Current biologic therapies in management of uveitis

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Introduction

The biologic agents are a group of therapeutic agents targeting mediators of inflammation including soluble factors (e.g., cytokines, chemokines), Cytokine/chemokine receptors, and immune cell surface markers, have been increasingly used in the treatment of ocular inflammatory diseases. As the pathogenic mechanisms underlying uveitis and ocular inflammation continue to be uncovered, the indications for specific immunomodulatory agents such as the biologic agents will likely continue to expand.

Clinical studies evaluating the aqueous, vitreous, and serum factors of patients have also provided valuable information about the various soluble and cellular mediators of inflammation in specific disease entities. Several agents have been designed to antagonize the action of tumor necrosis factor-alpha (TNF-alpha), and have been used for the treatment of ocular inflammatory diseases. These agents include infliximab, adalimumab, and etanercept. The interleukin-2 (IL-2) receptor antagonist daclizumab has also been utilized for the successful treatment of endogenous uveitis. Several other biologic agents, including alemtuzumab and anakinra, have also been reported in some series for ocular inflammatory diseases. This chapter will focus on the pharmacology, indications, contraindications, and side-effects associated with the TNF-alpha antagonists, IL-2 receptor antagonist daclizumab, and other biologic agents, which have been used for the treatment of uveitis.

Tumor Necrosis Factor-Alpha Antagonists

Histological studies have demonstrated a uveal infiltration of macrophages and T cells, resulting in an inflammatory cytokine and cellular milieu with subsequent loss of tissue architecture and function.

TNF-alpha appears to be a key inflammatory cytokine involved in EAU[1] and its presence has also been detected in the aqueous humor of uveitis patients.[2] Thus, TNF-alpha inhibition is an attractive target for therapy.

Three TNF-alpha inhibitors – **infliximab, adalimumab, and etanercept** – have been approved by the Food and Drug Administration (FDA) for systemic autoimmune indications, and all of these agents have been used for the treatment of ocular inflammatory diseases.

Infliximab

Infliximab is a mouse-derived chimeric monoclonal antibody, which antagonizes TNF-alpha. Its inhibition is mediated via interference of TNF binding to two known receptors – TNFr1, which binds to soluble TNF, and TNFr2, which binds to membrane-bound TNF. A mean terminal half-life between 9 and 12 days has been reported at doses between 5 and 20 mg/kg. Following its administration, infliximab has been detected in most patient sera from 8 to 12 weeks after infusion.[3] Infliximab is administered via intravenous infusion in doses ranging from 3 to 20 mg/kg for both systemic and ophthalmic indications.

Most studies in systemic autoimmune diseases have reported dosing intervals varying from 4- to 8-week dosing intervals. In the ophthalmic literature, doses vary from 3 to 10 mg/kg/dose. However, higher doses of infliximab have been reported for the treatment of refractory pediatric uveitis.

Ophthalmic Indications For Infliximab

The efficacy of infliximab has been evaluated for a number of ophthalmic inflammatory diseases. A paucity of prospective clinical trial data is available for infliximab use in ocular disease; however, its efficacy has been demonstrated for select conditions in a number of case reports and small case series.

Conditions for which infliximab has been used include Behçet's disease-associated panuveitis [4] and retinal vasculitis, juvenile idiopathic arthritis (JIA)-associated uveitis, human leukocyte antigen (HLA)-B27-associated uveitis, scleritis, and peripheral ulcerative keratitis. Suhler et al.[5] reported their experience in a prospective, phase II, open-label study of infliximab for refractory autoimmune uveitis. The various diagnoses from their series included pars planitis, sarcoidosis, Crohn's disease, and Behçet's disease. Infliximab was administered in 3- or 5-mg/kg doses via intravenous infusion at weeks 0, 2, and 6 with clinical assessment at week-10 follow-up. If the patient is stable, the regimen is then reduced to every 8 weeks. If the patient does not respond, however, the dose can be increased up to 10mg/kg and the interval decreased to every 4 weeks. A total of 18 (78%) of 23 patients treated with acuity, two-step decrease in intraocular inflammation, ability to taper immunosuppression, or decrease in inflammatory signs by optical coherence tomography or

