The timing of possible licensure by the FDA may allow PCV13 use during the 2009/2010 flu season, said Dr. Pekka Nuorti.

Panels Move PCV13 Closer to Approval

BY MIRIAM TUCKER & HEIDI SPLETE

ATLANTA & BETHESDA, Md. — A Food and Drug Administration advisory panel has recommended approval of Pfizer’s 13-valent pneumococcal conjugate vaccine for the prevention of invasive pneumococcal disease, while a Centers for Disease Control and Prevention advisory panel outlined draft guidelines for its use.

At a meeting last month, the FDA’s Vaccines and Related Biological Products Advisory Committee said that the data support efficacy and safety of Prevnar 13, based on two phase III trials involving a total of 2,362 subjects randomized to either PCV13 or PCV7 at 2, 4, 6, and 12-15 months of age.

If it is approved for use in the United States, a 13-valent pneumococcal conjugate vaccine in children would have recommendations mirroring those already in place for the 7-valent vaccine. At an earlier meeting in October, the Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices presented draft guidelines for PCV13 use.

The 13-valent formulation is composed of capsular polysaccharides derived from the seven pneumococcal serotypes contained in the current 7-valent Prevnar (1, 4, 6B, 9V, 14, 18C, 19F), and from six additional serotypes (1, 3, 5, 6A, 7F, and 19A). It is manufactured in the same way as Prevnar, by individual conjugation of each capsular polysaccharide to diphtheria protein, said Dr. Emilio A. Emnini, Pfizer Inc.’s chief scientific officer for vaccine research.

At the time PCV7 was licensed in 2000, its seven strains accounted for 80% of invasive pneumococcal disease (IPD) in young children in North America, according to Dr. Matthew R. Moore, an epidemiologist at the CDC. Although the rates of IPD from PCV7 strains then declined by 99%, overall IPD rates began to rise more than 72 hours of mechanical ventilation, placing them at high risk for VAP. Participants were stratified on the basis of APACHE II scores, and randomized to double-blind administration of 10^9 CFU of the commercially available probiotic Lactobacillus GG (68 patients) or placebo (70 patients) every 12 hours. The first daily dose was delivered in a slurry to the oropharynx, the second in sterile water via nasogastric tube to the stomach.

The primary end point was the incidence of microbiologically confirmed VAP, which was 19% in the probiotic group and 40% in the control patients, a significant difference, according to Dr. Morrow of Creighton University, Omaha, Neb.

The rate of clinically diagnosed VAP using the American Thoracic Society guidelines for consultation codes beginning Jan. 1, 2010. • 18

Guideline Revised for Stage IV NSCLC

BY BETSY BATES

CHEST Global Medical News

The current guideline does not advocate customizing therapeutic choices based on molecular marker analysis beyond epidermal growth factor receptor (EGFR) typing as routine practice, although the authors urged future research that could “build on these discoveries” to tailor antibiotic use also lower in ICU.

Probiotic Helped Prevent VAP, C. difficile Disease

BY BRUCE JANCIN

Elsevier Global Medical News

SAN DIEGO — Giving the probiotic Lactobacillus GG to critically ill patients on mechanical ventilation resulted in markedly reduced rates of ventilator-associated pneumonia and Clostridium difficile disease in a double-blind, placebo-controlled study.

“Probiotic therapy looks like it may provide us with a novel, inexpensive, and—most importantly—nonantibiotic opportunity for prevention of VAP (ventilator-associated pneumonia). It may also provide us with an opportunity to prevent other nosocomial infections,” Dr. Lee E. Morrow, FCCP, said at CHEST 2009, the annual meeting of the American College of Chest Physicians.

He reported on 138 patients admitted to a tertiary center ICU with an anticipated hospital stay greater than or equal to 72 hours. The first daily dose was delivered in a slurry to the oropharynx, the second in sterile water via nasogastric tube to the stomach.

The primary end point was the incidence of microbiologically confirmed VAP, which was 19% in the probiotic group and 40% in the control patients, a significant difference, according to Dr. Morrow of Creighton University, Omaha, Neb.

The rate of clinically diagnosed VAP using the American Thoracic Society guidelines for consultation codes beginning Jan. 1, 2010. • 18

Guideline Revised for Stage IV NSCLC

BY BETSY BATES

Elsevier Global Medical News

The first substantial revisions in the American Society of Clinical Oncology’s clinical guideline for the treatment of stage IV non-small cell lung cancer in 6 years acknowledges the burgeoning role for individualization of therapy according to patient characteristics, including epidermal growth factor receptor mutation status and performance status rather than age.

The guideline, which compiles evidence from 190 scientific papers published since 2002, was published online Nov 16 in the Journal of Clinical Oncology (DOI: 10.1200/JCO.2009.25.5622).
Pneumococcal Vaccine Reviewed

PCV13 • from page 1

to level off in 2002, because of an increase in the incidence of IPD caused by non-PCV7 strains, particularly 19A. The additional pneumococcal strains contained in PCV13 were responsible for approximately 62% of IPD cases in children younger than 5 years of age in 2007. In the same age group, the 13 serotypes contained in PCV11 were responsible for approximately 64% of IPD cases in 2007, Dr. Moore said.

At the FDA advisory panel meeting, some members questioned whether the data support an indication for PCV11 for prevention of otitis media, which was included in Pfizer’s licensing application. The committee didn’t vote on that issue, but several members requested further otitis media data for the six additional strains contained in PCV13 that were not in the current 7-valent Prevenar.

The timing of possible licensure by the FDA may allow for use of PCV13 during the 2009/2010 flu season, noted Dr. Pekka Nuorti of the CDC, who presented the draft recommendations at ACIP’s October meeting. ACIP member Dr. Michael Marcy cited recent data from the CDC’s Morbidity and Mortality Weekly Report that showed a significant association between bacterial coinfections and severe cases of pandemic influenza A (H1N1) virus.

To expedite a potential transition to PCV13, the CDC said provisions are in place for voting on vaccine recommendations in advance of the next scheduled ACIP meeting in February, noted Dr. Melinda Wharton, acting director of the CDC’s National Center for Immunization and Respiratory Diseases.

ACIP Outlines PCV13 Guidelines

ACIP’s draft recommendations involve four groups: unvaccinated infants and children, children who have started their PCV vaccine schedules with PCV7, children who have completed the PCV7 schedule, and immunocompromised children or children with chronic illness. For unvaccinated infants and children, the recommendations are the same as those currently recommended for the use of PCV7 with PCV13 replacing PCV 7 for all doses, said Dr. Nuorti.

The draft recommendations also state that children who began their vaccination series with PCV7 can complete the series with PCV13 at any point in the schedule, and children who have completed the primary infant series with PCV7 should receive a single PCV13 dose during the second year of life to provide protection against the six additional serotypes.

In addition, the draft recommendations propose a fifth “catch-up” dose for all children aged 12 through 23 months who have received all four PCV7 doses. The catch-up dose will provide protection against the six additional serotypes, Dr. Nuorti said.

Dr. Nuorti added that the proposed recommendations for the 23-valent pneumococcal polysaccharide vaccine (PPSV23) after PCV13 for individuals aged 2 years and older with underlying medical conditions are the same as those currently recommended for the use of PPSV23 after PCV7, although no safety and immunogenicity data are yet available for this vaccine sequence.

Dr. Peter Paradiso of Wyeth Pharmaceuticals presented safety and immunogenicity data. The studies suggest that the safety profiles and immune responses were similar to those seen with PCV7. Both Pfizer and the FDA announced plans to conduct phase IV postmarketing studies of efficacy and safety.

Dr. Burt Leminick, FCPA: comments

Pneumococcal vaccination rates are often low in those patients most at risk for bacterial pneumonias. This will likely become an important quality measure in the near future. The additional option of a 13-valent vaccine broadens coverage for young children, while the 21-valent vaccine remains the standard for those older than 24 months.

Prophylaxis Shows Promise

• from page 1

College of Chest Physicians (ACCP) criteria: 75% in the probiotic group, compared with 47% with placebo. The ACCP criteria consist of a new infiltrate on chest x-ray plus any two of the following three clinical criteria: fever, purulent sputum, or leukocytosis.

The incidence of C. difficile disease as diagnosed by cytotoxic assay was 6% in the probiotic group and 19% in controls. The duration of ICU-associated diarrhea also was significantly lower in the probiotic group: a mean of 3.1 days, compared with 6.2 days in controls.

Patients who received the probiotic received antibiotics for pneumonia for a mean of 6.9 days, significantly less than the 8.6 days in controls. They received antibiotics specifically for C. difficile infection for a mean of 0.5 days, compared with 2.1 days in controls.

Hospital charges averaged $66,000 more per patient in the placebo arm because of their longer ICU and overall hospital lengths of stay, along with their additional need for expensive antibiotics. Hospital cost data weren’t available.

Several secondary end points showed intriguingly consistent trends, albeit statistically nonsignificant, in favor of probiotic prophylaxis. For example, the probiotic group had a 12% hospital mortality rate, compared with 17% in controls. They also had a 38% incidence of bacteremia and a 21% urinary tract infection rate, compared with rates of 73% and 33%, respectively, with placebo. The probiotic prophylaxis had no side effects.

Serial cultures using oral swabs and gastric aspirates showed a clear trend toward preservation of a normal mixed upper respiratory flora in the probiotic group, with less appearance of potentially pathogenic species than in controls.

The probiotic treatment concept adopted measures to modify the gut flora in order to replace harmful microbes with useful ones. The mechanisms of benefit aren’t fully understood, but immunomodulation appears to figure prominently. Ligands on the communal organisms interact with toll-like receptors on gut-associated lymphatic tissue, which releases signals promoting immune system homeostasis, Dr. Morrow explained.

Dr. Morrow disclosed that the probiotic study was funded entirely by noncommercial entities, including the National Institutes of Health and the American College of Chest Physicians.

The next logical step, he said, would be a large multicenter trial powered to show whether the favorable mortality trend observed in the Omaha trial is real.
Panel Supports Spiriva to Reduce COPD Exacerbations

Inhaled tiotropium reduced number of COPD exacerbations, FDA advisory panel finds.

BY ELIZABETH MECHCA
Elsevier Global Medical News

Silver Spring, Md. — A Food and Drug Administration advisory panel on Nov. 19 voted 11 to 1 that evidence from two studies was sufficient to support approval of a claim that treatment with the inhaled, dry-powder formulation of tiotropium reduces exacerbations in patients with chronic obstructive pulmonary disease.

