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MIRIAM E. TUCKER/ELSEVIER GLOBAL MEDICAL NEWS

If adopted broadly, nurse-administered oral corticosteroids could reduce the burden of asthma, Dr. Roger L. Zemek said.

ED Nurses Should Give Meds in Acute Asthma

BY MIRIAM E. TUCKER
Elsevier Global Medical News

BOSTON – Emergency department administration of oral corticosteroids by a triage nurse prior to physician assessment significantly reduced the time to clinical improvement, total time in the ED, and risk of inpatient admission in a study of 644 children who presented with moderate to severe asthma exacerbations.

Medical directives allowing triage nurses to administer bronchodilator therapy are common, but nurse administration of oral corticosteroids has not previously been studied, even though earlier use of these agents in asthma patients with severe exacerbations has been shown to directly affect the risk of hospital admission. "We know that written clinical pathways improve physician ordering of oral steroids in acute asthma exacerbations, but delays to steroid administration are still long," said Dr. Roger L. Zemek, a pediatric emergency physician at Children's Hospital of Eastern Ontario, Ottawa.

The controlled trial used a "before-after" design, in which a 4-month phase of physician-ordered oral corticosteroids was compared with a 4-month period in which triage nurses administered them. The study was done in a tertiary children's hospital ED, with an annual patient population of about 60,000 visits a year, of which about 2,500 are for asthma, Dr. Zemek said at the annual meeting of the Society for Academic Emergency Medicine.

Eligible children were those aged 2-17 years who presented to the pediatric ED with a moderate to severe acute asthma exacerbation, with a Pediatric Respiratory Assessment Measure (PRAM) of 4 or greater. The PRAM is a validated scoring system that measures asthma severity based on the patient's symptoms on a scale of 1-12, with 12 being most severe. It has good nurse-to-nurse and nurse-to-physician interuser reliability, he said.

See **Nurses** • *page 4*

Maintenance Rx Slowed NSCLC Progression

Pemetrexed increased survival in trial.

BY PATRICE WENDLING
Elsevier Global Medical News

CHICAGO – Pemetrexed maintenance therapy after pemetrexed plus cisplatin induction reduced the risk of progression by 38% in patients with advanced nonsquamous non–small cell lung cancer in the phase III PARAMOUNT trial.

The study's primary end point of investigator-assessed progression-free survival was 4.1 months for pemetrexed (Alimta) plus best supportive care and 2.8 months for placebo plus best supportive care (log rank $P = .00006$; unadjusted hazard ratio, 0.62).

Independent review, completed in 88% of patients, confirmed the robustness of the primary end point, revealing a progression-free survival of 3.9 months for pemetrexed vs. 2.6 months for placebo (log rank $P = .0002$; HR, 0.64), lead author Dr. Luis Paz-Ares said at the annual meeting of the American Society of Clinical Oncology.

Overall survival data were not mature enough at the time of the analysis, with just 16 deaths.

"The magnitude of the benefit shown on progression-free survival, a 38% decrease in the risk of progression, is in favor of saying this is an effective treatment for patients with advanced nonsquamous non–small cell lung cancer," he said.

A previous trial (Lancet 2009;374:1432-40) showed that switching patients to pemetrexed maintenance improved the time free of cancer, but until now, it was unclear whether patients initially treated with pemetrexed would benefit from maintenance. "This trial answers that," Dr. Mark Kris, FCCP, chief of thoracic oncology at

See **NSCLC** • *page 8*

INSIDE

Secondary Infection Risk Higher in COPD

BY SUSAN LONDON
Elsevier Global Medical News

DENVER – The majority of patients with chronic obstructive pulmonary disease who acquire a rhinovirus infection develop a secondary bacterial infection shortly thereafter, suggesting that early antiviral therapy might do double duty.

In a study reported at the International Conference of the American Thoracic Society, 60% of patients with COPD who were experimentally infected with rhinovirus and who gave serial sputum samples developed a bacterial infection as well, approximately a week later. This rate was six times higher than the rates seen among smokers with normal lung function and among nonsmokers.

Temporal patterns of pathogen loads and molecular markers suggested that the virus may incite inflammation that, in turn, results in degradation of key defense peptides in the airways, leaving patients vulnerable to bacteria.

The findings raise the possibility that "dual infection is a lot

See **COPD** • *page 11*

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Tele-ICU Can Reduce Mortality and Length of Stay

BY MIRIAM E. TUCKER
Elsevier Global Medical News

DENVER – An intensive care unit telemedicine intervention was associated with lower hospital and ICU mortality and shorter hospital and ICU lengths of stay in a prospective, unblinded study conducted at one academic medical center over a 2-year period.

The intervention also was associated with significantly higher rates of adherence to critical care best practices and lower rates of complications. More rapid responses to alerts for physiologic instability and off-hours, off-site intensivist care plan reviews were identified as critical care process elements that may have contributed to the lower mortality and shorter lengths of stay associated with the tele-ICU intervention, Dr. Craig M. Lilly, FCCP, reported at an international conference of the American Thoracic Society. The study was simultaneously published online in JAMA (2011;305:E1-9).

VITALS

Major Finding: Unadjusted ICU mortality was significantly lower in the tele-ICU group, compared with the preintervention group (10.7% vs. 8.6%). Hospital mortality also was reduced with tele-ICU (13.6% vs. 11.8%). Both ICU and hospital mean length of stay were significantly shorter with tele-ICU (hospital stay, 9.8 days vs. 13.3 days; ICU stay, 4.5 vs. 6.4 days).

Data Source: Prospective study of 6,290 adult patients admitted over 2 years to seven ICUs in an academic medical center.

Disclosures: All study authors reported having no conflicts of interest.

Tele-ICU clinicians use audio, video, and electronic links to assist bedside caregivers in monitoring patients, oversee best practice adherence, and help create and execute care plans, said Dr. Lilly of the University of Massachusetts, Worcester.

Unlike previous studies of the effects of tele-ICU programs, this one focused on changes in the process of care rather than the ICU structure. Prior to the study start, best practices were standardized for the prevention of venous thrombosis, cardiovascular complications, ventilator-associated pneumonia, and stress ulcers. For the primary analysis, a representative sample of preintervention cases was obtained by identifying consecutive hospital discharges from an administrative database for cases managed in each of the seven ICUs (three medical, three surgical, and one mixed cardiovascular). Admission, discharge, and laboratory information was abstracted electronically.

The off-site team included an intensivist and used tele-ICU workstations. The tele-ICU team serially reviewed the care of individual patients, performed real-time audits of best practice adherence, performed workstation-assisted care plan reviews for patients admitted at night, monitored system-generated electronic alerts, audited bedside clinician responses to in-room alarms, and intervened when the responses of bedside clinicians were delayed and patients were deemed physiologically unstable. The off-site team was able to communicate with bedside clinicians or directly manage patients by recording clinician orders for tests, treatments, consultations, and management of life-support devices, Dr. Lilly said.

A total of 6,290 qualifying adult patients were identified from 6,465 electronic admission registrations to any of the seven ICUs, with 1,529 admitted during the preintervention period and 4,761 during the tele-ICU intervention period (the periods were staggered between 2005 and 2007).

Unadjusted ICU mortality was significantly lower in the tele-ICU group, compared with the preintervention group (10.7% vs. 8.6%). When adjusted for acuity, locus of care, physiologic parameters, laboratory values, and time trend, the odds ratio was 0.37. Hospital mortality also was reduced with tele-ICU (13.6% vs. 11.8%). The unadjusted difference was not statistically significant, but hospital mortality was significantly lower with tele-ICU after adjustment for acuity, locus of care, physiological parameters, laboratory values, and time trend, with an odds ratio of 0.40.

Both ICU and hospital mean lengths of stay were significantly lower with tele-ICU. The intervention group had a mean hospital stay of 9.8 days, compared with 13.3 days in the preintervention group. After adjustment for acuity, time trends, physiologic parameters, laboratory values, and locus of care, the hazard ratio was 1.44. For ICU stay, the mean was 4.5 days in the tele-ICU group vs. 6.4 days in the preintervention group. After adjustment for all of the previously listed factors, that hazard ratio was 1.26. Results for medical, surgical, and cardiovascular ICUs were similar, Dr. Lilly said.

To understand how tele-ICU team activities affected care processes and to evaluate the degree to which the association of the intervention with changes in mortality could be attributed to these process changes, another analysis examined adherence to best practices, incidence of ICU complications, intensivist involvement for cases admitted during nighttime hours, responses to alerts, and ICU type.

The tele-ICU intervention was linked with significantly better adherence to DVT prevention best practices and cardiovascular protection best practices, as well as lower rates of catheter-related bloodstream infection and ventilator-associated pneumonia. These factors also were linked with significantly lower ICU and hospital mortality. The proportion of the tele-ICU association with lower mortality that could be attributed to adherence to these best practices and complication measures was estimated to be 25% for hospital mortality and 30% for ICU mortality.

The study "suggests that the introduction of a tele-ICU program that collaborates with and supports bedside clinicians is one way" to provide better care and cut costs, Dr. Lilly said. ■

COMMENTARY

Dr. Carl A. Kaplan, FCCP, comments: This is a topic of much discussion and debate, and there is the possibility of a large paradigm change for ICU and hospital management and leadership. However, at this time, I do not believe the verdict is in yet, from this single-center study alone.

IN THIS ISSUE

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AMERICAN COLLEGE OF CHEST PHYSICIANS

CHEST PHYSICIAN

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Thrombolysis May Reduce Survival in Acute PE

BY MIRIAM E. TUCKER
Elsevier Global Medical News

DENVER – Adding thrombolytic therapy to standard anticoagulation with heparin did not significantly improve overall survival at 3 months in patients with acute symptomatic pulmonary embolism – and reduced survival rates for some normotensive patients, according to a large international retrospective cohort study.

Thrombolytic therapy as initial treatment did produce a nonsignificant trend toward survival among patients who presented with systolic hypotension, according to a subgroup analysis of the study data, while significantly worsening survival among normotensive patients.

However, thrombolysis had no significant impact on survival among normotensive patients when researchers accounted for differences in troponin and the presence of right ventricular dysfunction.

"Based on these findings, we cannot recommend thrombolysis in normotensive patients without more data from randomized controlled trials. We need to better determine how to risk stratify these patients," said Dr. David Jimenez of the Ramon y Cajal Hospital and Alcala de Henares University, Madrid.

Current guidelines from the American College of Chest Physicians recommend thrombolytic therapy in addition to anticoagulation for patients with evidence of hemodynamic compromise (grade 1B evidence) and for "selected high-risk patients without hypotension who are judged to have a low risk of bleeding (grade 2B)." The guidelines advise physicians to base that decision on the severity of the pulmonary embolism (PE), the patient's prognosis, and risk of bleeding (Chest 2008;133:454S-545S).

The current study was done to fill in the evidence gap for those recommendations, explained Dr. Jimenez, who presented the study results at an international meeting of the American Thoracic Society. He and his colleagues from Spain and the United States analyzed data from 15,944 patients with acute pulmonary embolism enrolled in the Spanish registry Registro Informatizado de la Enfermedad Tromboembólica. Thrombolytic therapy had been used in 2.7% (430) of the patients.

In general, those patients were younger, with fewer comorbid conditions and more signs of clinical severity. To overcome that bias, a propensity analysis was conducted to match patients for those differences.

Patients were also grouped into those with systolic blood pressure less than 100 mm Hg (hypotensive) and those with 100 mm Hg and higher (normotensive).

Comparing 94 propensity score–matched patients with systolic hypotension who received thrombolysis with 94 patients who did not, there was a trend in reduction in all-cause mortality with thrombolytic therapy, with an odds ratio of 0.72 (95% confidence interval, 0.36-1.46).

For two groups of 217 normotensive patients each who received or did not receive thrombolysis, there was a statistically significant increased risk of death for those receiving thrombolysis, with an odds ratio of 2.32 (95% CI, 1.15-4.68). However, when missing troponin and ECG data were added to the analysis, the effect of thrombolysis was no longer significant.

VITALS

Major Finding: Among 434 normotensive patients with acute symptomatic pulmonary embolism, there was a statistically significant increased risk of death for those receiving thrombolysis, with an odds ratio of 2.32. However, when troponin and right ventricular dysfunction were added to the analysis, the effect of thrombolysis on survival was no longer significant, with an odds ratio 1.67.

Data Source: A retrospective cohort study of data from 15,944 patients with acute pulmonary embolism enrolled in a Spanish registry.

Disclosures: Dr. Jimenez stated that he has no financial disclosures.

The reasons for the increased risks from thrombolysis for normotensive patients with PE aren't entirely clear, the investigators said.

However, because the risk of dying from pulmonary embolism is low among normotensive, hemodynamically stable PE patients, those patients' risk of dying from thrombolysis is therefore elevated by comparison and approaches that of hypotensive patients, Dr. Jimenez speculated. Only half of all patients with pulmonary embolism actually die of the embolism, he noted.

Indeed, there has been only one previous randomized clinical trial showing benefit from thrombolysis in patients with PE, Dr. Jimenez said, and that was in 10 patients with life-threatening PE (J. Thromb. Thrombolysis 1995;2:227-9).

"Thrombolysis is only useful for those who are at high risk for dying from PE," Dr. Jimenez said. "I think we have to test in a randomized, controlled trial whether thrombolysis is helpful in a subgroup of normotensive patients who have high risk due to right ventricular dysfunction and elevated troponin," Dr. Jimenez said.

Such a trial is now underway. The prospective, double-blind, placebo-controlled Pulmonary Embolism Thrombolysis Study (PEITHO) will examine the particular subgroup of normotensive patients with acute PE who have echocardiographic and laboratory evidence of right ventricular dysfunction.

The study investigators want to enroll 1,000 patients at 12 European centers, and they hope to have data by the end of 2012, said Dr. Jimenez, whose hospital is one of the study centers. ■

Risk of PE Higher in Patients With Traumatic Chest Injury

BY BRUCE JANCIN
Elsevier Global Medical News

BOCA RATON, FLA. – Severe chest injury constitutes a newly recognized independent risk factor for pulmonary embolism in trauma patients.

