American Thoracic Society, Digestive Disease Week 2007, and American Society of Hypertension

Reuben B. David

More than 16,300 people attended sessions of the American Thoracic Society, 17,000 attended Digestive Disease Week 2007, and 2,230 attended the American Society of Hypertension. Speakers discussed arformoterol and indacaterol for chronic obstructive pulmonary disease, pegylated interferon with or without ribavirin for hepatitis C virus infection, ambrisentan for pulmonary arterial hypertension, and olmesartan/amlodipine combinations for hypertension.

American Thoracic Society: May 18–23, 2007, San Francisco, California

Bronchodilators for Chronic Obstructive Pulmonary Disease

Presenter: Bartolome R. Celli, MD, Professor of Medicine, Tufts University, Boston, Massachusetts

The importance of treating hyperinflation emerged as a strong theme in several presentations on pharmacotherapy for chronic obstructive pulmonary disease (COPD) at the meeting. As a speaker at a symposium, Dr. Celli asked this question: Why do bronchodilators reduce exacerbations of COPD?

Although it is well known that steroids reduce inflammation, he suggested that bronchodilators help prevent exacerbations of COPD by countering the hyperinflation that ensues when disease progression, over years and decades, leads to a loss of lung elastic recoil, air trapping, and static hyperinflation. As a result, the patient breathes at a higher lung volume. During an exacerbation, triggering of systemic inflammation stimulates a syndrome somewhat similar to exercise in the laboratory.

"The only difference, Dr. Celli said, "is that the patient can't get off the bike. But I believe that it is possible that if we can influence hyperinflation, you may be able to decrease the threshold level at which patients perceive shortness of breath."

Arformoterol (Brovana)

Presenter: James Donahue, MD, Chief of Pulmonology and Critical Care Medicine, University of North Carolina, Chapel Hill

A 12-month trial compared once-daily bronchodilation plus arformoterol (Brovana, Sepracor) 50 mcg, administered via nebulization to 528 patients, with twice-daily dosing of the bronchodilator salmeterol (Serevent Diskus, GlaxoSmithKline) 42 mcg, given by a metered dose inhaler to 265 patients. He emphasized the potential value of longer-acting bronchodilation with a 24-hour agent.

"We've begun to think that the hyperinflation seen in COPD is actually inflammatory. So it's better to keep the airway open the whole time, because long-term bronchodilation deflates the lung."

Patients included in the study were 35 years of age and older with confirmed COPD. Endpoints were adverse events and changes in 1-second forced expiratory volume (FEV_1). The arformoterol dose was 1.7 times greater than the approved twice-daily dose.

The mean FEV_1 at baseline was 38.9% with arformoterol and 37% with salmeterol. At one year, the overall frequency of adverse events was similar for arformoterol and salmeterol, as was the frequency of serious adverse events (12.7% for arformoterol and 12.5% for salmeterol), and for respiratory serious adverse events (5.5% and 5.7%, respectively).

COPD exacerbations did not increase in frequency over 12 months. Stable decreases in the use of a rescue medication, albuterol, occurred in both groups at these approximate rates: with arformoterol, 1.1 days per week, 1 puff per day; with salmeterol, 0.9 days per week, 0.9 puffs per day.

The peak percent change in FEV_1 from a visit that included predosing with arformoterol over four hours was slightly better but not to a clinically significant degree, Dr. Donohue said. Three patients receiving arformoterol and two patients receiving salmeterol died.

Dr. Donahue concluded that the safety of nebulizer arformoterol 50 mcg once daily was similar to that of salmeterol 42 mcg twice a day. Long-acting bronchodilators were not associated with a loss of COPD control over 12 months, as indicated by stability in the need for rescue medication and by the frequency of COPD exacerbations.

"With all the concerns about beta-agonist safety, this study is reassuring," he said in an interview. "This higher dose would work once a day, no question," he added.

Indacaterol

In another study conducted by Dr. Donahue, supratherapeutic doses of indacaterol (QAB 149, Novartis) among patients with mild-to-moderate COPD were associated with changes of only minimal concern. Indacaterol is entering into large-scale, 2,000-patient pivotal phase 3 trials in 300 sites, 200 of them in the U.S.

Mr. David is a medical writer living in New York City.

"Indacaterol is an interesting compound," he stated. "It's a new agent, not a formoterol derivative, and it's an ultra-long-acting beta agonist with very fine efficacy for 24 hours. It's similar to tiotropium [Spiriva, Boehringer Ingelheim/Pfizer], in that it's long-acting and has comparable, if not better, efficacy in the short-duration, head-to-head studies conducted so far."