At the meeting, 11 of the 12 members of the FDA’s Pulmonary-Allergy Drugs Advisory Committee also voted that data from one of those studies, the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial, “adequately addressed” the potential safety signals of an increased risk of stroke and adverse cardiovascular outcomes associated with this product that have been recently identified in pooled data and meta-analyses of tiotropium studies.

The dry-powder formulation of tiotropium is marketed as the Spiriva HandiHaler by Boehringer Ingelheim and Pfizer. This medication was approved in the United States in January 2004 for the long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disorder (COPD), including chronic bronchitis and emphysema. It is administered once daily; each inhalation contains a dose of 18 mcg of tiotropium, an anticholinergic.

The companies proposed that Spiriva be approved for reductions in COPD exacerbations based on the UPLIFT trial and the Veterans Affairs (VA) Exacerbations Trial.

In the 6-month VA study, there were approximately 1,800 patients with COPD, most of whom were men and whose mean age was 68 years. The two primary end points—the proportion of patients with COPD exacerbations and the proportion of patients hospitalized for exacerbations—were significantly lower among those on Spiriva than in those on placebo: 27.9% of those on Spiriva and 32.3% of those on placebo had at least one exacerbation during the study, a significant difference (P value 0.037), and 7% of those on Spiriva had at least one exacerbation requiring hospitalization, compared with 9.5% of those on placebo, which approached significance (P = .056).

The median time to the first exacerbation and to the first exacerbation resulting in hospitalization, secondary end points, were also reduced among those on Spiriva, compared with those on placebo.

The UPLIFT study, a multinational, randomized, placebo-controlled, 4-year study comparing tiotropium to placebo in almost 3,000 COPD patients, the number of COPD exacerbations, which was a secondary end point, was significantly lower among those on Spiriva over 4 years than among those on placebo.

Also in the UPLIFT study, the risks for stroke, cardiovascular events, and mortality were all lower among those on Spiriva when compared with placebo. The FDA’s analysis concluded that the UPLIFT data did not suggest an increased risk for stroke or cardiovascular events, and suggested that the data supported a decrease in mortality associated with treatment. (The risk of mortality was reduced by 27% in this study.)

The FDA usually follows the recommendations of its advisory panels. Another treatment approved for COPD, the combination of butacaene propionate and salmeterol inhalation powder marketed as Advair Diskus, has been approved for reducing COPD exacerbations.

INLIGHT 2 Trial: Indacaterol Topped Salmeterol for COPD

By Bruce Jancin
Elsevier Global Medical News

San Diego — The investigational ultralong-acting inhaled beta-agonist indacaterol outperformed salmeterol and placebo in a double-blind, randomized clinical trial involving 998 patients with moderate to severe COPD.

Once-daily indacaterol provided sustained bronchodilation throughout the 24-hour day at 12 and 26 weeks that was superior to that of twice-daily salmeterol (Serevent) or placebo.

Moreover, indacaterol-treated patients experienced significantly less dyspnea and need for rescue medication and greater improvement in health status than patients in the other two study arms, Dr. Oliver Kornmann reported at CHEST 2009, the annual meeting of the American College of Chest Physicians.

The results of INLIGHT 2 (Indacaterol: Efficacy Evaluation Using 150 Mgc-Doses With COPD Patients-2) indicate that indacaterol administered via single-dose dry powder inhaler will be an attractive option for maintenance therapy in patients with moderate-to-severe COPD, according to Dr. Kornmann, a pulmonologist at Mainz (Germany) University Hospital.

The primary study end point was trough forced expiratory volume in 1 second (FEV1) at week 12, which was 60 mL greater with indacaterol than salmeterol and 170 mL more than with placebo. Although these differences were statistically significant, the prespecified definition of clinical significance was a 120 mL difference, he noted.

A key secondary end point was health status as assessed using the St. George’s Respiratory Questionnaire. At week 12, the total score in the indacaterol group was improved over baseline by 6.3 points more than placebo and 2.1 points more than salmeterol, which was dosed at 50 mcg twice daily using its proprietary dry powder inhaler. A total of 38% of indacaterol-treated patients achieved at least a 4-point improvement, as did 47% on salmeterol and 39% on placebo.

The odds of achieving a clinically meaningful improvement in health status by this measure with indacaterol therapy were 1.6-fold greater than with salmeterol and 2.4-fold greater than with placebo.

The indacaterol group didn’t require rescue albuterol on 60% of days over the course of 26 weeks of follow-up. That was significantly better than the 55% rate with salmeterol and 42% with placebo.

At week 12, 60% of indacaterol-treated patients had a meaningful reduction in dyspnea, vs. 51% of the salmeterol group.

Data Watch:
Respiratory Conditions Accounted for 9% of Hospital Costs in 2007

Note: Based on data from the Healthcare Cost and Utilization Project. Source: Agency for Healthcare Research and Quality.
Roflumilast Improved Lung Function in COPD

BY BRUCE JANCIN

San Diego — Roflumilast improved lung function and prevented exacerbations in patients with COPD with chronic bronchitis and severe airflow obstruction in a 12-month randomized trial.

Results of the 1,568-patient, double-blind, placebo-controlled study known as the M2-125 trial indicate roflumilast is an important potential new advance in the treatment of a subset of patients with COPD, Dr. Andrew McVor, FCCP, declared at CHEST 2009, the annual meeting of the American College of Chest Physicians.

Roflumilast (Daxas) is an investigational selective phosphodiesterase 4 inhibitor, a drug class that represents a novel approach to the treatment of COPD. Taken orally once daily, roflumilast targets the inflammation that’s a hallmark of the disease, explained Dr. McVor of St. Joseph’s Healthcare Hamilton, Ont.

Participants in the eight-nation M2-125 trial had to have at least one documented moderate or severe COPD exacerbation during the year prior to enrollment. They were randomized to roflumilast 500 mcg once daily or placebo for 1 year, on top of background long-acting beta agonist or short-acting anticholinergic therapy at stable doses, along with short-acting beta-agonists as needed. Long-acting anticholinergics and inhaled corticosteroids were not permitted.

The rate of moderate to severe COPD exacerbations requiring systemic steroids and/or treatment in a hospital—one of two co-primary study end points—was 1.21 cases per patient per year in the roflumilast group and 1.49 in controls, for a highly significant 18.5% relative risk reduction.

The other primary end point was improvement in lung function as reflected in mean change from baseline in forced expiratory volume in 1 second (FEV1) prior to administration of a bronchodilator. Again, roflumilast showed a highly significant advantage, with a 33-mL increase in FEV1, as compared to a 25-mL decrease with placebo over the course of a 12-month period.

The change in postbronchodilator FEV1, over time—a secondary end point—consisted of a 44-mL increase with roflumilast as compared to a 17-mL decrease with placebo, also a significant difference.

The other prespecified secondary end point was time to death from any cause, which was similar in the two study arms at 201 days for roflumilast and 215 days for placebo. All-cause mortality was 3% per year in each of the groups.

Adverse events were mostly mild in nature. The two that were more frequent in the roflumilast arm were diarrhea and weight loss, affecting 9% and 8% of patients, respectively.

In addition to the sort of patients enrolled in M2-125, the other subset of COPD patients in which roflumilast has shown compelling efficacy in large trials is those with moderate to severe COPD who are on long-acting bronchodilators, according to Dr. McVor.

The M2-125 study was sponsored by Nycomed, formerly Altana Pharma. Dr. McVor is a consultant to the company.

Dr. Philip Marcus, MPH, FCCP, comments: The management of COPD continues to evolve. The expected introduction of roflumilast, and probably other drugs in this class, should improve outcomes for many patients who remain symptomatic despite conventional therapies, including long-acting beta agonists, long-acting anticholinergics, and inhaled corticosteroids.

This study, like other recently published studies with this agent, has shown the ability to reduce exacerbations and improve pulmonary function in patients currently treated with other therapies. Where this will fit in the guideline approach to COPD management remains to be determined as more studies are undertaken.

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FDA Panel Backs Thermoplasty Device for Asthma

BY ELIZABETH MECHCATIE

GAITHERSBURG, MD. — A Food and Drug Administration advisory panel voted 6 to 1 that a novel device that uses thermal energy to ablate smooth muscle in the airway during bronchoscopy could be approved under certain conditions as a treatment for severe, persistent asthma in people aged 18 years and older.

At the October meeting, members of the FDA’s Anesthesiology and Respiratory Therapy Devices Panel agreed that there was reasonable evidence that the device was safe and effective for this indication, but stipulated several conditions for approval, reflecting concerns about the need for longer-term safety and efficacy data.

In the United States, 22 million people have asthma; 5%-10% of those people have severe asthma, according to the FDA.

The conditions included requiring the manufacturer to enroll all patients treated with the device after approval in a registry, which would follow the duration of the therapeutic effects and safety; and notifying the device in patients with impaired coagulation or on those who are on anticoagulant medication, because hemoptysis was reported in six treated patients in the pivotal study.

Other conditions for approval were that physicians who use the device be adequately trained, and that patients not be retreated with the device until clinical trial data on the effects of retreatment are available.

The panel also unanimously recommended postmarketing studies to further evaluate the safety and effectiveness of the device, including studies that include emergency department visits for respiratory symptoms, corticosteroid requirements, asthma exacerbations, and hospitalizations.

Components of the Alair Bronchial Thermoplasty system include a radiofrequency generator and a single-use catheter with an electrode basket at the tip that delivers radiofrequency (RF) energy to surrounding tissue.

Treatment results in clinical improvements in people with severe asthma using thermal energy “to reduce the airway smooth muscle responsible for airway constriction in asthma patients,” according to the device’s manufacturer, Asthmatx.

The pivotal study conducted in six countries compared treatment with the device in 190 patients to sham bronchoscopy in 98 patients (where the catheter was deployed, without RF). Patients, whose median age was 41 years, had severe persistent asthma that was “not well controlled” (30%) or “very poorly controlled” (70%), and required high doses of inhaled corticosteroids and long-acting beta agonist therapy. Treatment was administered during three separate outpatient bronchoscopies 3 weeks apart. Each procedure took about 30 minutes, according to Asthmatx.

The primary end point was the average of the changes in 6, 9, and 12 month Asthma Quality of Life Questionnaire (AQLQ) scores, a patient self-administered validated questionnaire, from baseline to 52 weeks in patients in both groups, but the average of the three scores was 0.21 points greater among these in the active treatment group, compared with those in the sham group, which just missed statistical significance, according to the FDA’s analysis.