fluorescein angiography). Of the 14 patients maintained on infliximab therapy for a full year, 7 (50%) patients maintained successful grades. However, the number of adverse events observed in their series was concerning and included congestive heart failure, pulmonary embolus, lupus-like reaction, and vitreous hemorrhage in 2 patients. Antinuclear antibodies were also identified in 15 (75%) of 20 patients who received more than three infusions. Based on this study, the authors recommended additional long-term studies to assess further the safety and efficacy of infliximab for ophthalmic inflammatory diseases.

Niccoli et al.[6] prospectively evaluated the efficacy of infliximab for Behçet's disease-associated posterior uveitis, which had failed therapy with at least one immunosuppressive medication prior to enrollment. In their series of 12 Behçet's disease patients, results were encouraging, with 9 (75%) patients demonstrating a complete remission at 12-month follow-up. The total number of ocular attacks across all patients decreased from 40 in the year prior to infliximab therapy to five attacks in the year following cessation of infliximab.[6]

Abu El-Asrar et al.[7] reported their experience with infliximab for refractory Behçet's disease-associated uveitis in 6 patients who had each failed at least on other immunosuppressive medication. In this small prospective trial, patients were treated with infliximab at a dosage of 5 mg/kg infusions at weeks 0, 2, 6, and every 8 weeks thereafter. All 6 patients achieved remission by the 2-month time period and 3 patients remained relapse free during the follow-up period (range, 16–36 months, mean, 23.6 months). From their study, it appeared that long-term remission could be maintained by repeated infusions.7 Tugal-Tutkun et al.[8] reported encouraging results from a prospective trial of infliximab for Behçet's disease-associated uveitis resistant to azathioprine, cyclosporine, and corticosteroids. Thirteen male patients were treated with infliximab (5 mg/kg) at weeks 0, 2, 6, and 14 in this trial, and uveitis exacerbations were documented during an infusion period (weeks 0–22) and observation period (weeks 23–54). One patient demonstrated a sustained remission with no ocular attacks during both infusion and observation periods, and 4 patients (30.8%) demonstrated remission during the infusion period. During the observation period, 36 attacks of uveitis in 12 patients were documented, and the treatment protocol was amended to allow the reinstitution of infliximab infusions because of the severity of sight-threatening ocular attacks. Three of the 12 patients required the reinstitution of infliximab therapy. Of note, the mean daily corticosteroid requirement and mean number of uveitis attacks were lower in the infusion period compared to the observation period (weeks 23–54). No serious adverse events were reported in this study. Accorinti et al.[9] also described their experience with

infliximab in 12 patients with Behçet's disease-associated ocular inflammatory disease. Of the 12 patients in their series, 11 patients demonstrated a decrease in the number of ocular relapses per month in the follow-up period. In addition, all 11 patients on corticosteroids prior to therapy were able to decrease their daily corticosteroid requirement. Significant side-effects observed included tuberculosis, herpetic keratitis, severe non-ocular herpetic infection, and recurrent urinary tract infections. Two of these 4 patients experienced uveitic exacerbations when infliximab infusions were delayed because of these side-effects. Thus, while infliximab appeared to benefit some patients, infectious complications possibly related to the medication in this series was concerning.9

Other retrospective studies have supported the efficacy of infliximab for Behçet's disease-associated panuveitis and retinal vasculitis.[10-14] Outcome measures have differed between these retrospective case series, making comparisons between studies difficult. Improvement in visual acuity, decreased intraocular inflammation, and reduction of daily corticosteroid requirements have been reported. However, the development of ocular and systemic tuberculosis in 1 patient[14] and an episode of thoracic herpes zoster in another patient[13] required systemic antimicrobial therapy.

