

Treating Comorbidities May Not Benefit Asthma

ARTICLES BY BRUCE JANCIN
Denver Bureau

KEYSTONE, COLO. — Optimal treatment of allergic rhinitis symptoms provides no added benefit in terms of improved control of coexistent asthma, Dr. Harold S. Nelson said at a meeting on allergy and respiratory disease sponsored by the National Jewish Medical and Research Center.

This conclusion, based on the negative findings of two large, well-conducted clinical trials, is a major disappointment, said Dr. Nelson, professor of medicine at the center as well as at the University of Colorado, Denver.



Several preliminary studies suggested that treating nasal symptoms might have a favorable effect on lower airway disease. These very small studies consistently showed that the use of intranasal corticosteroids in patients with allergic rhinitis and asthma resulted in improvement in bronchial hyperresponsiveness.

But then came the two definitive tests. Dr. Nelson was a coauthor of one—a 4-week, 92-site, double-blind, randomized clinical trial involving 863 patients with comorbid asthma and seasonal allergic rhinitis. All of the participants in the GlaxoSmithKline Inc.-sponsored study received open-label inhaled fluticasone propionate/salmeterol 100/50 mcg b.i.d. for their asthma, in addition to fluticasone propionate nasal spray, oral montelukast, or placebo for their allergic rhinitis. The addition of fluticasone nasal spray or montelukast significantly reduced nasal symptoms, compared with placebo, but it had no effect on asthma symptoms (Chest 2005;128:1910-20).

The other major double-blind multicenter trial, led by physicians at the Aarhus (Denmark) University, involved 262 patients with coexistent asthma and pollen-induced rhinitis. Beginning 2 weeks before the start of pollen season, they were randomized to 6 weeks of intranasal flutica-

sone propionate, inhaled fluticasone propionate, both, or dual placebo.

Only inhaled fluticasone significantly improved morning peak flow, methacholine responsiveness, and forced expiratory volume in 1 second, and quelled lower airway inflammation as reflected in blockage of the seasonal increase in sputum eosinophils. And only intranasal fluticasone effectively controlled nasal symptoms (Allergy 2005;60:875-81).

New data suggest that aggressive treatment of comorbidities has little impact on asthma control.

DR. GELFAND

son, because treatment began 2 weeks before onset of the pollen season, which is the right way to do it. In clinical practice, intranasal corticosteroids are far less effective when started only after patients become symptomatic, he stressed.

Dr. Erwin W. Gelfand noted that the message of these and several other studies is very different from the prevailing theory of the last decade. "It seems like we're moving away from the notion of comorbid conditions—sinusitis, [gastroesophageal reflux disease], rhinitis—impacting asthma. A series of studies has come up showing that aggressive treatment of the comorbid condition has little impact on asthma control," said Dr. Gelfand, chairman of the department of pediatrics at National Jewish Medical and Research Center and professor of pediatrics and immunology at the University of Colorado, Denver.

Dr. Nelson disclosed that he is a consultant to GlaxoSmithKline, Abbott Laboratories, APT Pharmaceuticals Inc., Curalogic A/S, Dey Laboratories, MediciNova Inc., Johnson and Johnson, Schering-Plough Corp., Dynavax Technologies Corp., Genentech Inc., and Novartis. Dr. Gelfand is a consultant to Teva Specialty Pharmaceuticals LLC, Novartis, Schering-Plough, and Altana Pharma U.S. Inc., and is on the Merck & Co. speakers bureau. ■

Extensively Drug-Resistant TB: Coming to a Location Near You

KEYSTONE, COLO. — Epidemiologic trends indicate that American physicians will increasingly encounter extensively drug-resistant tuberculosis in coming years, Dr. Charles L. Daley said at a meeting on allergy and respiratory disease sponsored by the National Jewish Medical and Research Center, Denver.

In the mid-1990s, TB in the United States occurred chiefly in U.S.-born persons. Indeed, U.S.-born patients with TB outnumbered foreign-born patients with TB 2:1. Since then, however, the annual number of TB cases among U.S.-born individuals has declined sharply, while the number of cases arising in the foreign born has remained constant. In each year since 2001 foreign-born persons have accounted for more than half of all TB cases in the United States.



"That's an important epidemiologic factor, because most of the XDR [extensively drug-resistant]-TB that's been reported has been outside the United States. With more cases here coming from those areas, no surprise, we're going to see more MDR [multidrug-resistant]- and XDR-TB," said Dr. Daley, head of the division of mycobacterial and respiratory infections at the center and professor of medicine at the University of Colorado, Denver.

