Aclidinium bromide, tofacitinib citrate, and teriflunomide

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Bronchodilator

Chronic obstructive pulmonary disease (COPD) is characterized by symptoms such as chest tightness, chronic cough, and excessive phlegm and is the fourth leading cause of death in the United States. Cigarette smoking is the most common cause of COPD. Treatment of COPD most often has involved use of a beta-2–adrenergic agonist and/or an anticholinergic (antimuscarinic) agent via oral inhalation. Patients with more severe forms of the disease may have an inhaled corticosteroid added to their regimen.

Aclidinium bromide (Tudorza Pressair—Almirall; Forest) is the third synthetic quaternary ammonium compound with anticholinergic activity to be approved for use by oral inhalation in the treatment of COPD, joining ipratropium (e.g., Atrovent) and tiotropium (Spiriva HandiHaler). The new drug is most similar structurally to clidinium, an anticholinergic agent that was at one time available for oral use as a single agent (e.g., Quarzan) and in combination with chlordiazepoxide (e.g., Librax). However, the use and route of administration of aclidinium are most similar to those of ipratropium and tiotropium.

Aclidinium is specifically indicated for the long-term maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema. It is administered twice a day via oral inhalation, whereas tiotropium is administered once a day and ipratropium is administered three or four times a day. The effectiveness of aclidinium was demonstrated in placebo-controlled studies in which the drug provided significantly greater bronchodilation. The primary efficacy endpoint was the increase from baseline in morning predose FEV_1 (forced expiratory volume in the first second of expiration) at 12 weeks. In the few studies of aclidinium in which some patients were treated with tiotropium, the efficacy of the two drugs was generally similar. Although some results suggested that aclidinium provided improved symptom control at night, data were insufficient to conclude that a difference existed in the effectiveness of the two drugs.

The indication for tiotropium goes beyond that for aclidinium by including use for reducing COPD exacerbations. However, this is not a labeled indication for aclidinium currently.

The risks and precautions associated with the use of aclidinium are very similar to those for tiotropium and ipratropium. There have been rare reports of immediate hypersensitivity reactions, including angioedema and anaphylaxis, and because of its structural similarity to atropine, patients with a history of hypersensitivity reactions to atropine should be closely monitored for similar reactions to aclidinium. In addition, aclidinium and tiotropium must be used with caution in patients with severe hypersensitivity to milk proteins. Paradoxical bronchospasm has been experienced by some patients, and treatment should be discontinued if this response occurs. Aclidinium, tiotropium, and ipratropium are not for acute use, and patients should be cautioned that they must not be used as a rescue medication.

Because of its anticholinergic action, aclidinium may cause new or worsened urinary retention or new or worsened narrow-angle glaucoma, and patients should be advised to immediately consult their physician if signs or symptoms of these complications occur. The activity of aclidinium may be increased by the use of other medications with anticholinergic activity (e.g., tolterodine [e.g., Detrol], diphenhydramine [e.g., Benadryl]), and the concurrent use of these agents should be avoided.

The most commonly experienced adverse events in the clinical studies of aclidinium included headache (7%), nasopharyngitis (6%), cough (3%), and diarrhea (3%). Like tiotropium, the new drug is classified in Pregnancy Category C and should only be used during pregnancy if the anticipated benefit justifies the risk to the fetus. COPD does not normally occur in children, and the effectiveness and safety of aclidinium in pediatric patients have not been evaluated.

Following administration by oral inhalation, the absolute bioavailability of aclidinium is approximately 6%. It is rapidly and extensively metabolized by hydrolysis to derivatives that do not have pharmacologic activity. Only approximately 0.1% of a dose is excreted in the urine. Tiotropium is more likely to be absorbed into the systemic circulation following oral inhalation, and approximately 14% of a dose is excreted in the urine, primarily as unchanged drug. Thus, in patients with moderate to severe renal impairment, tiotropium is more likely than aclidinium to cause anticholinergic adverse events.