Eighteen patients received single doses of indacaterol within the therapeutic range (400 mcg) via a dry-powder inhaler; after this, they received supratherapeutic doses at 1,000 mcg, 2,000 mcg, and 3,000 mcg. At the highest dose, the maximum mean decrease in fasting potassium (0.26 mmol/L), mean increase in fasting serum glucose (1.12 mmol/L), mean increase in heart rate (12 beats/minute), and mean decrease in the corrected QT interval (QTc) (7 milliseconds) were all considered to be within safe limits for a single dose. There were no clinically significant electrocardiographic abnormalities. Even in multiples of the therapeutic dose, Dr. Donahue said, indacaterol produced only mild-to-moderate changes in markers of systemic adrenergic stimulation in patients with COPD.

Ambrisentan (Letairis) for Pulmonary Arterial Hypertension

Presenter: Michael D. McGoon, MD, Professor of Medicine and Consultant in Cardiology, Mayo Clinic College of Medicine, Rochester, Minnesota

On June 15, 2007, after a priority review, the U.S. Food and Drug Administration (FDA) approved ambrisentan 5-mg and 10-mg tablets (Letairis, Gilead). This endothelin selective receptor antagonist is indicated for the once-daily treatment of pulmonary arterial hypertension (World Health Organization Group 1) in patients with WHO functional class 2 or 3 symptoms to improve exercise capacity and delay clinical worsening.

Because of the risks of liver injury and birth defects, the FDA required monthly monitoring of aminotransferases and urged that ambrisentan be discontinued under these circumstances: (1) if levels exceed more than five times the upper limit of normal (ULN), (2) if elevations are accompanied by bilirubin levels exceeding more than twice the ULN, or (3) if the patient had signs or symptoms of liver dysfunction.

The older endothelin receptor antagonists, bosentan (Tracleer, Actelion) and sitaxsentan (Thelin, Encysive), must also be monitored. On June 15th, 2007, the FDA concluded that the clinical development program for sitaxsentan did not demonstrate significant evidence of efficacy needed for approval; however, improvements in the six-minute walk test were noted. Encysive expects to file a request for formal dispute resolution with the FDA in the near term.

In a study of ambrisentan among patients who had discontinued bosentan or sitaxsentan because of abnormal serum aminotransferase levels, none of the patients discontinued ambrisentan therapy because of this abnormality.

The median duration of endothelin receptor antagonist therapy with bosentan or sitaxsentan before a first therapy failure caused by liver function test abnormalities had been 16 weeks. With ambrisentan at doses of 2.5, 5, or 10 mg/day, he said, only one of 31 evaluable patients required a temporary reduction in the ambrisentan dose because of elevated alanine aminotransferase (ALT) levels at 3.2 times the ULN at week 12. Furthermore, liver abnormalities did not show a trend toward increasing over time; one-year rates were similar to 12-week rates.

Dr. McGoon concluded that patients who had not responded to bosentan or sitaxsentan because of liver function abnormalities could be successfully treated with ambrisentan.

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Presenter: Ronald J. Oudiz, MD, Professor of Medicine, University of California, Los Angeles, School of Medicine, Torrance, California

Dr. Oudiz presented the long-term results of an extension study (ARIES-E), a 12-week trial of ambrisentan 2.5–10 mg among 383 patients with pulmonary arterial hypertension who had been exposed to ambrisentan for a mean of 1.4 years. In that trial, aspartate transaminase (AST) and ALT levels were between three and five times the ULN in 2.1% of the patients, and no discontinuations of ambrisentan were required. In one patient (0.3% of the total) with AST/ALT elevations above eight times the ULN, multiple drug therapy had to be discontinued. Dr. Oudiz pointed out that 2.3% of placebo patients in ARIES 1 and 2 had AST and ALT values exceeding three times the ULN.

In the ARIES-E trial, patients receiving ambrisentan improved their six-minute walking distance; the time to clinical worsening; WHO functional class symptoms; Borg dyspnea scores; Self-Help Health Survey (SF-36) status; and B-type natriuretic peptide levels, which correlate significantly with mean pulmonary arterial pressure and pulmonary vascular resistance.

Ambrisentan is being made available through the Letairis Education and Access Program (LEAP), a restricted distribution system designed to help patients learn about the risks of the drug.

Digestive Disease Week 2007: May 19–24, 2007, Washington, DC

Pegylated Interferon with or without Ribavirin for Hepatitis C Viral Infection

Presenter: Mark G. Swain, MD, Professor, Department of Medicine, Gastrointestinal Research Group, University of Calgary, Canada

Because clinical relapse is rare in patients with chronic hepatitis C virus (HCV) infection who achieve a sustained virological response (SVR) with peginterferon alfa-2a (Pegasys), with or without ribavirin (Copegus), both manufactured by Roche, it is possible that these patients might be considered "clinically cured."

Dr. Swain noted that SVR rates of up to 66% have been reported with peginterferon alfa-2a (40 kd) plus ribavirin in

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patients with HCV alone and of 40% in patients co-infected with HCV and human immunodeficiency virus (HIV). Pegasys is a modified form of interferon with a 40-kD polyethylene glycol strand attached to a recombinant interferon. This formulation increases the product's half-life from 7–10 hours to 77 hours.