The largest effects of treatment were seen at U.S. study sites. In Brazil, however, improvements in the scores were somewhat higher among those in the sham group, which panelists agreed was a concern. Some panelists thought that may have been due to the free maintenance medications received by all the patients enrolled at the Brazilian sites, possibly reflecting greater compliance with medication therapy.

Some of the study’s secondary end points, including rates of severe exacerbations after treatment; days lost from work, school, or other daily activities due to asthma symptoms; and emergency department visits for respiratory symptoms, were lower among those treated with the device. Nearly 79% of those on Alair had a change in the AQLQ score of at least 0.5 (which the company said is the threshold for a clinically meaningful change), compared with 64.3% of those on sham treatment, the company reported.

Respiratory-related events, including asthma symptoms, were higher among those on device-treated patients undergoing the treatment phase (from the time of the first bronchoscopy through 6 weeks after the third bronchoscopy) but lower than among those in the sham group after that time. A total of 6 patients (3%) treated with the device had hemoptysis, which typically occurred soon after the procedure and was self-limited; one patient developed severe hemoptysis 31 days after treatment. But there were no cases in sham-treated patients. There were no treatment-related deaths or withdrawals for worsening asthma in the study.

Although one of the primary effectiveness end points in the pivotal study was not met, panelists supporting approval said they considered some of the secondary end points clinically relevant.

The panel generally agreed that the device appeared to be safe, but that long-term safety should be monitored, including the potential for dysplastic changes and malignancy in the treated areas. (There has been no evidence of structural abnormalities or neoplasia during up to 3 years of follow-up, according to Asthmatx.)

Panelist Dr. Sharon Rounds said that, despite her concerns about the regional variability in the effectiveness results, she was impressed with the secondary end points. “On balance, the risks are offset by the reasonably effective nature of the intervention,” noted Dr. Rounds, chief of pulmonary/critical care at Providence VA Medical Center, Providence, R.I.

A long-term study following patients for at least 5 years after treatment is needed, however, to monitor treatment durability and potential long-term sequelae of “undoubted damage to the epithelium and other components of the airway wall, in addition to bronchial smooth muscle,” she cautioned.

The FDA usually follows the recommendations of its advisory panels. If approved, Asthmatx plans further studies, including one that will follow patients in the pivotal trial through 5 years. The company also will provide didactic and interactive training for physicians.

Dr. Philip Marcus, MPH, FCPP, comments: The management of patients with severe asthma, a group of patients generally felt to be difficult to treat, has evolved with the last update of the NAEPP guidelines. However, despite optimal therapy with essentially all available agents, a subgroup of patients exists for whom other options are needed. The use of this novel, nonpharmacologic therapy may be what we have been looking for. However, caution is needed until the technique is studied more to exactly define the group of patients who might benefit.

FDA Panel Says No to Expanded Indication for Omalizumab

BY ELIZABETH MECHCATIE

SILVER SPRING, MD. — The majority of a Food and Drug Administration advisory panel did not support expansion of the approval of omalizumab as a treatment for moderate to severe persistent asthma to include children aged 6-11 years, based on available safety and efficacy data.

The FDA’s Pulmonary-Allergy Drugs Advisory Committee voted 10-4 that the safety and efficacy data on omalizumab did not provide “substantial and convincing evidence” to support approval for the proposed indication: the treatment of asthma in patients aged 6-11 years with moderate to severe persistent asthma whose symptoms are inadequately controlled with inhaled corticosteroids (ICS) and who have a positive skin test or in vitro reactivity to a perennial allergen.

Omalizumab, a monoclonal antibody that reduces serum IgE levels, was approved in 2003 for the same indication in adolescents and adults aged 12 years and older. It is marketed as Xolair by Genentech USA Inc. and Novartis Pharmaceuticals.

A marginal effect on efficacy and outstanding safety issues, including concerns about long-term safety, anaphylaxis risk, and unknown implications of circulating levels of omalizumab-IgE immune complexes in some treated patients, were among the reasons panelsists said they voted against approval.

Omalizumab is administered subcutaneously, every 2-4 weeks in a health care setting, at a dose based on serum IgE levels and body weight. The current label has warnings about the potential risks of anaphylaxis and malignancies associated with treatment, based on clinical trial and postmarketing reports. In July 2009, the FDA reported that a cardiovascular safety signal associated with omalizumab was identified in postmarketing reports.

Omalizumab was evaluated in a pivotal 52-week study of 674 children aged 6-11 years with moderate to severe, persistent, inadequately controlled allergic asthma, despite treatment with fluticasone at dose of 200 mcg or more per day (or the equivalent), with or without other controller medications, which included short-acting beta-agonists (28.5%); leukotriene antagonists (37%). The primary end point, the rate of clinically significant asthma exacerbations (defined as worsening of symptoms requiring a doubling of the baseline ICS dose for 3 days or more and/or treatment with rescue systemic IV or oral steroids for 3 days) at 24 weeks, was 0.45 in those treated with omalizumab, versus 0.64 in those on placebo, a significant difference.

One secondary efficacy end point, the asthma exacerbation rate at 52 weeks, was significant in favor of omalizumab (0.78 among those on omalizumab, versus 1.30 among those on placebo). The other secondary end points—nocturnal symptom scores, asthma medication rescue use, and quality of life scores at 24 weeks—were not significantly different between the two groups.

The most common adverse effects in pediatric studies were nasopharyngitis, upper respiratory tract infections, and headache; these were reported at similar rates on placebo and omalizumab. No new safety signals were identified, and there were no malignancies among omalizumab-treated patients. The one case of anaphylaxis in an omalizumab-treated patient was associated with a meperidine hydrochloride injection.

The FDA usually follows the recommendations of its advisory panels.
temp: 101.9°F
O₂ sat: 89%
WBC: 18.1
PMNs: 80%, bands: 15%
creatinine: 2.6
CXR: LLL infiltrate
MRSA
nosocomial pneumonia
Some patients have ZYVOX written all over them

With proven efficacy, excellent tissue penetration, and clear and consistent dosing, count on ZYVOX to treat MRSA* in patients with nosocomial pneumonia whose conditions are complicated by renal insufficiency.1-3

ZYVOX is indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms:
Nosocomial pneumonia caused by Staphylococcus aureus (methicillin-susceptible and -resistant strains) or Streptococcus pneumoniae (including multidrug-resistant strains [MDRSP]).
Complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis, caused by Staphylococcus aureus (methicillin-susceptible and -resistant strains), Streptococcus pyogenes, or Streptococcus agalactiae. ZYVOX has not been studied in the treatment of decubitus ulcers.
ZYVOX use is contraindicated in patients with known hypersensitivity to linezolid or any of the other product components.
ZYVOX should not be used in patients taking any medicinal product which inhibits monoamine oxidases A or B (e.g. phenelzine, isocarboxazid) or within 2 weeks of taking any such product.
Unless patients are monitored for potential increases in blood pressure, ZYVOX should not be administered to patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis and/or patients taking any of the following: directly and indirectly acting sympathomimetic, vasopressive, and dopaminergic agents.
Unless patients are carefully observed for signs and/or symptoms of serotonin syndrome, ZYVOX should not be administered to patients with carcinoid syndrome and/or patients taking any of the following medications: serotonin reuptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists, meperidine, or buspirone.
Spontaneous reports of serotonin syndrome have been reported with the coadministration of ZYVOX and serotonergic agents. If signs or symptoms of serotonin syndrome, such as cognitive dysfunction, hyperpyrexia, hyperreflexia, and incoordination occur, discontinuation of one or both agents should be considered.
Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported in patients receiving ZYVOX. In cases where the outcome is known, when ZYVOX was discontinued, the affected hematologic parameters returned to pretreatment levels. Complete blood counts should be monitored weekly, particularly in patients who receive ZYVOX for longer than 2 weeks.
ZYVOX is not approved and should not be used for the treatment of patients with catheter-related bloodstream infections or catheter-site infections.
ZYVOX has no clinical activity against Gram-negative pathogens and is not indicated for the treatment of Gram-negative infections. It is critical that specific Gram-negative therapy be initiated immediately if a concomitant Gram-negative pathogen is documented or suspected.
Clostridium difficile associated diarrhoea has been reported with use of nearly all antibacterial agents, including ZYVOX, and may range in severity from mild diarrhoea to fatal colitis.
Lactic acidosis has been reported with the use of ZYVOX. Patients receiving ZYVOX who develop recurrent nausea, vomiting, unexplained acidosis, or a low bicarbonate level should receive immediate medical evaluation.
Peripheral and optic neuropathy have been reported primarily in patients treated with ZYVOX for longer than the maximum recommended duration of 28 days. If patients experience symptoms of visual impairment, prompt ophthalmic evaluation is recommended.
Convulsions have been reported in patients treated with ZYVOX. In some of these cases, a history of seizures or risk factors for seizures was reported. The most commonly reported adverse events in adults across phase 3 clinical trials were diarrhea, nausea, and headache.

* Methicillin-resistant Staphylococcus aureus.

References:

Please see brief summary on adjacent page.
treatment options according to which patients might benefit most. While research on NSCLC molecular markers is constantly changing, the guideline has to reflect the current state of published literature,” Dr. Giuseppe Giaccone, co-chair of the American Society of Clinical Oncology (ASCO) guideline committee and head of the thoracic oncology section branch of the National Cancer Institute, said in an interview.

“Treatments and NSCLC. NSCLC treatments are included in the treatment of the thoracic infections. Caused by susceptible strains of the designated microorganisms (Coxsackie B viruses, adenovirus, or respiratory syncytial virus (RSV)). Pneumocystis jiroveci (also known as Pneumocystis carinii), and infections including cases with concurrent bacterium. Pneumocystis pneumonia (also known as Pneumocystis carinii, Pneumocystis jiroveci, or PCP). Severe respiratory failure defined as a PaO2/FiO2 ratio less than 200. With symptoms including acute respiratory distress syndrome, and patients with the following criteria: 1. Severe respiratory failure. 2. Acute respiratory distress syndrome. 3. Patients 6 months of age or older with chronic respiratory failure. 4. Patients with the following symptoms: cough, fever, or respiratory distress.

The new guideline recommends combination chemotherapy as the first-line treatment in most patients, with either cisplatin or carboplatin deemed acceptable as the first drug in the combination.

Third-generation cytotoxic drugs are affirmed as acceptable in combination with cisplatin or carboplatin include docetaxel (Taxotere), gemcitabine (Gemzar), irinotecan (Camptosar), paclitaxel (Taxol), pemetrexed (Alimta), and vinorelbine (Navelbine). Based on moderate evidence, the committee noted that these drugs have a higher response rate than carboplatin and may improve survival when combined with third-generation agents. Carboplatin is less likely to cause nausea, nephrotoxicity, and myelosuppression than cisplatin, but is more likely to cause thrombocytopenia,” according to the new guideline.

