at www.accpmeeting.org. To make a donation to OneBreath, visit www.onebreath.org. ■

1-Day and Weekend Registration at CHEST 2012

If you'd like to attend CHEST 2012 but have trouble scheduling time away from your practice, consider coming for a shorter length of time. With the 1-day rate, you can register for any given day, Sunday through Thursday. Or, attend CHEST 2012 for the weekend by registering for the postgraduate course package or an additional Saturday course, along with a Sunday 1-day registration.

Saturday, October 20, Agenda

Postgraduate courses will be held Saturday. These courses are available as a package. Registration for the postgraduate course package permits admittance to any postgraduate course and electronic access to materials for all courses held on Saturday. Courses include:

- Critical Care: More Things You Wish You Had Learned in Fellowship
- An Integrated and Comprehensive Approach to the Management of Advanced Lung Disease
- Pulmonary Literature Review
- Sleep Medicine 2012: A Clinical Update
- Update in Thoracic Imaging for the Pulmonologist and Critical Care Physician

Two additional courses will be available Saturday. These courses are not part of the postgraduate course package, and registration will not permit admittance to other courses. However, you will be given electronic access to course materials for all Saturday courses. The additional courses include:

- Advanced Critical Care Echocardiography
- 20th Annual Assembly of the American Association for Bronchology and Interventional Pulmonology

CHEST 2012
October 20 - 25
Atlanta, Georgia

Sunday, October 21, Agenda

Sunday features more general education sessions than any other meeting day. And, a pulmonary focus on Sunday means busy pulmonologists can attend a concentration of relevant sessions. Sunday pulmonary-focused sessions include:

- Sleep Medicine for the Non-Sleep Specialist: Bottom-line Information for Managing Common Sleep Problems
- New Antithrombotic Guidelines: Diagnosis and Treatment of DVT and Pulmonary Embolism
- Critical Care Year in Review
- Coding and Reimbursement Update
- Interstitial Lung Disease in 2012

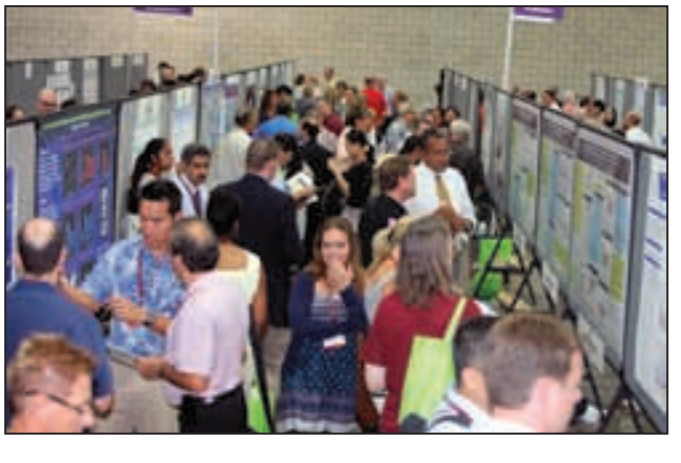
Cap off Sunday evening with an aquatic adventure to the Georgia Aquarium, the world's largest aquarium, while supporting The CHEST Foundation's OneBreath initiative at The OneBreath® Evening at the Georgia Aquarium. Two admission options allow you to choose your access to unique, don't miss attractions.

Learn about the special CHEST 2012 registration opportunities, The OneBreath Evening at the Georgia Aquarium, and more at accpmeeting.org. ■

Attendees Found All Kinds of Learning at CHEST 2011

Don't miss the August 31 deadline for discounts on CHEST 2012 registration.

Register at www.accpmeeting.org.



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Pulmonary Perspectives

Biomarkers in COPD

The National Institutes of Health (NIH) defines biomarkers as "a characteristic (or variable) that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention." In practical terms, a biomarker is an objective and reproducible measurement that reflects how patients or individuals feel, function, or survive with the disease in question. Clinically, biomarkers can be used for diagnosis, prognosis, severity assessment, staging of disease, and monitoring disease activity or clinical response to therapeutic interventions. In clinical trials, biomarkers are used as surrogate endpoints for patient-focused clinical outcomes such as survival. In COPD, the US Food and Drug Administration (FDA) currently indicates that "with exception of the lung function tests, there are no well-validated biomarkers or surrogate endpoints that can be used to establish efficacy of a drug for COPD." Although FEV_1 is relatively easy to obtain, highly reproducible, and tracks certain health outcomes in COPD, it is not an ideal biomarker for COPD because it is hard to modify with therapies, does not reflect disease activity, and correlates only loosely with clinically important health endpoints such as mortality, hospitalization, and even the quality of life of patients. Thus, over the past decade, there has been an explosion of research activities to identify and discover novel biomarkers in COPD. A quick search of PubMed using search terms "biomarker" and "COPD" reveals an exponential growth in the number of publications in the literature since 2000 (Fig 1), reflecting the growing interest in discovering novel biomarkers in COPD using noninvasive or minimally invasive procedures. This paper provides a short synopsis on the current state of knowledge on COPD biomarkers.

