Clinical Trials in Noninfectious Uveitis

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Abstract

The treatment of noninfectious uveitis continues to remain a challenge for many ophthalmologists. Historically, clinical trials in uveitis have been sparse, and thus, most treatment decisions have largely been based on clinical experience and consensus guidelines. The current treatment paradigm favors initiation then tapering of corticosteroids with addition of steroid-sparing immunosuppressive agents for persistence or recurrence of disease. Unfortunately, in spite of a multitude of highly unfavorable systemic effects, corticosteroids are still regarded as the mainstay of treatment for many patients with chronic and refractory noninfectious uveitis. However, with the success of other conventional and biologic immunomodulatory agents in treating systemic inflammatory and autoimmune conditions, interest in targeted treatment strategies for uveitis has been renewed. Multiple clinical trials on steroid-sparing immunosuppressive agents, biologic agents, intraocular corticosteroid implants, and topical ophthalmic solutions have already been completed, and many more are ongoing. This review discusses the results and implications of these clinical trials investigating both alternative and novel treatment options for noninfectious uveitis.

Keywords

uveitis; noninfectious uveitis; clinical trials; treatment; immunosuppression

Introduction

Uveitis encompasses a group of inflammatory eye diseases that can cause devastating damage to ocular structures. It is estimated to account for about 10% of visual loss or about 30,000 new cases of legal blindness in the United States each year.[1] Uveitis commonly affects patients in their prime working years, and as more recent epidemiological studies demonstrate higher prevalence and incidence rates than previously predicted, uveitis presents a significant burden to the American healthcare system.[2-4]

While individually tailored to each patient, the treatment paradigm for intraocular inflammation generally entails rapid initial control of inflammation, usually with systemic or

local corticosteroids, along with concomitant or subsequent initiation of steroid-sparing immunomodulatory therapy for severe inflammation requiring further control, or if the disease is known to be especially destructive, such as in granulomatosis with polyangiitis (previously known as Wegener granulomatosis), Behçet disease, and necrotizing scleritis. Once inflammation is controlled, systemic corticosteroids are tapered and discontinued to minimize and prevent adverse effects.

Currently, most treatment decisions are largely based on clinical experience and consensus guidelines,[5, 6] as clinical trials in uveitis are greatly lacking. However, with greater recognition and growing interest in targeted treatment strategies for uveitis, there has been a recent surge of randomized, controlled trials in the field. This review describes past, present, and future clinical trials in noninfectious forms of uveitis, focusing on landmark studies conducted within the last 10 years.

Clinical Trials of Nonbiologic Systemic Immunosuppressive Agents in Noninfectious Uveitis

Systemic Immunosuppressive Therapy for Eye Disease (SITE) Cohort Study

The SITE cohort study (Table 1) retrospectively reviewed medical records of all eligible patients seen at 5 tertiary uveitis referral clinics in the United States from 1979 to 2005.[7] Although it was not a clinical trial in itself, this landmark study addressed many clinically relevant treatment questions that would be difficult, if not impossible, to address through randomized, controlled clinical trials and is the largest retrospective study in uveitis to date. The primary outcome was overall and malignancy-related mortality in patients using systemic immunosuppression for ocular inflammatory disease. Patients taking oral corticosteroids, azathioprine, methotrexate, mycophenolate mofetil, or cyclosporine had similar overall and cancer-related mortality rates compared with patients not exposed to immunosuppression.[8] Patients on cyclophosphamide had a nonstatistically significant increase in cancer-related mortality rates, while patients taking anti-tumor necrosis factor (TNF)-α biologic agents had significantly increased overall and cancer-related mortality rates. However, this association was less robust due to the small number of patients receiving biologic therapy.

The SITE study also determined the rates of inflammatory control for several oral immunosuppressive therapies used as single agents in addition to corticosteroids. One year after starting therapy, sustained control of inflammation, defined as inactivity at least 2 visits over 28 days, was attained in 62.2%, 66.0%, 73.1%, 51.9%, and 76.3% of patients taking azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, and cyclophosphamide, respectively.[9-13] While substantial portions of these patients were able to taper oral prednisone to 5 mg daily, the rate of inflammatory control dropped precipitously when prednisone was stopped, regardless of the immunosuppressive agent.

Many other studies were conducted using the SITE cohort. In additional analyses from the SITE study, eyes with vision loss attributed to uveitic macular edema experienced visual improvement with immunosuppressive treatment.[14] In patients with Behçet-associated uveitis, uncontrolled intraocular inflammation, posterior synechiae, hypotony, and elevated

intraocular pressure (IOP) were associated with an increased risk of vision loss.[15] Similarly, worsening intraocular inflammation scores were associated with increased vision loss in juvenile idiopathic arthritis (JIA) patients with uveitis, while immunosuppressive treatment was associated with improved visual outcomes.[16] Treatment success with anti-TNF-α inhibitors was observed in 75% of pediatric uveitis patients.[17] In another study, hypopyon was found to be a rare occurrence in uveitis patients and was associated with Behçet disease, HLA-B27 positivity, and spondyloarthropathies.[18] A history of uveitis-associated hypopyon, however, was not associated with an increased risk of structural complications or vision loss. History of smoking among uveitis patients was associated with bilateral disease, lower visual acuity (VA) at presentation, and an increased risk of uveitis recurrence.[19] Other studies on the SITE cohort showed that periocular corticosteroid injections were effective in treating active intraocular inflammation and macular edema, with visual improvement by 6 months in approximately 50% of patients.[20] Hypotony incidence was also low among uveitis patients, but was associated with anterior-segment inflammation, uncontrolled inflammation, and a history of cataract surgery.[21] Relative risk of corticosteroid-induced hyperglycemia requiring treatment among nondiabetic uveitis patients was 4.4 times higher than those who did not use corticosteroids, but the cumulative risk was low at 1% per year.[22]

T-Cell Inhibitors: Cyclosporine A, Tacrolimus, Sirolimus, Voclosporin

T cells are thought to play a predominant role in the pathogenesis of noninfectious uveitis.[23] Pharmacologic agents classified as T-cell inhibitors (Table 2) block signaling pathways within activated T cells and are commonly used in the treatment of inflammatory T-cell-driven diseases, such solid organ transplant rejection and noninfectious uveitis. Cyclosporine A functions via calcineurin inhibition to block activated T-cell cytokine production and proliferation.[24] It was the first of its class shown to be effective in the treatment of noninfectious uveitis. In the late 1980s and early 1990s, 4 randomized, controlled trials established the efficacy of cyclosporine A in treating various inflammatory eye diseases.[25-28] Initial studies investigating high doses of cyclosporine A reported significant complications, including hypertension and nephrotoxicity. However, lower doses in the range of 3 to 5 mg/kg/day divided into twice daily doses provided equal efficacy with reduced incidence of adverse events.[12]

Tacrolimus, an alternative T-cell inhibitor, also functions through calcineurin inhibition, albeit via a slightly different mechanism than cyclosporine.[24] Tacrolimus dosed at 0.03 to 0.08 mg/kg daily was shown to be as equally effective as cyclosporine dosed at 2.5 to 5.0 mg/kg daily in suppressing posterior-segment inflammation with potentially fewer adverse effects.[29]

Unlike cyclosporine or tacrolimus, sirolimus inhibits T cells through blockade of the mammalian target of rapamycin (mTOR) pathway.[30] While little is known regarding the utility of systemically administered sirolimus in the treatment of noninfectious uveitis, 2 pilot studies recently reported on the ocular administration of sirolimus. Within 4 weeks, 3 of 5 patients with chronic active anterior uveitis met the primary outcome of at least a 2-step reduction in anterior chamber (AC) reaction with a single subconjunctival injection of sirolimus.[31] In the Sirolimus as a Therapeutic Approach for Uveitis (SAVE) study, a series

of subconjunctival or intravitreal sirolimus injections at days 0, 60, and 120 resulted in at least a 2-step reduction of vitreous haze scores in 6 of 15 patients (40%) with intermediate, posterior, or panuveitis by 6 months.[32]

