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ORIGINAL RESEARCH

The efficacy and safety of adalimumab in ocular inflammatory disease

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Objective: To evaluate the efficacy and safety of adalimumab in the management of ocular inflammation at our institution.

Methods: We performed a review of all patients with active ocular inflammation treated with adalimumab at our institution.

Results: Seventy eyes of 49 patients were reviewed. The mean duration of follow-up was 19.6 months. Therapy with an average of 2.1 immunomodulatory agents had been attempted prior to adalimumab therapy. At 1-year follow-up, adalimumab was effective in achieving quiescence in 33 eyes (47%). The most common side effects were injection-site reactions, arthralgias, and nausea, occurring in two patients each. Adalimumab was discontinued due to side effects in 12 patients.

Conclusion: These results suggest that adalimumab is an effective and safe therapeutic modality in ocular inflammation.

Keywords: uveitis, biologic response modifier, TNF-α, adverse effects, therapeutic outcomes, scleritis, peripheral ulcerative keratitis

Introduction

The pathogenesis of ocular inflammatory disease remains incompletely understood; however, cytokines seem to be critical mediators of ocular inflammation. The cytokines interleukin (IL)-2 and tumor necrosis factor α (TNF-α) and Th1 mediators such as interferon-γ and IL-12 are believed to be the primary factors contributing to the pathogenesis of uveitis. Supporting these hypotheses, these cytokines are found to be elevated in eyes with active uveitis.[1]

Biologic agents that target specific protein targets in the inflammatory cascade, such as anti-TNF agents or TNF inhibitors, have been used in systemic inflammatory diseases and ocular inflammation as corticosteroid-sparing agents to avoid the long-term side effects of prolonged corticosteroid therapy. Side effects include diabetes, dyslipidemia, osteoporosis, cushingoid changes, and so on.

Adalimumab is a recombinant human immunoglobulin G1 (IgG1) monoclonal antibody specific for TNF-α. The time to reach maximum serum concentration is 131±56 hours after a 40 mg subcutaneous administration in a healthy adult subject, with an average absolute bioavailability estimated at 64%. The mean terminal half-life is approximately 2 weeks (range: 10–20 days). Adalimumab is approved for juvenile idiopathic arthritis in children and for rheumatoid arthritis, ulcerative colitis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, and plaque psoriasis in adults.[1]

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Adalimumab has been shown, in case reports and small series,[2–28] to be effective in ocular inflammation. The purpose of this study is to evaluate the clinical outcomes of adalimumab for the management of noninfectious ocular inflammatory diseases at a tertiary eye care referral center.

Materials and methods

This was a retrospective, interventional, noncomparative cohort study conducted at the Massachusetts Eye Research and Surgery Institution (MERSI) in Cambridge, MA, USA. MERSI is a tertiary eye care referral center for ocular inflammatory diseases. The New England Institutional Review Board approved this study, and written informed consent was signed by all participants. This study adhered to the tenets of the Declaration of Helsinki and Health Insurance Portability and Accountability Act. Inclusion criteria for the study were: 1) treatment with adalimumab for noninfectious ocular inflammatory disease between September 2005 and July 2012; 2) active ocular inflammation at the time of initiation of adalimumab therapy; and 3) follow-up of 3 months after the commencement of therapy. Active inflammation was defined as a grade of inflammation of at least 1+ anterior and/or vitreous cells or the presence of conjunctival or scleral injection in scleritis cases. Exclusion criteria were: 1) therapy with adalimumab for a systemic disease without active ocular inflammation and 2) unavailability of case notes. Potential patients were identified through the MERSI patient database (n=166) between September 2005 and July 2012. From all charts reviewed, 70 eyes of 49 patients met our inclusion criteria.

A standardized set of information was entered in a Microsoft Excel database from electronic health records from the initiation of care at our facility until the last follow-up visit. Collected data included demographic characteristics, clinical diagnosis, ocular examination findings, prior therapies received, response to therapy, side effects, reasons for discontinuation of therapy, and complications.