"At our trauma center, we have a new venous thromboembolism risk algorithm, and patients with chest injury now go into the high-risk category. You have to give these patients some type of chemical prophylaxis as early as you feel safe, because if you're developing a pulmonary embolism without a deep vein thrombosis, the methods used to prevent DVT [such as a prophylactic inferior vena cava filter] are not going to prevent the pulmonary embolisms," Dr. Mary M. Knudson said at the annual meeting of the American Surgical Association.

This lack of benefit for prophylactic IVC filters in preventing pulmonary embolism (PE) was another one of the key findings in her study, in which she examined risk factors and outcomes for PE and DVT in 888,652 patients who were treated at 326 level I or II trauma centers that were included in the American College of Surgeons' National Trauma Data Bank (NTDB) for 2007-2009.

The incidence of DVT in this very large group of trauma patients was 1.06%, and for PE it was 0.42%. Only 20% of patients with PE also had a reported DVT, but because of how the data in the national registry are collected, it isn't known which came first.

The risk factors for PE and DVT were not the same. For example, patients with severe chest injury (defined as an Abbreviated Injury Scale score of 3 or higher) were 42% more likely to develop PE than were trauma patients without such an injury, but they weren't at increased risk for DVT. In contrast, patients with severe traumatic brain injury were 34% more likely to have DVT than were those without traumatic brain injury, but they were also 13% less likely to be diagnosed with a PE. And patients who were ventilator dependent longer than 3 days were at a 5.3-fold increased risk for DVT, but they were at a 3.8-fold increased risk for PE.

In contrast, several other significant predictors had overlapping risks for both PE and DVT, including shock, pelvic fracture, and spine injury, reported Dr. Knudson, a professor of surgery at the University of California, San Francisco.

She noted that compared with her previously reported analysis of the NTDB experience for 1994-2001, the PE incidence rate is rising, while PE-attributed mortality has declined. The likely explanation for these trends is that in recent years, the liberal use of chest CT after trauma has become routine, with resultant incidental detection of small PEs that are amenable to anticoagulation therapy. "I think we're recognizing a disease that's in an earlier stage, and one that we probably overlooked in the past," she said.

COMMENTARY

Dr. Richard Fischel, FCCP, comments: This well-done study's finding that thoracic trauma patients are significantly more likely to suffer a PE than a DVT has immediate clinical implications. It would appear that anticoagulation should play an integral role in the care of these patients and that IVC filters are not only not helpful but probably contraindicated in the absence of associated DVT. It is encouraging that even as the rate of detected PE increases, almost certainly due to more liberal use of CT to evaluate for PE, the mortality is decreasing due to increased recognition and aggressive intervention. Dr. Knudson's identification of severe chest injury as a novel contributor to the formation of PE is a significant clinical observation.

The incidence of PE in trauma patients more than doubled, from 0.21% in 1994-2001 to 0.49% in the same trauma centers in 2007-2009. Meanwhile, mortality in trauma patients with PE dropped from 15% in the earlier period to 11% more recently. In 1994-2001, PE was associated with an adjusted fourfold increased risk of mortality, whereas in 2007-2009 PE conferred a 2.4-fold increase in mortality.

Dr. Knudson concluded that prophylactic IVC filters are ineffective in preventing trauma-related PE because the use of such filters doubled between her first and second studies, even as the PE incidence rate more than doubled. "I'm not suggesting that prophylactic IVC filters cause pulmonary embolisms, but they certainly aren't preventing them," she said.

Severely injured patients who arrive at a trauma center in shock are already coagulopathic even before they receive transfusions. During the next 2-3 days, as they receive multiple transfusions, their protein C becomes depleted and they become hypercoagulable. At that point, patients with a chest injury (with its attendant profound inflammation) are more at risk for PE, whereas those with traumatic brain injury have stasis and may be more at risk for DVT, she explained.

Discussant Dr. David B. Hoyt, executive director of the American College of Surgeons, said that Dr. Knudson's identification of severe chest injury as a novel contributor to PE is a major new observation that will be an important consideration when clinicians are assessing a trauma patient's overall risk.

Dr. Knudson reported having no relevant conflicts. ■

Corticosteroids May Mitigate LABA Risks in Children

BY DAMIAN McNAMARA
Elsevier Global Medical News

DENVER – When you prescribe a long-acting beta-agonist for a child with asthma, you may want to consider adding an inhaled corticosteroid as well, according to a meta-analysis conducted by Food and Drug Administration investigators.

"Overall, there was an increased risk of asthma-related hospitalizations, intubation, or death to asthmatics of all ages using long-acting beta-agonists [LABAs]," said Dr. Ann W. McMahon at the meeting.

Dr. McMahon and her colleagues also found an age effect, with asthmatics aged 4-11 years at greater risk, compared with older patients. "Children are at increased risk, primarily of hospitalization, from asthma with LABA use compared to the overall population."

The elevated overall and age-related risks are no longer statistically significant, however, when patients are prescribed an inhaled corticosteroid (ICS) along with a LABA as part of a study protocol, Dr. McMahon said at the annual meeting of the Pediatric Academic Societies.

"Although further study is indicated, simultaneous use of inhaled corticosteroids and LABAs may mitigate this risk in children," said Dr. McMahon, deputy director of the division of pharmacovigilance at the FDA's Office of Surveillance and Epidemiology.

In a previous meta-analysis, LABA use was associated with a higher overall risk for adverse outcomes, a risk difference estimate of 2.80 for an asthma composite index of asthma-related hospitalizations, intubations, and deaths. In a 2008 meta-analysis that included 60,954 patients of all ages from 110 trials, Mark Levenson, Ph.D., one of Dr. McMahon's FDA colleagues, found the highest risk associated with LABA therapy was among those aged 4-11 years, who had a risk difference estimate of 14.83/1,000 participants.

VITALS

Major Finding: Asthma patients taking an ICS along with a LABA had a lower risk for asthma-related adverse events, 0.2/1,000 patients, compared with 6.3/1,000 among those taking a LABA regardless of concomitant therapy. Children aged 4-11 years had the greatest risks attributable to LABA use (19.8 events per 1,000 patients).

Data Source: Secondary analysis of risk by age from a meta-analysis of 60,954 asthma patients in 110 trials.

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

Dr. McMahon presented a secondary analysis of the 2008 meta-analysis in which she and her associates assessed a subset of patients assigned an ICS as part of their study regimen. Using a forest plot analysis, they compared 7,862 patients also treated with a LABA versus 7,330 who did not receive a LABA.

"What we see here is no overall risk for this subset of patients and no particular age trend either," Dr. McMahon said. The overall risk difference was 0.2/1,000 patients.

"This is a smaller group of patients, so whether we can conclude this is definitive, I would say probably not," Dr. McMahon said. "But it is very intriguing that this subgroup that took assigned inhaled corticosteroids really did not have an age effect or an overall increased risk."

In contrast, when all users and nonusers of inhaled corticosteroids were combined, overall risk associated with LABA use was 6.3 additional adverse events per 1,000 patients.

Another analysis of the data looked at all patients who took some concomitant ICS therapy (those intentionally prescribed an ICS and those noted to be taking an ICS at baseline). This analysis "looks very similar, with a slight increased risk overall" of 6.1 events per 1,000 patients, Dr. McMahon said.

Age again made a difference, with a point estimate risk of 19.8 per 1,000 participants for those aged 4-11 years, a statistically significant higher risk compared with that of patients aged 12-17 years, 18-64 years, and 65 years and older.

"Children are at increased risk primarily of [asthma-related] hospitalization," Dr. McMahon said. Data on intubations and deaths were insufficient to calculate these outcomes among children, she added.

Dr. McMahon's findings concur with those of other published studies. For example the Salmeterol Multicenter Asthma Research Trial (SMART) and the Serevent Nationwide Surveillance (SNS) study "both gave similar results to the extent that there was a three- to fourfold increase in risk of serious asthma outcomes such as asthma-related death and intubation" associated with LABA use (Chest 2006;129:15-26; BMJ 1993;306:1034-7). However, these trials did not include children younger than 12 years and did not include enough adolescents for investigators to be able to analyze those data separately, she added. ■

COMMENTARY

Dr. Burt Lesnick, FCCP, comments: The authors cannot say definitively that combinations of ICS and LABA are safe in children. However, this study suggests that if there is a negative effect from the addition of a LABA, it is likely to be small.

Triaging Acute Asthma

Nurses • *from page 1*

All of the children had either a prior physician diagnosis of asthma or three or more episodes of wheezing responsive to beta-2 agonists. Of 1,183 children with acute asthma presenting to the ED between September 2009 and May 2010, 644 were classified as having moderate to severe disease. There were 336 children in the physician-ordered phase and 308 in the triage nurse–administered phase. The children were similar in age (mean of about 6 years in both groups). About two-thirds of both groups were boys. Both groups had been experiencing respiratory distress for about a day and a half prior to ED arrival, with an initial average PRAM score of 6.7 (moderate exacerbation).

Other than the timing of oral steroid administration, the children were treated similarly in the ED. Children in the triage nurse–administered phase received steroids at just 30 minutes, compared with 75 minutes in the physician-ordered phase, a highly significant difference.

For the primary outcome, time until clinical improvement as defined by a reduction in initial PRAM score by 3 points, children who received steroids from the triage nurse improved a statistically significant 24 minutes faster (median, 158 minutes) than those treated during the physician-ordered phase (median, 182 minutes). They also improved to "mild" status 51 minutes sooner, with medians of 211 vs. 262 minutes.

Hospital admission was required for 19.0% of the physician group, compared with 11.7% of the triage nurse group, for a significant odds ratio of 0.56. Time to ED discharge was a significant 44 minutes sooner with steroid administration by a triage nurse, at 316 vs. 360 minutes.

Adjustments for a few significant although small differences at baseline in the proportion of patients with a preceding upper respiratory tract infection and in prior use of other asthma medications did not change the results, Dr. Zemek noted.

"While 44 minutes may seem short, when you add that over thousands of visits per year at most pediatric tertiary centers, you're talking about thousands of hours saved of nursing time [and] physician time," plus money saved from reduced hospital admissions. "If adopted broadly, this strategy to optimize multidisciplinary teams could have large health care implications with regard to reducing the burden of asthma and as a potential solution to overcrowding of our emergency rooms," he commented.

This study was funded by a grant from the Academic Health Sciences Alternate Funding Plan of Ontario. Dr. Zemek stated that he had no additional financial disclosures. ■

Pages 4a—4b

Salivary Markers May Help Assess Asthma Severity

BY DOUG BRUNK
Elsevier Global Medical News

SAN FRANCISCO – In the future, physicians may look no further than to a sample of saliva to assess asthma disease activity in children.

In a poster session at the annual meeting of the American Academy of Allergy, Asthma, and Immunology, Dr. Frédéric F. Little, of the department of medicine at Boston University, presented findings from a study that explored the efficacy of salivary inflammatory biomarkers as markers of disease activity in asthmatic children.

"It's premature to make any definitive clinical conclusions, but we have some insights that some of the traditional markers of allergic inflammation that are seen in blood, induced sputum, and nasal lavage, and correlate with disease control, can be readily detected in saliva," Dr. Little said in an interview.

For the study, which was conducted in collaboration with Dr. Elizabeth C. Matsui of Johns Hopkins University, Baltimore, 58 children aged 5-17 years who had moderate to severe asthma underwent measurements of exhaled nitric oxide, serum IgE quantification, and aeroallergen skin testing and filled out symptoms questionnaires. The researchers collected whole masticatory saliva, which was separated by centrifugation for supernatant harvest.

Slightly more than half of the children (52%) were boys, and 88% were black. Inflammatory mediators were detected in more than 95% of participants. The researchers found that salivary levels of eosinophil-related mediators such as interleukin (IL)-5 and the chemokines CCL11/eotaxin and CCL5/RANTES were strongly and positively correlated with each other. A similar strong association was seen in non–eosinophil-related mediators such as IL-1-beta and CXCL8/IL-8.

The researchers also found that salivary levels of vascular endothelial growth factor (VEGF) were positively correlated with certain markers of clinical disease activity. Also, VEGF correlated positively with non-Th2 markers of immune activation, including CXCL8/IL-8, CCL2/MCP1, and IL-1-beta, yet negatively with markers of atopic burden such as exhaled nitric oxide and total serum IgE. What that disconnect means going forward "we don't know," Dr. Little said. "That caught us by surprise."

In their poster, the researchers noted that "saliva profiling may offer complementary noninvasive assessment of disease activity beyond current markers of allergic inflammation." ■

COMMENTARY

Dr. Burt Lesnick, FCCP, comments: While much study has been made of exhaled breath condensate, the ability to test saliva directly may simplify biomarker analysis in the future. It will be interesting to see how this field develops.

VITALS

Major Finding: Inflammatory mediators were detected in the saliva of more than 95% of asthmatic children. Salivary levels of eosinophil-related mediators such as interleukin-5 and the chemokines CCL11/eotaxin and CCL5/RANTES were strongly and positively correlated with each other. A similar strong association was seen among non–eosinophil-related mediators such as IL-1-beta and CXCL8/IL-8.

Data Source: A study of 58 children aged 5-17 years who had moderate to severe asthma and who underwent measurements of exhaled nitric oxide, serum IgE quantification, and aeroallergen skin testing.

Disclosures: The study was funded with support from the National Institute of Dental and Craniofacial Research and the National Institute of Allergy and Infectious Diseases. Dr. Little said that he had no relevant financial disclosures.

Inner-City Families Struggle With Asthma Tx Compliance

BY MITCHEL L. ZOLER
Elsevier Global Medical News

It's challenging enough to control chronic asthma in children, but youngsters who live in low-income, inner-city households face some special barriers to optimal asthma management, including their family's difficulty paying for medication, lack of family understanding about optimal treatment, and denial by the family about treatment compliance.

