

A NEW OPTION FOR TREATMENT OF NONINFECTIOUS UVEITIS

A review of the evidence for adalimumab in this recently approved indication.

BY STEPHANIE B. ENGELHARD, BA, AND ASHVINI K. REDDY, MD



Adalimumab (Humira, AbbVie) is a fully human monoclonal immunoglobulin G 1 (IgG1) tumor necrosis factor alpha (TNF- α) antibody. It received regulatory approval from the US Food and Drug Administration (FDA) in June

for the treatment of noninfectious intermediate, posterior, and panuveitis in adults. Before this, adalimumab had FDA approval for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis (JIA), psoriatic arthritis, ankylosing spondylitis (AS), and Crohn disease, and a number of studies had reported outcomes of off-label use for uveitis.¹ This brief overview highlights key findings of those publications.

BACKGROUND

Corticosteroids are considered first-line treatment in the management of uveitis, but the potential for adverse events limits their long-term use.^{2,3} Therefore, systemic immunomodulatory therapy, which ideally serves to replace or reduce dependence on corticosteroids, is important in the management of refractory uveitis.⁴ Antimetabolites, alkylating agents, and T-cell inhibitors have demonstrated clinical efficacy in reducing ocular inflammation in certain groups of uveitis patients; however, long-term use has also been associated with undesirable effects including renal and hepatic toxicity, hypertension, and hematologic abnormalities.^{5,6}

Cytokines, including TNF- α , have been shown to play an important role in inflammation and apoptosis. They have been associated with autoimmune ocular inflammation, and elevated levels of TNF- α have been found in the aqueous humor and serum of uveitis patients.¹ TNF- α has also been associated with the development of cystoid macular edema (CME) and choroidal neovascularization in patients with uveitis, the development of which often portends poor outcomes.^{1,4,7}

Five anti-TNF- α drugs are on the market, but their success

in decreasing ocular inflammation is not well established, and no high-powered randomized clinical trials that could guide clinical judgment on their use have been performed. In a meta-analysis of the use of TNF- α inhibitors in chronic childhood uveitis, it was found that, across several studies, 87% of children responded to adalimumab, 72% responded to infliximab (Remicade, Janssen Biotech), and 33% responded to etanercept (Enbrel, Amgen).^{8,9} Another study found that infliximab and adalimumab were roughly equivalent in terms of their corticosteroid-sparing potential; however, patients on infliximab were more likely to require the continued use of antimetabolite therapy.⁹

There is considerable evidence that etanercept is inferior to both adalimumab and infliximab in the treatment of uveitis.^{8,10,11} Furthermore, although infliximab and adalimumab perform comparably in some groups of uveitis patients, adalimumab is much more convenient in that it can be self-administered subcutaneously on a biweekly basis, whereas infliximab must be administered intravenously.^{4,12} This can lead to better quality of life for patients taking the self-administered drug.



AT A GLANCE

- Adalimumab received regulatory approval from the FDA earlier this year for treatment of noninfectious intermediate, posterior, and panuveitis in adults.
- A number of open label trials, retrospective studies, and case series have already reported outcomes of off-label use of adalimumab for uveitis treatment.
- The available data suggest that adalimumab has the potential to serve an important role in management of chronic and refractory noninfectious uveitis with low rates of serious adverse events.

EVIDENCE

A number of open label trials, retrospective studies, and case series have detailed the success of adalimumab in the treatment of idiopathic uveitis and uveitis associated with systemic conditions including Behçet disease, JIA, sarcoidosis, HLA-B27–positive spondyloarthropathies, and other entities.

Several “all-comer” studies including patients with uveitis regardless of etiology or anatomic location have shown promising results with adalimumab. Suhler et al reported a clinical response to adalimumab in 68% of patients (21 of 31) after 10 weeks of treatment and a durable response in 39% at 50 weeks.¹² Dobner et al reported an effectiveness rate of 81.7% (49 of 60 patients). In that study, reported adverse events included liver enzyme elevation and furunculosis; however, most of the 13 patients who eventually discontinued adalimumab did so because of inefficacy, not because of serious adverse events.¹³

Although most reports center on subcutaneous injection of adalimumab, there have been reports of intravitreal use. One study in 2009 reported nonefficacy of intravitreal adalimumab in eight patients.¹⁴ A more recent study of the use of intravitreal adalimumab was more promising.⁵ In that study, patients were intravitreally injected with 0.03 mL (1.5 mg) adalimumab at baseline, at 2 weeks, and then every 4 weeks for 26 weeks. Of 12 eyes of patients completing the study, seven had an improvement of at least 2 ETDRS lines of visual acuity, three of three eyes had resolution of anterior chamber cells, and five of eight eyes had complete resolution of CME.⁵

There is additional evidence that adalimumab may benefit patients with CME. Durrani et al found that after 6 months of therapy with the drug, 47% of eyes with active inflammation became inactive, and CME resolved in the majority of cases.¹⁵ A study of 131 uveitis patients found that 28 of 40 eyes with CME at baseline had complete resolution of CME after 6 months of adalimumab treatment. Furthermore, 111 of the 131 patients were able to decrease their baseline immunosuppressive treatments by at least 50% at 6 months. Common adverse events included mostly mild injection site reactions and several infections, including one case each of infectious mononucleosis, herpes zoster, and reactivation of chronic hepatitis C infection; however, none of these required discontinuation of adalimumab.¹⁶

