Rituximab Therapy for Refractory Orbital Inflammation
Results of a Phase 1/2, Dose-Ranging, Randomized Clinical Trial

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**IMPORTANCE** Orbital inflammation is a potentially blinding and disfiguring disease process that 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, SETTING, AND PARTICIPANTS** A dose-ranging, randomized, double-masked phase 1/2 clinical trial was conducted at a tertiary referral ophthalmology clinic. Ten individuals with orbital inflammation refractory to systemic corticosteroids and at least 1 other immunosuppressive agent were enrolled from January 2007 to March 2010.

**INTERVENTIONS** Rituximab infusions were administered on study days 1 and 15 at doses of either 500 mg or 1000 mg. Initial responders with recurrent inflammation after week 24 were permitted reinfusion with an additional cycle of 2 open-label 1000-mg rituximab infusions.

**MAIN OUTCOMES AND MEASURES** The primary outcomes were reduction of inflammation measured with a validated orbital disease grading scale and corticosteroid dose reduction by at least 50%. The secondary outcomes were visual acuity, reduction in pain, and participant- and physician-reported global health assessment.

**RESULTS** Of 10 enrolled patients, 7 demonstrated improvement on the orbital disease grading scale at the 24-week end point with rituximab therapy. Of these 7 individuals, 4 were receiving corticosteroids at study inception and all achieved successful dose reduction. For the secondary outcome measures in the 10 participants, 7 patients and 8 patients improved in self-rated and physician global health scores, respectively, and 7 patients had reduction in pain by 25% or more at 24 weeks. Four patients who were positive responders at the week 24 end point experienced breakthrough inflammation after week 24 and received reinfusions between 24 and 48 weeks. Vision remained stable in all participants. Three of 10 patients had short-term objective or subjective worsening 2 to 8 weeks after receiving rituximab infusions, which was averted in subsequent patients with oral corticosteroids administered during the infusion and did not affect the eventual positive treatment outcome. No significant differences with regard to efficacy, toxicity, or likelihood of retreatment were noted between the dosing arms.

**CONCLUSIONS AND RELEVANCE** Rituximab was safe and effective in 7 of 10 patients with noninfectious orbital disease, although 4 required reinfusion with rituximab to maintain control of orbital inflammation. Substantial toxicity was not noted. Rituximab should be considered in the treatment of refractory orbital inflammation.

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he term orbital inflammatory disease (OID) describes a collection of disease processes that can cause pain, diplopia, and vision loss, resulting from either primary inflammatory conditions or secondary conditions related to inflammation, infection, trauma, congenital diseases, or malignant neoplasms. The primary inflammatory conditions that 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. These inflammatory conditions are usually treated with relatively high doses of oral corticosteroids. Investigators 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. In our experience, approximately one-third of patients fail to respond optimally to immunosuppressive therapy. Obviously, alternative forms of treatment are desirable.

Rituximab (Rituxan; Genentech, Inc) is a monoclonal antibody that recognizes CD20, an antigen expressed on the surface of mature B lymphocytes. Rituximab was initially approved by the US Food and Drug Administration for the treatment of B-cell lymphomas, chronic lymphocytic leukemia, and moderate to severe rheumatoid arthritis (RA), but investigators have reported success in the treatment of multiple other autoimmune conditions, such as pemphigus vulgaris, systemic lupus erythematosus, and autoimmune hemolytic anemia. Rituximab has been shown to be noninferior to cyclophosphamide in the treatment of GPA and microscopical polyangiitis and has been approved by the US Food and Drug Administration for that indication. Because 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 2 forms of OID. Previous reports have demonstrated the efficacy of CD20 blockade in the treatment of orbital orbitopathy and idiopathic OID. We conducted a randomized trial comparing 2 doses of rituximab for individuals with any form of noninfectious OID that had not been adequately controlled with oral corticosteroids and at least 1 additional systemic immunosuppressive medication.

Methods

All participants were recruited from the Uveitis Clinic of the Casey Eye Institute, Portland, Oregon, between January 1, 2007, and March 31, 2010. Approval was given by the Oregon Health and Science University Institutional Review Board and by the US Food and Drug Administration. Primary end points of the study were the ability to taper corticosteroid therapy and achieve improvement in disease activity based on validated grading systems. Secondary end points 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 participants were 18 years or older and had noninfectious OID refractory to therapy with oral corticosteroids and at least 1 other immunosuppressive medication or were intolerant of such therapy. The Box lists the inclusion and exclusion criteria. Participants provided written informed consent and did not receive financial compensation.

