Published in final edited form as:
JAMA Ophthalmol. 2014 May ; 132(5): 572–578. doi:10.1001/jamaophthalmol.2013.8179.

RITUXIMAB THERAPY FOR REFRACTORY ORBITAL INFLAMMATION: RESULTS OF A PHASE I/II DOSE-RANGING RANDOMIZED CLINICAL TRIAL

Eric B. Suhler, MD, MPH[1,2a,b], **Lyndell L. Lim, MD**[2a,3], **Robert M. Beardsley, MD**[2a], **Tracy R. Giles, BS**[2a], **Sirichai Pasadhika, MD**[2a], **Shelly T. Lee, MD**[2a], **Alexandre de Saint Sardos, MD**[2a], **Nicholas J. Butler, MD**[2a], **Justine R. Smith, MBBS, PhD**[2a,d,4], and **James T. Rosenbaum, MD**[2a,c,d,5]

[1]Portland Veterans Administration Medical Center, 3710 SW US Veterans Hospital Road, Portland, OR 97239-4197.

[2a]Oregon Health & Science University, Department of Ophthalmology/Casey Eye Institute, 3375 SW Terwilliger Blvd, Portland, OR 97239-4197

[b]Department of Public Health and Preventive Medicine, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, Portland, OR 97239-4197

[c]Department of Medicine, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, Portland, OR 97239-4197

[d]Department of Cell Biology, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, Portland, OR 97239-4197

[3]Centre for Eye Research Australia, University of Melbourne, Royal Victorian Eye and Ear Hospital, Melbourne, Australia

[4]Clinical and Molecular Medicine, Flinders University, Adelaide, Australia

[5]Devers Eye Institute, Portland, OR 97210

Abstract

Importance—Orbital inflammation is a potentially blinding and disfiguring disease process which is often treated with systemic corticosteroids and immunosuppression; better treatments are needed.

Objective—To determine whether rituximab, a monoclonal antibody against the B-lymphocyte antigen CD20, is effective in the treatment of refractory orbital inflammation.

Design—Prospective, dose-ranging, randomized, double-masked Phase I/II clinical trial

Setting—Tertiary referral ophthalmology clinic.

Correspondence and reprint requests: Eric B. Suhler, M.D., M.P.H., Casey Eye Institute, 3375 SW Terwilliger Blvd, Portland, OR 97239-4197. Phone 503-494-5023, FAX 503-494-6875, suhlere@ohsu.edu.

This paper was previously presented in part at the 2008, 2009, 2010, and 2011 Meetings of the Association for Research in Vision and Ophthalmology (ARVO), Fort Lauderdale, Fla.

Participants—10 patients with orbital inflammation refractory to systemic corticosteroids and at least one other immunosuppressive agent were enrolled from January 2007 to March 2010.

Intervention—Rituximab infusions at study days 1 and 15; either 500 mg or 1000 mg. Initial responders with recurrent inflammation after week 24 were permitted reinfusion with an additional cycle of two open-label rituximab 1000 mg infusions.

Main Outcome Measures—Primary: reduction of inflammation measured with a validated orbital disease grading scale (OGS) and corticosteroid dose reduction by at least 50%. Secondary: visual acuity, reduction in pain, and patient and physician-reported global health assessment.

Results—Of 10 enrolled patients, 7 demonstrated improvement in OGS. Of these 7, 4 were taking corticosteroids at study inception and all achieved successful dose reduction. With regard to secondary outcome measures, 7/10 and 8/10 patients improved in patient and physician global health scores, respectively, and 7/10 had reduction in pain by 25% or more. Four initial responders experienced breakthrough inflammation during the study period and were reinfused. Vision remained stable in all subjects. Three of 10 patients had significant short-term objective or subjective worsening 2-8 weeks after receiving rituximab infusions, which was averted in subsequent patients with peri-infusional oral corticosteroids and did not affect eventual positive treatment outcome. No differences with regard to efficacy, toxicity, or likelihood of retreatment were noted between the dosing arms.