Chest Imaging as Biomarkers in COPD

With the advent of high-resolution CT scans, several studies have evaluated the possibility of using CT scans to classify patients by phenotype to assess health outcomes in COPD. Compared with spirometry, the use of inspiratory and expiratory low-dose thoracic CT scans can provide diagnostic information regarding COPD with a positive predictive value of 76% and a negative predictive value of 79% (corresponding to a sensitivity of 63% and a specificity of 88%) in heavy current or ex-smokers with >16.5 pack-years of smoking history (Mets et al. *JAMA*. 2011;306[16]:1775). Low-dose CT scans can also provide prognostic information. For instance, one study (Mohamed Hoesein et al. *Thorax*. 2011;66[9]:782) found that heavy smokers with evidence of emphysema on baseline CT scans experienced a rapid fall in lung function, especially those with upper lobe predominance. Another study (Yuan et al. *Thorax*. 2009;64[11]:944) found that smokers with emphysema had, on average, 15 to 20 mL/y greater decline in FEV_1 on CT scans than those without emphysema. Moreover, the presence of emphysema on thoracic CT scan is associated with a two-fold increase in lung cancer risk compared with thoracic CT scans which do not demonstrate any emphysema (Zurawaska et al. *Chest*. 2012;[5]:). However, to date, there is little knowledge on whether the changes from emphysema on CT scans are modifiable or provide incremental prognostic or diagnostic information beyond that achieved with lung function measurements. Nevertheless, CT-based measurements are being used as surrogate endpoints for therapeutic evaluation of $alpha_1$-antitrypsin augmentation therapies for emphysema related to $alpha_1$-antitrypsin deficiency (Stockley et al. *Respir Res*. 2010;11:136).

Sputum Parameters as Biomarkers in COPD

Sputum is an attractive source of biomarker discovery because the primary site of disease in COPD is the airways. To facilitate this research, international guidelines have been developed to promote standardization of methods for sputum collection and processing to ensure comparability of results across centers and between studies (Efthimiadis et al. *Eur Respir J Suppl*. 2002;37:19s). The most promising data have been generated with the cellular components of induced sputum. Sputum eosinophilia, for instance, defined as eosinophil counts 3% in the sputum, which affects about 25% of patients with COPD, is associated with increased clinical responsiveness to both inhaled and oral corticosteroids (Brightling et al. *Lancet*. 2000;356[9240]:1480; Brightling et al. *Thorax*. 2005;60[3]:193). Sputum neutrophilia, on the other hand, is associated with poor therapeutic responses or no therapeutic responses to corticosteroids. Sputum cell counts may also be used to classify etiologies for exacerbations. For instance, in approximately 30% of exacerbations, patients demonstrate a significant increase in sputum eosinophils, and these patients may be more responsive to corticosteroids than those with "pauciinflammatory" features in sputum (Bafadhel et al. *Am J Respir Crit Care Med*. 2011;184[6]:662). Assessment of proteins or mediators in induced sputum, on the other hand, does not appear to provide incremental information beyond that achieved by sputum cell differentials (Liesker et al. *Respir Med*. 2011;105[12]:1853).

Blood Parameters as Biomarkers in COPD

The most promising source of biomarker in blood is plasma or serum. This area of investigation has ballooned in recent years with the realization that COPD is a systemic disorder with

Continued on following page

Figure 1. Number of Publications in PubMed Identified Using the Search Terms 'Biomarker' and 'COPD'

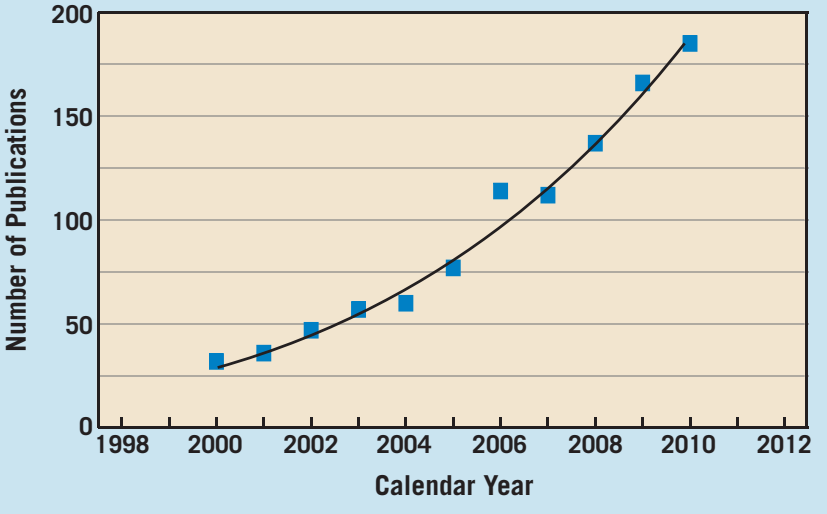

Table 1. Candidate Plasma or Serum Biomarkers Associated With Important Health Outcomes Reported in ECLIPSE Study and Lung Health Study