Recommendations for the duration of first-line therapy were also revised. However, based on moderate evidence, the new guideline recommends that the first-line treatment should be continued until disease progression or unacceptable toxicity. The duration of first-line therapy should be evaluated in controlled clinical trials. Prescribing ZYXIV in the absence of a strong baseline benefit or a prognostic indicator is unlikely to provide benefit to the patient and neither the full duration of the drug-resistant options is recommended. Patients with disease progression after first-line therapy may benefit from second-line therapy. This recommendation is based on evidence that the second-line therapy is less toxic than the first-line therapy, and that it is likely to prolong survival in patients with disease progression after first-line therapy. However, the duration of second-line therapy should be determined by the individual patient and their family, and the treatment should be continued until disease progression or unacceptable toxicity.

ZYXIV injection, tastes and for oral administration. Brief summary of prescribing information.

| **INDICATIONS AND USAGE** | **Zyvox** is indicated for the treatment of skin, flulike infections including, but not limited to, pyoderma gangrenosum, and infections including cases with concurrent bacterium. Pneumocystis pneumonia (also known as Pneumocystis carinii, Pneumocystis jiroveci, or PCP). Severe respiratory failure defined as a PaO2/FiO2 ratio less than 200. With symptoms including acute respiratory distress syndrome, and patients with the following criteria: 1. Severe respiratory failure. 2. Acute respiratory distress syndrome. 3. Patients 6 months of age or older with chronic respiratory failure. 4. Patients with the following symptoms: cough, fever, or respiratory distress.

**CONTRAINDICATIONS** | **Zyvox** should be used in patients who have had an adverse reaction to this drug.

**WARNINGS/ PRECAUTIONS** | **Zyvox** should be used in patients who have had an adverse reaction to this drug.

**ADVERSE REACTIONS** | **Zyvox** has been reported to cause adverse reactions in patients receiving this drug. The most common adverse reactions reported in patients receiving Zyvox include rash (5%); pruritus (3%); urticaria (2%); angioedema (1%); myalgia (2%); arthralgia (1%); urticaria (2%); angioedema (1%); myalgia (2%); arthralgia (1%); and fever (1%).

**DOSE AND ADMINISTRATION** | **Zyvox** should be administered once daily, with or without food. The recommended dose of Zyvox for the treatment of skin, flulike infections is 200 mg orally, once daily, for 7 days. The recommended dose of Zyvox for the treatment of skin, flulike infections is 200 mg orally, once daily, for 7 days.

**HOW SUPPLIED** | **Zyvox** is supplied as a white, round, scored tablet containing 160 mg of Zyvox, and as a white, round, scored tablet containing 320 mg of Zyrox.

**REFERENCES** | **Zyvox** should be used in patients who have had an adverse reaction to this drug.

**LYMPHOCYTOSIS** | **Zyvox** has been reported to cause adverse reactions in patients receiving this drug. The most common adverse reactions reported in patients receiving Zyvox include rash (5%); pruritus (3%); urticaria (2%); angioedema (1%); myalgia (2%); arthralgia (1%); urticaria (2%); angioedema (1%); myalgia (2%); arthralgia (1%); and fever (1%).

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December 2009 • CHEST PHYSICIAN

Cardiothoracic Surgery

A designation of acceptable, evidence-based second-line chemotherapy options, including docetaxel, erlotinib, gefitinib, or pemetrexed in patients with adequate performance status, regardless of age, in the face of disease progression or completion of a first-line platinum-based regimen.

An option of erlotinib as third-line chemotherapy in patients with performance status 0 to 3 who have not previously been exposed to erlotinib or gefitinib. The choice of third-line chemotherapy options should be considered within the context of clinical trials, experimental therapy, and best supportive care, the guideline suggests.

Elderly patients, those with limited vitality, and minorities receive special attention in the updated guideline, which advocates chemotherapy in the vast majority of patients with stage IV cancer, including those with

ECOG performance status of 0, 1, and possibly 2.

Evidence supports the use of single-agent chemotherapy, providing the patient with a personalized description of his or her individual risks and benefits.

Such efforts might improve outcomes in African Americans, for example, who receive first-line chemotherapy for stage IV NSCLC only 36% of the time.

A number of the authors of the updated ASCO guidelines disclosed potential financial conflicts of interest related to pharmaceutical companies that manufacture oncologic drugs.

The new ASCO guideline, along with decision aid tools, is available online at www.asco.org/guidelines/nsc

CHEMOTHERAPY BEYOND SPECIFIED LIMITS OR INITIATE DIFFERENT CHEMOTHERAPY PRIOR TO initiating first-line chemotherapy is considered as an acceptable first-line choice among patients whose tumors test positive for EGFR protein.

Cetuximab is generally available in the United States, except through a special program called the Iressa Access Program.

A recommendation to add bevacizumab (Avastin) (15 mg/kg every 2 weeks) to a first-line carboplatin/paclitaxel combination therapy until disease progression, except in patients with squamous cell carcinoma histology, brain metastasis, or clinically significant hemoptysis or cardiovascular disease, inadequate organ function, ECOG (Eastern Cooperative Oncology Group) performance status greater than 2, therapeutic antiangiogenesis, or medically uncontrolled hypertension.

A number of the authors of the updated guideline are affiliated with pharmaceutical companies that manufacture oncologic drugs, and an updated ASCO guidelines disclosure is available online at www.asco.org/guidelines/nsc.

The revised ASCO guidelines also disclose potential financial conflicts of interest related to pharmaceutical companies that manufacture oncologic drugs.

For the first time, the ASCO guideline calls for stopping chemotherapy beyond specified limits or initiating different chemotherapy prior to initiating first-line chemotherapy.

The updated ASCO guidelines disclose potential financial conflicts of interest related to pharmaceutical companies that manufacture oncologic drugs.

The new ASCO guideline, along with decision aid tools, is available online at www.asco.org/guidelines/nsc.

Elderly patients, those with limited vitality, and minorities receive special attention in the updated guideline, which advocates chemotherapy in the vast majority of patients with stage IV cancer, including those with
EGFR Testing Is Urged for Advanced NSCLC

BY ALICE GOODMAN
Elsevier Global Medical News

B R I M E R - T H E drumbeat calling for routine testing of non-small cell lung cancer patients for mutations in the epidermal growth factor receptor grew louder at the joint congress of the European Cancer Organization and the European Society for Medical Oncology.

New and updated data from trials conducted largely (but not exclusively) in Asia showed gains in progression-free survival when patients with these mutations were treated with gefitinib (Iressa) or erlotinib (Tarceva), which are epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs).

The consensus among the investigators was that EGFR testing should be usual care, especially in advanced patients with clinical characteristics suggesting that they would benefit from an EGFR TKI—namely, nonsmoking status, adenocarcinoma, Asian ethnicity, and female sex.

Test results would then guide the selection of therapy: Patients with EGFR mutations would receive first-line therapy with either erlotinib or gefitinib, whereas those with wild-type EGFR would be treated with standard chemotherapy.

“Front-line EGFR TKI should become the new standard of care for patients with advanced NSCLC who harbor EGFR mutations, similar to HER2 testing and trastuzumab for breast cancer. This is the new treatment paradigm,” Dr. Chandra P. Belani said in an interview after the meeting.

Evidence Favoring Patients From Asia

Asian populations are more likely to have EGFR mutations, which occur in about 10% of NSCLC patients from the Western world and about 40% of those in Asia, according to Dr. Belani, the M. am Beckner Distinguished Professor of Medicine at Pennsylvania State University, Hershey, and deputy director of the Penn State Hershey Cancer Institute in that city.

A key trial presented previously—the IRESSA Pan-Asia Study (IPASS) of 1,217 patients—showed that patients with EGFR mutations had longer progression-free survival when they were treated with gefitinib vs. chemotherapy. Dr. Tony Mok of the Chinese University of Hong Kong and colleagues reported that the testing of tissue samples from non-smoking Asian patients showed that 60% of them harbored EGFR mutations. Progression-free survival and response rates were significantly improved in this group, whereas those without EGFR mutations fared better with chemotherapy in the study, which was sponsored by AstraZeneca (N. Engl. J. Med. 2009; 361:947-57).

At this year’s joint congress, the following presentations reinforced the IPASS findings:

A new update of the Randomized Phase III Study Comparing Gefitinib With Carboplatin Plus Paclitaxel for the First-Line Treatment of Non-Small Cell Lung Cancer With Sensitive EGFR Mutations, also from Asia, showed a doubling of median progression-free survival (10.4 months vs. 5.5 months) with first-line gefitinib vs. standard carboplatin plus paclitaxel chemotherapy in patients with EGFR mutations. Despite a numerical improvement in survival on the gefitinib arm, this did not reach statistical significance in the data presented by Dr. Akinori Inoue of Tohoku University Hospital in Sendai, Japan, and colleagues.

Most patients who were assigned to the gefitinib arm were crossed over to chemotherapy at disease progression, Dr. Belani noted.

Dr. Junji Tsurutani of Kinki Universi-
y University in Osaka, Japan, presented the first data from the West Japan Thoracic Oncology Group (WJTGO) 3405 trial. This randomized, open-label study in 177 Asian NSCLC patients who harbored EGFR mutations found prolonged median progression-free survival with first-line gefitinib vs. a standard platinum-based chemotherapy doublet (9.2 months vs. 6.3 months).

Dr. Jean-Yves Douillard of Centre René Gauducheau, Nantes, France, and colleagues reported they have found that if tumor tissue at diagnosis is viable and accessible, CLIA-certified laboratories can perform EGFR testing. If they do get tested and are EGFR positive, insurance companies in the United States will not necessarily provide reimbursement for first-line TKI therapy.

No First-Line Approval in U.S.

Erlotinib is the only TKI EGFR inhibitor that is approved in the United States for advanced NSCLC, and it is approved as second- and third-line therapy—but not first-line therapy. Gefitinib is used in Europe and Asia, where it is approved as first-line therapy for patients with EGFR-mutation-positive advanced NSCLC; it is only selected in patients in the United States, however, under a risk-management program called the Iressa Access Plan.

“The discovery of EGFR mutations and their prediction for response to erlotinib and gefitinib in patients who harbor these mutations came after erlotinib was approved by the FDA,” Dr. Belani explained. It also followed the FDA’s scaling back of the indication for gefitinib in 2005.

