with moderately to severely active rheumatoid arthritis and Crohn's disease treated with REMICADE in clinical trials with a median of 1.1 years of follow-up, 3 patients developed lymphomas, for a rate of 0.07 cases per 100 patient-years of follow-up in patients with rheumatoid arthritis and 0.12 cases per 100 patient-years of follow up in the combined clinical trial data for rheumatoid arthritis and Crohn's disease patients. This is approximately 3-fold higher in the RA clinical trial population and 6-fold higher in the overall clinical trial population than expected in an age-, gender-, and race-matched general population based on the Surveillance, Epidemiology and End Results Database. Rates in clinical trials for REMICADE cannot be compared to rates of clinical trials of other TNF blockers and may not predict rates observed in a broader patient population. An increased rate of lymphoma up to several fold has been reported in the Crohn's disease and rheumatoid arthritis patient populations, and may be further increased in patients with more severe disease activity. Other than lymphoma, 13 patients developed malignancies, which was similar in number to what would be expected in the general population. Of these, the most common malignancies were breast, colorectal, and melanoma. (See *WARNINGS, Malignancies.*) Malignancies, including non-Hodgkin's lymphoma and Hodgkin's disease, have also been reported in patients receiving REMICADE during post-approval use. **Patients with Heart Failure** In a randomized study evaluating REMICADE in moderate to severe heart failure (NYHA Class III/IV; left ventricular ejection fraction ≤35%), 150 patients were randomized to receive treatment with 3 infusions of REMICADE 10 mg/kg, 5 mg/kg, or placebo, at 0, 2, and 6 weeks. Higher incidences of mortality and hospitalization due to worsening heart failure were observed in patients receiving the 10 mg/kg REMICADE dose. At 1 year, 8 patients in the 10 mg/kg REMICADE group had died compared with 4 deaths each in the 5 mg/kg REMICADE and the placebo groups. There were trends towards increased dyspnea, hypotension, angina, and dizziness in both the 10 mg/kg and 5 mg/kg REMICADE treatment groups, versus placebo. REMICADE has not been studied in patients with mild heart failure (NYHA Class I/II) (see *CONTRAINDICATIONS* and *WARNINGS, Patients with Heart Failure*). **Immunogenicity** Treatment with REMICADE can be associated with the development of antibodies to infliximab. The incidence of antibodies to infliximab in patients given a 3-dose induction regimen followed by maintenance dosing was approximately 10% as assessed through one to two years of REMICADE treatment. A higher incidence of antibodies to infliximab was observed in Crohn's disease patients receiving REMICADE after drug-free intervals >16 weeks. The majority of antibody-positive patients had low titers. Patients who were antibody-positive were more likely to have higher rates of clearance, reduced efficacy and to experience an infusion reaction (see *ADVERSE REACTIONS, Infusion-related Reactions*) than were patients who were antibody negative. Antibody development was lower among rheumatoid arthritis and Crohn's disease patients receiving immunosuppressant therapies such as 6-MP/AZA or MTX. The data reflect the percentage of patients whose test results were positive for antibodies to infliximab in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to infliximab with the incidence of antibodies to other products may be misleading. **Hepatotoxicity** Severe liver injury, including acute liver failure and autoimmune hepatitis, has been reported rarely in patients receiving REMICADE (see *WARNINGS, Hepatotoxicity*). Reactivation of hepatitis B has occurred in patients receiving REMICADE who are chronic carriers of this virus (i.e., surface antigen positive) (see *WARNINGS, Hepatotoxicity*). In clinical trials in RA, Crohn's disease and ankylosing spondylitis, elevations of aminotransferases were observed (ALT more common than AST) in a greater proportion of patients receiving REMICADE than in controls, both when REMICADE was given as monotherapy and when it was used in combination with other immunosuppressive agents. In general, patients who developed ALT and AST elevations were asymptomatic, and the abnormalities decreased or resolved with either continuation or discontinuation of REMICADE, or modification of concomitant medications. ALT elevations ≥5 times the upper limit of normal were observed in 1% of patients receiving REMICADE.In rheumatoid arthritis clinical trials, 34% of patients who received REMICADE + MTX experienced transient mild (<2 times the upper limit of normal) or moderate (≥2 but <3 times the upper limit of normal) elevations in ALT compared to 24% of patients treated with placebo + MTX. ALT elevations ≥3 times the upper limit of normal were observed in 3.9% of patients who received REMICADE + MTX compared with 3.2% of patients who received MTX alone (median follow up approximately 1 year). In Crohn's disease clinical