Much of the evidence for the utility of adalimumab in uveitis has come from studies of pediatric populations in which JIA-associated uveitis is the primary indication. Of all pediatric uveitis, 20% to 25% is associated with JIA, and 50% to 75% of children with severe uveitis develop significant ocular complications leading to visual impairment.⁶ Furthermore, many systemic immunomodulatory therapies that are effective in adults have reduced efficacy in the pediatric population.^{6,17} Of children with JIA-associated uveitis, 15% to 50% have refractory inflammation even with optimal methotrexate therapy.⁶



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In a study of 18 pediatric patients, 17 of whom had JIA-associated uveitis, adalimumab was found to be either very or moderately effective in 88% of patients. In that study, although rates of success for treatment of arthritis were similar among three drugs (adalimumab, infliximab, and etanercept), adalimumab was more effective in treating uveitis than the other two drugs.¹⁷ Other reports echo these findings.^{1,11,18–21} In order to systematically study the cost-effectiveness and efficacy of adalimumab in treating uveitis in patients with JIA, the randomized, controlled SYCAMORE trial is now enrolling patients in the United Kingdom.⁶

Adalimumab has shown promise in the treatment of uveitis associated with Behçet disease and AS. In a case series of three patients with bilateral panuveitis secondary to Behçet disease, in all three patients adalimumab maintained disease remission and prevented relapse when other drugs, including infliximab, failed to do so.²² Results were similar in a larger study of 124 patients with Behçet disease.²³ Similarly, studies have reported a decrease in AS-associated uveitis flares and decreased disease burden with adalimumab treatment.^{24,25}

ADMINISTRATION AND MONITORING

For the treatment of adults with intermediate, posterior, and panuveitis, the approved dosing and administration of adalimumab is an initial loading dose of 80 mg subcutaneously followed by an additional 40 mg subcutaneously every other week.²⁶ In most studies in uveitis, adalimumab has been administered 40 mg subcutaneously every other

week without the loading dose of 80 mg.^{4,10,12,16,24,25,27} For use of adalimumab in children, most studies have suggested weight-based dosing. For children weighing from 15 kg to 30 kg, 20-mg adalimumab is administered subcutaneously every other week. For children weighing more than 30 kg, the dose is the same as for adults.^{6,10,17,18}

Adalimumab has also been administered intravitreally in patients with uveitis. In one study, 0.5 mg/0.05 mL adalimumab was injected intravitreally at baseline and at 1 and 2 months, followed by an increased dose of 1 mg/0.05 mL if there was a decrease in BCVA of 5 letters or more compared with an earlier visit or an increase in foveal retinal thickness by 100 μ m or more compared with previous optical coherence tomography values.¹⁴ In that study, no adverse events were observed.¹⁴ In another study, 0.03 mL (1.5 mg) adalimumab was injected intravitreally every other week for a total of seven injections.⁵

In studies of adalimumab in uveitis, few adverse events have been observed. Adverse events reported have included pain and discomfort at the injection site, local reactions, and one case each of herpes simplex virus keratitis, infectious mononucleosis, reactivation of chronic hepatitis C infection, varicella zoster infection, and recurrent chest infection.^{8,16,25,27} Based on these studies, levels of adverse events with adalimumab are lower than has been observed with other anti-TNF- α agents.⁸ For all indications for adalimumab, rates of malignancies other than nonmelanoma (basal and squamous cell) skin cancer were similar between control and treatment groups.²⁶ Among uveitis patients, alanine transferase elevations greater than three times the upper normal limit were observed in 2.4% of treatment and control groups.²⁶

There is not a suggested monitoring schedule that is superior to others. In general, obtaining metabolic panels, liver function tests, and complete blood counts every 1 to 2 months or as needed is suggested.^{12,27} The use of any anti-TNF- α agent requires heightened vigilance against the development of infections and especially the reactivation of tuberculosis.¹⁰

CONCLUSIONS

Overall, available data suggest that adalimumab has the potential to serve an important role in management of chronic and refractory noninfectious uveitis and associated macular edema with low rates of serious adverse events in the long term.^{28,29} The recent FDA approval of adalimumab for the treatment of uveitis stands to benefit many patients; however, additional long-term, sufficiently powered, randomized controlled trials must be conducted to further evaluate the drug's effectiveness, cost-efficiency, and safety relative to other immunosuppressive therapies in distinct uveitis subpopulations in a systematic manner. ■

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Stephanie B. Engelhard, BA

- medical student in the department of ophthalmology at the University of Virginia, Charlottesville
- financial interest: none acknowledged
- sbe4bm@virginia.edu

Ashvini K. Reddy, MD

- assistant professor of ophthalmology in the Division of Ocular Immunology at the Wilmer Eye Institute, Johns Hopkins University School of Medicine, in Baltimore, Md.
- financial interest: none acknowledged
- areddy16@jhmi.edu