“Gefitinib should be resubmitted to the FDA for approval in patients with EGFR mutations on the basis of the available data from phase III trials performed outside” the United States, Dr. Belani urged.

“Based on the IPASS study, the NEJ002 study, and WJTGO 3405, patients with EGFR mutations should receive front-line therapy with either gefitinib or erlotinib,” he said.
Small Series Sheds Light on Flu in Transplanted Lungs

San Diego — Early experience with pandemic influenza A(H1N1) in lung transplant recipients suggests the infection may result in chronic allograft dysfunction.

Although our follow-up period is short, none of our patients (with H1N1 flu) have returned to their preinfection baseline respiratory status,” Dr. Vivek N. Ahya noted at CHEST 2009, the annual meeting of the American College of Chest Physicians.

Dr. Ahya, medical director of the lung transplant program at the University of Pennsylvania, Philadelphia, reported on the five patients in the program who have developed laboratory-confirmed H1N1 flu to date. The experience gleaned from the small series suggests the infection in lung transplant patients may differ in important ways from the disease pattern in the general population.

The 5 affected patients are among roughly 300 lung transplant recipients who are currently being followed in the program. Three of the five patients became sick in June, and the other two fell ill in October.

One striking difference about disease presentation in these patients is that only one of the five had fever, whereas fever is a prominent feature in more than 90% of cases of H1N1 flu in the general population.

One patient — the only one who died — developed H1N1 flu shortly after completing a course of radiotherapy for a squamous cell carcinoma in his native lung. That patient, the only one not immediately hospitalized for treatment, insisted on outpatient therapy. He had a DNR order in place because of his lung cancer, and he went to an outpatient hospital when he suddenly deteriorated, so it’s unclear whether his death was caused by H1N1 infection or something else, such as pulmonary embolism.

The first of the lung transplant recipients to develop H1N1 flu had a baseline FEV1 of 1.27 L, 44% of the predicted value. When he presented with influenza, his FEV1 had dropped to 0.7 L, or just 29% of the predicted value. Four months later, well after he had clinically recovered, his FEV1 was 1.06 L, 37% of the predicted value.

Another patient who developed H1N1 flu in June is now being evaluated for retransplantation, he added.

Treatment of H1N1 flu included a reduction in immunosuppressive therapy, antibiotics, and a standard 5-day course of oseltamivir (Tamiflu). The antiviral agent was well tolerated.

One patient who was already colonized with Pseudomonas did well for the first 4 days on oseltamivir in the hospital, then deteriorated, developing septic shock and pneumonia in his native lung. He remains in the ICU on a ventilator.

Once the H1N1 vaccine becomes more widely available, Dr. Ahya said, the plan is to immunize all patients in the lung transplant program with a single dose.

He noted that there is evidence to suggest lung transplant patients may be more vulnerable than other solid organ recipients to seasonal influenza. Some years ago, University of Pittsburgh investigators reported that the rate of seasonal influenza was 41.8 cases per 1,000 person-years among their lung transplant patients, compared with 4.3 per 1,000 among kidney recipients and 2.8 per 1,000 for liver transplant patients (Am. J. Transplant. 2002;2:287-91).

The explanation for those findings is unclear. Lung transplant patients are typically more heavily immunosuppressed than are other solid organ recipients, and transplant physicians tend to look more closely for infections in that population, according to Dr. Ahya.
**Drug Combo Effective for H1N1 Flu-Related ARDS**

**BY BRUCE JANCIN**

**Elsvier Global Medical News**

**SAN DIEGO** — Patients with suspected pandemic influenza A(H1N1)—associated acute respiratory distress syndrome responded favorably overall to an ICU treatment course of high-dose oseltamivir and prolonged low-to-moderate-dose corticosteroids in a pilot study.

Eleven of 13 patients showed a marked improvement in lung injury scores by day 7, and the 15% in-hospital mortality rate was lower than expected in such a critically ill population, Dr. G. Umberto Meduri said at CHEST 2009, the annual meeting of the American College of Chest Physicians.

On the basis of these findings and the extensive basic science rationale in support of prolonged steroid therapy in acute respiratory distress syndrome, the French Ministry of Health has announced it will fund a randomized controlled trial of this treatment protocol in patients with H1N1 influenza–associated ARDS. However, the results won’t be in until after the current seasonal outbreak of 2009 H1N1 flu has ebbed, said Dr. Meduri of the University of Tennessee, Memphis.

He reported on 13 consecutive patients who presented to an ICU in a tertiary-care hospital in Buenos Aires with suspected H1N1 influenza and hypoxemic respiratory failure during a 3-week period beginning June 24, 2009. Eight were in septic shock. Six had severe ARDS as defined by a \( \text{PaO}_2/\text{FiO}_2 \) (partial pressure of oxygen in arterial blood to the fraction of inspired oxygen) ratio of 120 or less and a positive end-expiratory pressure of at least 12 cm H\( _2 \)O; patients ill typically have an in-hospital mortality of about 55%, he said. By day 7 in the ICU, 11 of 13 patients showed significantly improved lung function as defined by at least a 1-point drop on the 4-point Lung Injury Scale, or a score below 2.

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**Monitoring for Delirium in ICU Gave No Benefit**

**SAN DIEGO** — Daily systematic monitoring for delirium in a surgical ICU proved no more beneficial than did routine clinical judgment in identifying affected patients early and initiating effective therapy in a randomized trial.

These results raise a key, unanswered question: Is delirium even a treatable condition? If not, early identification may be of little value, Dr. Ulrich H. Schmidt, FCCP, said at CHEST 2009, the annual meeting of the American College of Chest Physicians. “There is to date no validated active therapy for delirium,” noted Dr. Schmidt of Massachusetts General Hospital, Boston. Delirium entails substantial morbidity, including longer hospital stays, as well as prolonged neurocognitive deficits post discharge in many cases.

Dr. Schmidt and his colleagues hypothesized that daily administration of the Confusion Assessment Method for ICU patients (CAM-ICU), a validated screening tool (Crit. Care Nurse 2003;23:25-36), would result in earlier and more effective treatment of delirium than would clinical judgment alone.

To test this hypothesis, Dr. Schmidt had trained investigators administer the CAM-ICU daily to 283 patients after they had been in a surgical ICU for more than 48 hours. The findings for half of the patients were reported to the staff, but the information regarding the other half, which served as the control group, was withheld. Thus, staff had to rely on clinical judgment to detect delirium in controls.

In all, 35% of the 283 ICU patients developed delirium, as did 40% of the 116 who were mechanically ventilated. There was no difference between the intervention and control groups in the duration of delirium, or in ICU length of stay.

—Bruce Jancin

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**Important Safety Information**

Adcirca should not be used in patients taking medicines that contain nitrates, as the combination could cause a sudden, unsafe drop in blood pressure. If a patient experiences anginal chest pain after taking Adcirca they should seek immediate medical attention.

Adcirca contains the same ingredient (tadalafil) as Cialis, which is used to treat erectile dysfunction (ED). The safety and efficacy of combinations of Adcirca with Cialis or other PDE-5 inhibitors have not been studied. Therefore, the use of such combinations is not recommended.

Patients with a known serious hypersensitivity to Adcirca should not take Adcirca. PDE-5 inhibitors, including Adcirca, have mild systemic vasodilatory properties that may result in transient decreases in blood pressure. Before prescribing Adcirca, physicians should carefully consider whether their patients with underlying cardiovascular disease could be adversely affected by such actions. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD) and administration of Adcirca to these patients is not recommended. The use of Adcirca with alpha blockers, blood pressure medications, and alcohol may lower blood pressure significantly and may lead to symptomatic hypotension (fainting).

Adcirca is metabolized predominantly by CY3P3A in the liver. Use of Adcirca with potent CYP3A inhibitors, such as ketoconazole and itraconazole, should be avoided. For patients on Adcirca therapy that require treatment with ritonavir, Adcirca should be...
Five patients were extubated by day 7, another 6 by day 14, and 2 later. The mean hospital length of stay was 18.7 days. Four patients developed ventilator-associated pneumonia as a complication of their ICU stay, and 5 nondiabetic patients required insulin therapy. All 13 survivors were discharged home with no supplemental oxygen requirement.

One patient, an alcoholic with cirrhosis who developed septic shock and severe ARDS, died from progressive multisystem organ failure on day 15. The other patient, who developed septic shock and sepsis involving patients with early severe ARDS unrelated to H1N1 flu (CHEST 2007;131:954-63).

In the H1N1 pilot study, patients stayed on steroids for a mean of 21 days. If, however, a patient presents with severe ARDS or worsens to that status at any point, the methylprednisolone dose is 1 mg/kg per day, tapered as detailed in Dr. Meduri’s earlier randomized trial involving patients with early severe ARDS unrelated to H1N1 flu (CHEST 2007;131:954-63).

The 15% in-hospital mortality rate was lower than expected in such a critically ill population.

Dr. Meduri


ADCIRCA® (tadalafil) Tablets

The following is a brief summary of the full prescribing information on ADCIRCA (tadalafil). Please read the full prescribing information prior to prescribing ADCIRCA.

INDICATIONS AND USAGE

Pulmonary Arterial Hypertension

ADCIRCA is indicated for the treatment of pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability.

CONTRAINDICATIONS

Concomitant Organic Nitrates

Do not co-administer ADCIRCA with patients who are using any form of organic nitrates, either regularly or intermittently. (See CONTRAINDICATIONS AND PRECAUTIONS.)

WARNINGS AND PRECAUTIONS

Cardiovascular Effects

Discuss with patients the expected time in the day they experience exhaled carbon monoxide (CO) levels. The full prescribing information includes a discussion of cardiovascular effects and strategies for monitoring and management.

Sex-related Adverse Reactions

Sexual adverse reactions have been identified during post-approval use of tadalafil. These events have been chosen for inclusion in the listing because of their seriousness, potential for pharmacodynamic or pharmacokinetic interactions, or the potential for important management implications.

ADVERSE REACTIONS

The following adverse reactions have been identified during post-approval use of tadalafil. These events have been chosen for inclusion because of their seriousness, potential for pharmacodynamic or pharmacokinetic interactions, or the potential for important management implications.