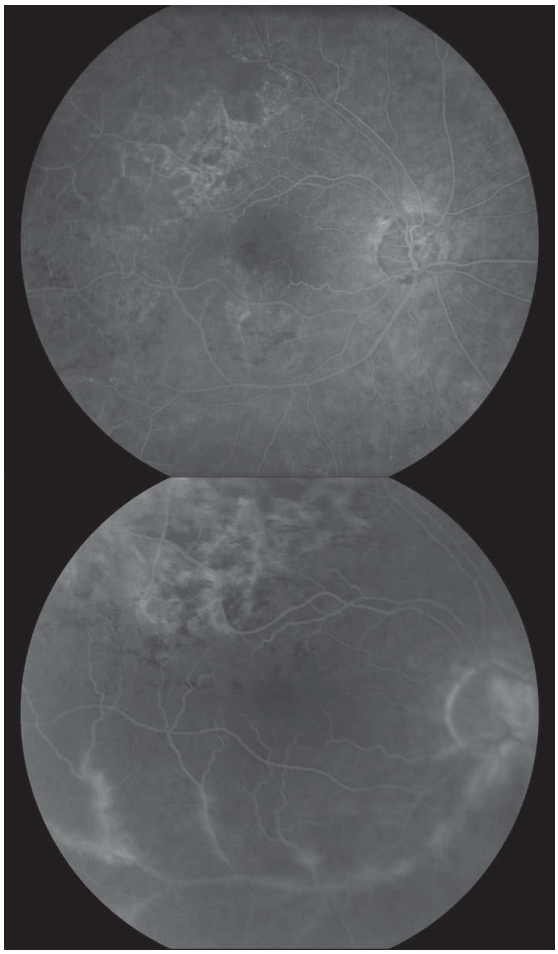
Besides Behçet's disease-associated uveitis, sarcoid-associated uveitis has also been treated successfully with infliximab therapy. Cruz et al.[15] reported the successful use of infliximab (3 mg/kg infusions given at day 0, week 2, and week 6) in 2 patients with retinal vasculitis and multisystem sarcoidosis. Other patients with sarcoid associated uveitis have also experienced therapeutic benefit with infliximab.[5, 12, 16] Other retrospective case series have reported a therapeutic benefit of infliximab for JIA-associated uveitis.[17, 18] Richards et al.[18] reported improved control of intraocular inflammation in 6 of 6 patients treated with infliximab and maintenance low-dose immunosuppression. This study suggested a role for infliximab as adjunctive therapy in JIA associated uveitis.

Rajaraman et al [17] also evaluated infliximab for pediatric uveitis due to a variety of etiologies, including JIA-associated uveitis (3 patients), pars planitis (1 patient), retinal vasculitis (1 patient), and idiopathic uveitis (1 patient). All patients demonstrated improvements in intraocular inflammation while on infliximab and 5 of 6 patients were able to wean completely off corticosteroid therapy by the end of the study period evaluated (mean follow-up 48 weeks). Vitreous hemorrhage developed in 1 patient while another patient experienced a transient upper respiratory infusion reaction. The use of high-dose infliximab (10–20 mg/kg) for pediatric patients with

refractory uveitis was reported by Kahn et al. In 17 patients evaluated, 13 individuals demonstrated quiescence of inflammation following two infliximab infusions, and the remaining 4 patients achieved this outcome after three to seven infusions. All patients receiving oral steroids before therapy discontinued steroid treatment over a period varying between 2 weeks and 2 years, and 15 of 17 patients were tapered off topical corticosteroids. One prospective non-comparative case series of infliximab as monotherapy for HLA-B27-associated anterior uveitis demonstrated a rapid decrease in anterior-chamber inflammation in 7 patients treated with infliximab (10 mg/kg) infusions. However, 1 patient required a second infusion after 3 weeks because of a flare-up, and median time to relapse in the 4 patients was 5+/-6.4 □□ months. Besides these reports of its efficacy for intraocular inflammation, infliximab has also been successfully utilized for the treatment of scleritis and peripheral ulcerative keratitis due to a variety of etiologies, including Wegener's granulomatosis, RA, and relapsing polychondritis. The efficacy of infliximab for posterior scleritis in a pediatric patient has also been reported.