Voclosporin (LX211 or Luveniq; Lux Biosciences Inc., Jersey City, NJ), a synthetic cyclosporine analog, has been reported to have a more stable pharmacokinetic profile and stronger calcineurin inhibition than cyclosporine A.[33] Following its success in animal models of uveitis,[34] voclosporin was recently tested in uveitis patients. The LX211 Uveitis Multicenter Investigation of a New Approach to Treatment (LUMINATE) study included 3 randomized, placebo-controlled, double-masked trials designed to test the efficacy of voclosporin in patients with active intermediate, posterior, or panuveitis (n = 218), quiescent intermediate, posterior, or panuveitis (n = 232), and active anterior uveitis (n = 108).[35] While the final results have yet to be published in manuscript form, conference abstracts revealed that voclosporin orally dosed at 0.4 mg/kg twice daily resulted in significant control of inflammation in active intermediate, posterior, or panuveitis patients at 16 and 24 weeks, compared with placebo.[36] For quiescent patients, voclosporin reduced the rate of inflammatory recurrence by 50% at 26 weeks of treatment, but the study failed to meet its primary endpoint. In a smaller study of patients with active anterior uveitis, no significant differences were observed between drug and placebo, but the study was underpowered.[35] While these results appeared initially promising, the study did not lead to approval by the Food and Drug Administration.[37] However, the company has plans to further develop and market voclosporin for lupus nephritis.[38]

Antimetabolites: Azathioprine, Methotrexate, Mycophenolate Mofetil

As discussed above in the SITE study, the antimetabolites azathioprine, methotrexate, and mycophenolate mofetil are commonly used immunosuppressive agents in the management of noninfectious uveitis (Table 3).[9-11] While a multitude of case series and retrospective cohort studies suggest their efficacy, very few randomized, controlled trials have investigated antimetabolites in inflammatory eye diseases. A prospective, randomized study comparing the combinations of prednisone and azathioprine (n = 12) versus prednisone and cyclosporine (n = 9) showed that both regimens were effective in reducing intraocular inflammation and improving vision in patients with chronic Vogt-Koyanagi-Harada (VKH) disease.[39] However, patients in the azathioprine group required significantly higher doses of prednisone, suggesting that cyclosporine may provide better steroid-sparing efficacy in chronic VKH.

A recent prospective, randomized trial conducted in India compared methotrexate (25 mg orally per week) to mycophenolate mofetil (1000 mg orally twice daily) in 80 patients with noninfectious intermediate, posterior, or panuveitis requiring steroid-sparing therapy.[40] A nonsignificantly higher percentage of patients receiving methotrexate (69%, 24/35), compared with mycophenolate mofetil (47%, 15/32), achieved treatment success, which was defined as AC cell, vitreous cell, and vitreous haze grades of 0.5+, absence of active retinal or choroidal lesions, 2 drops of prednisolone acetate 1% per day, 10 mg of oral prednisone per day (or the equivalent), and absence of treatment failure due to intolerance or safety concerns. There was no difference between methotrexate and mycophenolate mofetil

in the number of treatment failures, time to steroid-sparing control of inflammation, change in best-corrected visual acuity (BCVA), or resolution of macular edema. Taken together, the results from this randomized clinical trial and the SITE study suggest that methotrexate and mycophenolate mofetil are similarly effective in controlling intraocular inflammation in patients with noninfectious uveitis.

Clinical Trials of Biologic Agents in Noninfectious Uveitis

Biologic therapies generally refer to substances derived from living organisms or recombinant versions of such substances. Examples of biologic agents used in the treatment of noninfectious uveitis include interferon (IFN)-β and monoclonal antibodies (mAb) against specific cytokines, like TNF-α. Biologic agents that end with –umab indicate human antibodies, while those that end with –ximab are chimeric human-murine antibodies. Those ending with –cept represent native or modified receptor molecules.[41] Clinical trials investigating the use of biologic agents in the treatment of noninfectious uveitis are discussed below and are summarized in Table 4.

Type 1 Interferons

Type 1 IFNs, namely IFN-α and IFN-β, are named for their ability to interfere with viral replication, and IFN-α has been used extensively in the treatment of chronic hepatitis C virus infection.[42] Several noncontrolled, nonrandomized studies have also suggested long-lasting benefit of IFN-α treatment in patients with ocular manifestations of Behçet disease. Complete remission was reported in 84.9 to 98.1% of affected eyes in patients receiving subcutaneous IFN-α therapy,[43-45] and 1 study found that 50% of patients had clinically quiet eyes 45.9 months after discontinuing IFN-α treatment.[45]

Type 1 IFNs also have immunomodulatory properties, and IFN-β is commonly used to treat multiple sclerosis (MS).[46] Several nonrandomized, noncontrolled studies have suggested that systemic type 1 IFN therapy may be beneficial in treating uveitic macular edema and, in particular, treatment-refractory macular edema.[47-49] In support of these findings, a randomized, controlled clinical trial comparing systemic methotrexate (n = 10, treated with 20 mg subcutaneously per week) and IFN-β (n = 9, treated with 44 μg subcutaneously 3 times weekly) in the treatment of idiopathic or MS-related intermediate uveitis revealed significantly improved BCVA and macular edema in the IFN-β group.[50] No statistically significant differences were found in vitreous haze scores after 3 months of therapy; however, significantly more patients in the methotrexate group had at least a 2-step increase in AC or vitreous haze scores. These results suggest that type 1 IFNs may be beneficial for the treatment of uveitic macular edema.

Etanercept (Enbrel)

Etanercept (Enbrel; Amgen Inc., Thousand Oaks, CA) is a fusion protein consisting of the extracellular ligand-binding portion of TNF receptor 2 and the Fc portion of IgG1 that blocks both TNF-α and TNF-β.[51] Aside from small retrospective case series, few studies have examined the efficacy of etanercept in both adult and childhood uveitis. One prospective, randomized, placebo-controlled, double-masked trial evaluated the efficacy of

etanercept in preventing relapses compared with placebo in 20 patients whose uveitis was controlled with methotrexate and whose methotrexate dosage was thus being tapered.[52] No significant difference was observed between etanercept and placebo groups with respect to relapse rate or VA. Another prospective, randomized, placebo-controlled, double-masked trial examined the efficacy of etanercept versus placebo in 18 patients with chronically active ocular sarcoidosis.[53] Similarly, the authors found no significant difference in corticosteroid usage, VA, or ophthalmologist-graded global assessment score between etanercept and placebo. The authors, however, noted that more patients appeared to have their conditions worsened with etanercept (3 patients) than with placebo (1 patient).

As in adults, no significant difference in efficacy outcomes (eg, AC cell grade of ≤0.5+, ≥50% reduction in number or dose of immunosuppressive agents) was observed between etanercept and placebo in 12 children with treatment-refractory JIA-associated uveitis in a small, prospective, randomized, placebo-controlled, unmasked pilot study.[54] This is in contrast to the results of an earlier prospective, uncontrolled, open-label study that seemed to suggest a beneficial effect for etanercept in chronic, refractory uveitis in 10 children with JIA-associated uveitis.[55] Efforts to further investigate the efficacy of etanercept in treating chronic or treatment-resistant uveitis, especially in children, soon halted, as an association between etanercept use and new-onset or recurrent uveitis became evident.[56]

Infliximab (Remicade)

Infliximab (Remicade; Janssen Biotech Inc., Horsham, PA) is a chimeric IgG1 mAb that blocks both soluble and transmembrane forms of TNF-α.[57] Its use has been primarily evaluated with retrospective studies for the ocular manifestations of treatment-resistant Behçet disease as well as JIA-associated uveitis. However, there are many small, prospective, open-label studies examining its effect in ocular Behçet disease; a few of the larger reports are discussed here. One such study examined the efficacy of a single infliximab treatment in 25 patients with recurrent uveitis associated with Behçet disease.[58] Most patients were on systemic immunosuppression with corticosteroid and/or steroid-sparing agents. One day following infliximab treatment, acute inflammation was rapidly controlled in 96% of patients (24/25). By day 28, all patients with vitritis or retinitis showed a complete response, and at least 90% of patients with retinal vasculitis or cystoid macular edema (CME) had complete resolution. Among 15 patients who had at least 1 recent relapse, additional infliximab treatment was provided at weeks 4, 8, 16, and 24. Complete remission was achieved in 60% of these patients, and no patients withdrew from the study.