The best way to deal with at least some of these issues may be a new approach to educating families about their child's persistent asthma, said Dr. Marina Reznik, a pediatrician at the Children's Hospital at Montefiore Medical Center in New York. She has launched a study to test the ability of community health workers to improve family understanding of optimal asthma therapy and to see if this improves patient outcomes.

The study involves randomizing Bronx families who have a child with persistent asthma to receive either standard education materials or to get six visits from a community health worker every other week for 10 weeks. The health workers will instruct parents on optimal asthma therapy, teach them how to administer an inhaled corticosteroid to their young child, and continue to monitor the therapy for 10 weeks to make sure correct treatment continues. Dr. Reznik will compare the results between the intervention and control groups over the subsequent year.

She and her associates gained insight into the problems parents face with administering correct asthma treatment to their children from the results of a pair of studies they reported in March at the annual meeting of the Eastern Society for Pediatric Research in Philadelphia.

In one study, Dr. Reznik and associates tested parents' perceived compliance with their child's inhaled corticosteroid regimen, compared with their actual compliance. They recruited 40 parents of a child aged 2-9 years with persistent asthma who required twice-daily therapy with an inhaled corticosteroid, a total of four puffs per day. All children were patients of the community health care center run by Montefiore. The participating parents averaged 33 years old, two-thirds were Hispanic, and 29% had not graduated high school.

'There is a discrepancy between what physicians say and what parents hear.'

DR. REZNIK

Each parent received an inhaled corticosteroid actuator with an attached dose counter that recorded the number of puffs delivered. Thirty days later, the researchers surveyed the parents about their adherence to the two-puffs twice-daily regimen and checked the dose counter on the family's actuator.

Sixteen of the 40 parents (40%) claimed they had been 100% compliant with the regimen, while the dose counters revealed that only two families (5%) had achieved complete compliance. Only one parent (3%) owned up in an interview to being completely nonadherent, while the dose counters showed that four parents (10%) had actually failed to administer any treatment.

The results showed that parental self-reporting is "nonreliable" for assessing compliance with an asthma regimen, Dr. Reznik said. "The results may have implications for physicians using parental self-reports in managing children with persistent asthma."

The disparity between perceived and actual adherence may derive in part from parents' concerns about the safety of this treatment, she suggested. "They see improved symptoms [in their children], but they are terrified of the drugs. They have misconceptions."

The second set of results that her group reported at the meeting came from a study that focused on caregiver knowledge of inhaled corticosteroid delivery. Again, the study used parents of children aged 2-9 years old seen at the hospital's community outpatient pediatric clinic. This time, they enrolled 66 caregivers, who averaged 32 years old, with 96% of the study group comprising mothers; 27% of the parents had not finished high school, 59% were unemployed, and 59% were Hispanic and 26% were black.

Among the 66 participants, 92% said that they had used a spacer when delivering the inhaled corticosteroid to their child, with 78% saying they used the spacer for every treatment and 5% saying they never used a spacer. In addition, 97% of the caregivers said that a physician or nurse had explained to them how to use the metered dose inhaler and spacer, 91% said that a physician or nurse had demonstrated the correct technique, and 49% said that at some point a physician or nurse had watched their technique for administering the drug.

A researcher then watched each caregiver deliver two puffs of the inhaled corticosteroid to a doll. Only one of the participants (2%) correctly performed every step of drug administration with the metered dose inhaler and spacer. Although 97% correctly formed a tight seal with the inhaler, the most problematic steps involved waiting the appropriate interval between puffs, done by 27%, and instructing the recipient to exhale before the treatment inhalation, done by 24%. Other steps scored on the assessment involved shaking the inhaler for at least 5 seconds before administering a puff, pressing the inhaler just once for each puff, and administering the correct number of puffs.

Dr. Reznik and her associates concluded that the results highlighted the need for repeated training of caregivers to ensure ongoing, proper delivery of inhaled corticosteroids.

Most physicians don't have the time to properly teach parents on the correct delivery of inhaled corticosteroids, Dr. Reznik said. In addition, many parents favor treatment with an inhaled, short-acting beta-agonist, such as albuterol, because of the immediate symptom relief it provides. "They don't see the role of preventive treatment, compared with acute treatment," she said in an interview.

"There is a discrepancy between what physicians say and what parents hear, and there is more to this than education." Parents face the financial challenge of paying for the medications, and they fear the side effects of inhaled corticosteroids. "Physicians try to educate the family as much as possible, but with limited time, that may not be possible." The community health worker approach under development by Dr. Reznik features a user-friendly format in which the health worker goes to the family's home, a format that she hopes will lead to improved caregiver education and reinforcement, improved drug delivery, and better outcomes.

Dr. Reznik said that she had no disclosures. ■

Risk Factors Identified for Patients Weaned From VAD

With tighter criteria for weaning, freedom from heart failure recurrence reached 100% at 3 years.

BY CAROLINE HELWICK
Elsevier Global Medical News

NEW ORLEANS – Patients with chronic cardiomyopathy can be successfully weaned from ventricular assist devices, and certain parameters can predict long-term cardiac stability after explantation, according to German investigators.

"Unloading-promoted reversal of heart failure allows for long-term transplant-free outcomes after patients are removed from VADs. However, few patients with chronic cardiomyopathy have been weaned from VADs, and the majority only recently," said principal investigator Dr. Michael Dandel of the German Heart Institute Berlin. "The long-term outcomes of patients, therefore, and the reliability of criteria for making weaning decisions, are not well known."

At his clinic, 91 patients with chronic cardiomyopathy (CCM) as the underlying cause of heart failure were weaned from VADs between 1995 and 2010, including 75 weaned from left ventricular assist devices, 13 weaned from biventricular assist devices, and 3 weaned from right ventricular assist devices. Before VAD implantation, the patients had left ventricular ejection fraction (LVEF) values of 10%-20%.

These patients were evaluated as to the feasibility of weaning and to establish criteria that could predict long-term cardiac stability after VAD removal.

"With this information, we can improve future weaning decisions and postweaning patient management," Dr. Dandel said at the annual meeting of the American College of Cardiology.

A total of 47 patients were evaluated. Of these 41 (87.2%) had idiopathic cardiomyopathy, 4 (8.5%) had histologic evidence of chronic myocarditis before VAD implantation, and 2 (4.3%) had chronic ischemic cardiomyopathy with severe left ventricular dilation.

Before VAD insertion, all patients had irreversible end-stage heart failure and required continuous positive inotropic support. No attempts were made to use VADs electively with the aim of myocardial recovery only, Dr. Dandel said.

Postweaning Results

Cardiac stability lasting at least 15 years was achieved by 2 patients, while 10 patients have been stable at least 10 years and 3 at least 5 years, he reported.

"At 5 years, only five patients, 10.6%, had died due to heart failure recurrence or weaning-related complications. Several patients died of other causes," he said.

Postweaning freedom from heart failure recurrence for all evaluated patients was 74% at 3 years and 66% at 5 years, but these results included nine patients at very high risk for poor outcomes. After 2002, when the investigators tightened their criteria for weaning, freedom from heart failure recurrence reached 100% at 3 years, he noted.

Pre-Explantation Variables Predictive of Outcomes

"Echo data obtained during 'off pump' trials proved to be reliable for detection of recovery during mechanical unloading," Dr. Dandel said. "In particular, off-pump [left ventricle] size, geometry, and ejection fraction were predictive of outcome after weaning, especially when history of heart failure was also considered."

For cardiac stability lasting at least 5 years, pre-explantation "off pump" LVEF of 50% or more was associated with a positive predictive value of 91.7%, while LVEF of 45% or more had a positive predictive value of 79.1%.

The positive predictive value of LVEF of 45% or more was approximately 90% if additional parameters were considered: pre-explantation left ventricle size and geometry, stability of unloading-induced cardiac improvement before VAD removal, and heart failure duration before VAD implantation.

Time to cardiac recovery seemed important, Dr. Dandel said. "Patients who had recurrences needed more time to show an improvement. They needed twice the duration of VAD support as patients who did not have a recurrence," he said.

"Definite cutoff values for certain parameters – including tissue Doppler-derived LV wall motion velocity – allowed us to formulate weaning criteria with high predictability for postweaning stability," he said.

Risk Factors for Heart Failure Recurrence

Dr. Dandel and his colleagues also identified several risk factors that predicted heart failure recurrence during the first 3 years after VAD removal. These factors, and their associated probability for recurrence, were:

- Preweaning off-pump LVEF less than 45% plus history of heart failure longer than 5 years (100%).
- Preweaning LVEF less than 45% (88.9%).
- Preweaning off-pump LVEF less than 50% plus left ventricular internal diastolic diameter greater than 55 mm (90%).
- Pre-explantation LVEF less than 50% and preexisting alteration of greater than 10% best value (87.5%).
- LVEF less than 50% plus relative wall thickness decrease of less than 10% during final off-pump trial (83.3%).

Of these, Dr. Dandel emphasized the importance of the final off-pump trial values.

'WITH THIS INFORMATION, WE CAN IMPROVE FUTURE WEANING DECISIONS AND POSTWEANING PATIENT MANAGEMENT.'

"An off-pump ejection fraction less than 45% in patients with a history of heart failure for more than 5 years is an absolute contraindication for VAD removal," he noted. "All such patients in our study had a recurrence of heart failure," he said.

Early instability of ejection fraction and unstable geometry also confer a high probability of recurrence. "A wall thickness increase by more than 10% means the reverse in modeling is not stable enough," he added.

"The notion that we can actually wean patients from VADs is still a fairly new concept, and the European experience is larger than that of the United States. This is still a field that is wide open for determining patient selection and predictors of outcome after VAD removal," session moderator Dr. Gregory A. Ewald, medical director of heart transplantation at Barnes-Jewish Hospital, St. Louis, commented in an interview.

"Clearly, the echocardiographic appearance of the heart on and off support is a good predictor," Dr. Ewald said, but he noted that nonechocardiographic factors such as exercise tolerance were not studied.

He also noted that the field has moved to continuous-flow pumps rather than pulsatile pumps, which constituted much of the German experience. It remains to be determined if the same parameters are completely applicable to the newer-generation devices.

Dr. Dandel and Dr. Ewald both reported having no relevant conflicts of interest. ■

COMMENTARY

Dr. Jun Chiong, FCCP, comments: There have been case reports of LV function recovery while waiting for a donor heart. This, however, is the largest reported series that I am aware of and the authors were able to identify parameters that will increase its likelihood.

VAD Bridging to Heart Retransplant Fine for Some

BY SUSAN LONDON
Elsevier Global Medical News

SAN DIEGO – Ventricular assist devices appear to be a "reasonable strategy" for supporting certain patients who have failing cardiac grafts and are waiting for a new heart, concludes a retrospective review of more than 1,500 patients who had a second transplant.

In the group who had retransplantation at least 1 year after their first transplantation, median survival was about 7 years. There was no difference between patients bridged with a ventricular assist device (VAD) and those who did not have any type of mechanical circulatory support (MCS), according to results reported at the annual meeting of the International Society for Heart and Lung Transplantation.

But survival was poor for those who were bridged after any interval with extracorporeal membrane oxygenation (ECMO) and for those with primary graft failure or hyperacute rejection, regardless of whether they were mechanically supported.

"The use of ECMO to bridge any patient to retransplantation does not appear judicious, nor does the use of MCS to bridge patients with primary graft failure or hyperacute rejection to retransplantation," said coinvestigator Dr. David L.S. Morales of the departments of surgery and pediatrics at Texas Children's Hospital in Houston. "However, the use of VADs to bridge patients to transplant after a year could be a reasonable strategy."

Although MCS is widely accepted for bridging patients to initial heart transplantation, its use for bridging to retransplantation has not been well studied. The investigators therefore took a closer look at this issue, analyzing data from the United Network for Organ Sharing database for 1,535 patients who underwent cardiac retransplantation during 1982-2009.

Results showed that just 8% of the patients were bridged to retransplantation, with a VAD in about two-thirds of cases and ECMO in the other third. The mean age was 41 years in the former and 35 years in the latter, with children (younger than age 18) comprising 15% and 35%, respectively.

The patients bridged to retransplantation were significantly more likely than were their nonbridged counterparts to have primary graft failure or hyperacute rejection (54% vs. 11%) and significantly less likely to have chronic rejection (16% vs. 63%).

And the bridged patients by and large underwent retransplantation early, with 64% in the VAD group and 76% in the ECMO group retransplanted within 3 months of their primary transplantation, compared with just 12% of their nonbridged peers.

"Regardless of MCS, patients retransplanted for primary graft failure or hyperacute rejection do not do well," Dr. Morales commented. Specifically, in patients with these indications for retransplantation, the 1-year mortality rate was 83%, with essentially no difference according to whether they received bridging or the type received.

VITALS

Major Finding: Among patients retransplanted at least a year after an initial transplantation, median survival was 7 years and did not differ between those bridged with a VAD and those who did not receive any mechanical circulatory support.

Data Source: A retrospective review of 1,535 patients who underwent cardiac retransplantation during 1982-2009.

Disclosures: Dr. Morales disclosed having relationships with Berlin Heart, Syncardia Systems, and CircuLite as an investigator and/or consultant.

In the entire study population, median overall survival after retransplantation was 6.1 years in nonbridged patients, significantly longer than the 1.5 years in VAD-bridged patients and the 30 days in ECMO-bridged patients.

But when analyses were restricted to patients who underwent retransplantation at least 1 year after primary transplantation, median survival was similar in nonbridged and VAD-bridged patients, at 7.0 and 6.9 years. Compared with those groups, however, survival was significantly shorter – just 6 months – in the ECMO group.

"Patients bridged to retransplant with ECMO have poor outcomes regardless of timing or indication," Dr. Morales concluded of the findings. "And all patients retransplanted for hyperacute rejection or primary graft failure do poorly, regardless of MCS," he said.

"However, patients who are bridged with a VAD to retransplant that is done a year post primary transplant do have similar outcomes as compared to retransplant patients without MCS," he commented.