trials (median follow up 54 weeks), 39% of patients receiving REMICADE-maintenance experienced mild to moderate elevations in ALT, compared to 34% of patients treated with placebo-maintenance. ALT elevations ≥3 times the upper limit of normal were observed in 5.0% of patients who received REMICADE-maintenance compared with 4.0% of patients who received placebo-maintenance. In an ankylosing spondylitis clinical trial in which patients were not receiving MTX, 40% of patients who received REMICADE experienced mild to moderate elevations in ALT compared to 13% of patients treated with placebo. ALT elevations ≥3 times the upper limit of normal were observed in 12 (6%) REMICADE-treated patients compared to none in placebo-treated patients. **Other Adverse Reactions** Safety data are available from 2629 REMICADE-treated patients, including 1304 with rheumatoid arthritis, 1106 with Crohn's disease, 202 with ankylosing spondylitis and 17 with other conditions. Adverse events reported in ≥5% of all patients with rheumatoid arthritis receiving 4 or more infusions are listed below. The types and frequencies of adverse reactions observed were similar in REMICADE-treated rheumatoid arthritis, ankylosing spondylitis and Crohn's disease patients except for abdominal pain, which occurred in 26% of REMICADE-treated patients with Crohn's disease. In the Crohn's disease studies, there were insufficient numbers and duration of follow-up for patients who never received REMICADE to provide meaningful comparisons. The percentages of adverse events for placebo-treated patients (n=350; average weeks of follow-up 59) and REMICADE-treated patients (n=1129; average weeks of follow-up 66), respectively, are: *Gastrointestinal:* Nausea: 20, 21; Abdominal pain: 8, 12; Diarrhea: 12, 12; Dyspepsia: 7, 10. *Respiratory:* Upper respiratory tract infection: 25, 32; Sinusitis: 8, 14; Pharyngitis: 8, 12; Coughing: 8, 12; Bronchitis: 9, 10; Rhinitis: 5, 8; *Skin and appendages disorders:* Rash: 5, 10; Pruritis: 2, 7; *Body as a whole—general disorders:* Fatigue: 7, 9; Pain: 7, 8; *Resistance mechanism disorders:* Fever: 4, 7; Moniliasis: 3, 5; *Central and peripheral nervous system disorders:* Headache: 14, 18; *Musculoskeletal system disorders:* Back pain: 5, 8; Arthralgia: 7, 8; *Urinary system disorders:* Urinary tract infection: 6, 8; *Cardiovascular disorders, general:* Hypertension: 5, 7. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not predict the rates observed in broader patient populations in clinical practice. The most common serious adverse events observed in clinical trials were infections (see *ADVERSE REACTIONS, Infections*). Other serious, medically relevant adverse events ≥0.2% or clinically significant adverse events by body system were as follows: *Body as a whole:* allergic reaction, diaphragmatic hernia, edema, surgical/procedural sequela; *Blood:* pancytopenia; *Cardiovascular:* circulatory failure, hypotension, syncope; *Gastrointestinal:* constipation, gastrointestinal hemorrhage, ileus, intestinal obstruction, intestinal perforation, intestinal stenosis, pancreatitis, peritonitis, proctalgia; *Central and Peripheral Nervous:* meningitis, neuritis, peripheral neuropathy, dizziness; *Heart Rate and Rhythm:* arrhythmia, bradycardia, cardiac arrest, tachycardia; *Liver and Biliary:* biliary pain, cholecystitis, cholelithiasis, hepatitis; *Metabolic and Nutritional:* dehydration; *Musculoskeletal:* intervertebral disk herniation, tendon disorder; *Myo-, Endo-, Pericardial, and Coronary Valve:* myocardial infarction; *Platelet, Bleeding, and Clotting:* thrombocytopenia; *Neoplasms:* basal cell, breast, lymphoma; *Psychiatric:* confusion, suicide attempt; *Red Blood Cell:* anemia, hemolytic anemia; *Reproductive:* menstrual irregularity; *Resistance Mechanism:* cellulitis, sepsis, serum sickness; *Respiratory:* adult respiratory distress syndrome, lower respiratory tract infection (including pneumonia), pleural effusion, pleurisy, pulmonary edema, respiratory insufficiency; *Skin and Appendages:* increased sweating, ulceration; *Urinary:* renal calculus, renal failure; *Vascular (Extracardiac):* brain infarction, pulmonary embolism, thrombophlebitis; *White Cell and Reticuloendothelial:* leukopenia, lymphadenopathy. The following adverse events have been reported during post-approval use of REMICADE: neutropenia (see *WARNINGS, Hematologic Events*), interstitial pneumonitis/fibrosis, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, pericardial effusion, systemic and cutaneous vasculitis, Guillain-Barré syndrome, transverse myelitis, and neuropathies (additional neurologic events have also been observed, see *WARNINGS, Neurologic Events*). Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to REMICADE exposure. **OVERDOSAGE:** Single doses up to 20 mg/kg have been administered without any direct toxic effect. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately. **REFERENCE: 1.** American Thoracic Society, Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med* 2000;161:S221–S247.