Another prospective, open-label trial found that infliximab treatment (5 mg/kg) at weeks 0, 2, 6, and 14 resulted in significant reduction of both mean number of uveitic relapses and mean daily corticosteroid dose during the infusion period (weeks 0 to 22), compared with the pretreatment period.[59] This difference, however, did not last into the posttreatment observation period (weeks 23 to 54), suggesting that continued infliximab infusions may be necessary to maintain clinical effect. In a 1-year prospective study of patients with active Behçet disease resistant to corticosteroids and at least 1 other immunosuppressive agent, 17 of 19 patients with active posterior uveitis or retinal vasculitis achieved full remission with infliximab treatment at weeks 0, 2, and 6 followed by subsequent bimonthly infusions.[60] In

a larger, multicenter, prospective study examining the efficacy of infliximab in 48 patients with Behçet-associated uveoretinitis, at 1 year, 69% (33/48) had no relapses on continued infliximab treatment, 23% (11/48) had fewer ocular attacks, 8% (4/48) had no change in frequency, and no patients worsened on infliximab.[61]

In a 2-year, open-label, prospective, single-center trial, 77% of patients (24/31) with refractory noninfectious uveitis had initial improvements in VA, control of inflammation, tapering of corticosteroid and/or immunosuppressant dose, and reduction of CME with infliximab treatment (loading dose of 5 mg/kg at weeks 0, 2, and 6; maintenance dose starting at 5 mg/kg every 8 weeks with dose escalation as necessary).[62] Seven patients (23%) failed infliximab at 10 weeks, one of whom developed a pulmonary embolus, but 9 of 15 responders successfully completed the study at 1 year. Among the 9 responders who completed the study, 7 maintained quiescence at 2 years of follow-up. The remaining 2 completed the 1-year trial prior to its conversion to a 2-year study and thus were not followed beyond 1 year. In summary, continued infliximab treatment was reasonably effective in maintaining remission in early clinical responders with chronic, previously refractory noninfectious uveitis. Additionally, a small pilot trial found infliximab to be effective in treating active anterior nonnecrotizing scleritis.[63]

Adalimumab (Humira)

Adalimumab (Humira; AbbVie Inc., North Chicago, IL) is a fully humanized monoclonal IgG1 antibody that blocks TNF-α.[64] While there are no randomized, controlled trials investigating its use in adults with uveitis to date, several prospective, noncontrolled, open-label trials evaluating adalimumab's efficacy in treating and preventing recurrences of noninfectious uveitis—usually treatment-refractory—have been completed over the last few years. One such multicenter, open-label study conducted in Europe observed a substantial reduction in flare rates of anterior uveitis in 1250 patients with active ankylosing spondylitis.[65] When compared with anterior uveitis flare rates during the year prior to adalimumab treatment, flare rates were reduced by 51% in all patients, by 58% in patients with a history of anterior flares (n = 274), and by 45% in patients with chronic uveitis (n = 43) after starting adalimumab. Most anterior uveitis flares reported in the study were noted to be mild (67%) or moderate (29%). However, 2 patients with high ankylosing spondylitis disease activity developed new-onset anterior uveitis while being treated with adalimumab during the study period.

In another prospective case series of treatment-refractory ocular sarcoidosis, overall improvement in posterior disease activity was observed in 22 of 26 patients, and stabilization was noted in the rest.[66] Choroidal involvement resolved in 10 of 15 patients, and the remaining 5 had partial improvement. Macular edema also resolved in 5 of 8 patients, and the remaining 3 had partial improvement. Similar results were also observed in a larger, multicenter, prospective case series consisting of 131 patients from Spain, Mexico, and Venezuela with refractory noninfectious uveitis of various etiologies.[67] Six months after starting treatment, mean AC inflammation, vitreous inflammation, CME, and corticosteroid dose all significantly decreased ($P < 0.001$), and mean VA significantly increased from baseline ($P < 0.001$). In fact, 85% (111/131) achieved 50% reduction of their baseline

corticosteroid dose by 6 months. Adalimumab was generally well tolerated, except for 1 JIA patient who experienced severe recurrence of her anterior uveitis. Other complications included herpes zoster, infectious mononucleosis, and reactivation of a prior hepatitis C virus infection, all of which were treated medically and none of which required cessation of adalimumab therapy.

A more recent multicenter, open-label trial conducted in the United States observed that 21 of 31 patients (68%) with treatment-resistant uveitis responded to adalimumab at 10 weeks.[68] Twelve of these patients (39% of total) continued to demonstrate control of inflammation, improvement in VA, improvement in CME, and tapering of corticosteroid therapy at 1 year after starting adalimumab treatment.

The safety, efficacy, and cost-effectiveness of adalimumab is currently being examined in a prospective, randomized, double-masked, multicenter trial in the United Kingdom comparing the combinations of adalimumab and methotrexate versus placebo and methotrexate in pediatric patients with active JIA-associated uveitis.[69] To date, no such studies have been completed in children. However, 1 prospective, open-label, comparative study evaluating the clinical efficacy of adalimumab versus infliximab in chronic, refractory pediatric uveitis has been conducted.[70] While no significant differences in time to remission or time to corticosteroid discontinuation were observed, a higher probability of uveitis remission was associated with adalimumab. In fact, at 40 months into the study, 60% of patients (9/15) treated with adalimumab were still in remission, compared with 19% (3/16) on infliximab. However, infliximab was dosed at 5 mg/kg at weeks 0, 2, and 6 with subsequent infusions every 6 to 8 weeks, while adalimumab was dosed at 24 mg/m^2 every 2 weeks. The study was also nonrandomized, which may have biased the results in favor of adalimumab.

Daclizumab (Zenapax)

As mentioned above, T cells are important mediators of inflammatory eye disease.[23] Interleukin (IL)-2 is a cytokine critical to T-cell differentiation and survival and binds to the IL-2 receptor on T cells. The IL-2 receptor is made up of various combinations of 3 distinct subunits, α (CD25 or Tac), β (CD122), and γ (CD132) chains. Daclizumab (Zenapax; Hoffmann-La Roche, Inc., Nutley, NJ) is a humanized mAb against CD25 that has been used in the treatment of various immune-mediated diseases, including renal allograft rejection, MS, and human T-cell lymphotrophic virus 1 (HTLV-1)-associated disease.[71]

Small nonrandomized, noncontrolled studies investigating the use of daclizumab in the treatment of noninfectious uveitis showed favorable results in suppressing active disease, preventing reactivation of inflammation, and decreasing the concomitant use of other immunosuppressive medications.[72-76] However, a randomized, placebo-controlled, double-masked clinical trial of 17 patients with ocular Behçet disease demonstrated no difference between daclizumab- and placebo-treated patients receiving other forms of immunosuppression.[77] Although daclizumab was generally well tolerated, the manufacturer discontinued production of this medication due to declining market demand.[78]

Secukinumab (AIN457)

IL-17A is a pro-inflammatory cytokine implicated in the pathogenesis of several autoimmune diseases, including endogenous intraocular inflammation. Levels of IL-17A have been found to be increased in the serum of uveitis patients (eg, Behçet disease) compared with healthy controls and are particularly elevated in those with active disease.[79, 80] An initial open-label, nonrandomized, noncontrolled study of 16 noninfectious uveitis patients treated with 2 intravenous infusions of secukinumab (AIN457; Novartis Pharmaceuticals, East Hanover, NJ), a humanized mAb against IL-17A, showed promising results in terms of VA and intraocular inflammation scores.[81] However, in a multicenter, randomized, double-masked, placebo-controlled trial (SHIELD study) assessing the rate of uveitis recurrence during withdrawal of concomitant immunosuppressive medications in patients with posterior or panuveitis associated with Behçet disease (n = 118), subcutaneous treatment with secukinumab did not significantly reduce recurrences compared with placebo.[82] Secondary analyses revealed that treatment with secukinumab was associated with a significantly reduced use of concomitant immunosuppressive medications. Two additional multicenter, randomized, placebo-controlled, double-masked trials designed to investigate the use of secukinumab in patients with active noninfectious uveitis but without Behçet disease (INSURE study) and in patients with quiescent noninfectious uveitis but without Behçet disease (ENDURE study) were terminated early, without evidence of efficacy.[82] Thus, there is currently insufficient evidence to support the use of secukinumab in noninfectious uveitis. Further development of secukinumab for uveitis has since ceased, although studies for ankylosing spondylitis and psoriatic arthritis are still ongoing with promising early results.[83, 84]