Conclusions—Rituximab was safe and effective in 7 of 10 enrolled patients with non-infectious orbital disease within 24 weeks, although 4 required reinfusion with rituximab to maintain control of orbital inflammation. Significant toxicity was not noted. Peri-infusional inflammatory exacerbations were successfully treated with oral corticosteroids and did not affect eventual positive outcomes. Clinicaltrials.gov identifier NCT00415506

Keywords

orbital inflammatory disease; thyroid orbitopathy; rituximab; biologic response modifier; immunosuppression; treatment

---

The term orbital inflammatory disease (OID) describes a collection of disease processes which can cause pain, diplopia, and vision loss, either due to primary inflammatory conditions, or secondary conditions related to inflammation, infection, trauma, congenital diseases, or malignancy.[1] The primary inflammatory conditions which affect the orbit include Graves' disease, granulomatosis with polyangiitis (GPA, known previously as Wegener's granulomatosis), and nonspecific OID, which is also sometimes called orbital pseudotumor.[1,2] These inflammatory conditions are usually treated with relatively high doses of oral corticosteroid. We and others have advocated the use of corticosteroid-sparing drugs such as methotrexate for patients with OID to control the disease and spare patients the added morbidity of long-term corticosteroid use.[1-3] In our experience, about one-third of patients fail to respond optimally to immunosuppressive therapy. Obviously, alternative forms of treatment are desirable.

Rituximab (Rituxan; Genentech, Inc., South San Francisco, CA) is a monoclonal antibody that recognizes CD20, an antigen expressed on the surface of mature B-lymphocytes.

Rituximab initially was approved by the US Food and Drug Administration (USFDA) for the treatment of B-cell lymphomas, chronic lymphocytic leukemia and moderate-to-severe rheumatoid arthritis, but investigators have reported success in the treatment of multiple other autoimmune conditions such as pemphigus vulgaris,[4] systemic lupus erythematosus,[5] and autoimmune hemolytic anemia.[6] 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 US Food and Drug Administration for that indication.[7] Since B-lymphocytes are the progenitors of the plasma cells that make the autoantibodies characteristic of Graves' disease, we reasoned that there was a strong rationale for use of rituximab in at least two forms of OID. Previous reports have demonstrated efficacy of CD20 blockade in the treatment of thyroid orbitopathy[8,9] and idiopathic OID.[10,11] We elected to conduct a prospective, randomized trial comparing two doses of rituximab for patients with any form of non-infectious OID that had not been adequately controlled with oral corticosteroid and at least one additional systemic immunosuppressive medication.

METHODS

All patients were recruited from the Uveitis Clinic of the Casey Eye Institute, Portland, OR, between January 2007 and March 2010. Approval was given by the Oregon Health & Science University Institutional Review Board and by the USFDA (Clinicaltrials.gov identifier NCT00415506). Primary endpoints of the study were ability to taper corticosteroids (CS) and improvement in disease activity based on validated grading systems. Secondary endpoints included improvement in either the patient's or physician's global ocular health assessments and reduction in pain. The protocol permitted retreatment 24 to 48 weeks after initial infusion, with monthly safety assessment and outcome assessment at 24 and 48 weeks.

Before enrollment, all patients provided a detailed medical history and underwent complete ophthalmic examination and appropriate systemic evaluations to determine the cause of their orbital inflammation. All enrolled patients were required to be >18 years of age and have non-infectious OID refractory to therapy with corticosteroids and at least 1 other immunosuppressive medication, or to be intolerant of such therapy. Table 1 gives a complete list of inclusion and exclusion criteria.

All patients were required to have a purified protein derivative skin test, chest radiograph and electrocardiogram within 3 months of enrollment. All patients underwent orbital magnetic resonance imaging and ophthalmic ultrasound at enrollment and at weeks 24 and 48 for patients who reached these milestones in the study.

Treatment protocol

The first five subjects received open-label 1000 mg infusions of rituximab. Five subsequent patients were randomized to receive either 500 mg or 1000 mg infusions of rituximab at days 1 and 15. Preinfusion prophylaxis consisted of one dose each of oral acetaminophen (1 g), oral diphenhydramine HCl (50 mg, or equivalent dose of a similar agent), and intravenous methylprednisolone 100 mg.

Patients returned to clinic every 4 weeks for measurement of safety and efficacy endpoints. Patients who demonstrated an initial positive clinical response to rituximab measured at 24 weeks but relapsed subsequent to this were eligible for retreatment with 2 infusions of 1000 mg rituximab separated by 2 weeks.

Ophthalmic evaluation

Ophthalmic evaluation included best-corrected visual acuity with spectacle correction and pinhole on Snellen eye charts, applanation tonometry measurement of intraocular pressure, slit-lamp biomicroscopy and ophthalmoscopic fundus examinations. Orbital inflammation activity was graded using a modified grading system first devised by Werner (Table 2).[12] This grading system is comprised of measurement of physical signs and symptoms, proptosis, extraocular muscle involvement, corneal involvement, and optic nerve involvement. In addition, at each visit physician and patient marked a point along a continuous 10 cm line to indicate disease activity for that day, from worst to best (VAS; visual analog scale) andpatients similarly marked a a VAS line to indicate the subjective intensity of their pain.

