

Four Infusion Drugs Provide New Therapy Options

This article will briefly review four infusion drugs which were either recently approved by the FDA for the first time, or which had approval of significant new indications: Rituxan, Dacogen, Boniva Injection, and Myozyme. Clinicians are cautioned to review the complete prescribing information for each agent, including warnings and cautions, before use in a particular patient.

Rituxan for Rheumatoid Arthritis

Note: this drug has the potential for significant infusion-related side effects, and the complete prescribing information should be reviewed before use in a particular patient.

Rheumatoid arthritis (RA) is a debilitating autoimmune disease that affects more than 2 million Americans. Rituxan is a genetically-engineered therapeutic antibody (rituximab) that was initially approved in 1997 for treatment of certain types of non-Hodgkins lymphoma (NHL). It was FDA-approved in May 2006, in combination with methotrexate, for the treatment of moderate to severe RA in adult patients who have had an inadequate response to one or more tumor necrosis factor antagonist therapies such as Humira, Enbrel, or Remicade. The phase 3 "REFLEX" clinical trial was the basis for the FDA's decision. Patients in this trial who received Rituxan had significant improvement in joint pain, inflammation and physical function at 24 weeks (as compared to placebo) from a single course of therapy (2 infusions), along with a stable dose of methotrexate.

Rituxan binds to the antigen CD20, and selectively targets immune cells known as CD20-positive B-cells; it does not target stem cells or existing plasma cells. This drug may affect multiple pathways by which B-cells may contribute to the onset and progression of RA. It is the only agent with this mechanism of action that is approved for RA.

Infusion-related reactions: "Black Box" warning

It should be noted that extremely serious infusion reactions have been reported with Rituxan, some with fatal outcomes. The most severe symptoms of infusion-related reactions were pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, and anaphylactic-type reactions. In reported cases, the following factors were more frequently associated with fatal outcomes: female gender, pulmonary infiltrates, and chronic lymphocytic leukemia or mantle cell lymphoma.

Most patients experience some type of infusion-related symptoms with their first Rituxan infusion. Such reactions may occur within 30-120 minutes of the start of the first dose, which should be infused in a hospital or clinic setting where medical intervention is readily available. These symptoms could include flu-like illness, chills/rigors, nausea, urticaria, headache, bronchospasm, angioedema, hypotension, and hypoxia. These symptoms vary in their severity and are generally reversible with medical intervention. Less than 1 percent of acute infusion reactions were judged to be serious in the REFLEX trial.

Another potentially significant side effect of Rituxan is hypotension, which may occur during the infusion; therefore, it is recommended that antihypertensive agents be held for 12 hours prior to each dose. Also, about 5% of Rituxan-treated patients may develop anti-chimeric antibodies.

The current recommended dose for RA is one treatment course, consisting of two 1000 mg IV infusions separated by 2 weeks, in combination with methotrexate. Solu-Medrol 100 mg IV (or equivalent) is given as a pre-infusion medication 30 minutes before each Rituxan dose. The safety and effectiveness of additional Rituxan doses has not been established; a few patients have received additional courses, but none received subsequent courses sooner than 16 weeks after the previous course and most had subsequent courses 24 weeks after the previous one. Further research may clarify the appropriate use of additional doses in RA patients.

Rituxan is also being studied for treatment of other autoimmune diseases, including lupus nephritis, systemic lupus erythematosus (SLE), and multiple sclerosis (MS).



Dacogen (decitabine) for myelodysplastic syndrome

Dacogen is a new drug that has been approved for treatment of myelodysplastic syndromes (MDS), a group of bone-marrow disorders that can develop into cancer. A patient with MDS has too few of one or more types of healthy blood cells (red cells, white cells and/or platelets) in the blood or bone marrow. Dacogen therapy is indicated for patients at high or intermediate risk of developing acute myeloid leukemia (AML). Patients at low risk for developing AML were not included in the clinical trials.

Decitabine is an antimetabolite that can replace cytosine in DNA. Unlike cytosine, it cannot be methylated. The drug is thought to act by regulating DNA methylation, specifically by targeting methyltransferase. In some cancer cells, hypermethylation blocks the activity of tumor suppressor genes, which normally regulate cell division and prevent malignant transformation. Because hypermethylation occurs early in the malignant transformation of cells, decitabine may restore normal function to genes that are critical in controlling cellular differentiation and proliferation. This may prevent MDS from developing into cancer.