Clinical Trials of Local Ocular Corticosteroids in Noninfectious Uveitis

Fluocinolone Acetonide Uveitis Study

The Fluocinolone Acetonide Uveitis Study (Table 5) was an industry-sponsored, prospective, randomized, double-masked, multicenter trial that evaluated the safety and efficacy of 0.59-mg and 2.1-mg fluocinolone acetonide (FA) intravitreous implants (Retisert; Bausch & Lomb Inc., Rochester, NY) in noninfectious posterior-segment uveitis with a 3-year follow-up period.[85] Eligible patients were randomized 2:3, with 110 patients receiving 0.59-mg and 168 receiving 2.1-mg FA implants. Any patient with bilateral disease received the implant in the more severely affected eye, as long as ocular inflammation in the fellow, nonimplanted eye could be adequately controlled with topical medication or periocular steroid injections. Otherwise, the patient was not enrolled in the study. After surgical placement of the FA implant, systemic corticosteroids and immunosuppressive agents were tapered and discontinued. The primary outcome was difference in uveitis recurrence rates pre- and postimplantation in the implanted eye. Secondary outcomes included time to and rates of postimplantation uveitis recurrence between treatment groups, time to and rates of postimplantation uveitis recurrence between implanted and nonimplanted fellow eyes in patients with bilateral disease, need for adjunctive treatment in the implanted eye, reduction of CME, improvement in VA, elevation of IOP, incidence of cataracts, and quality of life (QOL) surveys.

By 3 years postimplantation, uveitis recurrence rates decreased from 62% to 20% in uveitic eyes implanted with the 0.59-mg FA implant ($P < 0.01$) and from 58% to 41% in uveitic eyes implanted with the 2.1-mg implant ($P < 0.01$).[85] Recurrence rates in nonimplanted eyes, however, increased from 30% to 59% in the 0.59-mg FA implant group ($P < 0.01$) and from 22% to 55% in the 2.1-mg implant group ($P < 0.01$). Similar trends were observed when comparing implanted and nonimplanted fellow eyes of the same patient. Implanted eyes also showed improvement in VA when compared with nonimplanted eyes ($P < 0.01$). However, implanted eyes had a higher incidence of 10-mm Hg IOP elevation ($P < 0.01$), IOP-lowering surgery ($P < 0.01$), and cataract extraction ($P < 0.01$). Thus, the FA implant significantly reduced uveitis recurrence rates and improved VA, but also led to significantly more ocular complications—mainly glaucoma and cataracts—in patients with posterior-segment uveitis.

The Fluocinolone Acetonide Uveitis Study Group also conducted an industry-sponsored, prospective, randomized (1:1), controlled, open-label trial comparing the safety and efficacy of a 0.59-mg FA intravitreal implant with that of standard systemic therapy (systemic corticosteroid monotherapy or combination steroid-immunosuppressive therapy) in treating noninfectious posterior-segment uveitis.[86] All 146 enrolled patients were required to have 10 AC cells and a vitreous haze grade of 2+, but patients were allowed to receive treatment prior to enrollment so that patients randomized to implant had clinically quiet eyes at the time of implantation. Patients with bilateral disease received the implant in the more severely affected eye, as long as ocular inflammation in the fellow, nonimplanted eye could be adequately controlled with periocular steroid injections. Upon enrollment, corticosteroids and other immunosuppressive agents were tapered according to protocol. The primary outcome was time to uveitis recurrence (within 24 months). Secondary outcomes included recurrence frequency pre- and poststudy enrollment, change in VA, change in CME, cataract formation, and IOP elevation.

During the 24 months, the survival distribution was considerably better for eyes treated with the FA implant than it was for eyes of patients who received systemic treatment ($P < 0.01$), although the mean time to first recurrence of uveitis was similar (6.4 ± 7.0 months in implanted eyes vs. 7.1 ± 7.2 months in nonimplanted eyes).[86] Implanted eyes also had a lower overall rate of uveitis recurrence than systemically treated eyes (18.2% vs. 63.5%, respectively; $P < 0.01$). The median, mean, and maximum number of recurrences in 24 months was also significantly lower in the FA group.

By 24 months, stabilized vision was observed in 71.2% of implanted eyes and 73.0% of nonimplanted, systemically treated eyes.[86] Improvement in VA of at least 3 lines was comparable between groups, with 17.2% in the FA group and 14.3% in the systemic therapy group ($P = 0.66$). Reduction in CME, however, was statistically more frequent in the FA group, as 96.5% (32/37) of implanted eyes had less CME by fluorescein angiography versus 74.4% (29/39) of eyes in the systemic treatment group ($P = 0.003$).

Despite greater efficacy of the intravitreal FA implant in reducing uveitis recurrence rates and CME, treatment-related adverse events occurred much more frequently in implanted eyes than in systemically treated eyes (95.5% vs. 39.2%, respectively).[86] By 24 months, a

change of at least 2 grades in lens opacity was seen more commonly in phakic implanted eyes than in phakic systemically treated eyes (89.6% vs. 23.2%, respectively; $P < 0.01$). More implanted eyes than systemically treated eyes also had an IOP elevation of 10 mm Hg at any visit during the 24 months (55.4% vs. 10.8%, respectively; $P < 0.01$). More patients randomized to the FA group also required IOP-lowering medications and glaucoma surgery. Severe ocular adverse events were observed in implanted eyes, with 3 cases of endophthalmitis (4.5%) reported in the FA group in comparison with none in the systemic therapy group. By 2 years of follow-up, 8 eyes in the implanted group were explanted (3 due to hypotony, 2 due to elevated IOP, 1 due to scleral thinning, 1 due to implant extrusion, and 1 due to postoperative complications).

Overall rates of nonocular adverse events were similar between the implant and systemic treatment groups; however, the frequency of moderate to severe nonocular adverse events was marginally higher in the systemic treatment group.[86] While none of these were considered to be related to the study treatment in the implant group, 25.7% of these nonocular adverse events were thought to be treatment-related in the systemic therapy group. The most common nonocular adverse effect was arthralgia (10.6%, 7/66) in the implant group and hypertension (8.1%, 6/74) in the systemic treatment group. One patient in the systemic treatment group died of causes unrelated to study participation.

Multicenter Uveitis Steroid Treatment (MUST) Trial

The MUST trial (Table 6) was a prospective, randomized (1:1), open-label, parallel-design clinical trial sponsored by the National Eye Institute and conducted at 23 tertiary care centers in the United States, United Kingdom, and Australia.[87] It sought to compare the effectiveness of local therapy using a 0.59-mg fluocinolone acetonide (FA) intravitreous implant with that of standard therapy (systemic corticosteroid monotherapy or combination steroid-immunosuppressive therapy). Patients were eligible if they had intermediate, posterior, or panuveitis of noninfectious etiology that was severe enough to warrant treatment with systemic corticosteroids. A total of 255 eligible patients (479 eyes with uveitis) were enrolled and randomly assigned to implant or systemic therapy from 2005 to 2008 and were followed for 24 months. Any patient with bilateral disease and randomized to implant received the implant in both eyes. Primary outcome was change in BCVA from baseline to 24 months in uveitic eyes. Secondary outcome measures included uveitis activity, change in macular edema, change in IOP, glaucoma incidence, cataract formation, change in self-reported vision-related function from baseline (as measured by the NEI 25-Item Visual Function Questionnaire [NEI-VFQ 25] vision-targeted composite score), change in SF-36 mental and physical component scores from baseline, and overall mortality at 24 months. An ancillary study also examined the cost-effectiveness of the FA implant compared with standard systemic therapy.[91]

At 24 months, patients treated with either implant or systemic therapy showed improvement in VA with a mean change of +6.0 or +3.2 letters, respectively, but no statistically significant difference was detected between the 2 groups ($P = 0.16$).[88] Additionally, 21% of eyes assigned to implant and 13% of those treated with systemic therapy gained at least 15 letters or 3 Snellen-equivalent lines of VA ($P = 0.065$). If eyes with VA 20/40 at baseline

were excluded, mean improvement was 12.9 and 9.3 letters in the implant and systemic therapy groups, respectively ($P = 0.25$). VA outcomes also followed similar trends regardless of baseline lens status ($P = 0.065$ for lens status-treatment interaction). These results were not sufficient to demonstrate superiority of the FA intravitreal implant over current standard systemic therapy. However, patients with implants showed significant and oftentimes greater improvement in VA numerically when compared with baseline.