Systemic evaluation and laboratory monitoring

Patients had a general physical examination before each infusion. Baseline laboratory tests included: complete blood count (CBC) with differential, comprehensive metabolic panel (CMP), urinalysis, serum uric acid, antineutrophil cytoplasmic antibody, erythrocyte sedimentation rate, C-reactive protein, and pregnancy testing; serologies for hepatitis B, hepatitis C, and HIV; and assays for the presence of human anti-chimeric antibodies (HACA), rituximab levels, and circulating CD19 and CD20-positive B-cell levels. CD19, similarly to 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, and therefore it is an ideal marker for detection of any circulating B-lymphocytes with rituximab bound to their CD20 cell surface antigen. Post-infusion laboratory monitoring included: CBC and CMP every 8 weeks. Monitoring of rituximab drug levels and HACA assays post-baseline occurred at weeks 24 and 36, and circulating CD19+ and CD20+ B-cells were measured at study weeks, 1, 2, 4, 12, 24, 36, and 48. Patients returned to clinic every 4 weeks for safety monitoring. A medical history and physical was performed at study enrollment, and every 8 weeks thereafter, or as needed for incident medical issues.

Outcome variables and definition of composite clinical endpoint

The primary efficacy endpoint was defined as improvement in either of the following criteria: a reduction in the dose of systemic corticosteroids or immunosuppressive therapy by at least 50% by 24 weeks; or a reduction in disease activity score by 2 or more, or an overall score of 3 or less by 24 weeks, as measured by the modified Werner grading system.

Secondary efficacy criteria were evaluated as follows: improved control of inflammation as evidenced by 25% improvement in both physician’s and patient’s global ocular health assessment on a 10 cm VAS scale; 25% reduction in ocular pain, as assessed by VAS; reduction in the analgesic dose for pain associated with orbital inflammation by both dose and/or frequency); improvement in Snellen visual acuity of 2 lines or more.

Orbital inflammation was considered active or uncontrolled if the orbital inflammation grading score was >3 at any examination or if the patient's and physician's global ocular health assessment was ≥ 5 cm on a 10 cm VAS. Tapering of systemic immunosuppressive therapy was attempted in patients with controlled disease. In general, prednisone therapy was tapered first unless it was medically necessary to first taper a concomitant immunosuppressive therapy owing to drug-related toxic effects. At each examination, the dose of prescribed immunosuppressive medications was recorded and patients were questioned about the development of any adverse effects. The components of our composite clinical endpoint each were graded dichotomously (yes or no for success).

RESULTS

Demographic information for enrolled patients is summarized in Table 3. Seven of the 10 patients (70%) were female. The age range was 28-86 years (mean 51, median 49 years). Three patients had Graves' disease, two patients had GPA, and five patients had idiopathic OID. Five patients had bilateral disease. Two patients had concurrent OID and scleritis and were followed both in this study and in a companion protocol ascertaining outcomes of rituximab treatment for scleritis (Suhler 2013, under review). Per protocol requirement, all patients had been treated previously with prednisone and at least one other immunomodulatory agent (range 1-5, mean 2).

The 24 week outcome measures are summarized in Table 4. With regard to primary outcome variables, 7 of 10 subjects noted improved control of orbital inflammation as graded on our orbital disease grading scale. Four of these patients enrolled in the study on oral corticosteroids and all were able to successfully reduce corticosteroid dose by at least 50%, with mean daily prednisone reduction from 17.5 mg to 6.875 mg. In addition, one patient was able to discontinue cyclophosphamide infusions in favor of subcutaneous methotrexate, which had previously been insufficient as a monotherapeutic agent. Another patient not on corticosteroids at baseline was able to discontinue methotrexate while on rituximab therapy. Seven subjects were able to achieve one or both primary endpoints and all subjects (including the 3 characterized as study failures) met multiple secondary outcome measures. With regard to these endpoints, 7 of 10 patients noted at least 25% improvement in self-assessed global health as measured on a VAS, and 8 of 10 had a similar improvement in physician-graded global health. Seven of 10 subjects noted at least 25% reduction in pain and/or analgesic use during the course of the study.

Three of the first 4 patients infused suffered exacerbations of ocular or systemic inflammatory disease in the early (2-8 week) period after infusion. All exacerbations were successfully treated with oral corticosteroids, usually in the range of 40 to 60 mg and gradually tapered over the following 1-2 months to their pre-infusion dose. The dosage was then tapered further per study protocol. All of the above patients went on to demonstrate positive treatment effect by week 24. Subsequent to these 3 patients, we pretreated with 40-60 mg oral prednisone per day for at least 3 days before and after all enrolled patients' initial infusions, with a more judicious tapering regimen over the first month after infusions, unless there was a specific contraindication to doing so. No further peri-infusional inflammatory flares were noted.

