Serious New Infections Continue With Biologics

BY NANCY WALSH
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LIVERPOOL, ENGLAND — Serious and even fatal infections continue to occur in patients being treated with tumor necrosis factor–blocking agents and other biologics, emphasizing the need for heightened vigilance.

This was demonstrated in a series of posters presented at the annual meeting of the British Society for Rheumatology. In one case report, a 49-year-old woman with rheumatoid arthritis (RA) who had been treated unsuccessfully with methotrexate, sulfasalazine, leflunomide, and high doses of prednisone was started on etanercept. She developed lesions on her palms and soles typical of pustular psoriasis, and was then switched to infliximab, prednisone, and methotrexate. Following the third infusion she was hospitalized with fever and a widespread vesicular rash, according to Dr. Elizabeth A. Justice of University Hospital Birmingham (England).

The patient's C-reactive protein level was 153 mg/L, but the results of a sepsis screen and chest x-ray were normal. Fluid from the skin vesicles was found to contain herpes simplex virus type 1 (HSV-1).

The TNF blocker was stopped and acyclovir was given in dosages of 800 mg five times daily. The rash began to resolve within 48 hours, and after 2 weeks the acyclovir dosage was reduced to 400 mg twice daily. Two months later she commenced adalimumab, 40 mg every other week, continuing on acyclovir prophylaxis in dosages of 200 mg every other day, with no recurrence of the HSV lesions.

"This is the first reported case of disseminated cutaneous HSV-1 infection following treatment with infliximab, an unusual adverse reaction we believe to be a direct result of her immunosuppressive therapy," Dr. Justice wrote.

A second case involved a 49-year-old man with a 14-year history of seropositive nonerosive eosinophilic RA. He presented with shortness of breath but no cough, fever, or chest pain, said Dr. Deepak R. Jadon. The patient had been treated previously with etanercept and adalimumab with limited benefit, and 2 months earlier he had begun treatment with rituximab. He also had previously been on sulfasalazine for 13 years, but 2 months earlier switched to leflunomide, 10 mg/day, plus methotrexate, 15 mg/wk. He developed low-grade fever, tachycardia, dyspnea, and orthopnea, with end-inspiratory crackles audible bilaterally in the mid-lower chest. Arterial blood gases showed saturation of 75% and partial pressure of oxygen of 5.63 mm Hg. He also had neutrophilia and eosinopenia, and his C-reactive protein level was 174 mg/L.

A case report of disseminated cutaneous HSV-1 infection following treatment with infliximab is believed to be the first of its kind.

A chest film showed patchy shadowing, and a CT scan revealed extensive ground glass parenchymal abnormalities affecting both mid and lower zones, according to Dr. Jadon of the department of rheumatology, Royal Berkshire Hospital, Reading (England).

Methotrexate and leflunomide were stopped, and calcium folinate (leucovorin calcium), 15 mg four times a day, and cholestyramine, 8 g three times a day, were administered. Three 1-g doses of intravenous methylprednisolone were given, along with amoxicillin with clavulanic acid in doses of 1.2 g intravenously three times daily. (There is no parenteral preparation of amoxicillin with clavulanic acid available in the United States.)

"This is the first-ever reported case of leflunomide-associated pneumonitis in a patient concurrently on rituximab and methotrexate. The patient was diagnosed early, therapy initiated promptly, and he survived the ordeal," Dr. Jadon wrote. Leflunomide should be used with caution in patients with preexisting lung disease or in combination with rituximab and methotrexate, he said.

A third case, presented by Dr. Ahmad A. Al-Shami, was a 51-year-old woman diagnosed with RA at age 37. She was treated initially with steroids and azathioprine, but developed neutropenia, which necessitated withdrawal of the azathioprine. She later was started on sulfasalazine and then methotrexate in dosages of 22.5 mg/wk.

Because the disease remained active she was started on infliximab, but after two doses she developed fever and headache. The results of blood cultures, chest x-ray, and cerebrospinal fluid were normal, so she was restarted on infliximab but 3 months later she was readmitted with dyspnea, erythema nodosum, and ocular pruritus. The TNF blocker was once again stopped.

A chest x-ray at this time showed bilateral hilar lymphadenopathy, pulmonary function testing found reduced gas transfer, and a CT scan of the chest confirmed the hilar lymphadenopathy as well as mediastinal lymphadenopathy. Test results for tuberculosis and fungi were negative.

Transbronchial biopsy showed nonnecrotizing granulomatous inflammation, and she was diagnosed with sarcoidosis and treated with prednisone. "Hitherto there have been two case reports of pulmonary and extrapulmonary sarcoidosis, both in patients on etanercept, and we believe this is the first report on infliximab as a possible cause for sarcoidosis. We should be vigilant for this new adverse event," wrote Dr. Al-Shami of University Hospitals of Leicester (England).