Biomarker	Mortality	Exacerbation	FEV1 Decline
ACRP-30	No	Yes	Yes
Clara cell secretary protein 16	Yes	No data	Possibly
C-reactive protein	Yes	Yes	No
Fibrinogen	Yes	Yes	No
Interleukin-6	Yes	Yes	No
Interferon-inducible protein 10	No data	Yes	No data
Matrix metalloproteinase 9	No data	Yes	No data
Myeloid progenitor inhibitory factor 1	No	Yes	No
PARC/CCL-18	Yes	Yes	No
Surfactant protein-D	Yes	Possibly	No
Tumor necrosis factor-infinity	No data	No data	No

ACRP-30 = adipocyte complement-related protein of 30 kDa
PARC/CCL-18 = pulmonary and activation-regulated chemokine/chemokine (C-C motif) ligand 18

Note: Adapted from Vestbo et al. *N Engl J Med* 2011;365[13]:1184; Sin et al. *Am J Respir Crit Care Med* 2011;183[9]:1187; Hurst et al. *N Engl J Med* 2010;363[12]:1128; Yoon H. et al. *Chest* Dec. 29, 2011 [doi:10.1378/chest.11-2173].

Continued from previous page

multiple extrapulmonary manifestations (Rabe et al. *Am J Respir Crit Care Med*. 2007;176[6]:532). There are several promising proteins that are candidate biomarkers in COPD (Table 1). The most promising are interleukin (IL)-6, surfactant protein-D, and Clara cell secretory protein (CC)-16. Of all the plasma proteins commonly assayed among patients with COPD, IL-6 has shown the strongest association with total mortality (Celli et al. *Am J Respir Crit Care Med*. 2012;185[10]:1065). Lung-predominant proteins, such as surfactant protein-D and CC-16, have been associated with mortality and accelerated decline in lung function, respectively (Vestbo et al. *N Engl J Med*. 2011;365[13]:1184; Hurst et al. *N Engl J Med*. 2010;363[12]:1128). Plasma C-reactive protein (CRP) is a promising biomarker for diagnosing acute (bacterial) exacerbations and blood eosinophilia, defined by a peripheral blood eosinophil count of 2%, and it may be a therapeutic biomarker to predict steroid responsiveness in acute exacerbations (Bafadhel et al. *Am J Respir Crit Care Med*. 2011;184[6]:662). However, none of these biomarkers has high enough performance characteristics to be useful as a clinical tool. To enrich the pool of candidate protein biomarkers, some investigators have used unbiased or multiplex proteomics platforms. Although several promising peptides and proteins have been identified through this process, none of them are ready for clinical translation owing to poor performance characteristics, lack of reproducibility, or the high cost of assay development. Other investigators (Bhattacharya et al. *J Clin Bioinforma*. 2011;1[1]:12) have explored the possibility of using gene expression data as biomarkers in COPD. While the use of microarrays has led to the discovery of many differentially expressed genes between COPD and control subjects, limitations, which include lack of consistent reproducibility of findings across studies, the large number of false-positive results (owing to multiple comparisons), and the variability in the measurement of gene expression levels, have precluded the translation of research findings into clinical practice.

Other Sources of Biomarkers

Various investigators have interrogated other sources for potential biomarkers. These include exhaled volatile gases such as nitric oxide, exhaled breath condensate, bronchoscopic brushings, and BAL fluid and urine. Although some interesting findings have been generated in these studies, there are major limitations with all of these sources, including invasiveness of test in the case of bronchoscopy and lack of reproducibility of data in the case of other sources, which preclude their use in the clinic.

Summary and Future Directions

Research on biomarker discovery in COPD is progressing at a rapid pace. There are several promising biomarkers on the horizon. In the sputum, eosinophilia is a promising biomarker for COPD exacerbation and steroid responsiveness. In the blood, promising plasma proteins include C-reactive protein (for exacerbation, especially if the levels are >10 mg/L), IL-6 (for predicting total mortality), and CC-16 (for predicting accelerated decline in lung function). Additionally, blood eosinophilia (>2% of total cell count) may be a good predictor of steroid responsiveness in acute exacerbations. Evolving technology in gene sequencing, micro-RNA interrogation, and robust, high throughput proteomics, coupled with large scale cohort studies in COPD (eg, ECLIPSE [Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints], SPIROMICS [Subpopulations and Intermediate Outcome Measures in COPD Study], COPDGene, CanCOLD [Canadian Cohort of Obstructive Lung Disease]) will enable identification, validation, and qualification of even better biomarkers in the near future for the diagnosis, prognosis, and monitoring of therapeutics in COPD.

Dr. Jin Woo Kim
UBC James Hogg Research Centre
Vancouver, BC, Canada
The Catholic University of Korea
Department of Internal Medicine
Division of Pulmonology
Seoul, Korea

Dr. Don D. Sin, FCCP
UBC James Hogg Research Centre
St. Paul's Hospital
Department of Medicine
Respiratory Division
Vancouver, BC, Canada

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