Decitabine is in Pregnancy Category D (may cause fetal harm) and pregnancy should be avoided during therapy. Men who are treated with Dacogen should be advised to avoid fathering a child during therapy, and for at least 2 months afterward. Side effects of Dacogen therapy may include neutropenia (87%), thrombocytopenia (85%), febrile neutropenia (23%), and leukopenia (22%). Other side effects may include fatigue, nausea, vomiting, cough, bleeding into the skin, constipation, diarrhea, and hyperglycemia.

The recommended dose of Dacogen is 15 mg/m² by continuous infusion over 3 hours, every 8 hours for 3 days; these nine doses are repeated every 6 weeks at least 4 times. More cycles may be needed for a complete or partial response; length of therapy is dependent on clinical response and toxicity. Standard anti-emetic therapy can be used before treatment. Treatment should be delayed if the patient's neutrophil and platelet counts do not reach minimally acceptable levels by the time the next cycle is due.

Decitabine should be handled according to hazardous drug precautions. Each 50 ml vial is reconstituted with 10 ml sterile water, and then immediately diluted further with normal saline, 5% dextrose, or Lactated Ringers' injection to a final concentration of 0.1-1 mg/ml. Administration of the diluted solution should start within 15 minutes of reconstituting the drug powder. If immediate administration is not possible, then a cold fluid must be used to dilute the reconstituted product; under these conditions the solution can be stored up to 7 hours under refrigeration.

Dacogen is also being studied for use in non-small cell lung cancer, in sickle-cell anemia and other thalassemias, and in other hematologic malignancies such as chronic lymphocytic leukemia (CML) and acute myeloid or lymphocytic leukemia.

Dacogen is marketed by MGI Pharma, which offers patient and professional information at dacogen.com and managemds.com. The drug should be commercially available by early June 2006.

Boniva Injection for Postmenopausal Osteoporosis

In 2004, the Surgeon General issued a report that elevated osteoporosis to a major public health threat similar to smoking and obesity in significance. Osteoporosis causes bones to become weak and more likely to break, and may result in severe pain, deformity, disability, hospitalization, and even death. 44 million Americans over age 50 are either affected by or are at risk for osteoporosis. Osteoporosis is responsible for approximately 300,000 hip fractures and 700,000 spinal fractures among men and women in the U.S. each year.

The bisphosphonates (Fosamax, Aredia, Actonel, Boniva) are well established for the treatment of postmenopausal osteoporosis. Bisphosphonates work by binding to calcified bone matrix, decreasing bone solubility, and decreasing the activity of osteoclasts. However, the oral forms are poorly absorbed from the GI tract (less than 1% bioavailability), and are associated with adverse gastrointestinal side effects such as an uncomfortable burning sensation in the esophagus shortly after taking the drug. Dosing guidelines include that the patient not eat or lie down for at least 30-60 minutes after taking oral bisphosphonates, a requirement that is inconvenient and may significantly impact compliance. Drugs in the same class that are dosed less often may result in better outcomes, due to increased patient acceptance.

Boniva (ibandronate sodium) injection is an intravenous treatment for postmenopausal osteoporosis. A 2.5 mg tablet for daily dosing was approved by the FDA in 2003, and a 150 mg tablet for monthly dosing was approved in 2005. The new injectable form is only administered once every 3 months, as an intravenous (IV) injection of 3 mg over 15-30 seconds. It is an alternative for patients who have difficulty with oral



Decitabine is a hazardous drug and must be prepared in a biological safety cabinet

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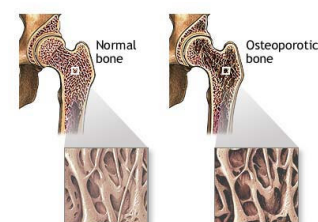
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In elderly patients with bones weakened by osteoporosis, very little trauma, even walking, may result in a hip fracture.

medications, such as the inability to sit upright for 30-60 minutes and/or swallow a pill. Boniva is also being tested in clinical trials for use in malignant hypercalcemia and Paget's disease.