Infliximab Toxicity

Herpetic keratitis, [9] vitreous hemorrhage, [5, 17] optic neuritis, and ocular tuberculosis [14] have been reported during infliximab therapy. A number of systemic complications have been associated with infliximab therapy, the most concerning of which include reactivation of latent tuberculosis, exacerbation of congestive heart failure, unmasking of demyelinating disease, the development of autoantibody formation (i.e., antinuclear antibodies, anti-dsDNA antibodies), and the formation of anti-infliximab antibodies. Severe hepatotoxicity complicating infliximab therapy has also been reported both with and without concomitant use of other medications with known hepatotoxicity.



Fluorescein angiography of patient with idiopathic retinal vasculitis and a history of bilateral, consecutive branch retinal vein

occlusions (A) Segmental hyperfluorescence of inferotemporal arcade (B). Following infliximab therapy, most retinal hemorrhages have resolved (B).

Adalimumab

Adalimumab is a fully human, anti-TNF-alpha IgG1 monoclonal antibody, which blocks the interaction of TNF-alpha with p55 and p75 cell surface receptors. Adalimumab is typically administered as a 20 or 40 mg dose via subcutaneous injection either weekly or every other week. The subcutaneous route of administration may be favorable to infliximab, which requires an intravenous infusion. The terminal half-life of adalimumab ranges from 15 to 19 days.

Ophthalmic Indications Of Adalimumab

The efficacy of adalimumab for uveitis has been reported in several retrospective series for adults and pediatric patients. Its efficacy for Behçet's disease-associated uveitis was reported in two retrospective reports.[19, 20] Mushtaq et al. reported 3 patients with Behçet's disease associated uveitis who were successfully switched from infliximab to adalimumab while in clinical remission. Follow-up was variable in this series, varying from 11 to 24 months; however, intraocular inflammation remained well controlled during the follow-up period. Administration of adalimumab for severe Vogt–Koyanagi–Harada syndrome allowed the successful tapering of corticosteroid and cyclosporine in one case report.[21] Vazquez-Cobian et al.[22] reported the successful treatment of pediatric uveitis (9 JIA-associated and 5 idiopathic) with adalimumab. In their series, adalimumab was well tolerated with no reports of serious adverse events. A total of 21 of 26 (80%) eyes with inflammation at baseline experienced a decrease in intraocular inflammation while 4 (15%) eyes remained stable and 1 (4%) eye worsened. A decrease in topical corticosteroid use was observed in 11 of 14 patients (79%) while 4 of 14 patients (29%) completely discontinued topical medications. In addition, other corticosteroid-sparing medications were decreased in a number of patients during the period of adalimumab therapy.

Another retrospective series by Biester et al.[23] described the efficacy of adalimumab for uveitis in 18 pediatric patients. Seventeen patients were JIA-associated while 1 was idiopathic. Ophthalmic efficacy was demonstrated in 16 of 18 patients (88%). Adalimumab also appeared effective or mildly effective for JIA-associated arthritis in 13 of 16 patients (81%) during the follow-up period.

Adalimumab Toxicity

Herpes simplex keratitis has been reported in one 5-year-old female patient treated with adalimumab for pauciarticular JIA-associated uveitis.[23]

Injection site reactions appear to be the most commonly reported adverse event and occur in up to 10% of patients treated. Elevation of liver enzymes requiring cessation of therapy has also been reported.