As for study limitations, "it is very important to note that we do not know the number of patients placed on MCS as a bridge to transplant who died while on support," he pointed out. ■

Biomarker Testing Key to MetMAb in Lung Cancer

BY PATRICE WENDLING
Elsevier Global Medical News

CHICAGO – Final efficacy results from the phase II OAM4458g trial confirm that the success of MetMAb in previously treated advanced lung cancer lies in accurate biomarker testing.

Some patients gained a striking survival advantage when given the investigational monoclonal antibody as second- or third-line therapy for non–small cell lung cancer (NSCLC). However, the study group as a whole did not benefit, and others actually did worse with the antibody. The difference appears to be driven by expression of the c-Met receptor.

MetMAb targets hepatocyte growth factor and its receptor, c-Met. Expression of c-Met is associated with a worse prognosis in many cancers, including NSCLC. Met activation by hepatocyte growth factor is thought to decrease sensitivity to erlotinib (Tarceva), hence the interest in combining MetMAb with erlotinib. In this trial, patients received either a combination of the two drugs or erlotinib with a placebo.

In NSCLC patients whose tumors were classified as Met positive, the addition of MetMAb to erlotinib nearly doubled the median time that they were free of disease from 1.5 months to 2.9 months (hazard ratio, 0.53; log rank $P = .04$) and tripled median overall survival from 3.8 months to 12.6 months (HR, 0.37; log rank $P = .002$), Dr. David Spigel said at the annual meeting of the American Society of Clinical Oncology.

When MetMAb plus erlotinib was given to patients with Met-negative tumors, however, median progression-free survival was significantly lower at 1.4 months, compared with 2.7 months in the control arm given erlotinib plus placebo (HR, 1.82; $P = .05$).

Median overall survival was also shorter with the combination in the Met-negative group – 8.1 months vs. 15.3 months with erlotinib and placebo – although the difference did not reach statistical significance (HR, 1.78; $P = .158$), said Dr. Spigel, director of lung cancer research at the Sarah Cannon Research Institute in Nashville, Tenn.

The Met diagnostic test used in the phase II study was developed by Ventana Medical Systems, which is owned by Roche, the parent company of the study sponsor, Genentech.

Of the 137 patients, 93% had adequate tissue for evaluation of c-Met by immunohistochemistry.

VITALS

Major Finding: Among Met-positive patients, median progression-free survival doubled from 1.5 months with erlotinib to 2.9 months with the addition of MetMAb (HR, 0.53; $P = .04$).

Data Source: Randomized phase II trial in 137 patients with advanced non–small cell lung cancer.

Disclosures: Dr. Spigel disclosed a consultant/advisory role with Genentech, which sponsored the study. His coauthors disclosed financial relationships with several firms including employment with Genentech.

In all, 52% of patients with evaluable tissue were "Met diagnostic positive," defined by at least 50% of tumor cells with moderate or strong staining intensity, Dr. Spigel said.

Patients were randomized to erlotinib 150 mg daily plus MetMAb 15 mg/kg IV every 3 weeks or the same dosing of erlotinib and placebo. Coprimary end points were progression-free survival in the Met diagnostic–positive and intention-to-treat populations.

In the latter, the combination of MetMAb and erlotinib failed to significantly improve median time to progression over erlotinib (2.2 months vs. 2.6 months; HR, 1.09; $P = .69$) or overall survival (8.9 months vs. 7.4 months; HR, 0.80; $P = .34$), he said.

The researchers performed additional analyses in key subpopulations, suggesting that the benefit from MetMAb is not related to epidermal growth factor receptor (EGFR) mutation or fluorescence in situ hybridization (FISH) status.

Although the patient numbers were small, an overall survival advantage was seen with MetMAb for patients with high Met expression (at least 5 copies) by FISH (HR, 0.60; $P = .35$), and was maintained in FISH-negative/Met diagnostic–positive patients (HR, 0.37; $P = .01$), Dr. Spigel said. Patients who were Met diagnostic positive and did not have an EGFR mutation also gained a survival advantage (HR, 0.42; $P = .01$).

"Outcomes in the diagnostic subpopulations highlight the importance of developing tools to identify patients who might best benefit from this treatment," he said, adding that immunohistochemistry appears to be more sensitive than FISH in determining benefit from combination MetMAb/erlotinib.

The study confirmed that Met expression by immunohistochemistry is associated with worse outcomes. An analysis of the 68 patients treated with erlotinib plus placebo confirmed that Met expression revealed that progression-free survival was worse among Met diagnostic–positive vs. Met diagnostic–negative patients (1.5 vs. 2.7 months; HR, 1.71; $P = .06$), as was overall survival (3.8 vs. 15.3 months; HR, 2.61; $P = .004$).

In response to audience questions, Dr. Spigel said it is unknown whether metastatic sites have different Met expression than primary tumor sites or why outcomes are worse in low Met tumors.

No new safety concerns emerged in the trial, although patients treated with MetMAb had more peripheral edema that was largely low grade, reversible, and manageable, he said.

A phase III study testing MetMAb plus erlotinib in Met diagnostic–positive patients is expected to start enrolling this year, he said. ■

Continued Therapy Beneficial

NSCLC • *from page 1*

Memorial Sloan-Kettering Cancer Center in New York, told reporters in a press briefing at the meeting. "I think it's very important in that it's an example of how we can achieve an incremental benefit in our patients by the optimal use of drugs that are already available."

Pemetrexed (Eli Lilly) is approved in combination with cisplatin as first-line therapy for advanced nonsquamous non–small cell lung cancer (NSCLC) and in the second line as maintenance therapy in patients initially treated with chemotherapy.

Standard treatment for nonsquamous NSCLC is to continue bevacizumab until disease progression, but on the basis of these results, clinicians will likely give bevacizumab with pemetrexed, Dr. Kris said in an interview.

"The guidelines don't say that because they didn't have any data, but this will be the data that I'm pretty confident will change the guidelines," said Dr. Kris, who also is the William and Joy Ruane Chair in Thoracic Oncology at Sloan-Kettering.

During the formal presentation of the data, invited discussant Dr. Martin Edelman, director of solid tumor oncology at the University of Maryland Greenebaum Cancer Center in Baltimore, described the use of maintenance therapy as a contentious issue. He noted that many questions remain regarding maintenance trials, including the value of progression-free survival as an end point, how and when control patients are crossed over to active treatment, and whether the RECIST criteria should be used to determine progression.

Dr. Edelman described progression-free survival as an arbitrary end point subject to testing interval and considerable bias. To the credit of the PARAMOUNT investigators, he pointed out that there was use of independent review for this end point, but he said it still does not answer the question of overall survival.

"If one is supposed to change practice based on progression-free survival, we really need to know if particularly small differences are really beneficial," Dr. Edelman said. "That is where quality of life analysis can help us."

The PARAMOUNT investigators assessed health-related quality of life using the EuroQol-5D at baseline, day 1 of each cycle of induction or maintenance therapy, and at the 30-day postdiscontinuation visit. Compliance at all time points during the maintenance phase was more than 80%, but no statistical differences in the EQ-5D index score or its visual analog scale were observed between treatment arms, said Dr. Paz-Ares of the Hospital Universitario Virgen del Rocío, Seville, Spain.

A total of 939 patients were enrolled in the trial. They received pemetrexed 500 mg/m^2 on day 1 of a 21-day cycle plus cisplatin 75 mg/m^2 induction. In all, 539 patients whose disease had not progressed and had a performance status of 0-2 were then randomized to pemetrexed maintenance 500 mg/m^2 on day 1 of a 21-day cycle plus best supportive care or placebo plus best supportive care until disease progression.

Dr. Paz-Ares said pemetrexed had a well-tolerated safety profile, similar to that seen in the previous pemetrexed switch maintenance trial. The pemetrexed and placebo groups had similar drug-related deaths (0.6% for both), drug-related serious adverse events (9% vs. 3%, respectively), and discontinuations due to adverse events (5.3% vs. 3.3%). Patients in the pemetrexed arm had significantly more grade 3/4 adverse fatigue (4.2% vs. 0.6%), anemia (4.5% vs. 0.6%), and neutropenia (3.6% vs. 0%). There was one on-study death with pemetrexed (pneumonia) and placebo (not specified), and one death within 30 days with pemetrexed (endocarditis), Dr. Paz-Ares said.

"While overall very reasonable, this still comes at a cost in terms of significant toxicity, not to mention the cost of additional treatment," Dr. Edelman observed. "We really need a cost-effectiveness analysis in this era to follow strategies of frequent visits and scanning with early institution of second-line therapy versus the maintenance approach."

Eli Lilly funded the study. Dr. Paz-Ares disclosed no relevant relationships. Several coauthors reported relationships with industry, including employment, stock ownership, honoraria, and consultancy with Lilly, which markets pemetrexed. ■

COMMENTARY

Dr. W. Michael Alberts, FCCP, comments: The ACCP Evidence-based Clinical Practice Guidelines on the Diagnosis and Management of Lung Cancer recommends that the duration of first-line therapy in patients with stage IV disease should be brief, consisting of three to four cycles. The study reviewed here and a number of other similarly positive recent articles will no doubt prompt a change in the recommendations in the next edition. Maintenance chemotherapy and so-called "early second-line" chemotherapy appear to provide significant benefit in some patients.

Pages 8a—8f

Rituximab Safe in RA Patients With Lung Disease

BY ELIZABETH MECHCATIE
Elsevier Global Medical News

To date, no new significant safety signals associated with rituximab therapy in patients with severe rheumatoid arthritis and lung disease have been identified in an ongoing observational study, Dr. Shouvik Dass said at the annual European Congress of Rheumatology.

No significant safety signals were observed 'beyond that which might be expected in this group of patients.'

DR. DASS

Overall, the incidence of serious infections in these patients has been low and is about what would be expected in this patient cohort, said Dr. Dass of the department of rheumatology, University of Leeds (England).

He and his associates reviewed the records of 67 patients with RA and concomitant lung disease who were treated with rituximab between 2004 and 2010 at their center, which he said has one of the largest single cohorts of RA patients treated with rituximab.

The patients' mean age was 60 years, and most (56) were female. The most common pulmonary diagnosis was interstitial lung disease, in 48 patients; 14 had COPD, and 5 had bronchiectasis; 2 also had had a previous pulmonary empyema.

All patients received two infusions of 1,000 mg rituximab with methylprednisolone per course, which was repeated when RA became active again, at intervals of no less than 6 months. Half of the patients received at least two treatment cycles.

Over a median of about 2 years of follow-up (range, 8 months to 6.5 years) after treatment with rituximab, 2 of the 48 patients with ILD and 1 of the 14 patients with COPD died. The patient with COPD died of an infective COPD exacerbation 12 months after the third cycle of rituximab. One of the patients with ILD died of pneumonia and possible acute progression of ILD, Dr. Dass said, noting that clinical and CT changes attributable to either condition were observed 4 weeks after the patient had been treated with the first cycle of rituximab. Suicide was the cause of death in the second patient with ILD, 3 months after treatment with the first course of rituximab.

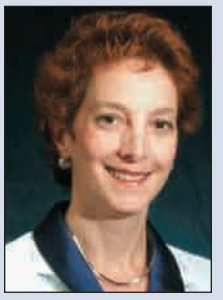
Another three patients had a single episode of serious respiratory tract infection that required hospital admission or treatment with intravenous antibiotics.

Based on these cases, no definite new significant safety signals were observed "beyond that which might be expected in this group of patients with long-standing severe RA and concomitant lung disease," Dr. Dass said. However, he pointed out that the one death caused by respiratory deterioration was temporally related to rituximab therapy.

"B-cell depletion is now an important therapy for RA, and therefore this study aims to add insight into the safety and practical usage of rituximab," he noted in an interview. "We hope that the results will be useful to fellow clinicians when making decisions about whether to use rituximab in such patients, and we hope to encourage ongoing review and follow-up of such patients."

In the United States, rituximab is marketed as Rituxan by Genentech, a member of the Roche Group. Dr. Dass and two of his six coauthors disclosed that they are consultants for Roche. Another coauthor is on Roche's speakers bureau; the remaining authors had no disclosures. ■

COMMENTARY



Dr. Jeana O'Brien, FCCP, comments: Some newer immunomodulating therapies have shown significant potential in the treatment of patients with rheumatoid arthritis. However, these patients often have concomitant interstitial lung disease, warranting concern that therapy may contribute to worsening ILD – similar to the situation with older RA therapies such as methotrexate. In the 60-patient cohort followed by Dr. Dass and his colleagues, this was not the case with rituximab. Although overall this is an encouraging finding, continued close attention is warranted, due to limitations of the small numbers and fairly brief follow-up for some patients.

Not All COPD Exacerbations Are Alike

BY SUSAN LONDON
Elsevier Global Medical News

DENVER – Exacerbations of COPD show distinctly different temporal patterns of onset and resolution, which may have implications for treatment and prognosis, researchers reported.

In a prospective cohort study in patients with COPD who kept daily diaries for at least 2 years, 56% of exacerbations started suddenly; the rest began gradually.

The sudden-onset type were 18% shorter in duration than were the gradual-onset type, reported presenting author Gavin C. Donaldson, Ph.D., a senior lecturer and respiratory medicine specialist at University College London.

The nature of onset of an exacerbation "is of particular interest because it is the prodrome that is reported to the physician when the patient comes into the clinic and dictates the courses of therapy," he noted at an international conference of the American Thoracic Society. Hence, a better understanding of these events could help physicians to time therapy more appropriately.

Study results additionally showed that patients frequently had episodes of symptom worsening that resolved without ever turning into exacerbations.

VITALS

Major Finding: Some 56% of exacerbations had a sudden onset, whereas 44% had a gradual onset. Recovery time was shorter for the sudden-onset type (11 vs. 13 days).

Data Source: A prospective cohort study of 212 patients with COPD.

Disclosures: Dr. Donaldson did not report any relevant conflicts of interest.

