

A NEW MONOCLONAL ANTIBODY TREATS SEVERE ASTHMA

- Reslizumab (Cinqair), a new human monoclonal antibody, has been approved to treat severe asthma in adults. Given intravenously, the drug is used as adjunct therapy, in conjunction with inhaled corticosteroids, to reduce the frequency of asthma exacerbations, relieve asthma symptoms, and improve lung function in patients with elevated blood eosinophil levels.
- Like all monoclonal antibodies, it carries a risk of anaphylaxis.

The Food and Drug Administration (FDA) has approved reslizumab (Cinqair), a new humanized monoclonal antibody, for the treatment of severe asthma (sometimes referred to as refractory asthma). Reslizumab is used as adjunct therapy in conjunction with inhaled corticosteroids to reduce the frequency of asthma exacerbations, relieve asthma symptoms, and improve lung function in patients 18 years of age and older who have an elevated blood eosinophil level (also referred to as eosinophilic phenotype) and whose asthma is not adequately controlled by inhaled corticosteroids.

Human interleukin-5 is the main cytokine involved in the growth and differentiation, recruitment, activation, and survival of eosinophils, one type of cell involved in inflammation. Reslizumab binds to interleukin-5, inhibiting the production and survival of eosinophils. The recommended dosage is 3 mg/kg, infused over 20 to 50 minutes, once every four weeks.

Before its approval, reslizumab was studied in four clinical trials, which found that use of the drug significantly decreased the incidence of asthma exacerbations, including those necessitating oral corticosteroid use, hospitalization, or an ED visit. Study participants

receiving reslizumab also showed greater improvement in forced expiratory volume in one second (FEV₁) from baseline, as compared with those receiving placebo.

Meeting in December 2015, the FDA's Pulmonary-Allergy Drugs Advisory Committee expressed two concerns related to the safety and efficacy of reslizumab. First, there were not enough data on adolescents to determine the safety and efficacy of reslizumab in that age group. Second, the trials involved too few U.S. participants to generalize the study findings to the American population at large.

Reslizumab's labeling carries a boxed warning that the drug can cause anaphylaxis, a known risk with biologic drugs, including monoclonal antibodies. Patients with severe asthma are also considered to be at greater risk for anaphylaxis because of their underlying disease. In the preapproval trials involving placebo, anaphylaxis occurred in 0.3% of patients. Symptoms of anaphylaxis included respiratory signs and symptoms (wheezing, dyspnea, and decreased oxygen saturation levels), dermatologic symptoms (wheals, urticaria, and facial swelling), and gastrointestinal symptoms (abdominal pain, nausea, and vomiting). Anaphylaxis was reported as early as the second infusion and occurred either during the infusion or within 20 minutes thereafter.

All of the patients who developed anaphylactic reactions recovered after treatment.

There are three other warnings and precautions listed in reslizumab's labeling. The first concerns malignancy. In the clinical trials that involved placebo, malignancies of various types were seen at twice the rate in patients receiving reslizumab (six of 1,028, or 0.6%) as in patients receiving placebo (two of 730, or 0.3%). The majority of malignancies were diagnosed less than six months after beginning reslizumab therapy. Some

patients died from malignancy during the study periods. Complicating the analysis of whether reslizumab increases the risk of cancer is that clinical trials allowed patients with preexisting cancers to be enrolled, and the diagnoses of cancers within six months after the start of reslizumab therapy suggest that they were present at baseline.

The second of the other precautions relates to the use of corticosteroids prior to infusion of reslizumab. Abrupt discontinuation of either systemic or inhaled corticosteroids should be avoided. Although no clinical trials formally assessed the best method of reducing corticosteroid dosages during reslizumab therapy, it is known that reducing the dosage of either type of corticosteroid can lead to systemic withdrawal symptoms or expose other types of physiologic conditions that have been suppressed by the corticosteroid therapy. If a reduction in corticosteroid dosage is deemed necessary, the decrease should be carried out slowly.

Finally, the labeling warns that if the patient has a preexisting helminth infection, the infection should be treated before reslizumab therapy is started. Although patients with known parasitic infections were excluded from the clinical trials, the immune response to some helminth infections can cause eosinophil elevation.

Anaphylaxis and malignancy were the most frequently reported serious adverse effects, although mouth pain also occurred.

