Arthritis Drug Shows Promise for Severe Vasculitis

BY NANCY WALSH
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SORRENTO, ITALY — Rituximab may provide a therapeutic option for patients with refractory, potentially life-threatening autoimmune vasculitic conditions that do not respond to conventional therapies or when dose-limiting toxicity occurs, Dr. Dario Roccatello said at the Fifth International Congress on Autoimmunity.

Although prognosis in the once rapidly fatal systemic vasculitides improved following the introduction of treatment with corticosteroids and cyclophosphamide, approximately one-fourth of patients cannot tolerate the associated side effects, and many relapse. Recent interest in the long-term management of these disorders therefore has centered on cyclophosphamide-sparing approaches, Dr. Roccatello said.

He reported on eight patients with systemic vasculitis who have been treated with this B cell–depleting agent. Their diagnoses included systemic micropolyangiitis, Wegener's granulomatosis, and Churg-Strauss syndrome. Six had kidney involvement, and necrotizing glomerulonephritis was present in four who underwent renal biopsy.

Intravenous rituximab was given in doses of 375 mg/m^2, with the first four doses being given at weekly intervals and the remaining two being given at monthly intervals.

Levels of the antineutrophil cytoplasmic antibodies (ANCA) that characterize these vasculitides decreased by fivefold following rituximab treatment, and one patient became ANCA-negative by week 4, said Dr. Roccatello of the University of Turin (Italy).

Treatment also resulted in significant decreases in pain and disease activity scores as measured on visual analog scales, with statistically significant decreases seen in levels of erythrocyte sedimentation rate (ESR), serum creatinine levels, proteinuria, and hematuria.

Weakness, paresthesias, arthralgias, and fever also resolved in the majority of patients.

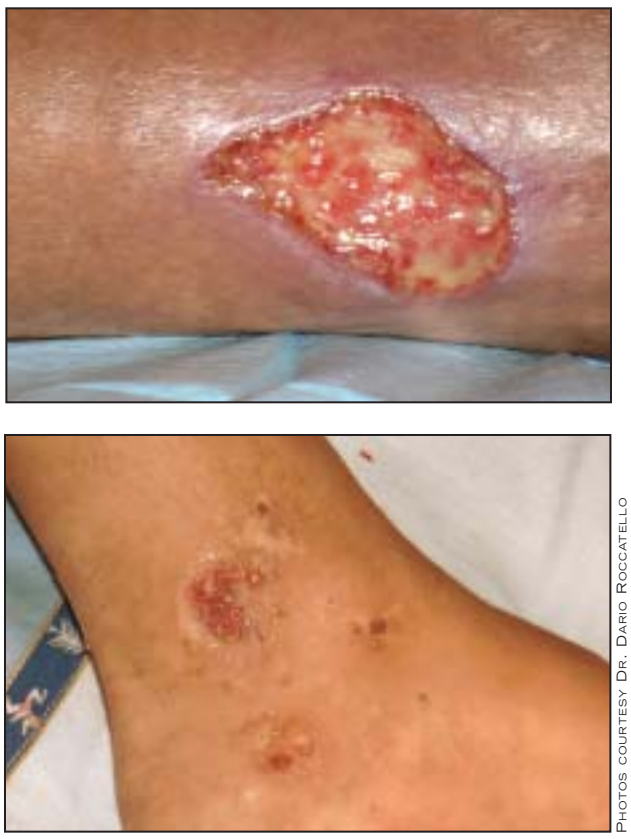
One of the patients was a 38-year-old man who had involvement of the left carotid artery and elevations of ESR, C-reactive protein, and rheumatoid factor (RF). He was antibody positive for phospholipids and perinuclear ANCA (p-ANCA), and had symptoms including hematuria, fever, severe weakness, and paresthesia.

Initially he was treated with anticoagulants, gabapentin, and high-dose immunoglobulins, but after 2 months he had further elevations of p-ANCA and RF, as well as worsening neuropathy, and was treated with three steroid pulses and mycophenolate mofetil. One month later, he developed a leukocytic vasculitis with motor disability and underwent plasma exchange. Methotrexate was substituted for the mycophenolate mofetil, which he was not tolerating.

The patient continued to experience severe neuropathy until given rituximab. Subsequent nerve conduction studies showed resolution of the neuropathic symptoms, with amelioration in velocity, amplitude, and latency, Dr. Roccatello said.

A second patient was a 61-year-old woman who had been treated for necrotizing glomerulonephritis with corticosteroids and cylophosphamide but was referred to Dr. Roccatello's center because of persistent fever, elevated cytoplasmic ANCA (c-ANCA) levels, weight loss, dyspnea, chest pain, and sinusitis characterized by complete blockage of the maxillary sinuses.

She also had multiple nodular lesions in the superior lobes of the lungs. Treatment with rituximab resulted in a 30% decrease in the number of pulmonary lesions by week 7, and in complete clearance by 9 months. Following treatment, this patient's urinary and inflammation markers and c-ANCA levels all normalized, he said.



PHOTOS COURTESY DR. DARIO ROCCATELLO

Necrotizing skin ulcers (above) developed in association with severe mixed cryoglobulinemia.