Participants recorded peak flow readings and various symptoms – including major (dyspnea, sputum purulence, and sputum volume) and minor (nasal discharge/congestion, wheeze, sore throat, and cough) symptoms – on a daily basis.

The investigators used the diary data to identify episodes of worsening symptoms and to identify exacerbations (defined as an increase in at least two symptoms, one of them major, on 2 consecutive days).

Results were based on 212 patients with an average age of 68 years. In all, 64% were men; 33% were current smokers. Their mean forced expiratory volume in 1 second (FEV_1) was 45% of predicted. All patients had at least 2 years of follow-up.

The patients experienced 4,439 episodes of worsening symptoms, slightly more than half of which resolved spontaneously and the rest of which resulted in a defined COPD exacerbation. The median number of exacerbations was 2.33 per patient per year.

Analyses revealed two distinct patterns of exacerbation onset. With the sudden-onset pattern (seen in 56%), the median time between initial worsening of symptoms and exacerbation was 0 days. With the gradual-onset pattern (seen in 44%), the time to exacerbation was 4 days.

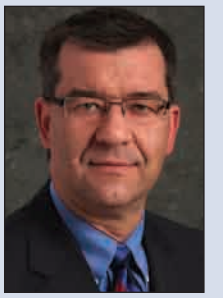
In addition, the time between the start of an exacerbation and recovery to baseline health status was a significant 18% shorter for sudden-onset vs. gradual-onset exacerbations (11 days vs. 13 days; *P* less than .001).

Treatment did not seem to affect these onset or recovery patterns, Dr. Donaldson noted.

Multiple logistic regression analyses showed that certain factors predicted the nature of onset and recovery, Dr. Donaldson said. Exacerbations were more likely to have a sudden onset in patients who were current smokers (odds ratio, 1.28), had cold symptoms (OR, 1.27), or had purulent sputum (OR, 13.47). There was less likelihood of a sudden onset in patients with a higher body mass index (OR, 0.98) or cardiovascular disease (OR, 0.78), or if the exacerbations occurred during the spring (OR, 0.71).

Exacerbations were more likely to have a long recovery time (defined as taking more than 12 days) if they had a gradual onset (OR, 1.39), and also if patients were male (OR, 1.27) or had cold symptoms (OR, 1.30), and if they occurred in the winter (OR, 1.36). There was less likelihood of a long recovery time in patients with purulent sputum (OR, 0.91). ■

COMMENTARY



Dr. Darcy Marciniuk, FCCP, comments: Exacerbations are an important and preventable adverse outcome in COPD, associated with higher mortality, reduced quality of life, and increased health care utilization. This study shows the diversity of exacerbations, as well as their frequency of occurrence and protracted recovery. The results highlight the importance of preventing exacerbations – optimal pharmacologic and nonpharmacologic therapies can help achieve that goal.

COPD Exacerbations Half as Common in Summer

BY SUSAN LONDON

Elsevier Global Medical News

DENVER – Exacerbations and deaths among patients with COPD follow a pronounced pattern of seasonal variation, according to an analysis of data from a randomized, controlled trial presented at in international conference of the American Thoracic Society.

The rate of exacerbations requiring treatment was about twice as high during the winter as during the summer, according to the analysis of data from the Prevention of Exacerbations With Tiotropium (POET) in COPD trial, which enrolled 7,376 patients with moderate to very severe COPD.

The rate of death from any cause followed a similar pattern, with about twice the rate of all-cause deaths occurring in the winter. In all, 142 of the patients died from any cause during the trial, said Dr. Thomas Glaab, head of respiratory medicine at Boehringer Ingelheim.

The randomized, double-blind trial enrolled patients from 25 countries and assigned them to treatment with tiotropium or salmeterol. Main results have been previously reported (N. Engl. J. Med. 2011;364:1093-103).

The participating patients had a mean age of 63 years, and 48% were current smokers. Most had stage II (49%) or stage III disease (43%), according to GOLD criteria. On average, their FEV_1 was 49% of that predicted.

COMMENTARY

Dr. Darcy Marciniuk, FCCP, comments: These results objectively confirm our clinical suspicion that acute exacerbations of COPD requiring therapy, as well as death from AECOPD, are twice as common in the winter compared to the summer. Antibiotic use demonstrated a similar pattern, suggesting a more frequent possible infective etiology. The results highlight the importance of instituting measures known to reduce the likelihood of exacerbations in this population, including optimal pharmacologic therapies, pulmonary rehabilitation, and vaccination.

During the 1-year trial, the patients had a total of 4,411 exacerbations that were moderate (defined as requiring treatment with systemic corticosteroids and/or antibiotics) or severe (requiring hospitalization).

Results showed that such exacerbations were twice as common during the winter versus summer months. Specifically, there were nearly 500 monthly exacerbations between December and February, compared with about 250 monthly exacerbations between June and August.

On an individual basis, the mean rate was 0.073-0.081 exacerbations per patient per month during the winter months, compared with 0.033-0.037 during the summer months, regardless of treatment group.

The pattern was stronger for exacerbations treated with antibiotics – likely reflecting the role of respiratory infections – than for exacerbations treated with steroids, Dr. Glaab commented.

The 2009 H1N1 influenza pandemic occurred during the middle of the study, he noted. "We expected a slight to moderate increase in exacerbations during this time," he said. But surprisingly, the rate was half as high during a period after the first documented case of H1N1 flu (April 2009 to March 2010) as during a period before (April 2008 to March 2009).

The investigators did not have data on the patients' immunization status. "One thing we have learned from POET and H1N1 is [that] it's very important to have the vaccination status for influenza at baseline," he commented. "We should have [these] data because we have problems explaining the difference in exacerbations before and during H1N1 without any vaccination status."

"Irrespective of the efficacy results of large COPD trials such as POET … we can learn much from studies like this," Dr. Glaab added. "And perhaps this may have an impact on how we plan and design studies on exacerbations more efficiently and more effectively in the future."

Dr. Glaab is an employee of Boehringer Ingelheim. The trial was funded by Boehringer Ingelheim and Pfizer. ■

Bacterial Follows Viral Infection

COPD • *from page 1*

more common than has been reported in [previous] studies," said lead investigator Dr. Patrick Mallia, a U.K. National Institute for Health Research clinical lecturer at the Imperial College London.

"In terms of therapeutics, this may suggest that antiviral drugs may not only be effective against virus-induced exacerbations, but also potentially could prevent or reduce secondary bacterial infection," he commented.

At his institution, COPD patients with an exacerbation are not routinely tested for viruses. But that may change, given the advent of rapid PCR (polymerase chain reaction) assays for detecting viruses and, possibly, expansion of the indications for antiviral agents. Interest in the role of viruses and of dual viral-bacterial infection in COPD exacerbations has intensified recently, according to Dr. Mallia. As both types of infections are common in this population, one might expect that dual infection is common as well; yet, on average, studies have found dual infection in only 13% of exacerbations.

"There are a number of reasons why these studies may have underestimated the rate of dual infection," he said, such as their cross-sectional or retrospective nature, and one-time testing for pathogens.

"Studies using a single sampling time point during exacerbation will probably underestimate the true prevalence of coinfection, and also can't tell us what the sequence of infection is," he explained.

To get around these issues, the study investigators used their newly developed model of experimental rhinovirus-induced COPD exacerbation. "These patients catch a cold, get lower respiratory symptoms, and get an exacerbation with increased airflow obstruction and airway inflammation," he said.

The study included 30 patients with GOLD stage II COPD who were using only short-acting bronchodilators, 28 smokers with normal lung function, and 18 nonsmokers. They were experimentally inoculated with rhinovirus, the virus most commonly detected in COPD exacerbations. Induced sputum was collected before inoculation and at 5, 9, 12, 15, 21, and 42 days afterward.

The load of rhinovirus in sputum was assessed with PCR assay. The load of bacteria that were classified as potentially pathogenic microorganisms was assessed with semiquantitative bacterial culture.

Study results showed that 20 of the COPD patients, 21 of the smokers, and 11 of the nonsmokers developed rhinovirus infection after inoculation.

Fully 60% of the rhinovirus-infected COPD patients developed secondary bacterial infections (mainly with *Haemophilus influenzae* and *Streptococcus pneumoniae*), compared with just 9.5% of the smokers and 10% of the nonsmokers (*P* less than .001).

Within the COPD group, bacterial infections were significantly more common among the patients who acquired rhinovirus infection than among those who did not. "This suggests that the bacterial infections we were detecting were a consequence of the rhinovirus infections," Dr. Mallia commented.

Both viral and bacterial loads rose and fell over time, but the former infection preceded the latter: The viral load peaked on day 9, whereas the bacterial load peaked almost a week later, on day 15. These are "really the first data that [show] a temporal sequence, that first you get the rhinovirus infection, and then you get the bacterial infection following this," he noted.

Moreover, "you can see immediately that if you take a single sample and you sample early, you may pick up a virus and call it a viral exacerbation, but not pick up the subsequent bacterial infection," he added. "Whereas if the patient happens to present later, you might detect the bacterial infection but not detect … the virus infection that actually initiated it."

To assess potential mechanisms whereby rhinovirus might induce bacterial infections, the investigators measured sputum levels of two antimicrobial peptides found in the airways that are part of the lung's innate defenses against infection: secretory leukocyte protease inhibitor (SLPI) and elafin.

Levels of both peptides fell in rhinovirus-infected COPD patients who developed bacterial infection before or at the time when bacterial load peaked. In contrast, levels remained the same or rose slightly in those who did not develop bacterial infection. Furthermore, lower levels of the peptides were correlated with higher bacterial loads. "This would suggest that bacterial infection is a consequence of low SLPI and elafin levels in the airways," Dr. Mallia said.

Finally, sputum levels of neutrophil elastase (an enzyme that could degrade the protective peptides) rose in rhinovirus-infected COPD patients who developed bacterial infection but remained essentially at baseline levels in their counterparts who did not.

"We hypothesize that possibly you have a sequence of events – viral infection, high neutrophil elastase levels, and degradation of SLPI and elafin – and that may progress to secondary bacterial infection," he said.

The study gives rise to several potential, related avenues of research. "Certainly, one of the things we are interested in is, Are there markers that can identify those people who are going to go on to develop bacterial infections?" he said. And some evidence suggests that in addition to having antibacterial activity, macrolide antibiotics also have antirhinovirus activity, which the investigators plan to test using their model.

Dr. Mallia reported previously having received research grants from Pfizer and GlaxoSmithKline, and currently receiving a travel grant from Boehringer Ingelheim. The study was funded in part by Pfizer and GlaxoSmithKline. ■

COMMENTARY

Dr. Marcos Restrepo, FCCP, comments: This is a very clever study with an important observation that may impact the future of the diagnosis, management, and prevention of acute exacerbations of COPD. The study authors showed that a significant number of rhinovirus-infected COPD patients developed secondary bacterial infections. In addition, there is a suggested mechanism, implicating viral infection activating the innate host response mediated by leukocytes, further facilitating the invasion of bacterial pathogens. These observations may explain why certain patients may benefit or not benefit from the use of antibiotics (e.g., macrolides), and the impact of outcomes in patients with acute exacerbations of COPD.

Important safety information

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

Liver injury

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

Teratogenicity

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

Contraindications

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

Warnings and precautions

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

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

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

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

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

Adverse events

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

CELEBRATING 10 YEARS OF PUTTING PATIENTS FIRST

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

NOVEMBER '11

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

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

Indication

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

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

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

ACTELION

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Tracleer® BOSENTAN TABLETS

WARNING: RISKS OF LIVER INJURY and TERATOGENICITY

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

Liver Injury

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

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

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

Teratogenicity

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

INDICATIONS AND USAGE

Pulmonary Arterial Hypertension

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

Considerations for use

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

DOSAGE AND ADMINISTRATION

Recommended Dosing

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

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

Required Monitoring

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

Dosage Adjustments for Patients Developing Aminotransferase Elevations

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

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

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

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

Use in Females of Childbearing Potential

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

Use in Patients with Pre-existing Hepatic Impairment

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

Patients with Low Body Weight

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

Use with Ritonavir

Co-administration of Tracleer in Patients on Ritonavir

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

Co-administration of Ritonavir in Patients on Tracleer

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

Treatment Discontinuation

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

DOSAGE FORMS AND STRENGTHS

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

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

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

CONTRAINDICATIONS

Pregnancy Category X *[see BOXED WARNING]*

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

Use with Cyclosporine A

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

Use with Glyburide

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

Hypersensitivity

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

WARNINGS AND PRECAUTIONS

Potential Liver Injury

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

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

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

Patients with Pre-existing Hepatic Impairment

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

Fluid Retention

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

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

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

Decreased Sperm Counts

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

Decreases in Hemoglobin and Hematocrit

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

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

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

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

Pulmonary Veno-Occlusive Disease

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

Prescribing and Distribution Program for Tracleer

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

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

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

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

ADVERSE REACTIONS

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

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

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

Clinical Studies Experience

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

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

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

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

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

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

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

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

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

Postmarketing Experience

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

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

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

DRUG INTERACTIONS

Cytochrome P450 Summary

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

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

Hormonal Contraceptives

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

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

Cyclosporine A

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

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

Glyburide

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

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

Lopinavir/Ritonavir or Other Ritonavir-containing HIV Regimens

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

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

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

Simvastatin and Other Statins

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

Rifampin

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

Tacrolimus

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

Ketoconazole

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

Warfarin

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

Digoxin, Nimodipine, and Losartan

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

Sildenafil

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

Iloprost

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category X: Teratogenic Effects [see Contraindications]

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

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

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

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

Nursing mothers

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

Pediatric use

Safety and efficacy in pediatric patients have not been established.

