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Rituximab Therapy for Refractory Scleritis

Results of a Phase I/II Dose-Ranging, Randomized, Clinical Trial

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Objective: To determine whether rituximab, a monoclonal antibody against the B-lymphocyte antigen CD20, is effective in the treatment of refractory noninfectious scleritis.

Design: Prospective, dose-ranging, randomized, double-masked phase I/II clinical trial.

Participants: Twelve patients with noninfectious scleritis refractory to systemic corticosteroid and ≥1 other systemic immunosuppressive agent were enrolled from January 2007 to March 2010.

Intervention: Subjects were randomly assigned to 500 (n = 5) or 1000 mg (n = 7) dosing arms of rituximab intravenous infusions (500 or 1000 mg), given at study days 1 and 15. Initial responders with breakthrough inflammation after study week 24 were offered treatment with an additional cycle of 2 open-label rituximab 1000 mg infusions.

Main Outcome Measures: Primary outcomes were reduction of inflammation, as measured with a validated scleritis disease grading scale (SGS) and reduction in corticosteroid dose by ≥50%. Patients were characterized as responders to study therapy if ≥1 of these endpoints showed improvement and neither showed evidence of worsening. Secondary outcomes were improvement in visual acuity, reduction in pain, and improvement in patient and physician-reported global health assessment.

Results: Of 12 enrolled patients, 9 met the SGS endpoint at or before week 24, and 4 additionally were able to reduce corticosteroid dose by ≥50%. With regard to secondary outcome measures, 11 and 9 patients showed improvement in patient and physician global health scores, respectively, and 7 patients had reduction in pain. Of 9 initial responders, 7 experienced breakthrough inflammation after 24 weeks and were treated with a second cycle of rituximab infusions. Four patients had significant objective or subjective worsening within 8 weeks of receiving rituximab; this event was averted in subsequent patients by treatment with peri-infusional oral corticosteroid. No other significant adverse events were noted. No differences in efficacy, toxicity, or likelihood of retreatment were noted between the dosing arms.

Conclusions: Rituximab was effective treatment for 9 of 12 enrolled patients with refractory, noninfectious scleritis at 24 weeks, although 7 required reinfusion with rituximab to maintain inflammatory control. The treatment was well-tolerated, and peri-infusional inflammatory exacerbations were managed successfully with oral corticosteroids. Further long-term studies are warranted to determine the safety and efficacy of rituximab in treating noninfectious scleritis and other ocular inflammatory diseases. *Ophthalmology 2014;121:1885-1891 © 2014 by the American Academy of Ophthalmology.*

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Scleritis is an inflammatory disease of the sclera that is often painful and, in severe cases, may cause loss of vision or even the eye. In most instances, it is presumed secondary to a vasculitis of scleral vessels,[1] and it may be caused by a heterogeneous collection of diseases, including severe or life-threatening inflammatory diseases such as severe rheumatoid arthritis (RA), granulomatosis with polyangiitis (GPA; formerly known as Wegener's granulomatosis), microscopic polyangiitis, inflammatory bowel disease, relapsing polychondritis, systemic lupus erythematosus, and other systemic vasculitides.[2–5] Mild scleritis responds to treatment with an oral nonsteroidal anti-inflammatory drug such as indomethacin, but more chronically or severely affected patients may require oral corticosteroid and/or corticosteroid-sparing systemic immunosuppressive medications, such as methotrexate, azathioprine, mycophenolate mofetil, cyclosporine, cyclophosphamide, and more recently, biologic response modifiers.[5,6] Each of these drugs, although effective in some patients, has potential toxicities, and many patients fail to respond to more than one of these medications, posing a therapeutic dilemma.[1,5,6]

Rituximab is a human–mouse chimeric monoclonal antibody that recognizes CD20, an antigen expressed on the surface of mature B lymphocytes. Rituximab is approved for

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the treatment of B-cell lymphomas and chronic lymphocytic leukemia, for moderate-to-severe RA, and has shown efficacy in a retrospective study in patients with refractory systemic lupus erythematosus.[7–10] More recently, rituximab has been shown to be noninferior to cyclosphosphamide in the treatment of GPA and microscopic polyangiitis, and it has been approved by the United States Food and Drug Administration (US FDA) for that indication.[11] There is a need for development of new therapies for scleritis patients who are refractory to currently available treatments. Scleritis is associated with or may have similar pathogenesis to many of these autoimmune or inflammatory diseases that respond to rituximab, which provided a strong scientific rationale to conduct a small, randomized, controlled trial evaluating 2 different rituximab dosing regimens in patients with refractory scleritis.