The primary outcome measured was the achievement of quiescence of inflammation at 1-year of follow-up. Quiescence was defined as a stage of inactivity (grade 0 cells) or resolution of conjunctival or scleral injection. For uveitis, the degree of anterior and vitreous cells was graded from 0 to 4 according to the Standardization of Uveitis Nomenclature Working Group validated grading system at baseline and at every visit. For diagnoses other than uveitis, ocular inflammation (conjunctival or scleral injection) was categorized as "quiescent", "mild activity", "moderate activity", "severe activity", and "extremely severe activity". A standard grading from 0 to 4 was used to record the data, where 0 ("quiescent") reflected a quiet eye with no clinical evidence of inflammation; 1 ("mild activity") described slight inflammation; 2 ("moderate activity") indicated the presence of ocular inflammation, not considered severe or mild; 3 ("severe activity") described severe inflammation; and 4 ("extremely severe activity") defined the most severe inflammation possible. All inflammation grading was evaluated by a single investigator.

Other outcomes evaluated were time to improved inflammation, time to achieve complete control of inflammation, efficacy of adalimumab as a corticosteroid-sparing agent, changes in visual acuity, and safety profile (reason for discontinuation, side effects, and complications). The best-corrected visual acuity was measured per eye, according to the Early Treatment Diabetic Retinopathy Study chart, and converted to logMAR (logarithm of the minimum angle of resolution) units for statistical analysis.

Data were analyzed using Stata software version 12 (StataCorp LP, College Station, TX, USA). Incidence rates (person-time) were computed. Median survival rates were estimated and Kaplan–Meier survival curves were generated.

Results

Baseline demographic characteristics are shown in Table 1. Forty-nine patients (70 eyes) with active inflammation were treated with adalimumab for anterior uveitis (35%), scleritis (22%), posterior or panuveitis (21%), intermediate uveitis (10%), or other inflammatory conditions (11%). The most common systemic diagnoses were idiopathic inflammation (24%), rheumatoid arthritis (20%), and human leukocyte antigen-B27-associated disease (18%). There were 28 (57%) females and 21 (43%) males, with a mean age of 35 years (range: 7–78 years) included in the study. The mean duration of follow-up was 19.6±16.0 months, and therapy with an average of 2.1 immunomodulatory agents had been attempted prior to adalimumab therapy. The majority of patients (41%) were on one immunomodulatory agent prior to adalimumab, but a significant proportion of patients (22%) have been on ≥ three agents in the past. The most common immunomodulatory agent used was methotrexate (76%), followed by mycophenolate mofetil (41%).

At 1-year follow-up, quiescence was achieved in 33 eyes (47%). The average grade of inflammation improved from 1.7±0.7 to 0.1±0.3 ($P<0.05$). The number of concomitant steroid-sparing immunomodulatory agents administered decreased from an average of 0.7±0.6 to 0.3±0.6 ($P<0.05$).

Table 1 Baseline demographic characteristics

Number of patients (eyes included [n])	49 (70)
Mean age (range), in years	35 (7–78)
Male sex, n (%)	21 (43)
Mean duration of follow-up ± SD, in months	19.6±16.0
Mean interval between onset of inflammation and adalimumab therapy ± SD, in years	5.8±5.4
Mean number of immunomodulatory agents prior to adalimumab (range)	2.1 (0–7)
Number of immunomodulatory agents prior to adalimumab, n (%)	
0	3 (6)
1	20 (41)
2	15 (31)
3–7	11 (22)
Prior immunomodulatory agents used, n (%)	
Methotrexate	37 (76)
Mycophenolate mofetil	20 (41)
Etanercept	7 (14)
Infliximab	7 (14)
Cyclosporine	5 (10)
Chlorambucil	5 (10)
Cyclophosphamide	3 (6)
Azathioprine	3 (6)
Daclizumab	2 (4)
Voclosporin	1 (2)
Rituximab	1 (2)
Leflunomide	1 (2)
Intravenous immunoglobulin	1 (2)
Ocular diagnosis, n (%)	
Anterior uveitis	24 (35)
Scleritis	15 (22)
Posterior or panuveitis	14 (21)
Intermediate uveitis	7 (10)
Peripheral ulcerative keratitis (PUK)	4 (6)
PUK with necrotizing scleritis	3 (4)
PUK with scleritis	1 (1)
Systemic diagnosis, n (%)	
Idiopathic	12 (24)
Rheumatoid arthritis	10 (20)
Human leukocyte antigen-B27-associated disease	9 (18)
Granulomatosis with polyangiitis (Wegener's granulomatosis)	5 (10)
Juvenile idiopathic arthritis	3 (6)
Crohn's disease	2 (4)
Psoriatic arthritis	2 (4)
Reactive arthritis	2 (4)
Sarcoidosis	1 (2)
Behçet's disease	1 (2)
Ankylosing spondylitis	1 (2)