Geriatric use

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

Hepatic Impairment

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

Renal Impairment

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

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carinogenesis and Mutagenesis

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

Reproductive and Developmental Toxicology

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

Impairment of Fertility/Testicular Function

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

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

PATIENT COUNSELING INFORMATION

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

Important Information

- Monthly monitoring of serum aminotransferases

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

- Pregnancy testing and avoidance of pregnancy

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

- Drug Interactions

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

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

ACTELION

PRESIDENT'S REPORT

ACCP Activities Abound

Do you want to know what is new at the ACCP? We have just completed an very productive meeting of the Board of Regents of the ACCP and Board of Trustees of The CHEST Foundation. So much is happening that I thought it would be timely to provide an update on major areas of progress and accomplishments at the College.

BY DR. DAVID D. GUTTERMAN, FCCP

1. **Global Initiatives.** One of the most exciting developments at the ACCP is the recruitment of **Dr. Mark Rosen, FCCP,** as Director, Global Education and Strategic Development. In this position, which begins July 1, 2011, Dr. Rosen will direct the College's efforts in international education and staff the newly approved **Global Education and Development Committee** that will replace the International Strategic Committee and oversee the ACCP international strategic plan. The newly constituted committee will work with ACCP leadership to develop international programs, evaluate proposals for international projects, and assist in the session development of Global Day at the annual CHEST meeting.
2. **Membership Review.** After an inquiry from an interested medical student, I formed a Membership Task Force, chaired by **Dr. Henri Colt, FCCP,** to review our membership categories and make recommendations for simplification and inclusiveness. Although the task force has not completed its analysis, one recommendation passed by the Board of Regents at the June meeting was to develop a category for student membership in the ACCP. Details and implementation plans will be provided soon. The task force is also looking at all membership categories, FCCP requirements, and all dues structures. Recommendations will be designed with input from member surveys and leadership interviews.
3. **Strategic Plan**. Important advancements were incorporated into the **ACCP Strategic Plan for 2011-2012**. Based on last year's plan, and with input from a Board strategic planning session earlier in the year, a revised Strategic Plan has been developed. This plan reflects our updated Vision statement that incorporates diversity and equity and lists six metric-driven goals that integrate all aspects of the ACCP. Kudos to **Nancy MacRae - Senior Vice President for Governance and Operations, and Stacy Seiden - Special Projects Manager**, for masterfully organizing this revision that was passed unanimously by the Board of Regents.
4. **Finances.** Our financial report, provided by **Dr. Ed Diamond, FCCP,** continues to reflect a positive bottom line as we expand our education efforts into new markets, grow our membership, and recruit new programs. This year, our investment income has been comparable to market increases, and revenues have exceeded expenses by more than $1 million (>$2 million if you include investment income). It is reassuring to know that in these fiscally uncertain times, the College is in an excellent financial position.
5. **NetWork Organization.** Last year, an ACCP task force was implemented to review and recommend enhancements to our NetWork structure, with the goal of improving efficiency and broadening participation of ACCP members. A brilliantly integrated NetWork structure was proposed in March, with a staged implementation plan. Providing momentum, three initial recommendations were approved by the Board of Regents at the June meeting. First, a motion was passed to revise the Council of NetWorks into a more nimble group of 23 members, down from the 51 current members. In addition, a new representative NetWork Executive Committee (11 members) was established to conduct the majority of business of the Council of NetWorks, including approval of NetWork projects. These changes are designed to prepare for the eventual launch of eCommunities and integration of NetWork activities throughout the College. The final action taken was the transition of the Affiliate NetWork to a Training and Transitions Committee to more effectively support the needs of subspecialty trainees and their advancement to regular membership in the College.
6. **Diversity and Equity.** The Board took action on a recommendation of the ACCP Presidential Task Force on Diversity established last fall. Chaired by **Dr. C. Sola Olopade, MPH, FCCP,** and **Dr. Marilyn Foreman, MS, FCCP**, the task force presented a comprehensive forward-thinking report for incorporating diversity and equity within the College and its projects. The Board of Regents approved the recommendation that a *Diversity Committee* be established to implement the task force recommendations—stay tuned for more on this landmark development.
7. **OneBreath™.** You do not need to hold your breath any longer! The OneBreath campaign of The CHEST Foundation is about to move into high gear. The College is in the midst of hiring a dynamic leader for the OneBreath campaign to coordinate efforts for The Foundation and across the College.
8. **Leadership Development.** An integrated program for leadership development in the College is being spearheaded by **Dr. Suhail Raoof, FCCP, President-Elect of the College**. This plan will assist those interested in moving through leadership tracks in the College, both domestically and internationally, and will serve to support and educate those already involved in leadership positions. As NetWorks restructure to involve more members, and as our international efforts grow, this program will become increasingly more important. As part of the leadership development plans, the Board is undergoing periodic self-assessment to help identify opportunities for leadership education. The first of these assessments was conducted this spring.

I hope you are as excited about all these activities as I am! ■

ACCP Delegation Visits China

BY DR. DAVID D. GUTTERMAN, FCCP; AND DR. DARCY MARCINIUK, FCCP

An ACCP delegation, led by President Dr. David Gutterman, embarked on a professional learning exchange with colleagues from China on April 8, 2011, visiting Beijing, Shanghai, and Hangzhou. Joining Dr. Gutterman was ACCP President-Designate Dr. Darcy Marciniuk, and ACCP members, Drs.Robert Baughman, FCCP; Kevin Brown, FCCP; Teofilo Lee-Chiong, FCCP; Bruce Davidson, FCCP; Renli Qiao, FCCP; Curtis Sessler, FCCP; and Momen Wahidi, FCCP. Marisa McCarren accompanied the team in her role as ACCP Global Education and Development Manager.

Our ACCP team, the largest ever to visit China, met with International Regent Dr. Chunxue Bai, FCCP, as well as ACCP Governors Dr. BoQiang Cai, FCCP, and Dr. Guangfa Wang, FCCP. We also met with Dr. Chen Wang, FCCP, President of the Chinese Thoracic Society, and Dr. Yang Ke, Vice-President of Peking University. We were most honored to meet with Dr. Qian Liu, Deputy Minister of Health in China, for what was a very productive gathering, addressing a number of important issues affecting respiratory health.

Our fellow ACCP delegation members shared the podium with distinguished Chinese lecturers at a number of outstanding and well-attended conferences, including the ACCP and Peking Union Medical College conference in Beijing; the ACCP and Shanghai Respiratory Society conference in Shanghai; and the Chinese Medical Association Respiratory Branch and *Chinese Journal of Respiratory Diseases and Tuberculosis* conference held in Hangzhou. We were also privileged to accept an official invitation to visit Peking University. In addition, we had the opportunity to meet with Mark Danderson, Vice-President of the *China Medical Tribune* (CMT), the broadest medical news publisher in China. The CMT publishes a monthly abstract selection from the journal *CHEST,* translated into Chinese. We were also honored to speak at Anzhem Hospital for a conference under the leadership of Dr. Shuang Liu and the Department of Pulmonary Diseases and Respiratory Critical Care Medicine; and, before

COURTESY ACCP

Pictured above are (from left to right) Dr. Darcy Marciniuk, FCCP; Dr. Chen Wang, FCCP; Dr. David D. Gutterman, FCCP; Dr. Luo Wei Ci; and Dr. Qian Liu.

Continued on following page

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leaving Beijing, we had an exploratory meeting with leadership of the Chinese Medical Association.

Lectures presented during the conferences covered a variety of topics directly relevant to the practicing clinician. These included the following: Cardiovascular Complications of Sleep Apnea (Gutterman); COPD and Pulmonary Hypertension (Qiao); COPD Exacerbations and Noninvasive Ventilation (Marciniuk); Non-ventilatory Management of ARDS (Sessler); Comprehensive Management of Idiopathic Pulmonary Fibrosis (Baughman); Connective Tissue Diseases and the Lung (Brown); Pulmonary Arterial Hypertension Associated With Connective Tissue Diseases (Brown); Advanced Diagnostic Pulmonary Procedures (Wahidi); Obstructive Sleep Apnea: A Systemic Disorder (Lee Chiong); Advances in the Diagnosis and Management of Malignant Pleural Effusions (Wahidi); Interesting Sarcoidosis Cases (Baughman); Venous Thromboembolism: New Opportunities (Davidson); Advanced Diagnostic Pulmonary Procedure Cases (Wahidi); Fellowship Training in Pulmonology (Qiao); Diffuse Interstitial Lung Disease-Idiopathic Interstitial Pneumonias (Brown); Diagnosis, Treatment, and Etiology of Sarcoidosis (Baughman); COPD State of the Art 2011 (Marciniuk); Nonrespiratory Sleep Disorders (Lee Chiong); and Lung Cancer in the Patient With COPD (Davidson).

We also contributed a number of presentations outlining the diverse activities, products, and services provided by the ACCP. We discussed the many practical benefits of ACCP membership, now realized by more than 18,000 worldwide members. In recognition of the rapidly growing ACCP membership in China, it was announced there will be an additional four ACCP Governors appointed in China. These appointments should be completed in time for CHEST 2011, which will be held in Honolulu, Hawaii, October 22-26, 2011, and will facilitate even greater representation and closer relations with our Chinese membership. These realities highlight the rapidly increasing international membership and international relationships in the ACCP.

One highlight of the trip included a visit to Zhongshan Hospital, Fudan University, where we were witness to innovative developments and advances in respiratory medicine by our Chinese colleagues. Throughout our travels and visits, it was repeatedly evident that the goals of the ACCP and its members are equally shared by our many colleagues from China. Other highlights of the trip included visits to the Summer Palace, the Great Wall, the Ming Tombs, the Imperial Palace, the Temple of Heaven, and the Olympic Village in Beijing. Shanghai was a very exciting and vibrant city, successfully balancing the past with the present, with so many famous landmarks and venues. The beauty and peacefulness of the Xi Lake in Hangzhou was extra special. Our entire group was genuinely impressed and appreciative of the hospitality, the openness, and the kindness exhibited by the Chinese hosts. We were also grateful for the practical expertise (and translation) provided by Renli, and the professional guidance throughout our travels by Marisa.

The visit to China was both rewarding and productive. While the ACCP recognizes that providing the very best educational offerings to our members and their patients knows no borders, we also recognize the sometimes differing needs of our international colleagues. We are working hard to meet these needs. With over 30% of the CHEST annual meeting attendance coming from outside North America in 2010, and with our international membership growing, the ACCP is devoting more resources and effort to support global health efforts.

The ACCP also realizes that in order to best serve all of our members, including those abroad, we must listen to and learn from others. By working together, we believe we will provide greater benefit for our patients. On behalf of the entire ACCP team, we very much appreciated the opportunity to have participated in this rewarding educational opportunity with our colleagues in China.

The ACCP will work hard to ensure that our colleagues in China will continue to benefit from their close association with the ACCP. ■

NETWORKS
Diversity Education, Global Warming, Home MV Online Resources

Cultural Diversity in Medicine

CHEST 2011 Meeting Highlights

The US Census Bureau (2010) reports just over one-third of the US population as a minority, with a 29% overall increase of minorities in the US population over the past decade.

The American Lung Association report, *State of Lung Disease in Diverse Communities: 2010* (www.lungusa.org/assets/documents/publications/lung-disease-data/solddc_2010.pdf), reveals improvements in lung diseases have not been equally distributed by income, race, ethnicity, education, and geography. Some minority groups may be at increased risk of lung disease because of genetic predisposition. The 2010 report finds that diverse communities experience a host of societal problems at a higher rate than Caucasians. Poverty contributes to substandard living conditions and exposures that increase risk of lung disease. Poor access to and utilization of health care not only stems from poverty but from poor provider-patient communication and health literacy.

These statistics confirm the relevance of cultural diversity education and the implementation of this knowledge alongside clinical practice. Understanding the values and traditions of individuals and the diversity that various cultures embrace and/or face is crucial for successful, holistic care of patients and family members and should be considered standard of care.

With this in mind, be sure to attend the following sessions at CHEST 2011, developed by the Cultural Diversity in Medicine NetWork:

- NetWork Feature Presentation and Open Meeting: "End of Life Discussions With Minority and Non-English-Speaking Populations," presented by Dr. Shankar Sundaram, NetWork member.
- NetWork Luncheon: "Diversity and Inclusion: A Health-care Imperative," presented by Dr. Anthony Carter, Vice President of Global Diversity & Inclusion, and Chief Diversity Officer for Johnson & Johnson.
- Economic Incentives to Reduce Health-care Disparities: Pro/Con Debate
- Census 2010: Lung Disease Management in a Changing Minority and Immigrant Population

Dr. Samir Fahmy, FCCP
Steering Committee Member

Disaster Response

Global Warming: Where Do We Stand?

While the debate on whether global warming (GW) really exists, and if so, will it have human or environmental impact rages on, our organization needs to become proactive in both our stance on the issue and on what we can do for health mitigation. Proponents of GW eschew a cataclysmic future. Others look at it as a natural cycle of nature, while unbelievers espouse that GW does not exist and is certainly not anthropomorphic in nature.

In the midst of the rhetoric and the hype, lines have been drawn. I would suggest that data (and conventional wisdom) do seem to suggest that we are undergoing a climate change. However, debate on the human health effects continues. Regardless of the true outcomes on our environment and human health (animal/plant effects will be significant, as well), a proactive dialogue needs to ensue on strategies we can field to mitigate potential ill-health.

The touted health effects appear to be twofold. First, effects of a rising world mean temperature and increase in solar radiation (ultraviolet) would include an increase in skin cancers and cataracts, and a reduction and maldistribution of world water. An increase in the distribution of endemic diseases has already been noted.

Second, important to us, is the increase in warming gases, such as water vapor, methane, and nitrous oxide, with the attendant, currently unknown, pulmonary and systemic health effects.

There are many more issues to raise and discuss, and in that vein, the Disaster Response Network would like to hear your thoughts and concerns on the issue of GW. Please send your comments to the NetWorks Department (networks@chestnet.org), and we will try to respond to all.