All participants were required to have a purified protein derivative skin test, chest radiograph, and electrocardiogram within 3 months of enrollment. In addition, all participants underwent orbital magnetic resonance imaging and ophthalmic ultrasonography at enrollment and at weeks 24 and 48 for those who reached these end points in the study.

The first 5 patients received open-label 1000-mg infusions of rituximab. Five subsequent participants were randomized to receive either 500-mg or 1000-mg infusions of rituximab on days 1 and 15. Preinfusion prophylaxis consisted of 1 dose each of oral acetaminophen (1 g), oral diphenhydramine hydrochloride (50 mg, or an 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 end points. Those who demonstrated an initial positive clinical response to rituximab measured at 24 weeks but experienced relapse subsequent to this were eligible for retreatment with 2 infusions of 1000 mg of rituximab separated by 2 weeks.

Ophthalmic Evaluation

Ophthalmic evaluation included determination of best-corrected visual acuity with spectacle correction and pinhole on Snellen eye charts, applanation tonometry measurement of intraocular pressure, slitlamp biomicroscopy, and ophthalmoscopic fundus examination. Orbital inflammation activity was graded using a modified grading system first devised by Werner (Table 1), comprising measurement of physical signs and symptoms, proptosis, extraocular muscle involvement, corneal involvement, and optic nerve involvement. In addition, at each visit, the physician and patient marked a point along a continuous 10-cm line to indicate disease activity for that day, from worst to best, on a visual analog scale (VAS). Participants similarly marked a VAS line to indicate the subjective intensity of their pain.

Systemic Evaluation and Laboratory Monitoring

Participants underwent a general physical examination before each infusion. Baseline laboratory tests included complete blood cell count with differential, comprehensive metabolic panel, urinalysis, serum uric acid, antineutrophil cytoplasmic antibody, erythrocyte sedimentation rate, C-reactive protein, and pregnancy testing; serologic reactions to detect hepatitis B, hepatitis C, and human immunodeficiency virus; and assays for the presence of human antichimeric antibodies, rituximab levels, and circulating CD19- and CD20-positive B-cell levels. CD19, similar to CD20, is a B-cell surface marker expressed by all B-lineage cells during development.
**Box. 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 treatment below prednisone ≥10 mg/d in addition to 1 systemic immunosuppressive agent
- Patients must be receiving a stable dosage of prednisone and ≥1 corticosteroid-sparing agent in the 30 d before screening/enrollment
- Active disease defined using physician’s judgment and supported by patient’s and physician’s global ocular disease assessment of disease ≥5 cm on a 10-cm visual analog scale
- Selected patients who are receiving biological agents, such as tumor necrosis factor blockers etanercept, infliximab, and adalimumab, with ongoing ocular disease are acceptable; there will be an 8-wk washout period of etanercept
- Concomitant systemic autoimmune diseases must be sufficiently stable to allow tapering of therapy with corticosteroids and/or immunosuppressive agents
- Adults of both sexes aged ≥18 y are eligible
- Have had a recent (<3 mo) purified protein derivative skin test and are considered eligible
- Acceptable screening laboratory test results
  - Chest radiograph within 3 mo before first infusion with no evidence of malignant lesions, infection, or fibrosis
  - Adequate renal function as indicated by normal urea nitrogen and creatinine levels
  - Able and willing to provide written informed consent and adhere to 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 12 mo 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, and progressive neuropathy or myocardy
- Hemoglobin <8.5 g/dL
- Platelets <100 x 10^9/L
- Aspartate aminotransferase or alanine aminotransferase >2.5 x upper limit of normal unless related to primary disease
- Positive hepatitis B or C serologic rest results (hepatitis B surface antigen and hepatitis C antibody)
- History of positive human immunodeficiency virus (testing conducted during screening if applicable)
- Treatment with any investigational agent within 4 wk of screening or 5 half-lives of the investigational drug (whichever is longer)
- Receipt of a live vaccine within 4 wk before randomization
- Previous treatment with rituximab (MabThera [Roche], Rituxan [Genentech])
- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies
- History of recurrent severe 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); any major episode of infection requiring hospitalization or treatment with intravenous antibiotics within 4 wk of screening; or oral antibiotics within 2 wk before screening
- Unstable corticosteroid dosage in the past 4 wk
- Lack of peripheral venous access
- History of drug, alcohol, or chemical abuse within 6 mo before screening
- Pregnancy (a negative serum pregnancy test result for all women of childbearing potential at screening and negative urine pregnancy test result before each infusion) or lactation
- Concomitant or previous malignant lesions, with the exception of cutaneously resected nonmelanoma skin carcinomas or carcinoma in situ of the cervix
- History of psychiatric disorder that would interfere with normal participation in this protocol
- Unstable or severe 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 for treatment complications