Table 1: Treatment-Emergent Adverse Events Reported by ≥2% of Patients in ADCIRCA and More Frequent than Placebo (% in Italic)

<table>
<thead>
<tr>
<th>EVENT</th>
<th>Placebo (%)</th>
<th>ADCIRCA 20 mg (%)</th>
<th>ADCIRCA 40 mg (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>0-2</td>
<td>2-8</td>
<td>4-10</td>
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<tr>
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<td>0-2</td>
<td>2-8</td>
<td>4-10</td>
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<td>0-2</td>
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<td>Nausea</td>
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Pharmacologic Experience

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Marketed by United Therapeutics Corporation, Research Triangle Park, NC 27709

Rx only - June 2009
H1N1 Mortality Highest in Elderly, Mexican Data Show

BY HEIDI SPLETE
Elsevier Global Medical News

Adults aged 60 years and older were more likely to die from the pandemic influenza A/H1N1 virus than were younger individuals, during the first wave of the outbreak in Mexico, based on data from nearly 7,000 cases of H1N1 influenza.

The researchers said. Factors that predict ed hospital admission and death included dyspnea, tachypnea, cyanosis, and confinement to bed.

The results were limited by incomplete data in some cases, as well as a lack of data on whether infection control measures such as school closings reduced the spread of disease, the researchers said.

Overall, the risk of infection was 35% lower among individuals who had been vaccinated for seasonal flu, but a protective effect of seasonal flu vaccination against H1N1 remains controversial, the researchers noted.

A significant finding in today’s report was that the infection risk was highest in children, but the disease was more severe (i.e., higher risk of death) in people older than 60 years,” noted the authors of an accompanying editorial, Dr. V. Alberro Laguna-Torres of the U.S. Naval Medical Research Center Detachment in Lima, Peru, and Dr. Jorge Gomez Benavides of San Marcos University in Lima (Lancet 2009 [doi: 10.1016/S0140-6736(09)61916-4]).

But the results also were limited by challenges of influenza surveillance, they noted, because not all patients who are ill seek medical care, and not all patients who sought care were tested for the H1N1 virus specifically.

The researchers declared no financial conflicts of interest.
Why end-of-life communication training is increasingly important for critical care medicine.

Because 20% of Americans die in ICUs, critical care has become a key ingredient in decision-making that better end-of-life communication can improve. Data supporting these are considered in three areas: quality of death and dying, the emotional impact on next of kin, and institutional outcomes (length of stay, cost).

Quality of Death and Dying
Assessing the quality of one’s own ICU death is quite challenging for obvious reasons. Thus, observers, either family members or nurses, can rate the dying experience on a scale, such as the Quality of Death and Dying Scale.

Using this scale, rated by nurses, Curtis and coworkers demonstrated that quality of death and dying can be improved by a multifaceted intervention that includes clinician education, local champions, academic detailing, feedback to clinicians, and system support (Curtis et al. Am J Respir Crit Care Med 2008; 178:269).

Thus, a tailored intervention that includes elements of better communication may improve the dying experience.

Emotional Impact of an ICU on Next of Kin
Family members of patients who both survive or die in the ICU are psychologically distressed by the experience. For example, 90 days after an ICU discharge, posttraumatic distress symptoms were seen in 29% of family members of patients who survived an ICU admission but increased to 50% in situations where the patient died.

Where next of kin participated in end-of-life decision-making, 82% scored above threshold for posttraumatic distress and also had higher rates of anxiety and depression (Azoalay et al. Am J Respir Crit Care Med 2005; 171:987). The emotional trauma of an ICU admission on next of kin thus presents a compelling reason to improve the quality of an ICU death.

A recent randomized controlled trial found that a rather simple intervention, a schema for conducting a family meeting and a brochure about what to expect from dying, reduced the rates of posttraumatic stress symptoms, depression, and anxiety in a grieving family member (Lautrette et al. N Engl J Med 2007; 356:469).


Imagine a husband with two young children whose wife recently died of cancer. Parenting is immeasurably more difficult in the presence of posttraumatic distress, depression, and anxiety. Connection to an emotionally absent father at a critical time of healing is also impeded.

Although improving post-ICU death outcomes has the potential to significantly impact the family, it is a new outcomes paradigm for critical care medicine.

Institutional Outcomes
The idea that so-called “soft” psychosocial interventions can positively impact ICU length-of-stay is quite remarkable.

Curtis, for example, found that his multifaceted ICU intervention promoting palliative care implementation, described above, reduced ICU length-of-stay from a median of 7.2 to 5.8 days.

A recent study found that only 31% of patients with advanced cancer reported end-of-life discussions with their oncologists. Health-care costs in the last week of life for patients who had discussed end-of-life care were 36% less than for those patients who had not discussed end-of-life care. Survival was identical in both groups (Zhang et al. Arch Intern Med 2009; 169:480). Thus, better end-of-life communication saves health dollars because people make better treatment choices.

What Is Communication Skill Training?
Communication skills are seen as core competencies by major health-care organizations (Liaison Committee on Medical Education [LCME], Accreditation Council for Graduate Medical Education [ACGME], National Board of Medical Examiners [US Medical Licensing Examination]).

Simulation communication training has been increasingly adopted nationally (eg, University of Pittsburgh, Institute for Doctor-Patient Communication; Children’s Hospital Boston, Program to Enhance Relational and Communication Skills; Temple University’s Institute for Clinical Simulation and Patient Safety; Center for Communication and Medicine, Northwestern University Feinberg School of Medicine; Children’s National Medical Center) and internationally (Israel, Australia, United Kingdom).

Cancer communication is, by nature, emotionally saturated, especially in regards to discussing dying. Most of us, given the choice, will avoid it. Recognizing this, Memorial Sloan-Kettering Cancer Center has developed the Communication Skills Research and Training Laboratory (Cornsh Lab), the only dedicated communication training facility at a comprehensive cancer center. A modular approach has been designed to help simulate dilemmas, such as breaking bad news, discussing prognosis, and discussing ICU end-of-life care.

The ICU modules focus on family communication rather than the traditional doctor-patient model, because most ICU patients are incapacitated. Actors portray family members. Before and after the training sessions, skill levels are assessed using a 12-min standardized assessment that is videotaped and scored.

This Month in CHEST: Editor’s Picks

► Association Between ICU Admission During Morning Rounds and Mortality. By Dr. B. Aftosiz, FCCP, et al.
► Achieved Anticoagulation vs Prosthesis Selection for Mitral Mechanical Valve Replacement: A Population-Based Outcome Study. By Dr. T. Le Tourneau, et al.
► Prevalence and Progression of Osteoporosis in Patients With COPD: Results From TORCH. By Dr. G. T. Ferguson, FCCP, et al.
► Physician Leadership for High Quality Care. By Dr. C. M. Clancy.
Continued from previous page

Different points in the dying trajectory are simulated (transition from curative to palliative goals of care, DNR discussions, withdrawal of life-extending treatments). A didactic program provides an evidence-based framework, and demonstration videos model proper communication techniques.

The steepest part of the learning curve comes from role-play, because training at this point is individualized to meet the physician’s deficits. Video-assisted feedback allows for recognition of inefficient techniques, reflection, and practice of better strategies.

What are some of the typical skills that a physician might work on in communication training? One is the centrality of empathic communication.

When a family member is overwhelmed by emotion, such as distress or sadness, then the understanding and processing of medical or prognostic data required for informed decision making is more difficult. Critical care medicine trainees learn to address these emotions first, prior to moving forward in the conversation.

There are many ways of ameliorating emotions: normalization (“It is normal to be upset …”) and paraphrasing and repeating back (“So, what you are saying is that …”), but critical care medicine physicians seem to find silence or listening most difficult. Silence represents understanding and sharing in the pain of suffering.

Video feedback can palpably demonstrate the efficacy of timely silence. Physicians who tend to lecture patients/families are often not aware of this until they view themselves on video feedback.

Doctors who talk less and listen more are actually perceived as being more empathic.

Communication training often addresses double-talk—physicians saying one thing when they mean another.

For example, discomfort talking directly about dying often drives physicians to use metaphors. “Would you like everything done?” is actually an attempt to say, “If you were close to death, we physicians would like to avoid futile resuscitation.”

The problem is that patients/families understand “everything” to mean a comprehensive approach. The opposite of “everything” is understood to be a halfhearted approach. Nobody would want a halfhearted professional, such as a mechanic or banker on their team and certainly not a halfhearted physician.

Communication training can unpack the metaphor “everything,” clarifying the real underlying issue, that CPR in dying cancer patients has an almost zero efficacy.

“Heroic measures is another metaphor for futile CPR that is understood in divergent ways by physicians and patients/families.

Would you prefer physicians to use heroics or the opposite, “cowardly” measures? I would select heroic measures. It reminds me of the movie, “Saving Private Ryan.”

But the real issue is physician discomfort discussing futile CPR and dying. This can be practiced in communication training, adding better lines to physicians’ end-of-life communication scripts, which more accurately reflect their good intent.

End-of-Life Communication: A Dilemma in the Best of Institutions

I was shocked recently when training a group of Eastern European palliative care physicians. One broke down in tears during role-play— he had never told a patient that he or she was dying. “Truth telling” is an old story in the West, so imagine my dismay when, 1 week later, I heard of a ventilated, brain dead patient, kept alive for weeks at a top US hospital. Earlier initiation of this painful negotiation would have helped the patient and family find their respective peace.

The physicians involved in this case were both competent and caring, yet they found it difficult to initiate the withdrawal of life-extending treatment conversation. Not wanting to displease the family, fears of litigation, a communication skill deficit, or cultural divergence may have impeded better communication. Nevertheless, earlier initiation of this painful negotiation would have helped the patient and family find their respective peace.

The need for ICU communication training is ubiquitous, even in the most prestigious medical institutions, because discussing death is so intrinsically difficult, even among kind-hearted, experienced critical care medicine physicians.

Although it seems obvious that communication training would be beneficial in the ICU setting, the challenge remains to demonstrate skill uptake and improved clinical outcomes. Currently, critical care medicine communication training is at an early, but exciting, stage of development.

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The decision directly impacts the ACCP membership.

The American College of Chest Physicians (ACCP) closely reviewed the Medicare Physician Fee Schedule (MPFS) proposed rule, and submitted written comments to CMS requesting that they remove the proposal to eliminate consultation codes or at least delay the implementation of the proposal. Similar requests were also made by other medical specialty societies, including the American College of Physicians and the American Thoracic Society.

CMS released its final ruling regarding the 2010 MPFS on October 30, and unfortunately, chose to proceed with elimination of payment for consultation codes as of January 1, 2010. This is a decision in the final rule that directly impacts the ACCP membership.

Robert DeMarco, MD, FCCP, Vice Chair Practice Management Committee and ACCP Governor for Ohio, wrote his Ohio constituents, “This does not mean that we will not be able to do consultative work; we will need to bill these services with different CPT codes.”