Etanercept

The third FDA-approved TNF antagonist is etanercept, which differs structurally from the monoclonal antibody structure of infliximab and adalimumab. Etanercept is a recombinant TNF-alpha receptor fusion protein composed of the constant (Fc) portion of human IgG1 and two copies of the extracellular ligand-binding portion of TNF receptor p75. Etanercept is given via subcutaneous injection at a dose of 25–50 mg twice weekly. Its elimination half-life is 102 hours following a single subcutaneous dose of 25 mg.[24]

Ophthalmic Indications Of Etanercept

Smith et al.[25] reported the results of a randomized, controlled, masked trial of etanercept for JIA-associated anterior uveitis. In their study, no apparent difference in anterior-segment inflammation was observed between etanercept and placebo.[26]

Another prospective study of etanercept for pediatric uveitis, including 7 juvenile RA patients, reported a decrease in anterior-chamber inflammation in 10 of 16 affected eyes (63%).[27] Patients in this study were treated with 0.4 mg/ kg subcutaneous injection twice weekly for 12 weeks, and the dose was increased to 25 mg twice weekly for patients with an incomplete response. While the majority of eyes experienced an improvement in anterior-chamber cellular reaction at 12 weeks, 7 responses were incomplete at 3-month follow-up, and no further improvement was demonstrated after 6 months of therapy. Mild injection reactions were observed, but no other significant adverse events were reported in their series. The successful use of etanercept for sight-threatening scleritis and sterile corneal ulceration has also been previously reported.[28] A retrospective study by Guignard et al.[29] evaluated the efficacy of anti-TNF agents for the prevention of uveitic flares. Their study found a decrease in the risk of a uveitic exacerbation in ankylosing spondylitis patients treated with monoclonal antibodies (i.e., infliximab, adalimumab) targeting TNF-alpha, but no such benefit was observed in patients treated with etanercept. A retrospective comparison of etanercept and infliximab for the treatment of uveitis by Galor et al.[30] was consistent with these findings. In their report, 17 of 18 (94%) patients on infliximab showed a reduction in intraocular inflammation at their final follow-up, whereas 0 of 4 patients on etanercept experienced a reduction in intraocular inflammation.

Findings from questionnaires from pediatric rheumatologists regarding the differential efficacy of the TNF-alpha

inhibitors for JIA-associated uveitis therapy and the prevention of uveitic exacerbations have reported greater efficacy of infliximab when compared to etanercept.[31] In addition, although arthritis appeared to respond to therapy in 87% of patients, etanercept did not appear to influence the frequency or severity of uveitis episodes.[32]

Etanercept Toxicity

New-onset uveitis and acute exacerbations of ocular inflammatory disease (i.e., scleritis, uveitis, and myositis) have been observed in patients treated with etanercept. Reports of optic neuritis and tuberculous pan uveitis have also been reported. The most commonly observed systemic adverse effects in both children and adults have been injection site reactions, infection, headache, rhinitis, and dizziness.[24] Serious infections and tuberculosis have been reported in patients receiving etanercept in post marketing surveillance.

Interleukin-2 Receptor Antagonists

Daclizumab

Daclizumab is a humanized monoclonal recombinant IgG1 antibody targeting Tac, a 55-kDa IL-2 alpha receptor subunit expressed by most T, B, and natural killer (NK) cells following activation by interaction with an antigen or with IL-2. The IL-2 receptor (IL-2R) system is a lymphokine receptor system composed of three subunits (alpha, beta and gamma) and plays a central role in the induction of the immune response. IL-2 binding to its receptor system facilitates antibody formation, cell-mediated immune responses, and NK cell responses.

The association of the Tac subunit with IL-2R beta and gamma subunits forms a high-affinity IL-2R complex, which is a critical step in the activation of all T cells, which are major contributors to autoimmune disease and allograft rejection. Doses of daclizumab 1 mg/kg in 2–4-week intervals have been reported in published studies to date for ocular inflammatory diseases, as 6-week intervals led to uveitis recurrences.