Methods

Enrollment Criteria and Study Screening

Noninfectious scleritis patients who had failed therapy with prednisone and ≥1 other systemic immunosuppressive drug were enrolled in our prospective study. This study was approved by the USFDA and the institutional review board, and it is HIPAA compliant between January 2007 and March 2010 (Clinical trial registration at Clinicaltrials.gov identifier NCT00415506). This research adhered to the tenets of the Declaration of Helsinki. Before enrollment, informed consent was obtained; all patients provided a detailed medical history and underwent complete ophthalmic and systemic evaluations to determine the cause of their eye disease. Enrolled patients had noninfectious scleritis refractory to therapy with corticosteroid and ≥1 other immunosuppressive medication, or were intolerant to such therapy. Only patients ≥18 years of age were eligible. Table 1 (available at www.aaojournal.org) provides a complete list of inclusion and exclusion criteria.

All patients were required to undergo a protein-purified derivative skin test, chest radiograph, and electrocardiogram within 3 months of enrollment. In addition, all patients underwent visual acuity testing, ocular B-mode ultrasonography, scleritis inflammation grading, and ocular health and pain assessments using a visual analog (Likert) scale at study enrollment and every 8 weeks subsequently for the duration of their participation in the study.

Treatment Protocol

Twelve patients were randomized to receive either 500 or 1000 mg infusions of rituximab at study days 1 and 15. Each infusion was preceded by a prophylactic dose of oral acetaminophen (1 g), oral diphenhydramine hydrochloride (HCl) (50 mg) or equivalent dose of a similar agent, and intravenous methylprednisolone (100 mg). Patients returned to the clinic every 4 weeks for measurement of safety and efficacy endpoints. Patients who demonstrated an initial positive clinical response to rituximab, but relapsed at ≥24 weeks, were eligible for retreatment with 2 infusions of 1000 mg rituximab separated by 2 weeks.

Ophthalmic Evaluation

Ophthalmic evaluation was performed at enrollment and every 8 weeks thereafter, and included best-corrected visual acuity on Snellen eye charts, measurement of intraocular pressure using applanation tonometry, and biomicroscopic and fundus examinations. Grading of scleritis activity was done using a modified 25-point McCluskey/Wakefield scleritis grading scale[12,13] (Table 2), evaluating number of scleral quadrants inflamed, globe tenderness, and presence or absence of nodules, scleral necrosis, corneal involvement, anterior chamber cells, vitreal activity, and retinal detachment. Scleritis grading was performed by 2 investigators and any differences were adjudicated before final recording. In addition, both the physician and patient separately marked a point along a continuous 10-cm line to indicate the disease activity for that day, from worst to best. Patients also marked a point along a continuous 10-cm line to indicate the subjective intensity of scleritis-related pain. A medical history was completed at each ophthalmic review.

Systemic Evaluation and Laboratory Monitoring

Patients underwent a general physical examination before each infusion. Preinfusion laboratory tests included complete blood count with differential, comprehensive metabolic panel; serum uric acid antineutrophil; antineutrophil cytoplasmic antibody titer; erythrocyte sedimentation rate; C-reactive protein; urinalysis; urine pregnancy testing; hepatitis B, C, and HIV serology; and percentage of leucocytes expressing CD19 and CD20 in the peripheral blood. CD19, like CD20, is a B-cell surface marker expressed by all B-lineage cells during development to B-cell blasts, but not on plasma cells. CD19 is not affected by rituximab; therefore, it is an ideal marker for detection of any circulating B lymphocytes with rituximab bound to the CD20 cell surface antigen. Postinfusion laboratory monitoring consisted of complete blood count and a comprehensive metabolic panel every 8 weeks, or more frequently if clinically indicated. Serum rituximab levels and human antichimeric antibodies (HACA) were monitored at baseline and at weeks 24 and 36; and circulating $CD19^+$ or $CD20^+$ lymphocytes were measured at weeks, 1, 2, 4, 12, 24, 36, and 48. Patients returned to the clinic every 4 weeks for safety monitoring.

Table 2. Modified McCluskey Grading of Scleritis Activity

Factor	Points	Score
Number of quadrants inflamed	0–4; 1 point per quadrant (with posterior scleritis ultrasound grading may be used)	
Tenderness	0–4; 0 = no pain, 4 = severe pain	
Nodules	0 = absent, 1 point = present	
Scleral necrosis	0 = absent/quiescent 4 = present 6 = progressive	
Corneal involvement (includes acute stromal keratitis, sclerosing keratitis, peripheral corneal melts and marginal corneal ulcers)	0 = absent/quiescent 2 = present 4 = progressive 0 = nil 2 = ≤20 cells 4 = >20 cells	
Anterior chamber cells	0 = nil	
Vitreal activity	1 = 1–2+ haze 2 = 3–4+ haze 0 = absent 2 = present	
Retinal detachment	Total (out of 25):	