Eyes treated with topical corticosteroid decreased from 41 (59%) to 12 (17%). Average logMAR visual acuity did not change significantly (0.27±0.52 vs 0.21±0.49) at 1-year follow-up. The number of eyes with glaucoma or elevated intraocular pressure decreased from 15 (21%) to 9 (13%), while that with macular edema decreased from 2 (3%) to 1 (1%). Therapeutic outcomes at 1-year follow-up are shown in Table 2.

The incidence rate of achieving complete control of inflammation was 144 per 1,000 person-months while inflammation improvement was 177 per 1,000 person-months (Table 3). The median time to achieve complete control of inflammation was 3 months (Figure 1). The incidence of decreasing immunomodulatory therapy (IMT) was 18 per 1,000 person-months, and the median time to decrease IMT was 24 months (Figure 2).

Table 4 shows the side effects and reasons for discontinuation of adalimumab. Discontinuation of adalimumab therapy occurred in 24 patients (49%) by 1 year, due to side effects in 12 (24%) patients, achievement of quiescence in five (10%), ineffectiveness in five (10%), and other reasons in two (4%). The most common side effects were injection-site reactions, arthralgia, and nausea, occurring in two patients each (4%). Although total numbers were too small to allow adequate subset analyses, the most common diagnoses among patients in whom adalimumab was discontinued due to side effects were rheumatoid arthritis-associated scleritis (three patients), and juvenile idiopathic arthritis-associated anterior uveitis (two patients). Among patients in whom side effects resulted in the discontinuation of adalimumab, five were receiving an additional immunomodulatory agent. The most common agents in these patients were methotrexate (three patients), followed by mycophenolate mofetil, and intravenous cyclophosphamide (one patient each). The most common side effects resulting in discontinuation of adalimumab were nausea

Table 2 Therapeutic outcomes of adalimumab therapy at 1-year follow-up

Outcomes	Baseline	1-year
Quiescence, n (%)	0	33 (47)
Grade of inflammation, mean ± SD	1.7±0.7	0.1±0.3*
Number of immunomodulatory agents, mean ± SD	0.7±0.6	0.3±0.6*
Eyes on topical corticosteroid, n (%)	41 (59)	12 (17)
Patients on systemic corticosteroid, n (%)	9 (18)	7 (14)
Visual acuity, mean ± SD (in logMAR)	0.27±0.52	0.21±0.49
Complications, n (%)		
Secondary glaucoma or elevated IOP	15 (21)	9 (13)
Cataract or pseudophakia	10 (14)	10 (14)
Macular edema	2 (3)	1 (1)
Posterior synechiae	1 (1)	1 (1)
Band keratopathy	1 (1)	1 (1)

Note: *Statistically significant result, $P<0.05$.
Abbreviations: IOP, intraocular pressure; logMAR, logarithm of the minimum angle of resolution.

Table 3 Incidence density rates of therapeutic outcomes

Outcome	n	Events (n)	Time at risk (months)	Incidence rate per 1,000 person-months	Time to achievement (months)
Complete control of inflammation	70	57	396	144	3
Improvement of inflammation	70	61	345	177	3
Decrease in immunomodulatory therapy	70	20	1,095	18	24

and arthralgias, which necessitated discontinuation of the drug in two patients each.

Discussion

The purpose of this study was to evaluate the safety and efficacy of adalimumab for the treatment of ocular inflammatory disease at our tertiary eye care referral center. Forty-nine patients (70 eyes) were treated with adalimumab for noninfectious ocular inflammation and were followed up for a mean of 19.6 months. At 1-year follow-up, quiescence was achieved in only 47% of eyes with active inflammation at baseline.