The No. 1 risk factor for MDR and XDR is foreign birth in areas where TB is endemic and TB control practices are poor. Russia and many of its neighboring former Soviet republics constitute the biggest problem area worldwide. In those regions, more than 40% of people who've previously been treated for TB have MDR-TB.

Drug resistance in Russia was created mainly in the prisons—and recent mass pardons have put many convicts with MDR-TB back into the community. A lot of transmission also took place in the country's hospitals because of the lack of infection control protocols. In

Russia, 14% of MDR-TB strains are XDR, compared with 6% in the United States and Western Europe. South Africa is another hotbed of XDR, though there is little TB drug resistance elsewhere on the continent.

Suspect MDR-TB in a patient with TB symptoms and who is from or has traveled to an endemic area, Dr. Daley advised.

Globally each year, there are more than 400,000 new cases of MDR-TB and 40,000 of XDR-TB. "The XDR strains aren't real virulent, so far as we know, but they're almost untreatable," according to Dr. Daley. A handful of published reports show cure rates of about 30% in U.S. patients with XDR-TB, compared with what's being reported elsewhere. In contrast, treatment success rates of 60%-80% are reported with systematic treatment for MDR-TB.

DR. DALEY

A Centers for Disease Control and Prevention case series reported last year highlighted the changing epidemiology of XDR-TB in the United States during 1993-2006.

In 1993-1999, 72% of cases in the series were men, 38% were foreign born, and 44% were HIV positive. In contrast, in 2000-2006, only 47% were men, 76% were foreign born, and just 12% were HIV infected.

"You might say, 'Well, this doesn't matter to my practice,'" Dr. Daley said, adding that in the past year and a half, there has been a handful of documented cases of MDR-TB diagnosed in Rocky Mountain states where TB hasn't historically been much of a problem. All involved foreign-born individuals.

Current treatment regimens for XDR-TB virtually always require utilization of third-line drugs that aren't very potent against *Mycobacterium tuberculosis*, such as amoxicillin/clavulanate, clofazimine, linezolid, and the macrolides. With cure rates for XDR-TB hovering around 30%, new drugs are clearly needed, Dr. Daley said. ■

Tuberculosis Pipeline Holds Promise for Drug-Resistant Strain

KEYSTONE, COLO. — New drugs are desperately needed to address the growing problem of extensively drug-resistant tuberculosis—and help appears to be on the way.

Indeed, the drug development pipeline for anti-TB medications is remarkably full as a result of recent, greatly increased global attention to what had long been a seriously neglected disease.

"These investigational drugs are very exciting," Dr. Charles L. Daley said at a meeting on allergy and respiratory disease sponsored

by the National Jewish Medical and Research Center, Denver.

Five new drugs are in or soon to enter phase II clinical trials, including several that are already slated for phase III. And more than a dozen other drugs in pre-clinical testing or the discovery phase are being developed by the National Institute of Allergy and Infectious Diseases, various universities in the United States and abroad, the TB Alliance, and pharmaceutical companies both large and small, according to Dr.

Daley, head of the division of mycobacterial and respiratory infections at the center and professor of medicine at the University of Colorado.

The drugs now in clinical trials are diarylquinoline TMC207, a Johnson and Johnson molecule with greater activity against *Mycobacterium tuberculosis* than treatment mainstays isoniazid and rifampin; the widely prescribed Bayer antibiotic moxifloxacin; nitroimidazole PA-824, being developed through a collaboration between Chiron

Corp. and the TB Alliance; nitroimidazole-oxazole OPC-67683, an Otsuka drug slated to go into phase II trials this summer; and the Lupin Ltd. drug pyrrole LL-3858, which is "probably a couple years behind the others," he said.

These are drugs with novel mechanisms of action against *M. tuberculosis*. Resistance won't immediately be an issue.

Dr. Daley forecasted favorable long-term prospects for an effective TB vaccine, the key words being "long term."

At least 10 new TB vaccines are now in phase I or II trials around the world. But because no surrogate markers for immunity exist, the only way to learn if a TB vaccine is effective is to vaccinate people, follow them for 10 years or so, and see how many get TB.

"That means that even the vaccines that show promise are still way, way off in terms of routine use. But they're coming," he predicted.

Dr. Daley had no financial conflicts to disclose. ■