Most eyes with active uveitis at baseline were controlled within 9 months for both treatment groups.[88] However, control was more frequently achieved in the implant group (88% vs. 71% at 24 months, $P = 0.001$). The rate of a 2-step improvement in vitreous haze was also faster in the implant group (hazard ratio [HR] = 1.47, $P = 0.014$). Despite similar baseline rates of macular edema, the implant group had fewer uveitic eyes with macular edema by 6 months (20% vs. 34% at 6 months, compared with 41% vs. 39% at baseline, $P < 0.001$). However, by 24 months, any statistically significant difference in change from baseline between groups was no longer observed (22% in implant group vs. 30% in systemic therapy group, $P = 0.071$).

Although systemic complication rates were low and similar between groups, ocular complications were unfortunately found to be more prevalent in the implant group than in the systemic therapy group.[88] The implant group had higher rates of first-incidence IOP elevation of 10 mm Hg (HR = 4.3, $P < 0.0001$), absolute IOP of 30 mm Hg (HR = 6.1, $P < 0.0001$), and need for IOP-lowering medical and surgical treatment (HR = 4.2 and 8.4, respectively; $P < 0.0001$ for both). Even when medical and surgical interventions were made for increased pressures, glaucoma developed in 17% of uveitic eyes in the implant group versus 4.0% in the systemic therapy group (HR = 4.2, $P = 0.001$). Furthermore, glaucomatous optic nerve damage was seen in 23% of the implant group versus 6% of the systemic therapy group ($P < 0.001$).[89] Among eyes at risk, a higher cumulative 24-month risk of cataract (91% vs. 45%) and cataract surgery (80% vs. 31%) was observed in the implant group compared with the systemic therapy group.[88]

Despite increased rates of ocular complications, vision-related and general health-related QOL scores were found to be higher in the implant group than in the systemic treatment group, with the greatest change from baseline occurring at 6 months.[88] In fact, vision-related QOL scores on a 100-unit scale improved by 9.4 units more in the implant group at 6 months ($P < 0.0001$). By 24 months, however, this value diminished to a 4.6-unit difference ($P = 0.04$), which would be considered a minimally important difference by a prior report.[90] General health-related QOL scores were also found to be marginally higher in the implant group at 24 months.[88]

The cost-effectiveness of the FA implant was also compared with that of standard systemic therapy in an ancillary study.[91] The incremental cost-effectiveness ratio (ICER), or the ratio of the difference in cost (ie, cost of all medications, surgeries, hospitalizations, and regular laboratory monitoring tests) to the difference in quality-adjusted life-years (QALYs), was determined over the 3 years of the study and was stratified by disease laterality. For patients treated with FA implants, upfront costs were significantly large with low maintenance costs, whereas the cost of systemic therapy was generally steady over the 3 years. Mean cost over

3 years for patients with unilateral disease was approximately $38,800 in the FA implant group and $33,400 in the systemic therapy group, and the difference was not statistically significant ($P = 0.44$). Mean 3-year cost for patients with bilateral uveitis, however, was much higher at $69,300 for the FA implant group and $52,500 for the systemic therapy group. This difference was significantly large at $16,900 (95% confidence interval [CI], $7,400-$26,300; $P < 0.001$). The ICER for bilateral disease over 3 years was also high at $297,800/QALY, compared with $41,200/QALY for unilateral uveitis. The probability of cost-effectiveness was 0.53 and 0.74 for ICER thresholds of $50,000/QALY and $100,000/QALY, respectively. Thus, at current costs, unilateral FA implants are considered to be reasonably cost-effective, while bilateral FA implants are not, given the exorbitantly high ICER for bilateral disease. However, if FA implant costs are reduced or if duration of treatment effect lasts longer than 3 years, then these implants may be cost-effective for bilateral disease. Nonetheless, these cost-effective analyses do not apply to patients with bilateral uveitis who have failed or have contraindications to systemic therapy, as the MUST trial demonstrated the safety and efficacy of FA implants in both unilateral and bilateral disease.[88]

Chronic Uveitis Evaluation of the Intravitreal Dexamethasone Implant (HURON) Study

The C*h*ronic *U*veitis Evaluation of the Intravit*r*eal Dexametha*son*e Implant (HURON) study (Table 7) was an industry-sponsored, randomized, placebo-controlled, double-masked, multicenter clinical trial comparing the dexamethasone intravitreal implant (Ozurdex; Allergan Inc., Irvine, CA) at 2 doses (0.35 mg and 0.70 mg) with a sham procedure in eyes affected with noninfectious intermediate or posterior uveitis.[92] The right eye was determined to be the study eye in patients with bilateral disease. Patients were allowed to continue topical corticosteroids and nonsteroidal anti-inflammatory agents if doses were stable for at least 2 weeks before screening until treatment day (day 0), systemic corticosteroids if doses of oral prednisone were 20 mg/day (or the equivalent) and were stable for at least 1 month before screening until 8 weeks posttreatment, and systemic immunosuppression (eg, cyclosporine) if doses were stable for at least 3 months before screening until 8 weeks posttreatment. Otherwise, patients were excluded from the study. Patients with any other active ocular disease or infection, uveitis previously unresponsive to corticosteroid therapy, and elevated IOP requiring IOP-lowering medications were also excluded from the study. A total of 229 patients with noninfectious intermediate (80%) or posterior uveitis (20%) were enrolled, were randomized 1:1:1 to 2 doses of study treatment and placebo, and were followed for 26 weeks posttreatment. Primary outcome was proportion of uveitic eyes with a vitreous haze grade of 0 at 8 weeks posttreatment. Secondary outcomes included time to vitreous haze grade of 0, change in VA, change in central macular thickness, need for rescue medication, change in IOP, incidence of ocular adverse events, and change in patient-reported vision-related function.

A mean vitreous haze grade of 2+ was observed in all patients at day 0, but by week 8, a greater proportion of uveitic eyes treated with dexamethasone implant had a vitreous haze grade of 0 compared with the sham group (47% and 36% of eyes treated with 0.70-mg and 0.35-mg dexamethasone implant, respectively, vs. 12% of eyes in the sham group; $P < 0.001$).[92] In fact, a statistically significant difference between implant and sham groups was

observed throughout most of the study period (*P* 0.014 for the 0.70-mg dexamethasone implant, weeks 6-26; *P* 0.030 for the 0.35-mg dexamethasone implant, weeks 6-12 and 20-26). If only eyes with a baseline vitreous haze grade of 1.5+ or 2+ from each treatment group were analyzed, this difference persisted throughout the entire study period (*P* < 0.05), except at week 16 for the 0.35-mg dexamethasone implant group. Vitreous haze grade improvement of 2 units was also more commonly seen in the 0.70-mg and 0.35-mg dexamethasone implant groups than in the sham group (*P* 0.023 and *P* 0.034, respectively).

During the study period, VA improvement of at least 15 letters or 3 Snellen-equivalent lines was 2- to 6-fold higher in the implant groups than in the sham group.[92] Mean VA improvement was also greater in the implant groups, and this difference was statistically significant throughout the study period (*P* 0.002 for the 0.7-mg dexamethasone implant, *P* 0.010 for the 0.35-mg dexamethasone implant), except at week 26 for the 0.35-mg dexamethasone implant group.

Central macular thickness at weeks 8 and 26 was significantly reduced from baseline values in the implant groups (*P* 0.004), but not in the sham group (*P* 0.092).[92] However, mean reduction in central macular thickness was only statistically significant at week 8, when comparing values of the 2 implant groups with those of the sham group (*P* 0.004). There was no significant difference in mean central macular thickness change between the implant groups.

Throughout the study period, the proportion of patients who required rescue medication was significantly greater in the sham group than in the implant groups (*P* 0.030), except at week 16.[92] Interestingly, more eyes in the 0.7-mg dexamethasone implant group needed rescue medication than those in the 0.35-mg dexamethasone implant group. However, this difference was not statistically significant.

At any point in the 26-week study period, <5% of study eyes developed an IOP of 35 mm Hg, and <10% had an IOP of 25 mm Hg.[92] The proportion of study eyes with IOP elevation of 10 mm Hg was not reported. However, the study authors noted that most patients with IOP elevation were either observed or treated with a single medication. The use of IOP-lowering medications was not reported for each treatment group, but 23% of the 0.7-mg dexamethasone implant group required IOP-lowering medications at any time during the study period. Only 1 of 229 patients in the study, who was randomized to the 0.35-mg dexamethasone implant group, required IOP-lowering surgery within the 26-week study period.