Prior studies have reported a wide range of success rates with adalimumab for noninfectious uveitis. In a pilot study of 19 patients by Diaz-Llopis et al,[13] it was reported that 63% of patients achieved control of inflammation at 1 year. Dobner et al[16] reported that adalimumab was effective in up to 80% of patients, while Suhler et al[15] reported that adalimumab was safe and effective in 68% of refractory uveitis patients at 10 weeks, which was maintained in only 39% after 1 year. In a prospective, multicenter study of 131 patients by Diaz-Llopis et al,[17] the anterior chamber and vitreous inflammation decreased significantly ($P<0.001$) from a mean of 1.51 and 1.03 at baseline to 0.25 and 0.14, respectively, at 6 months. This is similar to our finding of improvement in the average grade of inflammation from 1.7±0.7 to 0.1±0.3 at 1-year follow-up ($P<0.05$).

In our present study, the number of concomitant steroid-sparing immunomodulatory agents administered decreased from an average of 0.7±0.6 to 0.3±0.6 ($P<0.05$). Eyes treated with topical corticosteroids decreased from 41 (59%) to 12 (17%). The incidence of decreasing IMT was 18 per 1,000 person-months, and the median time to decrease IMT was 24 months. Suhler et al[15] reported an overall steroid-sparing effectiveness of adalimumab of 38%. Diaz-Llopis et al[13] reported that all patients in their pilot study were able to reduce at least 50% of the dose of the concomitant immunosuppressive drugs at the end of 1 year, while in his later study, only 111 patients (85%) were able to reduce at least 50% of their baseline immunosuppression load at 6 months.[17]

The results of this study showed that average logMAR visual acuity did not change significantly at 1-year follow-up. However, others have shown that adalimumab can have a positive effect on visual acuity in some patients. Diaz-Llopis et al[13] reported that visual acuity improved by –0.3 logMAR in 31% of eyes in patients treated with adalimumab and Dobner et al[16] also reported very similar results. In another study by Diaz-Llopis et al,[17] visual acuity improved in only 21.3% of eyes. Lower visual acuity values were noted in patients with increased macular thickness.

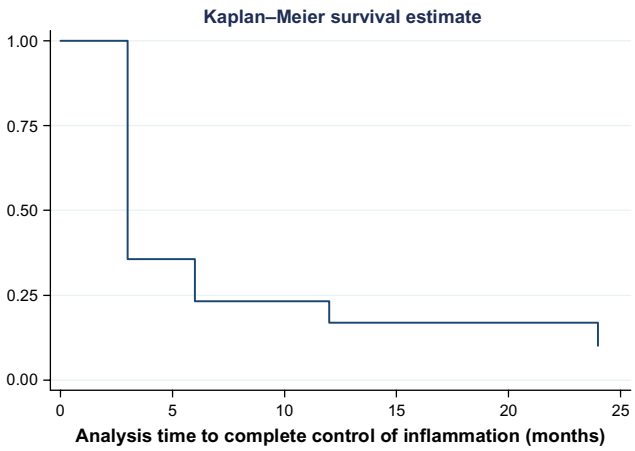

Figure 1 Kaplan–Meier curve of the time to achievement of complete control of inflammation.

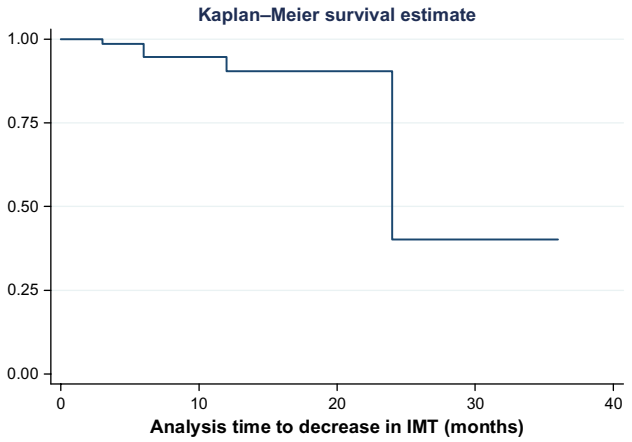

Figure 2 Kaplan–Meier curve of the time to decrease in immunomodulatory therapy (IMT).