Boniva injections must be given by a health professional, and should only be given by the intravenous route. The patient's serum creatinine must be checked before each dose. Boniva should not be used in patients with severe renal impairment (creatinine clearance < 30 ml/min.) Patients should be evaluated and treated for hypocalcemia, vitamin D deficiency, and other disturbances of bone and mineral metabolism before starting therapy. Patients must receive supplemental calcium and vitamin D. Osteonecrosis of the jaw is a rare complication that has been reported; most occurrences have been in cancer patients undergoing dental procedures who also received intravenous bisphosphonates. Co-administration of Boniva IV with other potentially nephrotoxic drugs could theoretically increase the risk of drug-related nephrotoxicity, and such patients should be monitored appropriately throughout therapy.

Injection site reactions (erythema, redness, or swelling) are infrequently observed with Boniva injection. Reactions tended to be mild to moderate in severity in clinical trials. Injection of Boniva other than by the IV route could cause tissue damage. Flu-like illness and fever were more common with IV versus oral Boniva. In most cases, no specific treatment was required, and the symptoms subsided within 24-48 hours. Other side effects commonly reported included diaphoresis and hot flashes. The ocular side effects seen with other drugs in this class could potentially occur with Boniva injection as well, such as eye inflammation, eye pain, or change in vision.

The complete prescribing information should be reviewed before use of this drug in an individual patient. The manufacturer offers a patient support program (see www.boniva.com) to help increase patient compliance with therapy.

Myozyme for Pompe's Disease

Myozyme (alglucosidase alfa) has been approved by the FDA for use in Pompe's Disease, a rare inherited neuromuscular disorder. The disease is deadly if it develops during infancy. Patients who develop the disease later in life may experience steadily progressive debilitation and premature mortality due to respiratory failure. They often require mechanical ventilation to assist breathing and wheelchairs for mobility. It is estimated that the disease affects about 5,000 to 10,000 persons worldwide.

Myozyme is a recombinant human enzyme-replacement product for endogenous acid alpha-glucosidase, and is the first treatment for any of the muscle diseases monitored by the Muscular Dystrophy Association (MDA). The alpha-glucosidase enzyme is required to break down glycogen in cell lysosomes. In Pompe's disease, excess glycogen builds up in the lysosomes. This progressively damages and weakens muscle tissue, including cardiac muscle, skeletal muscle, and muscles involved in breathing. Myozyme improves ventilator-free survival in patients with infantile-onset Pompe's disease as compared to historical data. Use of Myozyme in patients with other forms of Pompe's disease has not been studied sufficiently to assure safety or efficacy, but clinical trials are underway.

Myozyme 20 mg/kg is administered every 2 weeks by IV infusion over about 4 hours. There is a protocol for ramping up the infusion rate from a starting point of 1 mg/kg/hr, monitoring the patient's tolerance, and increasing the rate by 2 mg/kg/hour every 30 minutes. The maximum infusion rate is 7 mg/kg/hr. This product is stored in the refrigerator. Once reconstituted and diluted, it should be used immediately. The prepared solution is stable under refrigeration for 24 hours.

Serious and life-threatening allergic reactions, including anaphylaxis, were reported during clinical trials of the drug. These reactions occurred in 8 out of 280 patients (3 percent). Appropriate medical support measures should be available during Myozyme administration. Antibody formation occurs in 83% of patients and may be significant. One phase 2 clinical trial (Klinge, et. al, 2005) indicated that pre-medicating with corticosteroids and/or antihistamines may reduce the rate of infusion-related adverse reactions.

For more information on Pompe's disease, Myozyme, and the MDA, refer to www.pompe.com, www.genzyme.com (manufacturer of Myozyme) and www.mdausa.org.

References:

1. Manufacturer's information
2. American Society for Health-System Pharmacists News (May 1, 2006)
3. Clinical Pharmacology [database online], Tampa FL: Gold Standard, Inc.; 2006. URL: <http://cp.gsm.com>. Accessed May 18, 2006.



Boniva IV is in a prefilled syringe

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Infusion Partners is an alternate site healthcare organization whose cohesive team of professionals mission is dedicated to providing the highest quality care and services in an ethical, customer-focused environment.



Enzyme replacement therapy offers new hope to victims of Pompe's disease