Dr. Roccatello also has used rituximab in severe cryoglobulinemia, which is a systemic vasculitis usually associated with hepatitis C infection and sustained by the proliferation of oligoclonal B cells. A total of 12 patients with symptomatic type II mixed cryoglobulinemia were treated with six courses of rituximab in the same dose and schedule as the eight patients with ANCA-associated vasculitides, he said.

All 12 patients had polyneuropathy and renal involvement, with 6 having biopsy-proven diffuse membranoproliferative glomerulonephritis. Five patients had bone marrow clonal restriction, and three had large necrotizing skin ulcers.

Significant decreases were seen in levels of proteinuria, ESR, and RF during 18 months of follow-up, and bone marrow abnormalities were shown to have normalized in the three patients who underwent repeat biopsy. Skin ulcers and purpura, arthralgias, weakness, paresthesias, and fever improved or resolved in all patients, Dr. Roccatello reported.

Rituximab has been used in combination regimens, such as with corticosteroids and immunosuppressants for relapsing Wegener's granulomatosis. In another series presented at the congress, Dr. Achille Aouba reported on eight patients with Wegener's granulomatosis who experienced flares or failed to respond to multiple other immunomodulatory therapies, including anti–tumor necrosis factor–α blockers.

Disease manifestations included lung nodules in four patients, orbital pseudotumor in two, and gingival hyperplasia, mononeuritis multiplex, glomerulonephritis, rectal perforation, pyoderma gangrenosum, and myocardial involvement in one each.

While continuing on corticosteroids and immunosuppressants, seven of the patients received four weekly infusions of rituximab in doses of 375 mg/m^2, while the eighth patient received two infusions of 1 g on days 1 and 15.

The median Birmingham vasculitis activity score (BVAS) before rituximab treatment was 14.3, with a range of 0-30.

At 4 months, five patients had BVAS scores of zero and three were in complete remission, said Dr. Aouba of the National Reference Center for Vasculitides, Hospital Cochin, Paris, and of the French Vasculitis Study Group.

An additional three were in partial remission, with BVAS scores of zero but persistent lung nodules, and two failed to respond.

Constitutional and vasculitis-related symptoms resolved more quickly than granulomatous manifestations, which regressed slowly over several months, Dr. Aouba said.

Rituximab was well tolerated, with the only adverse event being an urticarial rash in one patient, which developed after the third infusion.

In conclusion, the addition of rituximab to conventional treatment for relapsing Wegener's granulomatosis improved clinical outcome, Dr. Aouba said. ■

Rituximab Effects More Than B Cells in Rheumatoid Arthritis

BY NANCY WALSH
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SORRENTO, ITALY — Evolving experience with rituximab is demonstrating that this monoclonal antibody has multiple complex effects other than B-cell depletion in rheumatoid arthritis, including the alteration of macrophage function, Dr. Elias Toubi said at the Fifth International Congress on Autoimmunity.

B cells have multiple immunomodulatory functions that may be involved in autoimmunity. Aside from the production of antibodies such as rheumatoid factor (RF) and anti–cyclic citrullinated peptide (CCP), other B-cell functions in RA and other autoimmune diseases include the production of proinflammatory cytokines, regulation of other effector cells, and acting as antigen-presenting cells. Dr. Toubi of Bnai Zion Medical Center, Haifa, Israel and his colleagues studied 10 patients with RA who had previously been treated with methotrexate without benefit.

Baseline assessments included measurement of serum RF, anti-CCP, and total IgG. Also, blood monocyte–derived macrophages were analyzed for messenger RNA expression of the costimulatory molecule CD86, the immunoregulatory cytokine interleukin (IL)-10, and B cell–activating factor (BAFF), he said.

The 10 patients then underwent a single course of rituximab therapy, which consisted of two infusions of 1,000 mg 2 weeks apart. B cells were depleted at 2 and 4 months in all patients. The mean B-cell count at baseline was 199 cells/mm^3; this fell to a mean of 16 cells/mm^3.

Six patients achieved an ACR 50 response and were classified as responders. An additional two had partial responses, and two failed to respond.

At baseline, seven of the patients had been positive for RF and anti-CCP. Among responders RF titers fell or disappeared, but the anti-CCP antibody levels remained high.

Because anti-CCP antibodies are produced by B cells, their persistence in the context of overall B-cell depletion suggests that certain pathogenic memory B cells survive, possibly in secondary lymphoid tissue, according to Dr. Toubi.

Treatment with rituximab also altered the expression of BAFF and IL-10, as was shown in an analysis of the supernatant of cultured macrophages.

The increased expression of these factors reflects compensatory efforts to restore B-cell homeostasis, he explained.

In cultured macrophages, the expression of messenger RNA of CD86 also was increased following treatment, reflecting the maintenance of a protective immune response despite depletion (Ann. Rheum. Dis. 2006; doi:10.1136/ard.2006.062505).

Furthermore, and most important, a significant reduction in tumor necrosis factor (TNF)–α following treatment also was seen in macrophages, Dr. Toubi said.

Immature macrophages are dominant in RA and are the primary producers of proinflammatory TNF-α, and a decrease in this cytokine following treatment with rituximab suggests that the immature macrophages are being replaced following depletion by more mature, less inflammatory macrophages, he said. ■