The following facts will help you understand how this new rule will change the way you will now document for what previously coded as consultations:

- Consultation codes 99241-99245 (outpatient/office) and 99251-99255 (inpatient) are eliminated for Medicare effective January 1, 2010. The telehealth consultation G-codes (G0425-G0427) will not be eliminated.
- In 2010, consultations in the office/outpatient setting will be coded using the existing CPT codes for new (99201-05) or established (99211-15) patients. In the inpatient hospital setting, the existing CPT codes for initial hospital care (99221-23) will be used and initial nursing facility codes (99304-06) will be used in the nursing facility consultations.
- A modifier will be developed to differentiate the admitting physician of record from the consultants for initial hospital inpatient and nursing facility admissions.
- Change would be budget neutral. Payment for outpatient/office codes will increase 6% from the same code payment in 2009. Initial hospital and facility visit E/Ms will increase 2% from the same code payment in 2009.
- Increases to other E/Ms will increase payment for ALL E/M coding, not just when reporting a former consultation.
- No information has been forthcoming from other third party payers about reporting consultations in 2010. However, CMS stated in the MPFS, “If the primary payer does continue to recognize those codes [consultation codes], the physician will need to decide whether to bill the primary payer using visit codes, which will preserve the possibility of receiving a secondary Medicare payment, or to bill the primary payer with the consultation codes, which will result in a denial of payment for invalid codes.” Ultimately, it is likely that most third party contracts will need to be renegotiated as these payers often follow the example set by CMS.

Individual Practice Analysis

To determine the extent of the loss of the consultation codes, each practice needs to estimate the percentage of Medicare consultations previously performed in a year. Members should be aware that “consultations” from a specialist will continue to be requested. However, they will now be billed using different CPT codes as annotated above. This may result in loss, gain, or no significant change in your practice revenue, dependent upon your payer mix.

A detailed explanation of the changes in the consultative services coding is provided in the ACCP publication Coding for Chest Medicine 2010—available in the ACCP store at www.chestnet.org.

This Month in PCCU

- Treatment of Lung Cancer in Older Patients.
  By Dr. Scott Gettinger
- Idiopathic Pulmonary Fibrosis and Pulmonary Hypertension: A Review.
  By Dr. Steven Nathan, FCCP
  www.chestnet.org
Board of Regents Approves Realignment of ACCP NetWorks and Institutes

BY TRACY GOODE, MBA, MHSA
Vice President, Member Activities

A t CHEST 2009 in San Diego, the ACCP Board of Regents approved three organizational changes to the ACCP NetWorks:

► The Practice Administration NetWork and Private Practice NetWork merged to become the Practice Operations NetWork.
► The Critical Care NetWork merged with the Critical Care Institute.
► The Sleep Medicine NetWork merged with the Sleep Institute.

All of these changes became effective at the close of CHEST 2009.

The Practice Administration and Private Practice NetWorks have always shared common goals and issues, as well as many common members. The two groups were already working together in many ways. The merger achieves resource and administrative efficiencies, as well as improved strength and effectiveness for its members.

The Practice Operations NetWork will stimulate the exchange of ideas and knowledge between physicians and practice administrators. The NetWork seeks to increase quality patient outcomes, aid in the delivery of prompt service, and maximize reimbursement by optimizing practice efficiency. The areas of focus are staffing, billing, coding, system infrastructure, and performance measurement. The NetWork is open to all members practicing clinical medicine in both academic and traditional private practice settings and to administrative and clinical staff responsible for the operations of the practice.

The 2010 co-chairs of the Practice Operations NetWork are Philip Marcus, MD, FCCP, and Michael McCormick, RRT.

The Critical Care NetWork and Institute merger resulted in one group that will retain the Critical Care Institute name and function as a member of the Council of NetWorks. Similarly, the Sleep Medicine NetWork and Sleep Institute merger resulted in one group that will retain the Sleep Institute name and function as a member of the Council of NetWorks. (The “Critical Care NetWork” and the “Sleep Medicine NetWork” names will no longer be used.) Both of these combinations will harness the strength in the number of members of the two NetWorks with the brand recognition that has been established by the Institutes. They will continue to collaborate with sister societies, industry partners, and other organizations on various projects, as well as conduct the standard business of NetWorks, such as development of sessions for CHEST annual meetings. Furthermore, the mergers will improve resource and staffing efficiencies and eliminate redundancies between the NetWorks and Institutes.

The 2010 co-chairs of the Critical Care Institute are Jeffrey Vender, MD, FCCP, and LTC Alexander Niven, MC, USA, FCCP. The 2010 co-chairs of the Sleep Institute are Barbara Phillips, MD, FCCP, and Teofilo Lee-Chiong, MD, FCCP.

The leaders of all three of these groups agree that it is the right time to make these transitions. They are working together to integrate their activities and improve ACCP’s presence in critical care, sleep, and the business of medicine.

For more information about the NetWorks and Institutes, contact networks@chestnet.org.

NEWS FROM THE COLLEGE

Al Lever Honored at ERS Congress

A t a speakers’ dinner gathering in the City Hall of Vienna, about 500 distinguished guests from around the world joined Professor O. C. Burghuber, FCCP Congress Chair, in acknowledging retiring Executive Vice President and CEO of the ACCP, Al Lever, for his leadership commitments.

Professor Burghuber announced Mr. Lever’s retirement to the audience and commented that the ERS, in particular, appreciated his kind concern to share his immense knowledge and experience with the leadership of ERS.

“He truly became a most valuable person within the society, known to many of us—people in the pulmonary field worldwide,” noted Burghuber. “We wish him the best for his next future steps and hope to keep in contact with him, as well with the ACCP, to further improve our relationship and common interests.”

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Al and Norine Lever Honorary Endowment Fund

A Legacy of Leadership
Al and Norine Lever have an 18-year history of noteworthy leadership on behalf of the ACCP and The CHEST Foundation. As CEO of the ACCP, Al has maintained high standards and has adhered to the ACCP mission to promote the prevention and treatment of diseases of the chest through leadership, education, research, and communication. Norine has been actively involved through The CHEST Foundation’s Ambassador Group, which she conceived to volunteer, network, and educate on behalf of The Foundation.

Continuing the Legacy
To honor the Lever’s accomplishments and successes as leaders, The CHEST Foundation has established the Al and Norine Lever Honorary Endowment Fund to foster exceptional leadership among health-care professionals. Show your appreciation for Al and Norine and continue their legacy by donating to this important fund.

Contribute today by contacting The CHEST Foundation.
www.chestfoundation.org
(800) 343-2227 or (947) 496-1400
Bosentan was teratogenic in rats given oral doses two times the maximum recommended human dose (MRHD) (24 mg/kg/dose). 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 10, 30, and 100 mg/kg/dose. Malformations observed included cleft palate, phenotypic dysmorphism, splenic dysgenesis, and in animals treated with other available 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 in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from bosentan, 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 of pediatric patients have not been established.

Geriatric Use

Clinical studies of Tracleer did not include sufficient numbers of subjects aged 65 or older to determine whether they respond differently from younger subjects. Clinical experience in patients with severe liver impairment on the pharmacokinetics of Tracleer has not been evaluated. There are no studies of Tracleer in patients with mildly impaired liver function. Tracleer should generally be avoided in patients with severe liver impairment. Because bosentan is a substrate for the CYP3A4 isoenzyme, drugs that are inhibitors of this enzyme, e.g., ketoconazole or clarithromycin, should be used with caution.

Pregnancy

Tracleer (bosentan) is effective and safe in the treatment of pulmonary arterial hypertension. However, bosentan has been shown in experimental studies to be teratogenic. Use of Tracleer in pregnant women is not recommended. Bosentan is a pregnancy category C drug. Bosentan was teratogenic in rat given oral doses two times the maximum recommended human dose (MRHD) (24 mg/kg/dose). In an embryofetal 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 10, 30, and 100 mg/kg/dose. Malformations observed included cleft palate, phenotypic dysmorphism, splenic dysgenesis, and in animals treated with other available endothelin receptor antagonists indicates that teratogenicity is a class effect of these drugs (see Nonclinical Toxicology).

The development of subcutaneous uterine rupture and impaired fertility has been linked with the chronic administration of certain endothelin receptor antagonists in rats. Treatment with bosentan at doses of up to 100 mg/kg/day for 26 months resulted in effects on spermatogenesis, ovulatory dysfunction, and impaired fertility. In rats, uterine rupture was observed in 2 of 70 bosentan-treated females at doses of 200 mg/kg/day. An increased incidence of uterine rupture was also observed in bosentan-treated rats at doses of 30 and 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 10, 30, and 100 mg/kg/dose. Malformations observed included cleft palate, phenotypic dysmorphism, splenic dysgenesis, and in animals treated with other available endothelin receptor antagonists indicates that teratogenicity is a class effect of these drugs (see Nonclinical Toxicology).

Management of fertility

The development of subcutaneous uterine rupture and impaired fertility has been linked with the chronic administration of certain endothelin receptor antagonists in rats.

The development of subcutaneous uterine rupture and impaired fertility has been linked with the chronic administration of certain endothelin receptor antagonists in rats. A “suspending physician” must be immediately available and accessible for medical consultations and emergencies. Physical therapy/occupational therapy codes cannot be reported for pulmonary rehabilitation programs.

Physician Quality Reporting Initiative (PQRI)

Claims-Based CAP Measures Group

Effective January 1, 2010, a Community-Acquired Pneumonia (CAP) Measures Group was approved for claims based reporting. Thirty patients would be reported in a one year period, or 15 patients if they represent 80% of the physician’s pneumonia patients, or 8 patients if the measure is reported starting July 1 through December 31, 2010. The consecutive patient requirement for 2009 has been deleted.
DNA Technology May Revolutionize Flu Vaccine

BY DOUG BRUNK
Elsevier Global Medical News

The way Dr. Joseph Kim sees it, the field of influenza vaccine development needs an extreme makeover. “Every year, three flu strains are selected by the flu experts around the world, which determines which strains the vaccine makers should make and stock for the coming fall,” Dr. Kim, president and CEO of San Diego-based Inovio Biomedical Corp., said in an interview. “They can guess right, or they can guess wrong, but every year, you have to change the vaccine. You can’t stockpile from the previous year, because the flu strains could change.”

Scientists don’t accept this approach for most other common vaccines, he noted, including the one for measles, mumps, and rubella. “That doesn’t get changed from year to year, but our society has accepted the fact that the one for influenza does,” he said. Dr. Kim wants to change that paradigm.