One other important adverse effect seen with reslizumab use was the elevation of creatine phosphokinase enzyme levels. In clinical studies, such elevations occurred across the spectrum of severity, at levels considered moderate, severe, and life threatening. The prevalence of life-threatening creatine phosphokinase elevations (greater than 10 times the upper limit of normal) was twice as high in

patients receiving reslizumab as in those receiving placebo (0.8% versus 0.4%).

None of the study subjects with life-threatening creatine phosphokinase elevations developed symptoms indicating rhabdomyolysis. No subjects with such high elevations stopped reslizumab therapy.

Other muscle-related adverse effects include myalgia (1% in study subjects receiving reslizumab versus 0.5% in subjects receiving placebo) and various other musculoskeletal symptoms that were reported on the day of reslizumab infusion, including musculoskeletal chest pain, neck pain, muscle spasms, extremity pain, muscle fatigue, and other musculoskeletal pain.

The mechanism underlying the elevations in creatine phosphokinase is unknown. Although monoclonal antibodies as a drug class are known to cause anaphylaxis, they are not known to cause creatine phosphokinase elevations. Because creatine phosphokinase levels had not been expected to rise with reslizumab use during clinical trials, levels were only measured immediately before administration, not in the hours after infusion. The advisory panel noted that the levels reported in the study most likely represented trough levels of the enzymes and that creatine phosphokinase elevations had likely been underreported. Complicating interpretation of the elevated creatine phosphokinase levels is that many of the patients had abnormal levels at baseline.

Reslizumab is given only as an iv infusion. Nurses should not administer the drug by iv push or as a bolus. They should flush the line with normal saline after administration to guarantee that the entire dose has been infused.

Nurses should be prepared for possible anaphylaxis and monitor the patient closely during and after infusions of reslizumab. An emergency cart should be readily

available. Patients should remain at the facility for observation after each infusion, but nurses should still teach patients the signs and symptoms of anaphylaxis and instruct them to seek immediate medical attention if symptoms develop. Nurses should also instruct patients not to stop taking their inhaled corticosteroid unless told to do so by their health care provider.

Reslizumab's complete FDA prescribing information, including detailed instructions on reconstitution and administration of the drug, can be accessed at <http://1.usa.gov/1TUKpNV>.

NEW WARNINGS FOR OPIOID ANALGESICS

- The Food and Drug Administration is revising the labeling of all opioid analgesics to warn that interactions between opioids and serotonergic drugs can produce serotonin syndrome, opioids have been linked to adrenal insufficiency, and decreases in levels of sex hormones may be associated with opioid use.

The Food and Drug Administration (FDA) is revising the labeling of all opioids to warn of three safety concerns.

The first issue is a drug interaction that can produce serotonin syndrome, a serious central nervous system reaction that occurs when serotonin levels rise too high, resulting in excessive stimulation.

Serotonergic drugs include medications taken for anxiety or depression, such as selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, tricyclic antidepressants, and monoamine oxidase inhibitors; certain psychiatric medicines, such as lithium, trazodone, and buspirone; medications used to treat migraine, such as triptans; antiemetics (the various serotonin 5-HT₃–receptor antagonists);

and other products, such as dextromethorphan, linezolid, and St. John's wort. For a complete listing of serotonergic drugs, see <http://1.usa.gov/1r14YOh>.)

Symptoms of serotonin syndrome include agitation, hallucinations, rapid heart rate, fever, excessive sweating, shivering or shaking, muscle twitching or stiffness, trouble with coordination, nausea or vomiting (or both), and diarrhea. According to data from the FDA Safety Information and Adverse Event Reporting Program, the opioids most frequently linked to serotonin syndrome are fentanyl and methadone. If serotonin syndrome is suspected, either the opioid or the serotonergic drug should be discontinued.

The second new warning concerns adrenal insufficiency, which has been determined to be a rare adverse effect of opioid use. Symptoms may include nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or low blood pressure. Diagnostic testing should be conducted in any patient in whom adrenal insufficiency is suspected. Treatment with corticosteroids may be necessary.

The third warning concerns a possible risk of diminished sex hormone levels. Effects reported include low libido, impotence, erectile dysfunction, amenorrhea, and infertility. Laboratory testing should be conducted to evaluate these symptoms. The FDA has decided to include the warning in the labeling of opioids despite the agency's admission that clinical trial data have not yet established a causal relationship between opioid use and diminished sex hormone levels.

The *FDA Drug Safety Communication* regarding all three warnings can be found at <http://1.usa.gov/1r14YOh>. ▼

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