Reduction of circulating B-cells occurred immediately in all treated patients and was usually sustained for the entire 48 week treatment period. The mean pretreatment percentages of circulating B-lymphocytes expressing CD19/CD20 was 12.2% (range 2.7-22.2%); in all patients, this was reduced to less than 1% after receiving the first of the two loading infusions. Three of six non-retreated patients had partial recovery of B-cells from 43-48 weeks after infusions to levels ranging from 1.4% to 3.8% which did not appear to be correlated with recurrence of inflammatory disease. No evidence of HACA formation was found in any study patient. No treatment limiting side effects or laboratory abnormalities were noted, although one patient did develop cellulitis 8 weeks after treatment which was successfully treated with antibiotics. The same patient also developed an esophageal abscess and thrush which were also successfully treated. With regard to dose effects, no evidence of differential effectiveness or toxicity was found on comparison of the three patients treated with 500 mg and seven patients treated with 1000 mg. Similarly, we did not note any clear differential effectiveness by diagnosis, with 2 of 3 patients with Graves' disease responding to therapy, one of whom required retreatment, as compared to 3 of 5 with idiopathic OID (1 retreatment) and 2 of 2 with GPA, both of whom were retreated. In total, four subjects who showed an initial beneficial effect at week 24 required retreatment between weeks 24 and 48, two from each dosage group.

DISCUSSION

This study is the first prospective interventional study of rituximab in the treatment of orbital inflammation. The classic treatment for OID has been the use of high-dose oral corticosteroids[1,13] with some authors advocating addition of orbital irradiation.[14,15] This therapy is often initially successful, but relapses are common as the underlying cause is not addressed.[16,17] Steroid-sparing agents have been successfully used to help reduce the effects of long-term prednisone.[3] Biologic response modifiers are becoming more commonly used in the treatment of refractory ocular inflammation and directly target the inflammatory mediators that induce and propagate ocular inflammation.[18] Previous reports have demonstrated success with tumor necrosis factor (TNF) blockers in the treatment of idiopathic OID,[19] as well as Graves' disease.[20] Rituximab has shown promise in numerous ocular inflammatory conditions in small series including rheumatoid arthritis (RA)-associated scleritis,[21] juvenile idiopathic arthritis-associated uveitis,[22] and ophthalmic manifestations of GPA.[23] For orbital disease, rituximab has shown efficacy in several small series in patients with Graves',[9] GPA,[23] nonspecific granulomatous inflammation,[24] and idiopathic OID.[11]

We chose to enroll patients with all forms of OID, with the rationale that rituximab had demonstrated preliminary efficacy in systemic forms of some of the most commonly encountered orbital diseases (GPA and Graves') as well as in idiopathic OID. Rituximab also has shown efficacy in cases of refractory RA that were nonresponsive to anti-TNF therapy.[25] In our study, rituximab showed efficacy in patients with OID due to GPA and Graves', as well as patients with idiopathic disease. Each of these subjects was previously refractory to traditional therapy with systemic corticosteroids and at least one other immunosuppressive medication. Not only was rituximab therapy efficacious, it worked in cases where multiple other medications had failed.

A retrospective interventional series from UCLA[9] of 6 patients with refractory Graves' disease treated with rituximab demonstrated good efficacy and safety. In one patient, a biopsy of orbital tissues taken 12 days after rituximab treatment demonstrated a reduction in infiltrating B cells, leading the authors to hypothesize that such reduction correlates with disease improvement. Salvi and colleagues also demonstrated decreased B-cells within orbital tissues of one patient treated with rituximab as compared to corticosteroid-treated controls,[26] and hypothesized that remnant autoreactive B cells were responsible for disease relapse. Rituximab also might have effects on extra-orbital lymphoid cells to account for its efficacy. 40% of our subjects required retreatment, suggesting that single-dose rituximab does not eliminate all autoreactive B-cells, and that in some patients, continued lymphodepletion is necessary to suppress disease activity. The long term effect of continuous B-cell suppression is not yet known, though a recent review of RA patients treated for over 9 years suggests that this state is systemically well tolerated.[27] In GPA, rituximab has demonstrated efficacy versus standard therapy with cyclophosphamide and often does not require maintenance therapy to sustain remission.[7,28] If we extrapolate this information to OID, disease remission may be possible, but not universally expected, with rituximab therapy.