Watch for Osteonecrosis With Long-Term Bisphosphonates

BY KATE JOHNSON
Montreal Bureau

Long-term bisphosphonate therapy can lead to osteonecrosis of the jaw—a previously unrecognized and potentially serious complication that can often be avoided, according to Salvatore Ruggiero, M.D., D.M.D.

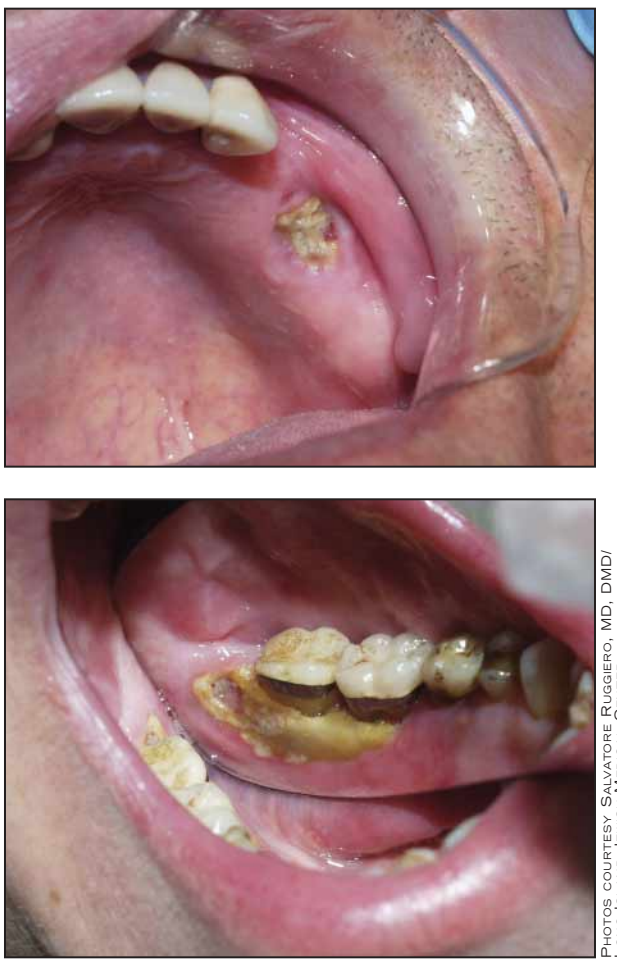
Patients on intravenous therapy, whether for cancer or osteoporosis, face the highest risk regardless of whether they are taking the medication for cancer or for osteoporosis, while the risk is lower, although not absent in those taking oral bisphosphonates, said Dr. Ruggiero, who is chief of oral and maxillofacial surgery at Long Island Jewish Medical Center in New Hyde Park, NY.

"The push is to alert physicians that this is a potential problem, so that before they start a patient on bisphosphonates, they send them to a dentist to extract any teeth that are nonrestorable," he told this newspaper. "Prevention and early detection are important for preserving the jawbone in these individuals."

In his experience, the majority of cases have been associated with infections following dental surgeries such as tooth extractions.

However, necrosis has also occurred spontaneously in a significant number of patients, he said.

For this reason Dr. Ruggiero recommends that all patients on long-term bisphosphonates have two or three preventive dental visits per year, and that physicians be alert for any early signs of necrosis.



PHOTOS COURTESY SALVATORE RUGGIERO, MD, DMD/ LONG ISLAND JEWISH MEDICAL CENTER

Spontaneous jaw osteonecrosis can occur in patients treated with long-term bisphosphonates; however, the majority of cases occur after tooth extraction or other dental surgeries.

Patients should be alert to "things like tooth pain, swelling, numbness of the lip and chin, or pain within the jaw.

"This is not a very difficult diagnosis to make. You basically have to look in the mouth and if you see exposed bone it is very clear," he said.

Dr. Ruggiero's research, published in the Journal of Oral and Maxillofacial Surgery (J. Oral Maxillofac. Surg. 62;2004:527-34), has prompted warnings from the Food and Drug Administration (FDA), as well as from Novartis, which manufactures the intravenous bisphosphonates pamidronate disodium (Aredia) and zoledronic acid (Zometa).

Novartis has also changed its package inserts to reflect this information. However, labeling for oral bisphosphonates has not changed.

His study identified 63 patients with osteonecrosis of the jaw (ONJ), all of whom were on long-term bisphosphonate therapy for a period ranging from 6 to 48 months.

Fifty-six of the patients had used intravenous bisphosphonates for cancer chemotherapy, while the remaining 7 had used oral bisphosphonates for treatment of osteoporosis.

Until these cases were identified, ONJ had been a rare clinical scenario, Dr. Ruggiero noted.

The typical presenting symptoms were pain and nonhealing exposed bone at the site of a previous tooth extraction. However, 9 patients (14%) had no history of a recent dentoalveolar procedure and presented with spontaneous exposure and necrosis of the alveolar bone. Biopsies of the lesions showed no evidence of metastatic disease, Dr. Ruggiero said.

The lesions had been refractory to conservative debridement procedures and antibiotic therapy.

The majority of patients required surgical procedures to remove all of the involved bone. These procedures included 45 sequestrectomies, 4 marginal mandibular resections, 6 segmental mandibular resections, 5 partial maxillectomies, and 1 complete maxillectomy. Despite these surgical procedures, 5 patients had persistent bone necrosis and developed new regions of exposed bone even after they stopped bisphosphonate therapy.

Dr. Ruggiero speculates that the impaired bone wound healing may result from a compromised vascular supply caused by the antiangiogenic effects of bisphosphonates. He suggests that the absence of bone problems elsewhere in the body may be due to the unique environment created by oral microflora. ■