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Outcome Variables and Definition of Composite Clinical End Point

The primary efficacy endpoint was defined as improvement in either of the following criteria: 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 the physician’s and participant’s global ocular health assessment on a 10-cm VAS scale; 25% reduction in ocular pain, as assessed using the VAS; reduction in the analgesic dose for pain...
Table 1. Modified Werner Classification for the Grading of Orbital Inflammation

<table>
<thead>
<tr>
<th>Description</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>No physical signs or symptoms</td>
<td>0</td>
</tr>
<tr>
<td>Only signs (no symptoms), ie, proptosis ≥22 mm, minimal lid swelling, with no pain</td>
<td>1</td>
</tr>
<tr>
<td>Pain</td>
<td></td>
</tr>
<tr>
<td>Minimal</td>
<td>1</td>
</tr>
<tr>
<td>Mild</td>
<td>2</td>
</tr>
<tr>
<td>Moderate</td>
<td>3</td>
</tr>
<tr>
<td>Severe</td>
<td>4</td>
</tr>
<tr>
<td>Soft-tissue involvement with symptoms and signs</td>
<td></td>
</tr>
<tr>
<td>Minimal</td>
<td>2</td>
</tr>
<tr>
<td>Moderate</td>
<td>3</td>
</tr>
<tr>
<td>Marked</td>
<td>4</td>
</tr>
<tr>
<td>Proptosis</td>
<td></td>
</tr>
<tr>
<td>3-4 mm over the upper limit of normal (ie, 22 mm) with or without symptoms</td>
<td>3</td>
</tr>
<tr>
<td>5-8 mm increase over the upper limit</td>
<td>4</td>
</tr>
<tr>
<td>&gt;8 mm increase over the upper limit</td>
<td>6</td>
</tr>
<tr>
<td>EOM involvement (usually with diplopia and other symptoms and signs)</td>
<td>4</td>
</tr>
<tr>
<td>Limitation of movement at the extremes of gaze</td>
<td>6</td>
</tr>
<tr>
<td>Marked restriction of EOM</td>
<td>8</td>
</tr>
<tr>
<td>Fixation of globes</td>
<td></td>
</tr>
<tr>
<td>Corneal involvement primarily caused by lid restriction/lagophthalmos</td>
<td>5</td>
</tr>
<tr>
<td>Stippling of cornea</td>
<td>6</td>
</tr>
<tr>
<td>Corneal ulceration</td>
<td>8</td>
</tr>
<tr>
<td>Corneal clouding/necrosis/perforation</td>
<td></td>
</tr>
<tr>
<td>Sight loss caused by optic nerve involvement</td>
<td></td>
</tr>
<tr>
<td>Disc pallor/swelling and/or visual field defect, VA 20/20-20/60</td>
<td>6</td>
</tr>
<tr>
<td>As above, VA 20/70-20/200</td>
<td>8</td>
</tr>
<tr>
<td>Legal blindness, VA &lt;20/200</td>
<td>10</td>
</tr>
<tr>
<td>Possible total</td>
<td>40</td>
</tr>
</tbody>
</table>

Abbreviations: EOM, extraocular movement; VA, visual acuity.
grading scale. Four of these people enrolled in the study while receiving oral corticosteroids, and all were able to successfully reduce the corticosteroid dose by at least 50%, with mean daily prednisone dose reduced from 17.5 mg to 6.9 mg. In addition, 1 person was able to discontinue the cyclophosphamide infusions in favor of subcutaneous methotrexate, which had previously been insufficient as a monotherapeutic agent. Another patient not receiving corticosteroids at baseline was able to discontinue use of methotrexate while receiving rituximab therapy. Seven participants were able to achieve one or both primary end points and all (including the 3 characterized as study failures) met multiple secondary outcome measures. With regard to these end points, 7 of 10 participants noted 25% or more 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 individuals noted a 25% or more reduction in pain and/or analgesic use during the course of the study.