Doses of 2 mg/kg given in 4–5-week intervals via intravenous infusion or subcutaneous injection have been utilized for maintenance immunosuppression in a number of patients.[33]

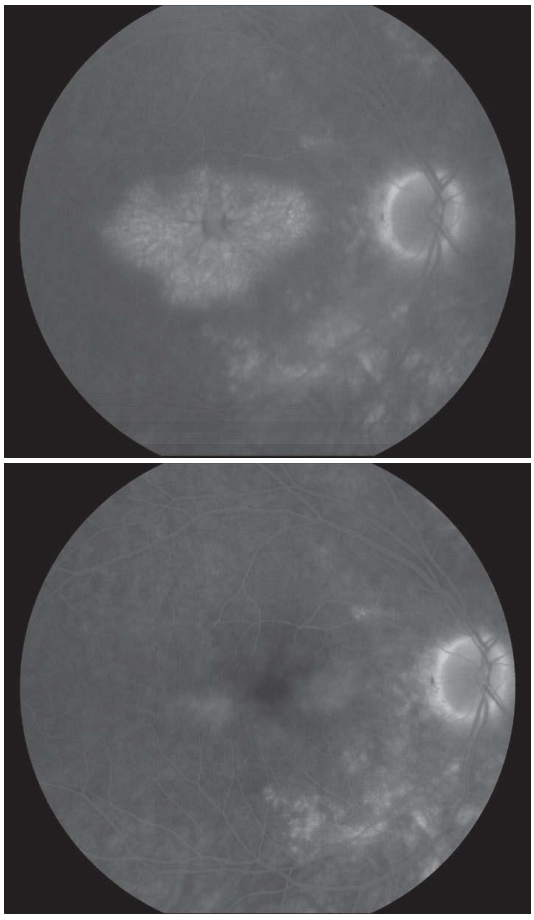
Ophthalmic Indications Ofdaclizumab

In the initial nonrandomized, open-label pilot study of daclizumab for uveitis, intravenous daclizumab therapy in up to 4-week intervals allowed the successful tapering of immunosuppressive medication (i.e., corticosteroids,

cyclosporine) in 8 of 10 patients enrolled during the first 8 weeks of therapy. Of note, daclizumab prevented the expression of sight-threatening inflammatory disease in these patients treated over a 12-month follow-up period.

Uveitic syndromes treated with daclizumab included sarcoidosis, Vogt–Koyanagi–Harada's disease, idiopathic intermediate uveitis, idiopathic panuveitis, and multifocal choroiditis.[26] A longer-term (>4-year) phase I/II interventional study of intravenous daclizumab and a short-term phase II study using subcutaneous daclizumab further supported the efficacy of daclizumab for the long term control of uveitis. Of the 10 patients enrolled in this study, 7 patients were able to taper off all other immunosuppressive medications and were maintained exclusively on daclizumab for over 4 years.[33] In the long-term study, a dosing interval of 6 weeks resulted in recurrent uveitis, whereas 2–4-week intervals did not. In the short-term phase II study evaluating the preliminary safety and activity of subcutaneous daclizumab, 4 of 5 patients enrolled met their primary study endpoint for success by 12 weeks of therapy (i.e., 50% reduction in immunosuppressive medication and maintenance of visual acuity within 5 letters), and all 5 patients met this endpoint by week 26. None of the patients in the long-term study stopped daclizumab due to adverse events attributable to daclizumab. In a randomized, double-masked, placebo-controlled trial evaluating the efficacy of daclizumab for Behçet's disease, there was no suggestion that daclizumab was beneficial in comparison with placebo. Specifically, efficacy outcomes (i.e., number of ocular attacks per year, visual acuity change from baseline, and immunosuppressive medication load) were comparable between the daclizumab and placebo arms.[34] Several other retrospective studies have reported the use of daclizumab for a variety of ocular inflammatory diseases in both children and adults.[35,36] Papaliodis et al.[36] described the use of daclizumab for 14 patients with a variety of inflammatory conditions, including scleritis, ocular cicatricial pemphigoid, and panuveitis. An improvement in visual acuity was seen in 12 of 27 eyes (44%) and in 5 of 14 (36%) patients. Intraocular inflammation improved in 16 of 27 eyes (59%), remained stable in 3 of 27 (11%) eyes, and worsened in 8 of 27 (30%) eyes. A decrease in ocular inflammation was observed in 59% of eyes in their series. Efficacy of daclizumab has also been observed for birdshot retino-choroidopathy, leading to improvements in visual acuity and resolution in vitreous inflammation in the majority of patients treated. [37] Gallagher et al.[35] described the use of biologic response modifier therapy in 23 pediatric patients with uveitis: 5 patients in this series were treated with daclizumab. Conditions treated with daclizumab in this series included sarcoidosis, panuveitis, keratouveitis, and uveitis. Of these 5 patients, 4 of 10

eyes demonstrated improvements in visual acuity and 8 of 10 eyes showed improvements in ocular inflammatory grade.