Cataracts developed in 15% (9/62), 12% (6/51), and 7% (4/55) of phakic study eyes in the 0.7-mg and 0.35-mg dexamethasone implant groups and sham group, respectively.[92] Conjunctival hemorrhage, ocular discomfort, eye pain, iridocyclitis, and retinal detachment were also reported as adverse effects in the study. One case of possible culture-negative endophthalmitis versus uveitis flare was also reported. No significant difference was observed between groups for any of these ocular adverse effects.

Although no significant differences in ocular adverse effects were seen between groups,[92] statistically significant improvements in the total patient-reported NEI VFQ-25 score (P 0.012) and various vision-related subscores ($P < 0.05$) were observed in both dexamethasone implant groups when compared with the sham group at week 8.[93] Even after 26 weeks, statistically significant increases in the total NEI VFQ-25 score ($P = 0.001$) and several of its subscores (P 0.032) persisted in both implant groups. It is important to note that the NEI VFQ-25 composite score and few of its subscores were higher at baseline in the sham group than in the implant groups, but the change from baseline was significantly greater in the implant groups than in the sham group, even though improvements in vision-related function were observed in all treatment groups.

Clinical Trials of Topical Agents in Noninfectious Anterior Uveitis

Multiple topical agents, including several topical corticosteroids, have been tested in patients with noninfectious uveitis. These studies are discussed below and are summarized in Table 8.

Topical Corticosteroids: Difluprednate 0.05% (Durezol), Prednisolone Acetate 1% (Pred Forte)

The safety and efficacy of difluprednate ophthalmic solution 0.05% (Durezol; Alcon Laboratories Inc., Fort Worth, TX), a potent difluorinated prednisolone derivative, was compared with that of prednisolone acetate ophthalmic solution 1% (Pred Forte; Allergan Inc., Irvine, CA) in treating anterior uveitis in an industry-sponsored, prospective, randomized, double-masked, multicenter, noninferiority clinical trial.[94] Ninety patients with acutely active anterior uveitis, defined as anterior uveitis of <2-week duration with >10 AC cells and AC flare grade of 2+ in at least 1 eye, were enrolled in the study. Topical difluprednate (n = 50) was dosed at 4 times per day (alternating with vehicle 4 times per day), and topical prednisolone (n = 40) was dosed at 8 times per day. The treatment period was 14 days followed by another 14 days or so of tapering; patients were followed for another 14 days. Any patients stably taking corticosteroids and/or steroid-sparing agents were allowed to continue taking their systemic immunosuppressive medications throughout the 6-week study period. The primary outcome was change in mean AC cell grade at day 14 from baseline. Secondary outcomes included AC clearing, AC flare, total sign and symptom scores, pain score, VA, adverse effects, and QOL surveys. The total sign score was calculated by summing the individual scores for AC cells, AC flare, posterior synechiae, peripheral anterior synechiae, hypopyon, limbal injection, and keratic precipitates for a maximum of 23 points. The total symptom score was determined by adding the individual scores for pain, photophobia, blurred vision, and lacrimation, each of which was on a 0- to 100-mm visual analog scale. QOL was assessed by the NEI VFQ-39 and Work Limitations Questionnaire.

At all time points throughout the study, topical difluprednate was found to be noninferior to topical prednisolone.[94] In fact, by day 14, mean AC cell grade improved by 2.1 in the difluprednate group versus 1.9 in the prednisolone group (upper 95% confidence limit on the difference being 0.22, where <0.5 is required to be noninferior). AC clearing was nonsignificantly greater in the difluprednate group than in the prednisolone group (68.8%

vs. 61.5%, respectively). Resolution of AC flare also occurred more rapidly in the difluprednate group compared with the prednisolone group, but any differences were not statistically significant. Improvements in total sign, total symptom, and pain scores were numerically higher in the difluprednate group than in the prednisolone group.

VA improved significantly and much more rapidly in the difluprednate group compared with the prednisolone group.[94] Improvements in VA occurred as early as day 3 ($P = 0.02$), with significant differences between groups noted until day 35 ($P = 0.04$), with the exception of day 14. Patients in the difluprednate group also had higher scores on QOL surveys than patients in the prednisolone group, but the study was not powered to determine the significance of these QOL measures.

Adverse effects were reported in 68% of patients on difluprednate and in 70% of patients on prednisolone.[94] Most were mild to moderate and ocular in nature. IOP elevation was observed in 6 patients (12%) on difluprednate and 2 patients (5%) on prednisolone, although clinically significant IOP elevation occurred in 3 patients (6%) taking difluprednate and 2 patients (5%) taking prednisolone. One of the patients on prednisolone had an IOP elevation of 10 mm Hg; the others had an IOP elevation of 8 mm Hg. Only 1 patient required IOP-lowering medication, while IOP elevation resolved spontaneously in the other patients. One patient on difluprednate experienced noncardiac chest pain that required hospitalization, but continued with the study. Five patients (12.5%) on prednisolone had worsening anterior uveitis despite topical corticosteroid treatment and therefore discontinued the study.

In 2010 to 2011, a similarly designed, industry-sponsored, prospective, randomized, double-masked, multicenter, noninferiority clinical trial was conducted to compare the safety and efficacy of difluprednate versus prednisolone in treating anterior uveitis.[95] Similar to the study by Foster et al,[94] difluprednate was found to be noninferior to prednisolone.[95] Adverse effects were reported in 45% of patients on difluprednate and in 35% of patients on prednisolone, and most were mild and ocular. IOP elevation of 10 mm Hg was observed in 9 patients (16%) on difluprednate and 6 patients (11%) on prednisolone. One patient developed severe necrotizing retinitis while on difluprednate and discontinued the study drug. One patient also experienced nausea, weakness, malaise, and sinusitis while participating in the study and discontinued the study medication for these symptoms. One patient with a history of hypertension had moderate systemic hypertension during the study period, but continued on difluprednate. One patient on prednisolone reported moderate recurrent iritis and subsequently withdrew from the study for treatment failure. A total of 8 patients discontinued prednisolone for treatment failure. In summary, both studies similarly showed that difluprednate 0.05% dosed 4 times daily was noninferior to prednisolone acetate 1% dosed 8 times daily, with slightly more ocular adverse effects—mainly in the form of IOP elevation—in the difluprednate-treated group.

Iontophoretic Administration of Dexamethasone Phosphate (EGP-437)

An industry-sponsored, prospective, randomized, double-masked, parallel-design, multicenter clinical trial sought to determine the safety and efficacy of ocular iontophoretic application of dexamethasone phosphate (EGP-437 using the EyeGate II Delivery System; EyeGate Pharmaceuticals Inc., Waltham, MA).[96] Forty patients with anterior uveitis were

enrolled, and 1 uveitic eye per patient was randomly assigned to 1 of 4 iontophoresis dose groups (1.6, 4.8, 10.0, or 14.0 mA-min). After a single treatment on day 0, patients were followed for 28 days. Any patient with 0.5 increase in AC cell grade on day 1 or who had worsening of or no change in AC cell count by day 7 was treated with topical prednisolone. Primary outcome was AC cell grade of 0 at days 14 and 28. Secondary outcome measures included time to AC cell grade of 0, mean change in AC cell grade from baseline at day 28, and adverse effects.

By day 14, 55% of patients (22/40) had an AC cell grade of 0.[96] Most of these patients achieved an AC cell grade of 0 with a single treatment of iontophoretic dexamethasone alone. Three of 22 patients did require rescue therapy with topical prednisolone. By day 28, 80% (32/40) had an AC cell grade of 0, and 8 of these patients received topical prednisolone during the study period. All except 1 patient achieved an AC cell grade reduction of at least 0.5 by day 28. Mean change in AC cell grade from baseline was -2.14 for all dose groups by day 28 (median, -2.00). The highest mean change in AC cell grade was observed in the 1.6 mA-min dose group, and the lowest was seen in the 14.0 mA-min dose group. The 1.6 mA-min dose group also had the highest proportion of patients achieving an AC cell grade of 0 and the lowest proportion of patients requiring adjunctive therapy. Interestingly, an inverse dose response was observed with respect to time to AC cell grade of 0—specifically, the median number of days to AC cell grade of 0 was 11.5 days in the 1.6 mA-min dose group, 15.0 days in the 4.8 mA-min dose group, 22.0 days in the 10.0 mA-min dose group, and 31.0 days in the 14.0 mA-min dose group. Furthermore, a mean AC cell grade of 0 was seen in both 1.6 and 4.8 mA-min dose groups by days 14 and 28, but this was not the case for either the 10.0 or 14.0 mA-min dose groups.