Three of the first 4 patients who received rituximab infusions developed exacerbations of ocular or systemic inflammatory disease in the early (2- to 8-week) period after infusion. All exacerbations were treated successfully with oral corticosteroids, usually in the range of 40 to 60 mg, and therapy was gradually tapered during the following 1 to 2 months to their preinfusion dosage. The dosage was then tapered further per the study protocol. All 4 of these individuals went on to demonstrate a positive treatment effect by week 24. Subsequent to the 3 participants who developed exacerbations, we administered 40 to 60 mg/d of oral prednisone as pretreatment for at least 3 days before and after all patients' initial infusions, with a more judicious tapering regimen during 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 patients who received treatment and was usually sustained for the entire 48-week treatment period. The mean pretreatment percentage of circulating B lymphocytes expressing CD19 and 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 2 loading infusions. Three of 6 individuals who did not receive retreatment had partial recovery of B cells from 43 to 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 human antichimeric antibodies formation was found in any patient. No treatment-limiting adverse effects or laboratory abnormalities were noted, although one patient developed cellulitis 8 weeks after treatment, which was successfully treated with antibiotics. The same person 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 3 patients who received 500 mg and 7 who received 1000 mg. Similarly, we noted no clear differential effectiveness by diagnosis, with 2 of 3 individuals with Graves disease responding to therapy, 1 of whom required retreatment, compared with 3 of 5 with idiopathic OID (1 retreatment) and 2 of 2 with GPA, both of whom received retreatment. In total, 4 patients (2 from each dosage group) who showed an initial beneficial effect at week 24 required retreatment between weeks 24 and 48.

### Discussion

To our knowledge, this study is the first prospective interventional trial of rituximab in the treatment of orbital inflammation. The classic treatment for OID has been the use of high-dose oral corticosteroids, with some authors advocating the addition of orbital irradiation. This therapy is often initially successful, but relapses are common because the underlying cause is not addressed. Corticosteroid-sparing agents have been successfully used to help reduce the effects of long-term prednisone. 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. Previous reports have demonstrated success with tumor necrosis factor

### Table 3. Week 24 Outcomes

<table>
<thead>
<tr>
<th>Patient</th>
<th>Corticosteroid Decrease</th>
<th>OGS</th>
<th>Physician Global Decrease</th>
<th>Pain Decrease</th>
<th>Vision</th>
<th>Weeks of Follow-up</th>
<th>Re-treated</th>
<th>Early Flare</th>
<th>Rituximab Dose, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yes (20 mg → 10 mg)</td>
<td>Yes</td>
<td>Yes*</td>
<td>Yes</td>
<td>Yes</td>
<td>Stable</td>
<td>52</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>NA (0 at enrollment)</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Stable</td>
<td>48</td>
<td>No</td>
<td>1000</td>
</tr>
<tr>
<td>3</td>
<td>NA (0 at enrollment)</td>
<td>Yes</td>
<td>Yes*</td>
<td>Yes</td>
<td>No</td>
<td>Stable</td>
<td>48</td>
<td>Yes</td>
<td>1000</td>
</tr>
<tr>
<td>4</td>
<td>No (10 mg → 15 mg)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Stable</td>
<td>48</td>
<td>Yes</td>
<td>1000</td>
</tr>
<tr>
<td>5</td>
<td>NA (0 at enrollment)</td>
<td>Yes</td>
<td>Yes*</td>
<td>Yes</td>
<td>Yes</td>
<td>Stable</td>
<td>48</td>
<td>No</td>
<td>1000</td>
</tr>
<tr>
<td>6</td>
<td>Yes (20 mg → 10 mg)</td>
<td>Yes</td>
<td>Yes*</td>
<td>Yes*</td>
<td>Yes*</td>
<td>Stable</td>
<td>48</td>
<td>Yes</td>
<td>1000</td>
</tr>
<tr>
<td>7</td>
<td>Yes (20 mg → 25 mg)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Stable</td>
<td>48</td>
<td>Yes</td>
<td>500</td>
</tr>
<tr>
<td>8</td>
<td>Yes (10 mg → 5 mg)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Stable</td>
<td>54</td>
<td>500</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>No (10 mg → 20 mg)</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Stable</td>
<td>28</td>
<td>(Discontinued from the study)</td>
<td>1000</td>
</tr>
<tr>
<td>10</td>
<td>NA (0 at enrollment)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Stable</td>
<td>48</td>
<td>Yes</td>
<td>500</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable; OGS, Orbital Grading Scale.