In our study, subjects were randomized into two groups with different rituximab dosing regimens for their initial treatment. Initially approved for use in B-cell lymphoma in 1997 at 375 mg/m^2 weekly dosing for four weeks,[29] rituximab was subsequently approved for use in refractory RA with concurrent methotrexate therapy in two 1000 mg infusions over two weeks.[30] Newer studies have demonstrated similar efficacy to the standard 1000 mg doses with two doses of 500 mg given 2 weeks apart in RA, and a recent small study suggested rapid effectiveness of doses as low as 100 mg.[31, 32] We found no statistical difference in efficacy, duration of effect, B-cell depletion, or toxicity between the two studied dosages, although a study of this size would be able to distinguish only a very large differential effect. Further studies are needed to support this observation in order to mitigate the potential risks of toxicity with overtreatment and increased cost without clinical benefit.

Rituximab is known to be very safe in large cohorts of rheumatic disease patients. A pooled case analysis of nearly 3200 patients found no difference in rates of serious infections, malignancy, or death compared to those in the general RA population.[27] The drug's safety in ophthalmic disease is less well established; however, we found no significant toxicity with this medication that was definitely attributable to study therapy. We did note the interesting finding that 3 of our initially treated subjects experienced a disease exacerbation within 2-8 weeks of the initial infusion of 1000 mg rituximab. Each responded to corticosteroid therapy. Interestingly, this acute disease flare was also seen in a previously reported pemphigus series[4] and more recently in a series of rituximab-treated patients with Graves' orbitopathy[32], and we have also observed this in patients with scleritis (Suhler 2013, under concurrent review). We hypothesize, as have previous investigators, that this effect is due to rapid B-cell elimination causing cytokine release and creating a tumor lysis-like effect within the affected orbit. Corticosteroid therapy successfully blunted peri-infusional flares in all subsequent patients and is now part of our standard protocol for rituximab therapy in patients with inflammatory eye disease. The occurrence of these flares did not seem to negatively impact 24 and 48 week outcomes.

In summary, this prospective, dose-ranging study noted a positive effect of rituximab therapy in the treatment of patients with non-infectious OID of any etiology, with 7 of 10 patients characterized as clinical responders after 24 weeks of therapy. Further study is necessary to determine subsets of patients who may benefit most from rituximab therapy for OID, and appropriate doses and intervals for optimal treatment.

Acknowledgements

Dr. Suhler had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study expenses and drug were provided by Genentech (San Francisco, CA). Genentech did not contribute to study design, conduct, data analysis, or interpretation, or manuscript preparation or approval, but were allowed to review the final manuscript prior to submission. Additional research support was provided by the Department of Veterans' Affairs (EBS), Research to Prevent Blindness (unrestricted grant to Casey Eye Institute, Senior Scholar Award to JTR), the Rosenfeld Family Trust (JTR) and the William and Mary Bauman Foundation. Dr. Suhler has served as a paid consultant to LuxBio, Abbott/Abbvie, and Eleven Biotheraputics. Dr. Rosenbaum has served as a paid consultant to Amgen, LuxBio, Xoma, Centocor, Genentech, Pfizer, Santen, Teva, Sanofi, Regeneron, Elan, Celtic Therapeutics, Mitotech, and Abbott/Abbvie. Dr. Lim has served as a paid consultant to Bayer. The OHSU Uveitis Clinic has received research support from Abbott/Abbvie, Bristol-Myers-Squibb, EyeGate, LuxBio, and Novartis. The authors gratefully acknowledge Dr. Russell Van Gelder (University of Washington) for assistance in the successful enrollment of this study.

References

1. Gordon LK. Orbital inflammatory disease: a diagnostic and therapeutic challenge. Eye (Lond). 2006; 20(10):1196–206. [PubMed: 17019419]
2. Lutt JR, Lim LL, Phal PM, Rosenbaum JT. Orbital inflammatory disease. Semin Arthritis Rheum. 2008; 37(4):207–22. [PubMed: 17765951]
3. Smith JR, Rosenbaum JT. A role for methotrexate in the management of non-infectious orbital inflammatory disease. Br J Ophthalmol. 2001; 85(10):1220–4. [PubMed: 11567968]
4. Leshem YA, Hodak E, David M, Anhalt GJ, Mimouni D. Successful treatment of pemphigus with biweekly 1-g infusions of rituximab: A retrospective study of 47 patients. J Am Acad Dermatol. Oct 5.2012
5. Merrill JT, Neuwelt CM, Wallace DJ, et al. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. Arthritis Rheum. 2010; 62(1):222–33. [PubMed: 20039413]
6. Zecca M, Nobili B, Ramenghi U, et al. Rituximab for the treatment of refractory autoimmune hemolytic anemia in children. Blood. 2003; 101(10):3857–61. [PubMed: 12531800]
7. Stone JH, Merkel PA, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med. 2010; 363(3):221–32. 15. [PubMed: 20647199]
8. Silkiss RZ, Reier A, Coleman M, Lauer SA. Rituximab for thyroid eye disease. Ophthal Plast Reconstr Surg. 2010; 26(5):310–4.
9. Khanna D, Chong KK, Afifiyan NF, et al. Rituximab treatment of patients with severe, corticosteroid-resistant thyroid-associated ophthalmopathy. Ophthalmology. 2010; 117(1):133–139.e2. [PubMed: 19818507]
10. Schafranski MD. Idiopathic orbital inflammatory disease successfully treated with rituximab. Clin Rheumatol. 2009; 28(2):225–6. [PubMed: 19015801]
11. Kurz PA, Suhler EB, Choi D, Rosenbaum JT. Rituximab for treatment of ocular inflammatory disease: a series of four cases. Br J Ophthalmol. 2009; 93(4):546–8. [PubMed: 19321476]
12. Werner SC. Modification of the classification of the eye changes of Graves' disease: recommendations of the Ad Hoc Committee of the American Thyroid Association. J Clin Endocrinol Metab. 1977; 44(1):203–4. [PubMed: 576230]
13. Rubin PA, Foster CS. Etiology and management of idiopathic orbital inflammation. Am J Ophthalmol. 2004; 138(6):1041–3. [PubMed: 15629299]