The overall durability of these sustained responses, however, is less well known. To quantify the long-term durability of responses with peginterferon alfa-2a (40 kd), given as monotherapy or with ribavirin, Dr. Swain evaluated 997 patients who achieved undetectable HCV RNA levels (below 50 IU/mL) at 24 weeks' follow-up in nine randomized, multicenter trials of peginterferon alfa-2a (40 kd) therapy for HCV infection. Three trials involved monotherapy, and six involved combination therapy. Patients underwent five years of annual follow-up serum testing of HCV RNA levels. Ninety-three of the patients, all of whom received combination therapy, had HIV co-infection.

At a mean follow-up of 4.1 years, response rates were durable in 99.2% of patients. HCV RNA levels were detectable in eight patients.

Analyzing the type and duration of therapy, the incidence of co-infection, age, sex, race, genotype, viral load, days off treatment, and the presence of cirrhosis (none), Dr. Swain observed no suggestion of common risk factors. It was unclear whether the eight patients whose HCV RNA viral load became detectable during follow-up had experienced re-infection or a virological relapse.

He concluded that patients who achieve a sustained response could be considered cured of chronic HCV.

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Peginterferon alfa-2b and Peginterferon alfa-2a

Presenter: Vinod K. Rustgi, MD, Clinical Professor of Medicine, Georgetown University, Washington, DC

In a poster presented by Dr. Rustgi, patients with HCV who were intolerant of peginterferon alfa-2b (Peg-Intron, Schering) plus ribavirin, because of flu-like symptoms, fatigue, injection-site reactions, or depression, were more likely to tolerate peginterferon alfa-2a (Pegasys) plus ribavirin (96% completed 36 weeks of treatment). As a result, they achieved higher sustained virological response rates in a multicenter trial compared with non-responders.

American Society of Hypertension: 22nd Annual Scientific Meeting and Exposition, May 19–22, 2007, Chicago, Illinois

Olmesartan/Hydrochlorothiazide (Benicar HCT) versus Amlodipine/Benazepril (Lotrel)

Presenter: Henry Punzi, MD, Director, Punzi Medical Center and Hypertension Research Institute, Carrollton, Texas

Current hypertension guidelines call for a step approach, beginning first with one drug, then adding others. Advocates of initial combination therapy have long complained that antihypertensive monotherapy rarely achieves treatment goals, but they have not had the data to make their case for first-line combination therapy. Results from trials of combination therapy, however, may fill that void.

Dr. Punzi acknowledged the reluctance of many clinicians to start off with a strong combination therapy.

"The drugs in the old days dropped pressure so rapidly that it was dangerous, and a lot of family physicians became very concerned. But now we have much better drugs. The fixed-dose combinations are very carefully put together."

He presented the results of a 12-week study that compared olmesartan medoxomil plus a thiazide (Benicar HCT, Daiichi Sankyo) with amlodipine besylate/benazepril (Lotrel, Novartis) in 190 patients with stage 2 hypertension. Both combinations were more effective in lowering systolic blood pressure (BP) than either olmesartan (Benicar) or amlodipine (Norvasc, Pfizer) alone. Compared head-to-head, olmesartan/hydrochlorothiazide (40 mg/12.5 or 25 mg) outperformed amlodipine plus benazepril (5–10 mg/20 mg). The former combination resulted in a mean reduction of 33 mm Hg in systolic BP from baseline, compared with a decline of 27 mm Hg for the latter.

Among the olmesartan/thiazide patients, 66% reached a goal of 140/90 mm Hg or lower, and 33% achieved 130/80 mm Hg or lower. In the amlodipine/benazepril group, 45% reached the first goal, and 14% reached the second goal.

Dr. Punzi concluded that hesitation to use combination therapy might do more harm than good.

"The VALUE [Valsartan Antihypertensive Long-term Use Evaluation] trial showed us that if you don't control blood pressure well within the first six months, you get higher morbidity and mortality. Why mess around with monotherapy when we have safe and effective combination therapies?"

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Olmesartan and Amlodipine

Presenter: Steven Chrysant, MD, Oklahoma Cardiovascular and Hypertension Center, Oklahoma City, Oklahoma

Dr. Chrysant demonstrated that a calcium-channel blocker/angiotensin receptor blocker (CCB/ARB) combination improved blood pressure control without increasing the risk of adverse effects. He compared combinations of olmesartan medoxomil, 10 to 40 mg daily, plus amlodipine, 5 to 10 mg daily (Azor, Daiichi Sankyo), with either drug alone or placebo in 1,940 patients with mild-to-severe hypertension.

High-dose monotherapy with both amlodipine and olmesartan produced good reductions in BP, he said, "but only the combination can get you below 140 mm Hg systolic."

In addition to reducing systolic pressure, the combination produced a strong lowering effect in diastolic BP. By adding progressively higher doses of olmesartan while lowering the amlodipine dose, he suggested that foot edema could be reduced. ■