* Patient met end point before week 24 but not at week 24.
Rituximab has shown promise in multiple ocular inflammatory conditions in small series, including 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 disease,24 GPA,25 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 disease) as well as in idiopathic OID. Rituximab also has shown26 efficacy in cases of refractory RA that were nonresponsive to anti–tumor necrosis factor therapy. In our study, rituximab showed efficacy in patients with OID due to GPA and Graves disease as well as in those with idiopathic disease. Each of these patients was previously refractory to traditional therapy with systemic corticosteroids and at least 1 other immunosuppressive medication. Not only was rituximab therapy efficacious, it worked in cases for which multiple other medications had failed.

A retrospective interventional series from the University of California, Los Angeles,9 of 6 patients with refractory Graves disease treated with rituximab demonstrated good efficacy and safety. In one patient, a biopsy of orbital tissues performed 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 colleagues26 also demonstrated decreased B cells within orbital tissues of a patient who received rituximab compared with those in the general RA population.27 The drug’s safety in ophthalmic disease is less well established; however, we found no treatment-limiting toxic effects with this medication that were definitely attributable to study therapy. However, 3 of our patients who received initial treatment experienced disease exacerbation within 2 to 8 weeks of the first infusion of 1000 mg of rituximab. Each responded to corticosteroid therapy. Interestingly, this acute disease flare was also seen in a previously reported pemphigus series28 and more recently in a series of rituximab-treated patients with Graves orbitopathy.29 We have also observed this in patients with scleritis (unpublished findings). We hypothesize, as have previous investigators, that this effect is due to rapid B-cell elimination causing cytokine release and creating a tumor lysislike effect within the affected orbit. Corticosteroid therapy successfully blunted peri-influenzial flares in all subsequent patients and is now part of our standard protocol for rituximab therapy in all patients with inflammatory eye disease. The occurrence of these flares did not appear to negatively affect 24- and 48-week outcomes.

Conclusions

Rituximab appears to be safe, and it improved orbital inflammation in 7 of 10 patients, suggesting potential effectiveness in patients similar to those enrolled in this trial through at least 48 weeks of treatment. Findings from a small study with a heterogeneous population and multiple dosing arms must be interpreted cautiously. Further study is necessary to determine subsets of patients who may benefit most from rituximab therapy for OID, as well as optimal dosing and intervals for treatment.
Rituximab Therapy for Refractory Orbital Inflammation

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Author Contributions: Dr Suhler has served as a paid consultant to Lux Bio, Abbott/AbbVie, and Eleven Biotherapeutics. Dr Lim has served as a paid consultant to Bayer. Dr Rosenbaum has served as a paid consultant to Amgen, Lux Bio, Xoma, Centocor, Genentech, Pfizer, Santen, Teva, sanofi-aventis, Regeneron, Elian, Catalan Therapeutics, Mitotech, and Abbott/AbbVie. The Oregon Health and Science University Uveitis Clinic has received research support from Abbott/AbbVie, Bristol-Myers Squibb, EyeGate, LuxBio, and Novartis. No other disclosures were reported.

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Role of the Sponsor: The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication, but Genentech reviewed the manuscript prior to submission.

Previous Presentations: This study was presented in part at the 2008, 2009, 2010, and 2011 Meetings of the Association for Research in Vision and Ophthalmology; May 2008; May 2009; May 4, 2010; and May 5, 2011; all in Fort Lauderdale, Florida.

Additional Contributions: Russell Van Gelder, MD, PhD, University of Washington, provided assistance with enrollment of the participants. Dr Van Gelder received no financial compensation for his work.

REFERENCES