Since 2005, he and his associates at Inovio have been developing DNA-based influenza vaccines capable of providing broad protection against existing as well as newly emerging, unknown seasonal and pandemic influenza strains. To design vaccines, the company developed a process known as SynCon, a way of targeting consenso proteins from multiple strains of H1N1, H2N2, H3N2, and H5N1, “which have collectively caused greater than 90% of all seasonal and pandemic flu events in people in the last 100-plus years,” Dr. Kim said. “We felt that those were very good targets.”

What separates Inovio’s SynCon approach from that of other DNA vaccine manufacturers is that the SynCon vaccines demonstrate potential to protect against new strains of influenza that do not specifically match the vaccine. “So, if the 2009 H1N1 virus mutates, there is no plan B,” Dr. Kim said. “There is no backup option; 2009 swine flu could be a big problem or not. No one can predict accurately.”

Origins of an Alternative
DNA-based influenza vaccines began to draw serious attention about 6 years ago, when infectious diseases experts around the globe expressed concern about a pandemic of H5N1 influenza virus, noted Dr. William Schaffner, chair of the Department of Preventive Medicine at Vanderbilt University, Nashville, Tenn.

That galvanized the international community,” said Dr. Schaffner. “Since that time, the United States government and private capital have gone into research to develop more improved influenza vaccines and to improve the vaccine technology. There has been more research into those areas in the past 5 or 6 years than there has been in the previous 50 years. That’s stunning.”

The concept of DNA vaccines first emerged in the early 1990s, when researchers discovered that immunizing animals with plasmids—a circular string of DNA that encodes for a specific antigen or vaccine target—generates vaccine responses.

“The beauty of this technology is speed,” said Vijay B. Samant, president and CEO of San Diego-based Vical, which develops DNA vaccines. “It’s not cell culture. It’s not egg-based. It’s simple fermentation and two purification steps. It does not require the manufacturer to handle the pathogen. All it needs is a gene sequence; that’s good enough for us to make the vaccine.”

“Instead of delivering the viruses themselves in some form, you’re taking a very simple plasmid, which is a circular piece of DNA, and you’re putting in a genetic blueprint designed for a specific target, in this case hemagglutinin,” Dr. Kim explained. “Once you inject that into muscle cells or skin cells, it uses our own cellular machinery to manufacture those proteins as antigens, and presents them in a customized way. It’s like mimicking viral infection without the side effects and replication. DNA vaccines can never replicate. They do not infect; they do not cause disease, ever. There are zero reversion effects.”

Delivery Poses Challenges
Until recently, Dr. Kim and other researchers in the field faced a barrier to the advancement of DNA vaccines: inefficient delivery. Delivery methods such as “naked” DNA formulated in water or salt solution, or formulated in lipids or even traditional adjuvants such as aluminum sulfate, and then injected in a syringe were not efficient.

However, a technology developed in the 1990s known as in vivo electroporation is proving to be an effective way to deliver DNA vaccines. Electroporation works as follows: After a DNA vaccine is injected via syringe into the upper arm or into skin, a short, controlled electrical pulse is delivered directly into that tissue, either from the same needle or from a surrounding needle. This brief pulse of electric current “coaxes the cell membranes to open up their pores,” Dr. Kim said. “That brings in the DNA. We remove the electric field and the pores close up. This has been shown in animal species to be effective in up to a 1,000-fold increase in DNA vaccine uptake. The whole procedure takes a couple of seconds.”

Not all DNA vaccine manufacturers are using electroporation as a delivery method.

Vical, the first company to produce a vaccine against the pandemic influenza A (H1N1) virus after initial reports of outbreaks in Mexico, uses a patented adjuvant known as Vaxfectin, “which does an amazing job of protecting the DNA before it enters the skeletal muscle cells,” Mr. Samant said. “Being a proinflammatory, it attracts the immune system toward the site of the injection to facilitate creation of the right immune response and immune memory.”

Mr. Samant noted that the “gentleness” of the Vical vaccination approach, compared with electroporation, allows it to trigger both innate and adaptive immunity “with that dual response, hopefully that will lead to broader cross protection.”

Phase I Trials Begin
On Oct. 1, 2009, the U.S. Navy awarded Vical a $1.25 million contract to support a phase 1 clinical trial of its vaccine against H1N1 influenza. “Our goal is to get that trial done by later this year,” Mr. Samant said.

In a virus challenge and protection study of Inovio’s SynCon H1N1 vaccine, mice were injected with the H1N1 virus that caused the 1918 Spanish flu. Mice that received the H1N1 vaccine were completely protected from the virus, whereas all of the unvaccinated animals died within 1 week.

A more recent study of the SynCon H1N1 vaccine tested in ferrets—a model considered to be on par with human influenza—showed that protective antibody responses occurred in 100% of the animals, with a titer of 1:40 or higher. “This is as good as or better than what the matched strains of vaccines have been able to do,” Dr. Kim said.

In 2010, the SynCon H1N1 vaccine will undergo human testing in healthy volunteers, followed by tests in combination with the SynCon H1N1 vaccine. Addition of H2N2 and other strains could soon follow.

‘Proof Is in the Pudding’
“If we are correct, we can revolutionize how flu vaccines are made and delivered,” Dr. Kim said. “Potentially, we can gather enough clinical evidence to show that because you’re injecting the same vaccine and generating a memory response, you may not have to take it annually. It could be a booster regimen every few years.”

“I cannot predict what the frequencies will be,” he added, “but if we can make Continued on following page
Prep Work Paid Off When H1N1 Emerged in Cities

BY HEIDI SPLETE
Elsevier Global Medical News

The response to the pandemic influenza A(H1N1) virus by the governments and public health officials of Mexico City and New York City in the spring of 2009 reveals successful strategies, but also points to issues that need to be addressed, according to a report published online in the journal Emerging Infectious Diseases.

“In each case, advance planning laid the foundation for enhanced surveillance and a generally effective response, made possible by an extensive public communications campaign and effective political leadership,” wrote Dr. David M. Bell of the Centers for Disease Control and Prevention, Atlanta, and his associates.

The researchers summarized the responses of Mexico City and New York City to the H1N1 virus in spring 2009 (Emerg. Infect. Dis. 2009 [doi: 10.3201/ eid512.090322]).

“These megacities may not be representative of cities in low-income countries, which face more daunting problems,” the researchers noted.

After the novel H1N1 virus was identified on April 23, 2009, Mexico City followed a pandemic influenza preparedness plan that had been developed for any virus that originated outside Mexico.

Efforts to decrease the spread of the virus included an intense media campaign encouraging people to stay home if they were sick and to avoid close contact such as hugging or kissing in greeting.

“Early in the epidemic, the federal government released antiviral drugs from the national strategic reserve and controlled their distribution,” Dr. Bell and his colleagues wrote.

“The government successfully introduced a mass media campaign that addressed Mexico City’s diverse population and range of literacy rates. In addition, it mobilized private businesses, such as grocery stores and pharmacies, to deliver health messages. The Ministry of Health also used text messages and e-mails to convey public health messages.

“The closure of thousands of businesses in Mexico City and throughout Mexico is estimated to have cost the country more than $2.3 billion, and large gatherings such as sporting events were cancelled or postponed, the researchers said.

Despite these costs, the researchers concluded that Mexico City’s preparations paid off. “The preexisting pandemic plan and planning process facilitated collaboration, decision making, and rapid development of a communications campaign,” they said. But the emergency of the pandemic illustrated several areas in need of improvement, including a limited capacity of laboratories to handle tests and a lack of criteria for reopening schools that closed because of the outbreak.

In New York City, 77% of emergency departments collected electronic information from more than 90% of patient visits. “During spring 2009, these systems were essential for real-time monitoring of the pandemic in NYC,” allowing public health officials to track the spread of the virus through the city.

The New York City government kept the public informed during the spring 2009 H1N1 outbreak with press conferences in both English and Spanish, and a government information hotline staffed with live operators answered 98% of calls within 30 seconds, the researchers said. About 50 schools in New York City closed for approximately 1 week.

Unlike Mexico City, New York City did not distribute antiviral drugs from the emergency stockpile because “normal distribution channels sufficed,” Dr. Bell and his associates said, but emergency plans called for the distribution of antivirals from the stockpile if necessary.

Decision making based on flu severity in New York City proved challenging given that the case-fatality ratio was unknown. Other challenges included deciding when and whether to close and reopen schools and how to keep children from gathering in groups elsewhere when schools were closed.

“In response to the surge in emergency department visits from individuals with flu-like symptoms, New York City hospitals were able to plan for additional care sites to handle the expected surge in cases of influenza-like illness in the fall and winter of 2009,” the researchers said.

Overall, they concluded that the early responses of Mexico City and New York City to the H1N1 virus outbreak were promising. “The problems that did occur would likely have been worse if the disease were more severe or if schools and businesses had remained closed for longer periods, they wrote.

The Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices has been “inclined toward” a recommendation for universal influenza vaccination over the past few years, he noted.

“If you read the current recommendations carefully, we have a quasi-universal recommendation,” explained Dr. Schaffner, who is a liaison member of the committee.

“This has drawn manufacturers into the U.S. market, and it further stimulated the rationale and the financing of research into developing and improving influenza vaccine,” he said. It can only be stimulated further by novel H1N1 that’s out there now, and by increasing the publicity (about) the kinds of severe illness of healthy people that H1N1 and seasonal influenza illnesses produce.

“I think it will be just a matter of time before we get a universal recommendation,” Dr. Schaffner predicted. “An improved vaccine would clearly stimulate such a recommendation.”

Dr. Schaffner disclosed that he has been a consultant for various vaccine manufacturers.

He is also a member of a data safety committee for Merck for experimental vaccines.

Continued from previous page

it longer than 2-3 years, there will also be a dose-savings and a better way of delivering vaccines to people.”

One potential pitfall of the DNA vaccine technology is the impending back-lash from vaccine naysayers, cautioned Dr. Schaffner.

“We have a hardcore group of vaccine skeptics,” he said. “This is a group of people who look askance at vaccines, are dubious about their benefits, and are concerned about how they’re manufactured and what’s in them. Any innovation, whether it’s the addition of an adjuvant, or a new technology such as this, will come to their attention and draw some of their skepticism and opposition. We have to brace for this.”

Then there’s the fact that DNA influenza vaccines have yet to be studied in rigorous, randomized controlled trials.

“The proof is in the pudding,” he said. “The studies have to be done. We await these phase I clinical trials with great interest.”

Universal Vaccination Next?

If clinical success is achieved with new influenza vaccines, it could catalyze a significant shift in public health policy, Dr. Schaffner predicted.
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