Table 4 Side effects and reasons for discontinuation of adalimumab therapy

	Patients, n (%)
Reasons for discontinuation of therapy	24 (49)
Side effects	12 (24)
Quiescence	5 (10)
Ineffectiveness	5 (10)
Others	2 (4)
Side effects	
Injection site reaction	2 (4)
Arthralgia	2 (4)
Nausea	2 (4)
Bronchitis	1 (2)
Upper respiratory tract infection	1 (2)
Headache	1 (2)
Extremity edema	1 (2)
Fever	1 (2)
Myalgia	1 (2)
Flu-like symptoms	1 (2)
Rash	1 (2)
Skin abscess	1 (2)
Dyspnea	1 (2)

Adalimumab therapy was stopped due to negative side effects in 24% of patients in this study. Reported side effects included dyspnea, rash, fever and flu-like symptoms, arthralgia, skin abscess, fungal infections, headache, nausea, swelling, and joint pain. Injection-related side effects included swelling, discomfort, and redness at the injection site. Other studies reported additional side effects that included liver enzyme elevation and furunculosis,[16] fatigue, hypertension, herpes zoster, and reactivation of hepatitis C virus.[17] However, the side effects were rare and did not require cessation of treatment in any patients. The ability to assess the safety of adalimumab in this study and others is limited. Studies with longer follow-up periods are vital in order to determine the long-term safety and ideal dosing regimen. Recently, clinical trials have explored the safety and efficacy of adalimumab in patients with active, noninfectious, intermediate-, posterior-, or panuveitis.[29] The results of this study and others may provide additional insight on the safety of adalimumab for uveitis specifically.

Conclusion

Adalimumab was effective as an immunosuppressive drug in a heterogeneous group of ocular inflammatory disease cases managed in a tertiary setting, generally after treatment with other immunosuppressive agents failed. Discontinuation of adalimumab for toxicity was common.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Levy-Clarke G, Jabs DA, Read RW, Rosenbaum JT, Vitale A, Van Gelder RN. Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. *Ophthalmology*. 2014;121:785–796. e3.
2. Sen ES, Sharma S, Hinchcliffe A, Dick AD, Ramanan AV. Use of adalimumab in refractory non-infectious childhood chronic uveitis: efficacy in ocular disease – a case cohort interventional study. *Rheumatology (Oxford)*. 2012;51:2199–2203.
3. Kotaniemi K, Saila H, Kautiainen H. Long-term efficacy of adalimumab in the treatment of uveitis associated with juvenile idiopathic arthritis. *Clin Ophthalmol*. 2011;5:1425–1429.
4. Trachana M, Pratsidou-Gertsi P, Pardalos G, Kozeis N, Badouraki M, Kanakoudi-Tsakalidou F. Safety and efficacy of adalimumab treatment in Greek children with juvenile idiopathic arthritis. *Scand J Rheumatol*. 2011;40:101–107.
5. Tynjala P, Kotaniemi K, Lindahl P, et al. Adalimumab in juvenile idiopathic arthritis-associated chronic anterior uveitis. *Rheumatology (Oxford)*. 2008;47:339–344.
6. Vazquez-Cobian LB, Flynn T, Lehman TJ. Adalimumab therapy for childhood uveitis. *J Pediatr*. 2006;149:572–575.
7. Simonini G, Taddio A, Cattalini M, et al. Prevention of flare recurrences in childhood-refractory chronic uveitis: an open-label comparative study of adalimumab versus infliximab. *Arthritis Care Res*. 2011;63:612–618.
8. Zannin ME, Birolo C, Gerloni VM, et al. Safety and efficacy of infliximab and adalimumab for refractory uveitis in juvenile idiopathic arthritis: 1-year followup data from the Italian Registry. *J Rheumatol*. 2013;40:74–79.
9. Adams AB, Kazim M, Lehman TJ. Treatment of orbital myositis with adalimumab (Humira). *J Rheumatol*. 2005;32:1374–1375.
10. Callejas-Rubio JL, Ortego-Centeno N, Lopez-Perez L, Benticuaga MN. Treatment of therapy-resistant sarcoidosis with adalimumab. *Clin Rheumatol*. 2006;25:596–597.
11. van Laar JA, Missotten T, van Daele PL, Jamnitski A, Baarsma GS, van Hagen PM. Adalimumab: a new modality for Behcet's disease? *Ann Rheum Dis*. 2007;66:565–566.
12. Winterhalter S, Niehues T. TNFalpha-blocking agents or conventional immunosuppressive drugs in the therapy of children with uveitis? – an evidence based approach. *Klin Padiatr*. 2008;220:342–347.
13. Diaz-Llopis M, Garcia-Delpech S, Salom D, et al. Adalimumab therapy for refractory uveitis: a pilot study. *J Ocul Pharmacol Ther*. 2008;24:351–361.
14. Biester S, Deuter C, Michels H, et al. Adalimumab in the therapy of uveitis in childhood. *Br J Ophthalmol*. 2007;91:319–324.
15. Suhler EB, Lowder CY, Goldstein DA, et al. Adalimumab therapy for refractory uveitis: results of a multicentre, open-label, prospective trial. *Br J Ophthalmol*. 2013;97:481–486.
16. Dobner BC, Max R, Becker MD, et al. A three-centre experience with adalimumab for the treatment of non-infectious uveitis. *Br J Ophthalmol*. 2013;97:134–138.
17. Diaz-Llopis M, Salom D, Garcia-de-Vicuna C, et al. Treatment of refractory uveitis with adalimumab: a prospective multicenter study of 131 patients. *Ophthalmology*. 2012;119:1575–1581.
18. Rudwaleit M, Rodevand E, Holck P, et al. Adalimumab effectively reduces the rate of anterior uveitis flares in patients with active ankylosing spondylitis: results of a prospective open-label study. *Ann Rheum Dis*. 2009;68:696–701.
19. Garcia-De-Vicuna C, Diaz-Llopis M, Salom D, et al. Usefulness of adalimumab in the treatment of refractory uveitis associated with juvenile idiopathic arthritis. *Mediators Inflamm*. 2013;2013:560632.
20. Doycheva D, Zierhut M, Blumenstock G, et al. Immunomodulatory therapy with tumour necrosis factor alpha inhibitors in children with antinuclear antibody-associated chronic anterior uveitis: long-term results. *Br J Ophthalmol*. 2014;98:523–528.
21. Bravo-Ljubetic L, Peralta-Calvo J, Noval S, Pastora-Salvador N, Abelairas-Gomez J, Merino R. Adalimumab therapy for refractory childhood uveitis. *J AAPOS*. 2013;17:456–459.

