Biologics inch ahead in asthma treatment

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CHICAGO – Targeted biological therapies are working in rheumatoid arthritis, cancer, and irritable bowel disease, leading some experts to question whether their time in asthma has finally arrived.

“We’re still not there yet, but perhaps we can see the light at the end of the tunnel,” Dr. Diego J. Maselli said at CHEST 2013.

Early successes in animal models of asthma have not translated to human patients, in part because of disparities in immunology, biology, and anatomy, but also because of the heterogeneous nature of the disease.

The benchmark so far for asthma biologics is the anti-immunoglobulin E (anti-IgE) monoclonal antibody omalizumab (Xolair), indicated for moderate to severe persistent asthma that is uncontrolled with inhaled corticosteroids.

Omalizumab gained approval after cutting exacerbations in two trials involving patients with a forced expiratory volume in one second (FEV1) between 40% and 80% predicted, but the drug had no effect on exacerbations in a third trial that did not restrict screening FEV1 and allowed use of long-acting beta2-agonists. In all three studies, exacerbations were not reduced in patients requiring oral steroids as maintenance therapy or those with an FEV1 over 80%.

There is now significant experience with omalizumab, and although there was a concern regarding a slight increase in the incidence of malignancy in the initial studies, large registries have shown no risk for malignant neoplasms or cardiovascular effects, said Dr. Maselli, of the University of Texas Health Science Center, San Antonio.

Promising results with several new agents, however, suggest that phenotypical markers such as IgE, eosinophils, and periostin are necessary to identify patients most likely to benefit from targeted therapy, he noted.

For example, the investigational interleukin-5 (IL-5) antagonist mepolizumab produced mixed initial results, but reduced asthma exacerbations over the course of 50 weeks from a mean of 3.4 to 2 in one study (N. Engl. J. Med. 2009;360:973-84), and by 48% over placebo in a second study when used in highly selected asthma patient populations with confirmed sputum or serum eosinophilia (Lancet 2012;380:651-9).

A recent meta-analysis (PLOS One 2013 March 27 [10.1371/journal.pone.0059872]) of seven mepolizumab studies echoed these findings, but also concluded the drug fails to significantly improve lung function, Dr. Maselli observed.

Provocative results from another...
biologic suggest that the presence of nasal polyps in eosinophilic asthma may be useful in further selecting patients for IL-5 antagonist therapy. Intravenous treatment with the anti-IL-5 antibody reslizumab (Cinquill) had a greater effect on sputum eosinophilia and asthma exacerbations in poorly controlled asthmatics with nasal polyps (Am. J. Respir. Crit. Care. Med. 2011;184:1125-32).

Serum levels of the matricellular protein periostin are also being used to better target interleukin-13 (IL-13)-directed therapy, Dr. Maselli said. IL-13 induces bronchial epithelial cells to secrete periostin and is thought to play a central role in asthma by promoting mucus secretion and airway remodeling and hyper-reactivity.

Six monthly injections of the experimental anti-IL-13 monoclonal antibody lebrikizumab significantly improved lung function over placebo in asthmatics who were poorly controlled on inhaled corticosteroids, but produced a more robust increase in FEV1, and a 60% reduction in exacerbations only in the subgroup with high pretreatment periostin levels (N. Engl. J. Med. 2011;365:1088-98). Interestingly, the investigators had hypothesized that high serum IgE plus high peripheral-blood eosinophil counts would serve as a marker for patients with high IL-13 expression.

To further complicate IL-13 blockade, a more recent lebrikizumab study in asthmatic patients not receiving inhaled steroids reported no meaningful differences in FEV1 between various lebrikizumab dose groups and placebo in a periostin subgroup (J. Allergy Clin. Immunol. 2013;132:567-574.e12).

The investigational anti-IL-13 monoclonal antibody tralokinumab also recently failed to meet its primary endpoint of improving Asthma Control Questionnaire scores compared with placebo and modestly improved FEV1, in a phase II study (Eur. Respir. J. 2013;41:330-8).

Finally, strong phase II results are being seen with dupilumab, a monoclonal antibody that inhibits both IL-4 and IL-13 signaling, Dr. Maselli said. Dupilumab cut exacerbations by a dramatic 87%, improved lung function, and decreased biomarkers associated with type 2 helper T-cell-driven inflammation in patients with elevated eosinophil levels and moderate to severe uncontrolled asthma despite use of glucocorticosteroids and long-acting beta-agonists (N. Engl. J. Med. 2013;368:2455-66).

“These agents allow clinicians to target specific asthma phenotypes with the aid of biomarkers such as IgE, eosinophilia, and periostin, and show a glimpse of what the future of ‘personalized medicine’ may offer,” he said in an interview.

Dr. Maselli reported having no financial disclosures.

Dr. Vera DePalo, FCCP, comments: Targeted biological therapies offer the promise of broadening the array of treatments for asthma, giving providers more options for better outcomes.

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