14. Li Yim JF, Sandinha T, Kerr JM, Ritchie D, Kemp EG. Low dose orbital radiotherapy for thyroid eye disease. Orbit. 2011; 30(6):269–74. [PubMed: 22132844]
15. Rajendram R, Bunce C, Lee RW, Morley AM. Orbital radiotherapy for adult thyroid eye disease. Cochrane Database Syst Rev. Jul 11.2012 7:CD007114. [PubMed: 22786503]
16. Bradley EA, Gower EW, Bradley DJ, et al. Orbital radiation for graves' ophthalmopathy: a report by the American Academy of Ophthalmology. Ophthalmology. 2008; 115(2):398–409. [PubMed: 18082885]
17. Zoumalan CI, Cockerham KP, Turbin RE, et al. Efficacy of corticosteroids and external beam radiation in the management of moderate to severe thyroid eye disease. J Neuroophthalmol. 2007; 27(3):205–14. [PubMed: 17895822]
18. Lim L, Suhler EB, Smith JR. Biologic therapies for inflammatory eye disease. Clin Experiment Ophthalmol. 2006; 34(4):365–74. [PubMed: 16764659]
19. Garrity JA, Coleman AW, Matteson EL, Eggenberger ER, Waitzman DM. Treatment of recalcitrant idiopathic orbital inflammation (chronic orbital myositis) with infliximab. Am J Ophthalmol. 2004; 138(6):925–30. [PubMed: 15629282]
20. Durrani OM, Reuser TQ, Murray PI. Infliximab: a novel treatment for sight-threatening thyroid associated ophthalmopathy. Orbit. 2005; 24(2):117–9. [PubMed: 16191800]
21. Iaccheri B, Androudi S, Bocci EB, Gerli R, Cagini C, Fiore T. Rituximab treatment for persistent scleritis associated with rheumatoid arthritis. Ocul Immunol Inflamm. 2010; 18(3):223–5. [PubMed: 20482403]
22. Heiligenhaus A, Miserocchi E, Heinz C, Gerloni V, Kotaniemi K. Treatment of severe uveitis associated with juvenile idiopathic arthritis with anti-CD20 monoclonal antibody (rituximab). Rheumatology (Oxford). 2011; 50(8):1390–4. [PubMed: 21378109]
23. Taylor SR, Salama AD, Joshi L, Pusey CD, Lightman SL. Rituximab is effective in the treatment of refractory ophthalmic Wegener's granulomatosis. Arthritis Rheum. 2009; 60(5):1540–7. [PubMed: 19404964]
24. Lower EE, Baughman RP, Kaufman AH. Rituximab for refractory granulomatous eye disease. Clin Ophthalmol. 2012; 6:1613–8. [PubMed: 23055686]
25. Keystone EC, Cohen SB, Emery P, et al. Multiple Courses of Rituximab Produce Sustained Clinical and Radiographic Efficacy and Safety in Patients with Rheumatoid Arthritis and an Inadequate Response to 1 or More Tumor Necrosis Factor Inhibitors: 5-Year Data from the REFLEX Study. J Rheumatol. 2012; 39(12):2238–46. [PubMed: 23027887]
26. Salvi M, Vannucchi G, Campi I, et al. Rituximab treatment in a patient with severe thyroid-associated ophthalmopathy: effects on orbital lymphocytic infiltrates. Clin Immunol. 2009; 131(2): 360–5. [PubMed: 19195932]
27. Van Vollenhoven RF, Emery P, Bingham CO 3rd, et al. Long-term safety of rituximab in rheumatoid arthritis: 9.5-year follow-up of the global clinical trial programme with a focus on adverse events of interest in RA patients. Ann Rheum Dis. Nov 7.2012 [Epub ahead of print].
28. Jones RB, Tervaert JW, Hauser T, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med. 2010; 363(3):211–20. [PubMed: 20647198]
29. Maloney DG, Grillo-López AJ, White CA, et al. IDEC-C2B8 (Rituximab) anti-CD20 monoclonal antibody therapy in patients with relapsed low-grade non-Hodgkin's lymphoma. Blood. 1997; 90(6):2188–95. [PubMed: 9310469]
30. Edwards JC, Szczepanski L, Szechinski J, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med. 2004; 350(25):2572–81. [PubMed: 15201414]
31. Mease PJ, Revicki DA, Szechinski J, et al. Improved health-related quality of life for patients with active rheumatoid arthritis receiving rituximab: Results of the Dose-Ranging Assessment: International Clinical Evaluation of Rituximab in Rheumatoid Arthritis (DANCER) Trial. J Rheumatol. 2008; 35(1):20–30. [PubMed: 18050385]
32. Salvi M, Vannucchi G, Currò N, et al. Small dose of rituximab for graves orbitopathy: new insights into the mechanism of action. Arch Ophthalmol. Jan; 2012 130(1):122–4. [PubMed: 22232486]