Dr. Dennis Amundson, FCCP
NetWork Chair

Home Care

The Home Mechanical Ventilation Online Resource Center

The Home Mechanical Ventilation Resource Center is now available on the ACCP Web site, www.chestnet.org/accp/article/home-mechanical-ventilation-resource-center. This is the culmination of several years of work by the Home Care NetWork. There are four major resource documents: Home Ventilation 101, Home Ventilator Directory, a Ventilator-Support Equipment Directory, and a series of ventilator acquisition checklists, designed to address a variety of specific patient populations and ventilation-related equipment.

Home Ventilation 101 - directed to physicians, caregivers, and patients who need a global understanding of home mechanical ventilation. The goal is for readers to understand the different methods of home ventilation and appreciate the distinction between invasive (tracheotomy) and noninvasive ventilation. In addition, the selection of and considerations for appropriate candidates for each form of ventilation are discussed.

Home Ventilator Directory - includes specifications and options for portable ventilators used in the home.

Ventilator-Support Equipment Directory - lists support equipment.

Ventilator Acquisition Checklist - provides detailed information on the necessary equipment for a variety of patients, such as those using a volume-cycled ventilator via a noninvasive interface, or a bilevel ventilator through a tracheotomy.

The Home Mechanical Ventilation Resource Center provides an unparalleled, convenient source of information on home ventilation for experienced clinicians, fellows-in-training, home care providers, patients, and caregivers.

Dr. Noah Lechtzin, FCCP
NetWork Chair

Interstitial and Diffuse Lung Disease

Update in Interstitial Lung Disease (ILD) Clinical Trials

Results of the Multicenter International Lymphangioleiomyomatosis Efficacy and Safety of Sirolimus (MILES) Trial were presented at this year's American Thoracic Society International Meeting.

The MILES trial randomized 89 patients with lymphangioleiomyomatosis (LAM) (mean FEV_1 48 ± 13.8%) to receive the mTOR inhibitor sirolimus (Rapamycin, N=46) or placebo (N=43) in a 12-month, double-blind, placebo-controlled study followed by a 12-month observation period during which no subject received study medications. The primary endpoint was the rate of change in FEV_1 (the FEV_1 slope). Secondary endpoints included change in forced vital capacity (FVC), lung volumes, and DLCO, as well as 6-min hall walk distance, serum VEGF-D levels, and quality of life measures.

Investigators found that, over 12 months, FEV_1 decreased significantly in subjects receiving placebo compared with those receiving sirolimus, in whom FEV_1 remained essentially stable. Similar findings were observed for the FVC, and subjects receiving sirolimus had a significant decrease in serum VEGF-D levels compared with those receiving placebo. There were no significant differences between groups with respect to other secondary endpoints. Over the course of the subsequent 12-month observation period, FEV_1 declined by similar amounts in both groups, suggesting that withdrawal of sirolimus did not enhance FEV_1 decline. Serum VEGF-D levels remained lower during the observation period in subjects receiving sirolimus. There were significantly more adverse events in the sirolimus group, with serious adverse cardiac events (pericarditis, atrial dysrhythmia, and tachycardia) only occurring in the sirolimus group.

The authors conclude that sirolimus therapy may be beneficial for select patients with moderately severe LAM-related lung disease, although future studies are needed to evaluate optimal dosing and duration of therapy. Study results have been published in the *New England Journal of Medicine* (McCormack et al. 2011;364[17]:1595).

Dr. Eric S. White, FCCP
Steering Committee Member

Family Time. Hawaiian Style.

CHEST 2011 offers more than essential updates on patient care and practice management strategies. It offers an opportunity for family time you will never forget. The CHEST 2011 program has been designed with Hawaii in mind. Education sessions will end by mid to late afternoon, so you and your family will have time to make memories. To get you started, your ACCP colleagues who live in Hawaii have shared their favorite family activities and hikes. As you're making plans for Hawaii, be sure to check out these suggestions.

CHEST 2011

October 22 - 26
Honolulu, Hawaii

Favorite Family Activities

- Beach, beach, and more beach!
- Hanging out at Hilton Hawaiian Village
- Picnicking at Ala Moana, Koolina, or Waikiki
- Beaches (stay for the sunset)
- Body surfing and beach time at Bellows or Sherwoods Beaches
- Eating out at Hakone Restaurant, Hawaii Prince Hotel
- Taking the kids for shave ice on a hot day
- Taking a catamaran cruise at sunset

Favorite Places to Hike

All these hikes, except Kilauea, are on Oahu, which is the island where CHEST 2011 will be held.

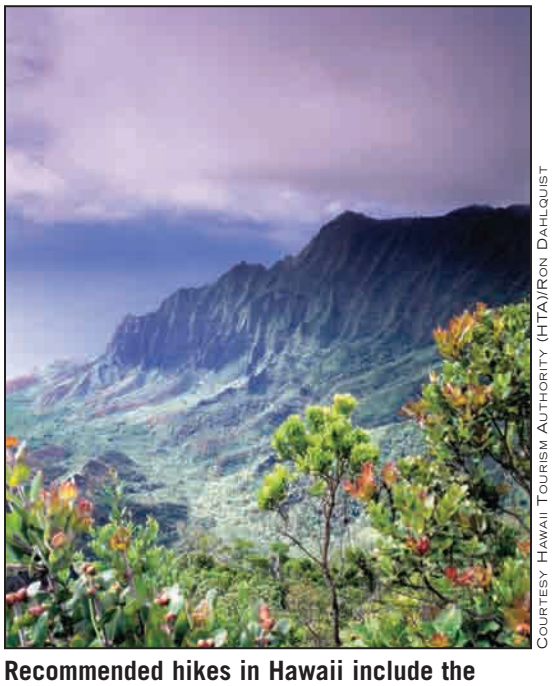
- Diamond Head
- Koko Head Stairs
- Kuliouou Trail
- Kilauea (located on the Big Island)
- Monoa Falls

Dr. Warren Tamamoto, FCCP, says, "There are many great hiking spots. Be sure to get a reliable guide book and stay on the trails. The hike to the top of Diamond Head Crater is a relatively easy hike, with great views of the entire southwest Oahu coastline. Highly recommended!"

Dr. Christine Fukui offers additional good advice, "Exercise care with any of the hikes in the mountains. The mountains are not tall but can be dangerous due to drop offs, wet trails, and vegetation."

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

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



Courtesy Hawaii Tourism Authority (HTA)/Ron Dahlquist

Recommended hikes in Hawaii include the Koko Head Stairs and the Kuliouou Trail.

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PRACTICE MANAGEMENT UPDATE

There's an App for That: mHealth Takes Center Stage

BY RICK KROHN, MA, MAS

That it will ever come into general use, notwithstanding its value, is extremely doubtful because its beneficial application requires much time and gives a good bit of trouble, both to the patient and the practitioner. That's an appraisal of the stethoscope from the London Times in 1834, but it could just as easily refer to our contemporary experience in attempting to introduce useful health technologies like CPOE and EMR – an experience characterized by skepticism and tepid growth.

There is, however, one technology that has bucked the trend and taken root in healthcare with astonishing speed – mobile health. Mobile devices and applications have come a long way from the "bag" phone and walkie-talkie-sized devices of the mid 90's, and are now a truly practical – and ubiquitous feature of daily life.

The healthcare industry has taken note, and is deploying mobile networks and point of care devices to support the electronic exchange of medical information. "mHealth "offers an elegant solution to a chronic problem facing clinicians: accessing the right information where and when it is needed within highly fluid, distributed organizations.

Healthcare is fertile ground for mHealth, because it removes geography and time as barriers to care by establishing connectivity with remote locations and remote workers, and by creating new points of contact with patients. It establishes effective new treatment modalities—telehealth, remote patient monitoring, self care, and home health among them.

But beyond clinical connectivity, mHealth holds the promise of quality improvement, cost reduction, wholesale gains in population health, access to care, and a better allocation of health delivery resources. It's becoming imbedded into healthcare operations – mHealth is integral to a number of care delivery strategies including the medical home, the health information exchange, the care team, and the personalization of healthcare.

The underlying infrastructure of mHealth is growing at breakneck speed. Consider the following:

- Healthcare telecom spending will increase 44 percent within three years from $8.6 billion and wireless will account for 2/3 of that increase.[1]
- 4G wireless technology will incorporate increased data security-allowing large high resolution imaging, live surgeries, and ever-expanding communities of care.[2]
- The US market for wireless home-based healthcare applications and services will grow at a 5 year cumulative annual rate of over 180 percent ($4.4 billion) in 2013.[3]
- 95 percent of healthcare enterprises rely on smart phones.[4]
- The FCC's National Broadband Plan aims to bring 100 megabit connections to 100 million Americans (by 2020). The Plan has a specific focus on healthcare connectivity, particularly in rural areas.[5]

So why is mHealth surging while other clinical technologies continue to sputter? There are a number of confluent factors.

Low barrier to entry. The infrastructure of mHealth (broadband and wireless networks) is either already in place or quick to implement. Add to this the fact that, as Epocrates CTO Bob Quinn observes, "The long-awaited mobile convergence is finally here." More than 64% of physicians in the U.S. are using a PDA or smartphone, in part because the convenience and power of smartphones today provide physicians one device for personal email or multimedia, as well as clinical point-of-care software." This is mobile convergence with a vengeance, a seamless intersection of personal and professional uses during a physician's workday. To meet this demand devices like iPhone® are being architected to meet the HIPAA benchmarks for privacy and security.

Consumerism. Consumers are becoming increasingly accountable for their health, and are embracing health technologies that are convenient, effective, and offer an alternate and affordable healthcare settings and solutions.

Healthcare reform. mHealth mitigates the crippling cash drain in healthcare caused by a lack of care coordination, unnecessary utilization, spiraling insurance premiums and uneven quality by recalibrating the process of care delivery – getting caregivers connected and coordinated, rewarding outcomes, getting patients invested in their own health, and shifting facility based episodes of treatment to a holistic, patient-centric model of health maintenance.

Value-based purchasing and reimbursement. The seismic shift from volume to value will trigger a heightened focus on payor/provider/patient communications.

Innovative applications. Mobile technologies like GPS, RF, cellular, and evolving wireless standards like 4G and Zigbee are creating an explosion of mHealth solutions and devices. The result is a breathtaking assortment of apps and devices tailored to the healthcare market. Some are truly innovative, like home monitors to manage COPD, CHF, hypertension, and diabetes, two way provider/patient video and voice messaging, even mental health brainware monitoring.

There's a lot going for mHealth but like every other health technology, it faces speed bumps along the road to industry saturation. There are the standard business issues – demonstrated cost savings, reimbursable services, and a common business model remain unclear.

"Every time we add technology to affect professional communications, the cost goes up" says Kaveh Safvi, Vice President of Cisco's Internet Business Solutions Group Global Healthcare Practice. He adds "there's a trust/value calculus facing the mHealth customer. It's this – is there enough value for the provider and the patient in sharing clinical information via mobile networks, in terms of convenience and utility, to trump industry apprehension about privacy and security?"

From the technology perspective, there are issues about a lack of uniform standards, of serious concerns regarding privacy and security within public networks, of capacity, latency and reliability. And then there is adoption.

mHealth will require clinicians to adopt a vastly different mode of clinical activity, which includes communicating with and treating patients remotely, acting as members of multiple care teams, and intervening proactively in the collective health of their patients. Finally, the physical attributes of mobile devices limit their functionality – form factor reduces the PDA and smart-phone to a text-only device, and mobile devices cannot be de-featured to attract a mobile-Lite customer. Additionally, hand-held devices along with their resident data are more susceptible to loss or theft.

Those limitations are unlikely to suppress the growth of mHealth, however. "Mid-size mobile devices will resolve form factor limitations, and cloud applications will address the PDA security issue," says Glenn Keet, President of Axolotl. mHealth may even act as a catalyst of EMR adoption.

"If an EMR offers 100 features, and doctors regularly use perhaps 20 of those – such as results review, medications, problems, allergies and alerts, and those select features can be delivered effectively to a mobile device – the device will rapidly gain adoption" suggests Todd Fisher, President, MobileMD.

As an industry vertical, mHealth is far from maturity, but there are clues to its possible trajectory. Joe Caper, Vice President Global Customer Solutions at MedPlus says "if it fits in the lab coat pocket, it's more likely to be used."

MEDecision President Scott Storrer notes "in the US the payor market is showing interest, but although cost savings have been demonstrated in lower level pilots and demonstration projects, mHealth hasn't rung the bell in the C suite." In the next term, the spike in mobile convergence may occur at the grass roots level, among providers and consumers. Through social media and viral marketing, mHealth apps and devices are finding their way directly to the clinician and the patient – and that market dynamic may soon propel mHealth to the "must have now" class of clinical technologies. JHIM ■

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2. Dan Hess Sprint CEO, Keynote Address HIMSS10
3. Park Associates, 2009.
4. Managing and Securing Mobile Healthcare Data and Devices. Forrester Research, March 2010.
5. http://www.broadband.gov/

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Product of the Month

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Watch for an opportunity to earn CME with PCCSU lessons offered in the ACCP Self-study Clinical Library at CHEST 2011 in Honolulu, Hawaii.

PCCSU Lessons for July

PCCSU
PULMONARY, CRITICAL CARE, SLEEP UPDATE

- **Upper Airway Resistance Syndrome.** *By Dr. Olukayode A. Ogunrinde; Dr. Herbert J. Yue; and Dr. Christian Guilleminault, BiolD*
- **Sarcoidosis: New Concepts in Cause and Treatment.** *By Dr. Antonio D. Gomez; and Dr. Laura L. Koth*

SLEEP STRATEGIES

The Society of Anesthesia and Sleep Medicine: A New Collaboration

While mankind has always shown interest in sleep and dreaming, it has been the scientific study of sleep over the last 3 centuries that has established the roots of modern sleep medicine. From the first descriptions of circadian rhythms in the late 1700s, to the discovery of REM sleep in the 1950s, to the establishment of the first sleep disorders clinics to manage patients with narcolepsy and insomnia in the 1970s, sleep medicine has evolved into a multidisciplinary field responsible for the evaluation and management of over 90 recognized sleep disorders. Given the breadth of pathophysiology that has been associated with sleep, practitioners of sleep medicine come from a variety of backgrounds but share a common interest in sleep and sleep disorders. The field of anesthesiology is now added to the growing list of specialties with a vested interest in sleep medicine.