The recommended dosage of aclidinium is one oral inhalation of 400 µg twice a day. If a dose is missed, that dose should be skipped and the

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next dose administered at the usual time. The drug is provided in a dry powder formulation in a breath-actuated multidose inhaler that is supplied in a pouch. Each actuation provides a metered dose of 13 mg of the formulation, which contains lactose monohydrate (which may contain milk proteins) as the carrier and 400 µg aclidinium bromide. Each actuation delivers 375 µg aclidinium bromide from the mouthpiece.

Tudorza Pressair is a unit containing 60 doses of aclidinium bromide, and the product labeling should be consulted for the instructions for use. The unit contains a button that is pressed and released to make a dose available and a control window that confirms a dose is available for inhalation. The patient should breathe out completely (but not into the inhaler) before placing the mouthpiece in the mouth. After placing the lips tightly around the mouthpiece, a quick, deep breath provides the delivery of the dose of medication. The patient should breathe in until a "click" sound is heard and should continue breathing in to be sure the full dose is delivered. The mouthpiece then is removed from the mouth and patients should hold their breath for as long as is comfortable and then breathe out slowly through the nose. The control window should be checked to confirm that the dose has been inhaled correctly. The inhalation device does not have to be cleaned. The inhaler should be discarded and a new one obtained when the dose indicator has a marking of 0, when the device locks out, or 45 days after the inhaler was removed from the sealed pouch, whichever comes first.

Although aclidinium is administered more frequently (twice a day) than tiotropium (once a day), the administration of doses of aclidinium is more convenient than with tiotropium, which is supplied in capsules that are placed in the inhalation device and pierced to release the medication.

Antiarthritic agent

The development of biologic agents that reduce inflammation and associated complications by altering immune function has resulted in important progress in the treatment of rheumatoid arthritis and other diseases. These agents include the tumor necrosis factor (TNF) inhibitors etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira), certolizumab (Cimzia), and golimumab (Simponi), the selective costimulation modulator abatacept (Orencia), and the interleukin-6 antagonist tocilizumab (Actemra). In addition to relieving inflammation and pain associated with rheumatoid arthritis, certain of these agents have been demonstrated to be effective in inducing a major clinical response, inhibiting progression of structural damage, and improving physical function. However, a disadvantage of each of these agents is that they must be administered by injection.

Janus kinases (JAKs) are intracellular enzymes that mediate the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. In 2011, ruxolitinib (Jakafi) was the first JAK inhibitor to be marketed. It is administered orally for the treatment of myelofibrosis, a disease involving the bone marrow that is associated with the dysregulation of two JAKs.

Tofacitinib citrate (Xeljanz—Pfizer) is a JAK inhibitor that is effective following oral administration in the treatment of rheumatoid arthritis. It is specifically indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. It may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs). Because of the potential for an excessive effect on immune function, tofacitinib should not be used in combination with a biologic DMARD or a potent immunosuppressant such as azathioprine and cyclosporine (e.g., Neoral).

The effectiveness of tofacitinib following oral administration in patients who have had an inadequate response or intolerance to methotrexate or a TNF inhibitor offers the hope that it may be as effective as the parenterally administered biologic antiarthritic agents. However, it is not indicated for first-line use in patients with rheumatoid arthritis and its labeled indication is more limited than those for the biologic agents with respect to the clinical benefits that can be anticipated. In addition, although some of the risks associated with the use of tofacitinib are the same as those for the biologic agents, tofacitinib has other potential problems that require periodic monitoring.

Tofacitinib was evaluated in seven clinical trials in patients with moderately to severely active rheumatoid arthritis who had an inadequate response to methotrexate and/or another DMARD. Two of the studies included patients who had experienced an inadequate response to a biologic DMARD (e.g., adalimumab). In all seven studies, patients treated with tofacitinib experienced improvement in clinical response and physical functioning compared with patients receiving placebo. Therefore, the new drug represents an important advance in the therapeutic options available for the treatment of patients with rheumatoid arthritis.

Certain of the risks associated with the use of tofacitinib are the same as those for the biologic DMARDs (e.g., TNF inhibitors). Serious infections have occurred, including active tuberculosis, invasive fungal infections, and bacterial, viral, and other infections caused by opportunistic pathogens. These are the subject of a boxed warning in the labeling for tofacitinib, as well as for the TNF inhibitors. Most patients who have experienced serious