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NEW DRUGS

Reslizumab, ixekizumab, and pimavanserin tartrate

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Antiasthmatic agent

The symptoms of many patients with asthma are effectively managed with the use of a beta$_2$-adrenergic agonist (e.g., salmeterol), muscarinic antagonist (e.g., tiotropium), or a corticosteroid (e.g., fluticasone) administered by oral inhalation. Certain corticosteroids (e.g., prednisone) are sometimes administered orally in patients with more severe symptoms. Even though these regimens are effective in most of the more that 20 million Americans with asthma, many patients do not experience adequate reduction of symptoms and associated complications with conventional therapy, and there are more than 400,000 asthma-related hospitalizations each year.

Multiple cell types, including eosinophils, and mediators (e.g., cytokines) are involved in the inflammatory process that occurs in the airways of the lungs. Interleukin (IL) 5 is the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils. In 2015, mepolizumab (Nucala) was approved as the first IL-5 antagonist for add-on maintenance treatment for patients with severe asthma and with an eosinophilic phenotype. It is administered subcutaneously and acts by reducing the production and survival of eosinophils.

Reslizumab (Cinqair—Teva) is the second IL-5 antagonist to be approved. Like mepolizumab, it is a monoclonal antibody and is indicated for add-on maintenance treatment of patients with severe asthma and with an eosinophilic phenotype. However, unlike its predecessor, it is administered by intravenous infusion and is not indicated in patients younger than 18 years of age, whereas the labeled indications for mepolizumab include patients as young as 12 years of age. Neither reslizumab nor mepolizumab is indicated for the treatment of other eosinophilic conditions or for the relief of acute bronchospasm or status asthmaticus.

The effectiveness of reslizumab was demonstrated in 4 placebo-controlled studies in patients with severe asthma who were being treated with other antiasthmatic medications. Two of the studies continued for 52 weeks, and reslizumab provided a significant reduction in the rate of asthma exacerbations, including those that required the use of a systemic corticosteroid as well as those that required hospitalization or an emergency room visit. The use of reslizumab resulted in a significant improvement in lung function as reflected by increases in 1-second forced expiratory volume determinations.

Although its properties and indications differ from those of reslizumab and mepolizumab, a third monoclonal antibody, omalizumab (Xolair), also has been used for the treatment of patients with asthma. Omalizumab is administered subcutaneously for the treatment of moderate to severe persistent asthma in patients with a positive skin test or *in vitro* reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with the use of an inhaled corticosteroid. It is also indicated for the treatment of chronic idiopathic urticaria in patients who remain symptomatic despite antihistamine treatment.

The most important risk associated with the use of reslizumab is anaphylaxis, which was reported in 0.3% of the patients in the clinical studies. This is the subject of a boxed warning in the labeling for the new drug, and it should be administered in a health care setting by a health care professional who is prepared to manage anaphylaxis. Patients should be observed for an appropriate period of time after the intravenous infusion of reslizumab. If severe systemic reactions, including anaphylaxis, occur, the administration of the drug should be stopped immediately and appropriate medical treatment provided. Reslizumab is contraindicated in patients with known hypersensitivity to the drug or any excipients in the formulation. Although hypersensitivity reactions are also a risk with the use of mepolizumab, the strength of the concern does not rise to the level of a boxed warning as included in the labeling for reslizumab.

Reslizumab was well tolerated in the clinical studies, and the most commonly experienced adverse events included oropharyngeal pain (3%) and myalgia (1%). Malignant neoplasms occurred in a small number of patients (0.6% compared with 0.3% of those in the placebo group). These responses were diverse and not

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associated with any particular tissue type. However, this risk is identified in the warnings in the labeling for reslizumab, whereas it is not included in the labeling for mepolizumab.

The use of reslizumab or mepolizumab may permit a reduction in the dosage of corticosteroids that have been part of a patient's maintenance treatment. The reduction of dosage of a corticosteroid may be associated with systemic withdrawal symptoms and unmask conditions previously suppressed by systemic corticosteroid therapy. Therefore, treatment with a systemic or inhaled corticosteroid should not be discontinued abruptly but should be done on a gradual basis.

Because eosinophils may be involved in the immunologic response to some helminth infections, patients with known parasitic infections were excluded from participation in the clinical studies of reslizumab. It is not known whether reslizumab would influence a patient's response against a parasitic infection, and preexisting helminth infections should be treated before initiating therapy with the new drug. If a helminth infection occurs during treatment with reslizumab, and does not respond to antihelminth treatment, the new drug should be discontinued until the infection resolves.