Adverse effects were reported in 90% of patients (36/40), and most were mild and ocular.[96] Of 134 reported adverse events, conjunctival hyperemia (n = 21, 16%), punctate keratitis (n = 15, 11%), conjunctival edema (n = 13, 10%), eyelid edema (n = 8, 6%), and eye pain (n = 8, 6%) were the most commonly reported ocular adverse effects. IOP elevation was observed in 2 patients (5%), but this resolved within 48 hours. No serious adverse events were reported, and no nonocular, systemic corticosteroid effects were observed, as based on serum corticosteroid levels. No patients discontinued the study due to medication-related adverse effects. Overall, single iontophoretic dexamethasone treatment was most effective in lower doses and was well tolerated. However, placebo-controlled, double-masked studies are still needed to determine its true efficacy.

Topical anti-TNF-α single-chain antibody (ESBA105)

A pilot study on the safety and efficacy of a topical TNF-α antagonist (ESBA105; ESBATech AG, Zurich-Schlieren, Switzerland) in treating acute anterior uveitis was terminated early due to recruitment difficulties (personal correspondence). However, the company is pursuing further development of ESBA105 in other ophthalmic applications, such as severe dry eye.[97]

Conclusion

With renewed interest in more effective targeted treatment strategies for uveitis, multiple clinical trials have investigated steroid-sparing immunosuppressive agents as treatment options for noninfectious uveitis. Clinical trials completed over 30 years ago have established the efficacy of cyclosporine A, a calcineurin inhibitor that blocks proliferation and effector functions of activated T cells, and this medication is still commonly being used today. Newer T-cell inhibitors, such as tacrolimus, may have fewer adverse effects and are more frequently used, especially in Europe. The antimetabolites methotrexate, mycophenolate mofetil, and azathioprine have also been shown to be effective in treating noninfectious uveitis in multiple retrospective chart reviews and small prospective clinical trials and are regularly used in clinical practice. There has also been increasing recent evidence to suggest the efficacy of biologic agents, especially mAb directed against TNF-α, but there is some level of concern for malignancy potential with their continued use. There are additional ongoing and planned trials investigating other potential therapeutic agents for uveitis, which are listed in Table 9.

Although several clinical trials have demonstrated the safety and efficacy of steroid-sparing immunosuppressive agents in uveitis, corticosteroids administered either systemically or locally in and around the eye still remain critically important in the treatment of noninfectious uveitis, given their broad immunosuppressive effects and rapid onset of action. In fact, the SITE study revealed that when systemic corticosteroids were completely discontinued in patients with inflammatory eye disease treated with corticosteroids and 1 other immunosuppressive agent, the percentage of uveitis patients with quiescent disease decreased precipitously. These findings demonstrate that even low doses of corticosteroids (eg, 5 mg of prednisone) provide significant immunosuppressive effects. Nevertheless, chronic corticosteroid use can lead to unwanted and potentially serious adverse effects. Fortunately, extended-release intravitreal corticosteroid implants can provide long-acting local immunosuppression without the dreaded systemic complications of systemically administered corticosteroids, and they are approved by the Food and Drug Administration for use in patients with noninfectious uveitis. However, ocular side effects of cataract and glaucoma are not insignificant and must be considered before using these implants.

In general, prospective, randomized, controlled clinical trials in uveitis enroll small numbers of patients, and many of these studies include patients with various conditions under the umbrella term "uveitis." While all forms of uveitis are proposed to have an inflammatory etiology, the precise immunopathological mechanisms remain elusive for individual entities. This becomes critically important when testing pharmacologic agents that target certain inflammatory pathways, such as mAb directed against specific cytokines. If the pathogenesis of a particular form of uveitis is not largely mediated by a specific cytokine of interest, then blocking it will unlikely be of strong clinical benefit. Thus, as our understanding of the basic immunological mechanisms underlying the pathogenesis of noninfectious uveitis expands, so will the breadth of prospective therapeutic targets, but only with continued basic and clinical research efforts will effective targeted therapies be discovered and successfully implemented for patients suffering from potentially blinding inflammatory eye diseases.

Acknowledgments

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Table 1

Summary of Systemic Immunosuppressive Therapy for Eye Disease (SITE) cohort study results

- Patients taking oral corticosteroids, azathioprine, methotrexate, mycophenolate mofetil, or cyclosporine had similar overall and cancer-related mortality rates compared with patients not exposed to immunosuppression.[8]

- Patients on cyclophosphamide had a nonstatistically significant increase in cancer-related mortality rates.[8]

- Patients taking anti-TNF-α biologic agents had significantly increased overall and cancer-related mortality rates, but this association was less robust due to the small number of patients receiving biologic therapy.[8]

- One year after starting therapy, sustained control of inflammation was attained in 62.2%, 66.0%, 73.1%, 51.9%, and 76.3% of patients taking azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, and cyclophosphamide, respectively.[9-13]

TNF indicates tumor necrosis factor.

Table 2

Summary of select clinical trials on T-cell inhibitors

Cyclosporine A

FDA-approved for use in solid organ transplantation, RA, and psoriasis

- Cyclosporine A has been shown to be effective in treating several noninfectious uveitic entities.[25-28]

- Doses of 151-250 mg/day provided equal efficacy with reduced incidence of adverse events when compared with higher doses.[12]

Tacrolimus

FDA-approved for use in solid organ transplantation

- Tacrolimus (0.03-0.08 mg/kg daily) was shown to be as equally effective as cyclosporine (2.5-5.0 mg/kg daily) in suppressing posterior segment inflammation with potentially fewer adverse effects.[29]

Sirolimus

FDA-approved for use in solid organ transplantation

- Within 4 weeks, a single subconjunctival injection of sirolimus resulted in at least a 2-step reduction of anterior chamber reaction in 3 of 5 patients with chronic active anterior uveitis.[31]

- At 6 months, a series of subconjunctival or intravitreal sirolimus injections at days 0, 60, and 120 resulted in at least a 2-step reduction of vitreous haze scores in 6 of 15 patients with intermediate, posterior, or panuveitis.[32]

Voclosporin

Not currently FDA-approved for any indication

- Significant control of intraocular inflammation was achieved with voclosporin in patients with active intermediate, posterior, or panuveitis (n = 218) at 16 and 24 weeks.[35, 36]

- By 26 weeks, voclosporin reduced recurrence rates by 50% in patients with quiescent intermediate, posterior, or panuveitis (n = 232), but the study failed to meet its primary endpoint.[35-37]

- No significant differences were demonstrated between voclosporin and placebo in patients with active anterior uveitis (n = 108), but the study was underpowered.[35]

FDA indicates Food and Drug Administration; RA, rheumatoid arthritis.

Table 3

Summary of select clinical trials on antimetabolites

Azathioprine vs. cyclosporine A

- Both prednisone-azathioprine (n = 12) and prednisone-cyclosporine (n = 9) combination therapies were effective in reducing intraocular inflammation and improving vision in patients with chronic VKH. However, patients in the azathioprine group required significantly higher doses of prednisone, suggesting that cyclosporine may provide better steroid-sparing efficacy in chronic VKH.[39]

Methotrexate vs. mycophenolate mofetil

- A nonsignificantly higher percentage of patients receiving methotrexate (69%, 24/35) versus mycophenolate mofetil (47%, 15/32) achieved treatment success, but there was no significant difference in the number of treatment failures, time to steroid-sparing control of inflammation, change in best-corrected visual acuity, or resolution of macular edema observed between the 2 groups.[40]

- Methotrexate and mycophenolate mofetil are similarly effective in controlling intraocular inflammation in patients with noninfectious uveitis.[10, 11, 40]

VKH indicates Vogt-Koyanagi-Harada disease.