Table 1

Inclusion and Exclusion Criteria

Inclusion Criteria

- Idiopathic orbital inflammatory disease requiring chronic immunosuppressive treatment for disease control.
- Intolerance, failure to respond to, or inability to taper below prednisone ≥ 10mg/day in addition to one systemic immunosuppressive
- Patients must be on a stable dosage of prednisone and at least one steroid-sparing agent in the 30 days prior to screening/ enrollment.
- Active disease defined using physician judgment and supported by patient and physician global ocular disease assessment of disease≥ 5 cm on a 10cm visual analog scale.
- Selected patients who are on biological agents such as TNF blockers etanercept, infliximab and adalimumab with ongoing ocular disease are acceptable. There will be an 8 week washout period of etanercept
- Concomitant systemic autoimmune diseases must be sufficiently stable to allow tapering of steroids and/or immunosuppressive agents
- Adults of both genders ≥ 18 years old.
- Have had a recent (<3 months old) PPD skin test and are considered eligible
- Acceptable screening laboratory test results
- Chest radiograph within 3 months prior to first infusion with no evidence of malignancy, infection or fibrosis.
- Adequate renal function as indicated by normal BUN and creatinine levels.
- Able and willing to give written informed consent and comply with the requirements of the study protocol
- Men and women of reproductive potential must agree to use an acceptable method of birth control during treatment and for twelve months (1 year) after completion of treatment.

Exclusion Criteria

- Untreated thyroid disease
- Organ threatening systemic disease as evidenced by rapidly progressive glomerulonephritis, pulmonary hemorrhage or respiratory failure, seizures or psychosis, progressive neuropathy or myopathy
- Hemoglobin: < 8.5 gm/dL
- Platelets: <100,000/mm
- AST or ALT >2.5 × Upper Limit of Normal unless related to primary disease.
- Positive Hepatitis B or C serology (Hep B Surface antigen and Hep C antibody)
- History of positive HIV (HIV conducted during screening if applicable)
- Treatment with any investigational agent within 4 weeks of screening or 5 half-lives of the investigational drug (whichever is longer)
- Receipt of a live vaccine within 4 weeks prior to randomization
- Previous Treatment with Rituximab (MabThera® / Rituxan®)
- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies
- History of recurrent significant infection or history of recurrent bacterial infections
- Known active bacterial, viral, fungal, mycobacterial, or other infection (including tuberculosis or atypical mycobacterial disease, but excluding fungal infections of nail beds) or any major episode of infection requiring hospitalization or treatment with i.v. antibiotics within 4 weeks of screening, or oral antibiotics within 2 weeks prior to screening
- Unstable steroid dose in the past 4 weeks
- Lack of peripheral venous access
- History of drug, alcohol, or chemical abuse within 6 months prior to screening
- Pregnancy (a negative serum pregnancy for all women of childbearing potential at screening and negative urine pregnancy test prior to each infusion) or lactation
- Concomitant or previous malignancies, with the exception of curatively resected non-melanoma skin carcinomas or carcinoma in situ of the cervix

- History of psychiatric disorder that would interfere with normal participation in this protocol
- Significant cardiac or pulmonary disease (including obstructive pulmonary disease)
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications
- Inability to comply with study and follow-up procedures