Finally, a 33-year-old man with stage IVB non-Hodgkin's lymphoma presented following a third cycle of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy. He had received a total of 2,190 mg of rituximab in three divided doses given at 21-day intervals, according to Dr. Charlotte M. Ford of the department of hematology, Newham University, London.

He had pyrexia, diarrhea, and a dry cough, along with clinical and radiologic evidence of left lower lobe pneumonia that persisted despite treatment with antibiotics and granulocyte colony-stimulating factor.

Adenovirus was isolated from bronchoalveolar lavage fluid, blood, and stool samples, and despite treatment with immunoglobulin and cidofovir plus intensive supportive care, he died on day 22.

Adenoviridae are lytic DNA viruses with varying degrees of pathogenicity, and infection is rarely fatal in otherwise healthy patients. "To our knowledge, this is the first case of fulminant adenovirus infection following rituximab therapy in doses similar to those used in the treatment of RA. Adenovirus infection should be considered in any patient presenting post rituximab with a febrile illness," Dr. Ford wrote. ■

Rituximab Effective for Rheumatoid Arthritis in Real World Use

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LIVERPOOL, ENGLAND — Rituximab has been used successfully in a real-world setting as a first-line biologic therapy for rheumatoid arthritis that does not respond to conventional disease-modifying drugs, Dr. Ai Lyn Tan reported at the annual meeting of the British Society for Rheumatology.

Rituximab is licensed in the United Kingdom for the treatment of adults with rheumatoid arthritis (RA) who have had an inadequate response to, or who are intolerant of, conventional disease-modifying anti-rheumatic drugs (DMARDs) and to one or more tumor necrosis factor (TNF) inhibitors. In the United States it is licensed for use in combination with methotrexate for management of moderately to severely active RA that has not responded to treatment with one or more anti-TNF agents.

Licensure of the TNF inhibitors posed financial strains on the U.K. health care system, and the drugs were restricted in availability in some areas. Because of this lack of availability and the fact that rituximab had been shown to be effective in RA in trials of patients who had not previously received anti-TNF therapy, this drug has been used as a first-line biologic since 2004 by Dr. Tan and her colleagues at the University of Leeds (England) and Chapel Allerton Hospital, Leeds.

A total of 39 patients who had failed at least one DMARD have received two initial infusions of rituximab 2 weeks apart. In 17 patients the doses were 1,000 mg each, and in 22 the doses were 500 mg each.

Two-thirds of the patients were women. Their median age was 58 years and median disease duration was 7 years. Thirty of the patients were rheumatoid factor (RF) positive at baseline, and 16 were also antinuclear antibody (ANA) positive.

Clinical outcome data were available for 37 patients and safety data for all 39.

Clinical assessments using the Disease Activity Score (DAS)28 and EULAR response criteria were done at 3, 6, 9, and 12 months. The EULAR response criteria use the change in DAS and the level of DAS achieved to classify patients as good, moderate, or nonresponders.

At all time points, there was a significant improvement in DAS28. EULAR good responses were seen in 40% of patients at 3 months and in 50% of patients at 12 months, while overall EULAR responses were seen in 88% and 77%, respectively, at those time points.

By 6 months ANA became negative in 40% of patients in whom it had been positive at baseline, and in 88% of RF-positive patients the antibody level had fallen. Four of the previously RF-positive patients became seronegative by 6 months, and these reductions were sustained at 12 months, Dr. Tan wrote in a poster presented at the meeting.

Slightly better responses were seen in patients who received the higher dose, with 82% in the 500-mg group and 94% of those in the 1,000-mg group achieving EULAR responses. Nonetheless, she suggested that it might be "prudent" to start on lower doses since treatment is likely to be needed long term.

Thus far 25 patients have been retreated, at a median of 13 months after the initial infusions, and 7 have received a third treatment, at a median of 11 months after the second treatment.

Two patients were switched to anti-TNF therapy following early treatment failure and a third was switched following an allergic reaction to the second infusion of rituximab, according to Dr. Tan, who declared no conflicts of interest.

One 67-year-old patient with preexisting lung disease died 3 months after treatment from presumed bilateral bronchopneumonia and possible methotrexate pneumonitis, and a second 61-year-old man died of a myocardial infarction while awaiting coronary angiography for angina pectoris. This outcome was not considered to be related to therapy.

In an interview, Dr. Tan said that her study showed that rituximab is effective as first-line therapy in patients with severe RA. "This is important because it can be used in patients in whom the TNF blockers are contraindicated," she said.

Almost half of the patients in this study had disease features that could have caused concerns with TNF blockade, such as risks of infection and strong ANA positivity (Rheumatology 2008:47;865-7).

"I think this will be an important role for rituximab in RA," Dr. Tan said. ■