Table 4

Summary of select clinical trials on biologic agents to treat noninfectious uveitis

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Type 1 Interferons (IFN-α, IFN-β)

IFN-α: FDA-approved for multiple malignancies and hepatitis virus infections

IFN-β: FDA-approved for multiple sclerosis

- Noncontrolled, nonrandomized studies suggest IFN-α to be beneficial in the treatment of ocular Behçet disease.[43-45]

- Compared with methotrexate, IFN-β treatment improved visual acuity and macular edema in patients with intermediate uveitis.[50]

Etanercept (Enbrel)

FDA-approved for RA, JIA, ankylosing spondylitis, and psoriasis

- No significant differences (eg, in relapse rate, visual acuity, corticosteroid dosage) were observed between etanercept and placebo in either adults or children, despite prior reports of a beneficial effect.[52-55]

- Efforts to further investigate the efficacy of etanercept in treating chronic or treatment-resistant uveitis, especially in children, has halted, as an association between etanercept use and new-onset or recurrent uveitis has become evident.[56]

Infliximab (Remicade)

FDA-approved for RA, ankylosing spondylitis, psoriasis, and IBD

- Continued infliximab treatment (5 mg/kg every 8 weeks) resulted in both resolution of posterior disease and reduction of relapse rates in patients with refractory noninfectious uveitis, including Behçet disease.[59-62]

Adalimumab (Humira)

FDA-approved for RA, JIA, ankylosing spondylitis, psoriasis, and IBD

- Anterior uveitis flare rates were reduced by 51% with adalimumab in 1250 patients with ankylosing spondylitis, although 2 patients with high ankylosing spondylitis disease activity developed new-onset anterior uveitis during the study period.[65]

- Significant differences (e.g., in visual acuity, cystoid macular edema, corticosteroid dosage) were observed in patients with refractory noninfectious uveitis after the initiation of adalimumab therapy.[66-68]

Daclizumab (Zenapax)

FDA-approved for prevention of renal transplant rejection, but no longer commercially available

- No significant differences were observed between daclizumab and placebo in 17 patients with ocular Behçet disease receiving other forms of immunosuppression.[77]

Secukinumab (AIN457)

FDA-approved for plaque psoriasis

- In the SHIELD study, secukinumab treatment was associated with significantly reduced use of concomitant immunosuppressive medications in 118 patients with posterior or panuveitis associated with Behçet disease.[82]

- The INSURE and ENDURE studies were terminated early, without evidence of efficacy.[82]

FDA indicates Food and Drug Administration; IBD, inflammatory bowel disease; IFN, interferon; JIA, juvenile idiopathic arthritis; RA, rheumatoid arthritis.

Table 5

Summary of Fluocinolone Acetonide Uveitis Study results[85, 86]

- Although mean time to first recurrence of uveitis was similar between groups, overall recurrence rates were significantly lower in eyes treated with the fluocinolone acetonide intravitreous implant than in eyes of patients who were treated with systemic therapy.

- Reduction in cystoid macular edema was statistically more frequent in the implant group, but improvement in visual acuity was comparable between groups.

- Treatment-related adverse events—notably glaucoma and cataracts—occurred much more frequently in implanted eyes than in nonimplanted, systemically treated eyes.

- Overall rates of nonocular adverse events were similar between implant and systemic treatment groups; however, the frequency of moderate to severe nonocular adverse events was marginally higher in the systemic treatment group.

Table 6

Summary of the Multicenter Uveitis Steroid Treatment (MUST) Trial[88, 89, 91]

- Overall uveitic control (eg, by vitreous haze score, macular edema) was significantly more frequently achieved in eyes treated with the fluocinolone acetonide intravitreous implant than in eyes of patients who were treated with systemic therapy.

- Improvement in visual acuity was comparable between groups. However, patients with implants showed significant and oftentimes greater improvement in visual acuity numerically when compared with baseline.

- Ocular complications—notably glaucoma and cataracts—occurred significantly more frequently in implanted eyes than in nonimplanted, systemically treated eyes, but overall rates of systemic adverse events were similar between groups.

- Despite a significant increase in ocular adverse effects, vision-related and general health-related quality of life scores were found to be higher in the implant group than in the systemic treatment group.

- Whereas the cost of systemic therapy was generally steady over the 3 years of the study, upfront costs for implants were significantly large, with an incremental cost-effectiveness ratio of $297,800 per quality-adjusted life year (QALY) for bilateral disease and $41,200/QALY for unilateral disease, albeit with low maintenance costs. Thus, at current costs, unilateral implants are considered to be reasonably cost-effective, while bilateral FA implants are not. However, these cost-effective analyses do not apply to patients with bilateral uveitis who have failed or have contraindications to systemic therapy.

Table 7

Summary of Chronic Uveitis Evaluation of Intravitreal Dexamethasone Implant (HURON) Study results[92]

- Throughout the study period, a significantly greater proportion of eyes treated with the dexamethasone implant had a vitreous haze grade of 0 and a vitreous haze grade improvement of 2 units compared with the sham group.

- Improvement in visual acuity was also significantly greater in the 2 implant groups than in the sham group.

- Reduction of central macular edema was generally nonsignificantly greater in the implant groups than in the sham group.

- The proportion of patients requiring rescue medication was significantly greater in the sham group than in the implant groups.

- Although there were no significant differences in the rate of ocular adverse events between groups, intraocular pressure elevation and cataracts were the most commonly reported treatment-related ocular adverse effects in this study.

- Significant improvements in vision-related function were observed in implant groups compared with the sham group.

Table 8

Summary of clinical trials on topical agents to treat noninfectious anterior uveitis

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Difluprednate 0.05% (Durezol) vs. prednisolone acetate 1% (Pred Forte)

- Difluprednate 0.05% dosed 4 times daily was noninferior to prednisolone acetate 1% dosed 8 times daily, with slightly more ocular adverse effects—mainly in the form of IOP elevation—in the difluprednate-treated group.[94, 95]

Iontophoretic administration of dexamethasone phosphate (EGP-437)

- Single iontophoretic dexamethasone treatment was most effective in lower doses (1.6 or 4.8 mA-min vs. 10.0 or 14.0 mA-min) and was well tolerated.[96]

Topical anti-TNF-α single-chain antibody (ESBA105)

- A pilot study on the safety and efficacy of the topical TNF-α antagonist ESBA105 in treating acute anterior uveitis was terminated early due to recruitment difficulties.

IOP indicates intraocular pressure; TNF, tumor necrosis factor.

Table 9

Currently ongoing and future clinical trials in noninfectious uveitis

Compound	Company	Structure	Mechanism of action	Development stage
Abatacept (Orencia)	Bristol-Myers Squibb	Recombinant fusion protein (CTLA-4–Ig)	Binds CD80 and CD86	Phase II
Adalimumab (Humira)	AbbVie Inc.	Humanized mAb	Binds soluble and transmembrane TNF-α	Phases II-III
B27PD (Optiquel)	Enzo Biochem Inc.	Peptide	Multiple; induces oral tolerance	Phases I-II
Celecoxib (Celebrex)	Pfizer Inc.	Selective enzyme inhibitor	Selectively binds COX-2	Phase I
Gevokizumab (XOMA 052)	XOMA Ltd.	Humanized mAb	Binds IL-1β	Phase III
Golimumab (Simponi)	Janssen Biotech Inc.	Humanized mAb	Binds soluble and transmembrane TNF-α	Phase IV
IB-MECA (CF101)	Can-Fite BioPharma	Small molecule agonist	Agonizes adenosine A3 receptor	Phase II
LFG316	Novartis Pharmaceuticals	Humanized mAb	Binds complement C5	Phase II
Sarilumab (SAR153191/REGN88)	Sanofi SA	Humanized mAb	Binds IL-6 receptor	Phase II
Simvastatin (Zocor)	Merck & Co. Inc.	Selective enzyme inhibitor	Inhibits HMG-CoA reductase	Phases II-III
Sirolimus (DE-109)	Santen Pharmaceutical Co., Ltd.	Macrolide antibiotic	Inhibits mTOR	Phase III
Tocilizumab (Actemra)	Genentech Inc. (Roche)	Humanized mAb	Binds IL-6 receptor	Phases I-II
Ustekinumab (Stelara)	Janssen Biotech Inc.	Humanized mAb	Binds p-40 subunit of IL-12 and IL-23	Phases I-II
V404 PDS	ForSight Labs	Unknown	Unknown	Phases I-II

COX indicates cyclooxygenase; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; Ig, immunoglobulin; IL, interleukin; mAb, monoclonal antibody; mTOR, mammalian target of rapamycin; TNF, tumor necrosis factor.

Source: https://www.clinicaltrials.gov