Information regarding the use of reslizumab in pregnant women is very limited, although there was no evidence of fetal harm in animal studies. The labeling for reslizumab notes that its safety and effectiveness in patients younger than 18 years of age have not been established. Although 39 patients in the clinical studies were in the age range of 12 to 17 years, the asthma exacerbation rate was actually higher in these patients than in those receiving placebo. Therefore, reslizumab is not indicated for use in patients younger than 18 years of age, whereas the indications for mepolizumab include patients as young as 12 years of age.

As with other monoclonal antibodies, reslizumab is degraded by enzymatic proteolysis into small peptides and amino acids.

Reslizumab is administered by intravenous infusion, and should not be used as an intravenous push or bolus. The recommended dosage is 3 mg/kg once every 4 weeks, infused over a period of 20 to 50 minutes.

The injection is supplied in single-use vials containing the drug in a concentration of 100 mg/10 mL. The vials should be stored in a refrigerator. The dose of the drug should be prepared and administered by a health care professional. The volume of solution needed to provide the dose of reslizumab should be withdrawn from the vial and slowly added to an infusion bag containing 50 mL 0.9% sodium chloride injection. To minimize foaming, neither the vial nor the infusion bag should be shaken.

Agent for psoriasis

Psoriasis is a chronic immune-mediated disease that affects an estimated 7.5 million Americans. It is characterized by thick and extensive skin lesions (plaques) which can cause itching, scaling, and pain. Mild and limited lesions can often be effectively treated with topically applied medications (e.g., corticosteroids and calcipotriene [a vitamin D analogue]). Options for the treatment of more widespread and severe lesions, as well as lesions that have not responded adequately to topical treatment, include phototherapy with ultraviolet light and systemic therapy with the use of an orally administered medication (e.g., methotrexate, apremilast [Otezla]) or a parenterally administered medication (e.g., a tumor necrosis factor inhibitor, e.g., adalimumab [Humira], etanercept [Enbrel]).

Certain naturally occurring interleukins (ILs) have been identified as having a role in the occurrence and worsening of psoriasis, and the development of IL receptor antagonists has been a focus of research efforts. Ustekinumab (Stelara) inhibits IL-12 and IL-23 and was the first IL antagonist to be approved for the treatment of psoriasis. IL-17A is another interleukin that is present in elevated concentrations in psoriatic plaques, and the IL-17A antagonist secukinumab (Cosentyx) was marketed in 2015 for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. It has also been subsequently approved for the treatment of patients with psoriatic arthritis and ankylosing spondylitis.

Like secukinumab, ixekizumab (Taltz—Lilly) is a monoclonal antibody that inhibits IL-17A. Both agents are administered subcutaneously, and ixekizumab was approved in early 2016 for the same indication for which secukinumab was initially approved: the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

The effectiveness of ixekizumab was demonstrated in 3 placebo-controlled studies that included almost 4000 participants. The primary endpoints were a reduction in the Psoriasis Area and Severity Index (PASI) score of at least 75% (PASI 75) from baseline to week 12, and an improvement in the Physician Global Assessment (PGA) to clear or minimal. From 87% to 90% of the patients treated with ixekizumab attained PASI 75, compared with 7% or fewer of those who received placebo. Approximately 70% of those treated with the new drug attained PASI 90, compared with fewer than 3% of those receiving placebo. Approximately 40% of the patients treated with ixekizumab received a PGA of clear, compared with 0% of those receiving placebo. In 2 studies, ixekizumab was compared with etanercept (50 mg twice a week). PASI 75 and PASI 90 scores for patients treated with ixekizumab for 12 weeks were obtained by 87% and 64%, respectively, compared with 41% and 18%, respectively, of those treated with etanercept.

As with other medications that suppress immune function, ixekizumab increases the risk of infection, with upper respiratory tract infections (14%) being one of the most commonly experienced events. Oral candidiasis, conjunctivitis, and tinea infections also occurred more frequently in patients treated with ixekizumab compared with those in the placebo group. If a serious infection occurs during treatment, the drug should be discontinued until the infection resolves, and the patient should be closely monitored. Patients treated with ixekizumab should not be treated with live vaccines, and before initiating treatment with the new drug, consideration should be given to completing all age-appropriate immunizations.

Patients should be evaluated for tuberculosis infection before initiating treatment with ixekizumab. In patients with a history of latent or active tuberculosis in whom an adequate course of antitubercular therapy cannot be confirmed, such treatment should be considered before initiating treatment with the new drug.

In the clinical studies, there were infrequent reports of Crohn's disease (0.1%) and ulcerative colitis (0.2%), including exacerbations. Although these