22. Simonini G, Taddio A, Cattalini M, et al. Superior efficacy of Adalimumab in treating childhood refractory chronic uveitis when used as first biologic modifier drug: Adalimumab as starting anti-TNF-alpha therapy in childhood chronic uveitis. *Pediatr Rheumatol Online J*. 2013;11:16.
23. Magli A, Forte R, Navarro P, et al. Adalimumab for juvenile idiopathic arthritis-associated uveitis. *Graefes Arch Clin Exp Ophthalmol*. 2013;251:1601–1606.
24. Perra D, Alba MA, Callejas JL, et al. Adalimumab for the treatment of Behcet's disease: experience in 19 patients. *Rheumatology (Oxford)*. 2012;51:1825–1831.
25. Cordero-Coma M, Mendez RS, Blanco AC, Corral AL, Calleja-Antolin S, de Morales JM. Adalimumab for refractory peripheral ulcerative keratitis. *J Ophthalmic Inflamm Infect*. 2012;2:227–229.
26. Erckens RJ, Mostard RL, Wijnen PA, Schouten JS, Drent M. Adalimumab successful in sarcoidosis patients with refractory chronic non-infectious uveitis. *Graefes Arch Clin Exp Ophthalmol*. 2012;250:713–720.
27. Olivieri I, Leccese P, D'Angelo S, et al. Efficacy of adalimumab in patients with Behcet's disease unsuccessfully treated with infliximab. *Clin Exp Rheumatol*. 2011;29:S54–S57.
28. Bawazeer A, Raffa LH, Nizamuddin SH. Clinical experience with adalimumab in the treatment of ocular Behcet disease. *Ocul Immunol Inflamm*. 2010;18:226–232.
29. ClinicalTrials.gov [search results for adalimumab and uvetis studies]. US National Institutes of Health. Available at: https://clinicaltrials.gov/ct2/results?term=%22adalimumab%22+and+%22uveitis%22&Search=Search. Accessed February 24, 2015.