Table 2

Modified Werner Classification for the Grading of Orbital Inflammation

Description	Points	Score
No physical signs or symptoms	**0**	
Only signs (no symptoms) ie. Proptosis ≤ 22mm, minimal lid swelling, etc **with no pain**	1	
Pain Minimal	**1**	
Mild	**2**	
Moderate	**3**	
Severe	**4**	
Soft tissue involvement with symptoms and signs Minimal	**2**	
Moderate	**3**	
Marked	**4**	
Proptosis 3-4mm over the upper limit of normal (ie. 22mm) with or without symptoms	**3**	
Proptosis of 5-8mrn increase over the upper limit	**4**	
Proptosis of >8mm increase over the upper limit	6	
EOM involvement (Usually with Msm other symptoms & signs) Limitation of movement at the extremes of gaze only	**4**	
Marked restriction of EOM	**6**	
Fixation of globe(s)	8	
Corneal involvement primarily caused by lid restriction/lagophthalmos Stippling of cornea	**5**	
Corneal ulceration	**6**	
Corneal clouding/necrosis/perforation	**8**	
Sight loss caused by optic nerve involvement Diisc pallor/swelling and/or visual field defect, VA 20/20-20/60	**6**	
As above, VA 20/70-20/200	**8**	
Legal blindness, VA < 20/200	**10**	
	TOTAL (out of 40)	___

Table 3

Demographics

Anatomic Diagnosis	Laterality	Secondary Cause	Age/ Gender	Prior Treatment	Treatment at Enrollment
Orbital Disease	Unilateral	GPA	30/F	CTX (PO, IV), MTX, Pred	CTX IV, Pred 20 mg
Orbital Disease	Bilateral OS>OD	Thyroid	53/F	MMF	MMF 1g/day
Orbital Disease	Bilateral	Thyroid	57/F	MTX, MMF, Pred	MMF 2g/day
Orbital Disease	Unilateral (OS)	Idiopathic	82/F	MTX, MMF, Pred	MTX 15 mg po, Pred 10 mg
Orbital Myositis	Bilateral	Idiopathic	86/F	MTX, Pred	MTX 20 mg po, Pred 30 mg
Orbital Disease	Unilateral (OS)	Idiopathic	43/M	MTX, Pred	MTX 25 mg SC, Pred 20 mg
Orbital Disease	Unilateral (OD)	GPA	34/M	Corticosteroids (PO,IV), Etanercept, MTX, AZA, Cyclophosphamide	AZA 150 mg, Pred 20mg
Scleritis, Orbital Disease	Unilateral (OS)	Idiopathic	28/M	Pred, MTX	MTX 20 mg po, Pred 10 mg
Scleritis, Orbital Disease	Bilateral	Idiopathic	46/F	Pred, MTX, MMF	MTX 20 mg po, Pred 10 mg
Orbital Disease	Bilateral	Thyroid	52/F	Pred, MTX, Radiation	MTX 25mg

GPA- granulomatosis with polyangiitis MTX- methotrexate, MMF- mycophenolate mofetil, Pred- prednsione, AZA- azathioprine, CTX- cytoxan, IV- intravenous, SC- subcutaneous, po- oral, g- gram, OD- right eye, OS- left eye

Table 4

Week 24 Outcomes

Patient	Steroid Decrease	OGS	Patient Global	MD Global	Pain Decrease	Vision	Weeks of follow up	Re-Treated	Early Flare?	RTX Dose
101	Yes (20 mg → 10 mg)	Yes	Yes[a]	Yes	Yes	Stable	52	Yes	Yes	1000
102	N/A (0 enrollment)	No	No	Yes	Yes	Stable	48		No	1000
103	N/A (0 enrollment)	Yes	Yes	Yes	No	Stable	48		Yes	1000
104	No (10 mg →15 mg)	No	Yes	Yes	Yes	Stable	48		Yes	1000
105	N/A (0 enrollment)	Yes	Yes	Yes	Yes	Stable	48		No	1000
106	Yes (20 mg → 10 mg)	Yes	Yes[a]	Yes[a]	Yes[a]	Stable	48	Yes	No	1000
107	Yes (20 mg → 2.5 mg)	Yes	Yes	Yes	Yes	Stable	48	Yes		500
108	Yes (10 mg → 5 mg)	Yes	Yes	Yes	Yes	Stable	54			500
109	No (10 mg → 20 mg)	No	Yes	No	No	Stable	28-d/c			1000
110	N/A (0 enrollment)	Yes	Yes	Yes	Yes	Stable	48	Yes		500

[a]Patient met endpoint prior to week 24 but not at week 24.

OGS- Orbital Grading Scale