As early as 1985, descriptions of significant episodic hypoxia during sleep associated with the use of IV narcotics following major surgery under general anesthesia were reported (Catley et al. *Anesthesiology*. 1985;63[1]:20). Subsequent studies by anesthesiologists examined the effects of general anesthesia on airway collapse (Nandi et al. *Br J Anaesth*. 1991;66[2]:153) and sleep architecture (Knill et al. *Anesthesiology*. 1990:73[1];52), offering potential explanations for the intermittent hypoxia found postoperatively during sleep. These reports prompted others to take a closer look at patients with obstructive sleep apnea (OSA) undergoing general anesthesia and postoperative analgesia. Case series emerged suggesting patients with OSA were at risk for a variety of adverse postoperative outcomes (Rennotte et al. *Chest*. 1995;107[2]:367; Ostermeier et al. *Anesth Analg*. 1997;85[2]:452), but this was not confirmed until well-controlled studies were performed (Mooe et al. *Coron Artery Dis*. 1996;7[6]:475; Gupta et al. *Mayo Clin Proc*. 2001;76[9]:897). In addition to postoperative concerns, data began to emerge regarding intraoperative management problems in patients with OSA (Siyam and Benhamo. *Anesth Analg*. 2002;95[4]:1098). As a result of these findings, both the American Academy of Sleep Medicine and the American Society of Anesthesiology (ASA) published reviews on the topic of the perioperative management of patients with OSA, recognizing that much is unknown (Meoli et al. *Sleep*. 2003;26[8]:1060; Gross et al. *Anesthesiology*. 2006;104[5]:1081). The issues related to surgery and sleep apnea are quite broad, ranging from preoperative screening to intraoperative management to postoperative monitoring and management. These were recently reviewed in the Sleep Strategies section in *CHEST Physician* last November (Auckley and Bolden. *CHEST Physician*. 2010; 5[11]:13), as well as in a recent extensive review article (Seet and Chung. *Can J Anaesth*. 2010; 57[9]:849).

Due to the complex and interdisciplinary nature of OSA in the perioperative setting, it is clear that collaborations are required in order to make significant progress in education and knowledge about this issue. As such, a group of anesthesiologists, sleep physicians, surgeons, emergency physicians, and basic scientists with an interest in sleep and anesthesia organized a symposium on this topic prior to the annual meeting of the American Society of Anesthesiologists (ASA) in October 2010. Out of this symposium emerged the formation of the "Society of Anesthesia and Sleep Medicine (SASM)," whose purpose is to promote discussion, education, development of clinical standards, and research related to issues common to anesthesia and sleep.

The SASM objectives are to:

- Promote the cross-fertilization of ideas between anesthesiology and sleep medicine.
- Stimulate research aiming to better understand the similarities and differences between sleep and anesthesia, as well as their impact on physiologic control systems.
- Encourage clinical and epidemiologic studies determining the associations between sleep-disordered breathing and perioperative risk.
- Examine methods of minimizing perioperative risk of upper airway obstruction or ventilatory insufficiency in predisposed individuals.
- Explore the use of noninvasive positive airway pressure therapies to prevent and treat perioperative upper airway obstruction or hypoventilation.

As stated in the first two objectives, the intersection of anesthesiology and sleep medicine is much broader than just sleep-disordered breathing in the perioperative setting. Fostering collaborations between these two disciplines should give rise to a better understanding of the physiology and pathophysiology of the sleep/wake states, the impact of medications and medical interventions on these states, and potentially new and safer forms of anesthesia, as well as novel therapies for sleep disorders. Recognizing the extensive overlap in the basic science and anatomic, physiologic, and clinical realms of anesthesiology and sleep medicine, the America Board of Medical Specialties has recently announced the availability of subspecialty certification in Sleep Medicine to anesthesiologists. This requires that the anesthesiologist be board-certified in anesthesiology and either complete a 1-year ACGME-certified sleep fellowship training program, or have the equivalence of 12 months of practice experience in sleep medicine (to include a minimum of 400 patient evaluations, 200 polysomnogram interpretations, and 25 multiple sleep latency interpretations). More details regarding the pathways for anesthesiologists to achieve sleep medicine board certification can be found at the American Board of Anesthesiology Web site (www.theaba.org).

The SASM has established a steering committee, and the society is now incorporated and taking applications for membership. Interested individuals can contact Dr. Norman Bolden at nbolden@metrohealth.org. For further information, visit the SASM Web site (www.anesthesiaandsleep.org).

The SASM is also organizing its first annual conference to be held on October 14, 2011, just prior to the start of the annual ASA meeting in Chicago. The objectives of the inaugural meeting are to provide a forum for discussions regarding the common areas of OSA, sleep, and anesthesia, and to promote excellence in medical care, research, and education in sleep medicine, anesthesiology, and perioperative medicine. The meeting will include the election of board members, presentations of basic science and clinical research abstracts (deadline was June 30, 2011), and three sessions with invited speakers. The sessions scheduled for this inaugural meeting include:

- Session 1 - "Unconsciousness and the Upper Airway - Shared Considerations for Anesthesiology and Sleep Medicine"
- Session 2 - "Obstructive Sleep Apnea - A Perioperative Challenge"
- Session 3 - "Sleep, Anesthesia, and Ventilatory Control"

This is an exciting time for a new partnership between anesthesiology and sleep medicine. A companion announcement of this collaboration is currently being published in the anesthesia literature (Chung et al. *Anesthesiology*. 2011;114[6]:1261), and all those with an interest in this field are encouraged to become involved with the new society.

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This Month in *CHEST:* Editor's Picks

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

Point/Counterpoint Editorials

- **Point: Is Low Tidal Volume Mechanical Ventilation Preferred for All Patients on Ventilation? Yes.** *By Dr. R. D. Hubmayr, FCCP.*
- **Counterpoint: Is Low Tidal Volume Mechanical Ventilation Preferred for All Patients on Ventilation? No.** *By Dr. Luciano Gattinoni.*

Original Research

- **Delay in Recognition of Pulmonary Arterial Hypertension: Factors Identified From the REVEAL Registry.** *By Dr. L. M. Brown et al.*
- **The Effect of Catheter to Vein Ratio on Blood Flow Rates in a Simulated Model of Peripherally Inserted Central Venous Catheters.** *By Dr. T. P. Nifong; and Dr. T. J. McDevitt.*

Special Features

- **Long-term Course and Prognosis of Idiopathic Pulmonary Fibrosis in the New Millennium.** *By Dr. S. D. Nathan, FCCP, et al.*
- **The Research Agenda in ICU Telemedicine: A Statement From the Critical Care Societies Collaborative.** *By Dr. J. M. Kahn et al.*

FROM THE DESK OF THE PRACTICE MANAGEMENT COMMITTEE

New Subcommittee to Support EHR/Health IT Integration

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

Practice Management EHR/Health IT Subcommittee Description

The ACCP has formed an Electronic Health Record (EHR)/Health Information Technology (IT) Subcommittee of its Practice Management Committee. The impetus to form this group was in response to the growing need to provide physicians and allied health professionals with technology-based resources, tools, and education for them to provide the highest level of patient care and be able to respond to external forces impacting their practice.

Charges to the Subcommittee

- Regularly monitor and provide comment, when appropriate, on the health IT environment (federal, CMS regulations, regional extension centers, vendor certification, etc).
- Inform ACCP and its members of relevant opportunities and changes that can and will affect ACCP members and their practices.
- Initiate the development of resources that integrate ACCP evidence-based guideline (EBG) recommendations and quality indicators into EHR clinical management systems.
- Respond to and provide expertise when ACCP members have questions or concerns regarding EHR/health IT.
- Provide resources to assist physicians in understanding the American Recovery and Reinvestment Act (ARRA) incentive program, as it relates to EHR adoption and "meaningful use."
- Proactively collaborate with outside professional organizations and other specialty societies (ie, HIMSS, ACP, KLAS) to secure educational opportunities and resources for EHR/health IT.
- Facilitate and lead educational initiatives regarding EHR/health IT.
- Collaborate with the ACCP Quality Improvement Committee and its AQuIRE Subcommittee to identify ways to efficiently collect practice data.
- Identify opportunities to integrate targeted medical education opportunities into EHR/health IT clinical management systems.

Subcommittee Composition and Appointment

When fully constituted, the subcommittee shall have a minimum of seven members. Full voting members of the subcommittee must join or already be members of the ACCP.

- *Chair:* In addition to the usual duties of the Chair, the Chair of this subcommittee will also report, on a regular basis, to the ACCP Practice Management Committee and, when appropriate, to other standing committees of the ACCP. The Chair shall be appointed by the Practice Management Committee. The term of the Chair shall last 2 years.
- *Vice-Chair:* Shall assist the Chair. In the absence of the Chair, shall conduct meetings and represent the ACCP at external meetings. Shall be appointed by the Practice Management Committee. The term of Vice-Chair shall last 2 years. At termination of the Chair's term, the Vice-Chair shall assume the position of Chair, pending approval of the President-Elect of the College.
- *Members:* Shall serve a 1-year term with eligibility for up to 3 reappointments. Member terms should be staggered, if possible, to provide continuity. Members shall represent the following ACCP committees and report back to their respective Committees when appropriate:
  - Health and Science Policy
  - Quality Improvement Committee/AQuIRE
  - Education Committee
  - Two ACCP members, 5 years in practice, with expertise in health IT preferred

  HIMSS Liaisons (Stephanie Serra, CAE; and Mary Griskewicz, MS)
  AMA Liaison (Robert Herling)
  ACCP Staff Liaison (Marla Brichta) ■

AMA Delegates Affirm Support of Individual Mandate

BY ALICIA AULT

Elsevier Global Medical News

CHICAGO – The American Medical Association's House of Delegates voted to support the premise that all Americans should be required to buy health insurance if they can afford to do so.

The so-called individual mandate is an essential element of the Affordable Care Act, but the AMA itself has had a long-standing policy backing the purchase of insurance. On June 20, the House of Delegates voted 326-165 in favor of keeping the policy adopted in 2010 that more formally backed the individual mandate. The vote was a resounding rejection of an effort by a vocal minority to overturn that policy.

A resolution had been offered by the American Academy of Facial Plastic and Reconstructive Surgery, the American Association of Neurological Surgeons, the American Society of General Surgeons, and state delegations from Kansas, Arkansas, the District of Columbia, Florida, Georgia, and Oklahoma. They sought a new policy stating that the AMA believed that health insurance purchase should be an individual's responsibility, but not a requirement.

Counter-resolutions were offered by delegates led by the American Academy of Family Physicians and the American College of Physicians.

Passions ran high on both sides of the issue. Delegates who sought to overturn the AMA policy said that it took away choice and would not guarantee that more Americans would get access to health care.

After the vote, Dr. Cecil Wilson, AMA president, said that the organization was gratified that the House supported the mandate. The vote shows that "fully two-thirds of the House said today our policy is good," he said. ■

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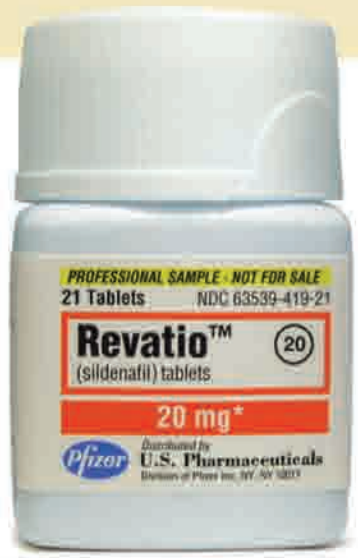

Important Safety Information

Do not use REVATIO in patients taking organic nitrates in any form, either regularly or intermittently. Consistent with its known effects on the nitric oxide/cGMP pathway, sildenafil was shown to potentiate the hypotensive effects of nitrates.

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

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

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

Co-administration of REVATIO with potent CYP3A4 inhibitors, eg, ketoconazole, itraconazole, and ritonavir, is not recommended as serum concentrations of sildenafil substantially increase. Co-administration of REVATIO with CYP3A4 inducers, including bosentan; and more potent inducers such as barbiturates, carbamazepine, phenytoin, efavirenz, nevirapine, rifampin, and rifabutin, may alter plasma levels of either or both medications. Dosage adjustment may be necessary.

Non-arteritic anterior ischemic optic neuropathy (NAION) has been reported post-marketing in temporal association with the use of PDE5 inhibitors for the treatment of erectile dysfunction, including sildenafil.

It is not possible to determine if these events are related to PDE5 inhibitors or to other factors. Physicians should advise patients to seek immediate medical attention in the event of sudden loss of vision while taking PDE5 inhibitors, including REVATIO.

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

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

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

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

Patients with the following characteristics did not participate in the preapproval clinical trial: patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months, unstable angina, hypertension (BP >170/110), retinitis pigmentosa, or patients on bosentan. The safety of REVATIO is unknown in patients with bleeding disorders and patients with active peptic ulceration. In these patients, physicians should prescribe REVATIO with caution.

The most common side effects of REVATIO (placebo-subtracted) were epistaxis (8%), headache (7%), dyspepsia (6%), flushing (6%), and insomnia (6%). Adverse events of REVATIO injection were similar to those seen with oral tablets.

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

Indication

REVATIO is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to improve exercise ability and delay clinical worsening. Delay in clinical worsening was demonstrated when REVATIO was added to background epoprostenol therapy. Studies establishing effectiveness included predominantly patients with NYHA Functional Class II-III symptoms and etiologies of primary pulmonary hypertension (71%) or pulmonary hypertension associated with connective tissue disease (25%). The efficacy of REVATIO has not been adequately evaluated in patients taking bosentan concurrently.

Revatio®
sildenafil
20 mg tablets
Start With Confidence™

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

www.REVATIO.com