Fluorescein angiogram of patient with birdshot retino-choroidopathy and history of bilateral, recurrent, cystoid macular edema despite multiple partiocular corticosteroid injections. Following repeat sub-Tenon

triamcinolone and monthly daclizumab infusions at a dosage of 2 mg/kg, the cystoid macular edema has resolved without recurrence.

Daclizumab Toxicity

No known ocular toxicities have been reported in patients on daclizumab therapy. No difference in serious infectious complications or cancer has been observed when comparing patients receiving daclizumab or placebo.

Other Biologic Agents

Other biologic agents, which have been used in several retrospective series and case reports for the treatment of uveitis, include **anakinra, alemtuzumab, and interferon-alpha (IFN-alpha). Rituximab,** an anti-CD20 monoclonal antibody targeting B cells, has been reported for the treatment of primary intraocular lymphoma.

Anakinra , a is recombinant human IL-1 receptor antagonist that binds to IL-1 type 1 receptors, down-regulating the proinflammatory effects of IL-1. Its efficacy for the treatment of ocular inflammation has been demonstrated in murine models of uveitis.[38] Recently, several reports have described the efficacy of anakinra for the treatment of specific uveitic syndromes thought to be IL-1-mediated. Specifically, pediatric patients with uveitis associated with chronic infantile neurologic, cutaneous, and articular (CINCA) syndrome [39] and the NOD2 gene-associated pediatric granulomatous arthritis were treated successfully with anakinra therapy.[40]

Alemtuzumab (Campath-1H), the anti-CD52 monoclonal antibody that targets T and B lymphocytes, has been used for a variety of hematologic indications, including myelodysplastic syndrome, aplastic anemia, chronic lymphocytic leukemia, and a number of T-cell leukemias/ lymphomas.[41-43] Dick et al.[44] reported the use of alemtuzumab for severe, recalcitrant ocular inflammation in 10 patients with a variety of ophthalmic inflammatory diseases, which included Wegener's granulomatosis-associated peripheral ulcerative keratitis and pseudotumor, retinal vasculitis, sympathetic ophthalmia, and Behçet's disease.[44] All patients showed an initial improvement following Campath-1H administration; however 2 of 10 patients required retreatment. Remission was observed in 8 patients who received Campath-1H, and no opportunistic infections or malignancies were observed at short term Follow-up.

IFN-alpha has been utilized for its antineoplastic and antiviral effects; however its precise mechanism of action is unknown. Its use in the prevention of ocular relapses, as well as in the treatment of Behçet's disease-associated ocular inflammation in the doses of 3 to 6 million IU by subcutaneous injection daily to three times per week has been reported previously. [9,45] Kotter et al.[45] reported that IFN-2 alpha in combination with low-dose steroid led to remission of ocular disease in 7 patients with Behçet's disease-associated panuveitis. A more recent report suggested a potential benefit of **IFN-2alpha** for treatment-resistant CME, with 6 of 8 patients responding to IFN-2alpha with resolution of CME during the first 6 months of therapy.[46] Further studies into IFN-2alpha as a therapeutic modality are required before its implementation into routine clinical practice.

Rituximab, a monoclonal anti-CD20 antibody targeting B cells, has been used systemically for the treatment of a number of hematologic malignancies and lymphoproliferative disease processes, including primary central nervous system lymphoma.[47,48] Recent studies have supported its use for ocular adnexal lymphomas, [49, 50] and limited case series have also reported its benefit for the treatment of primary intraocular lymphoma. While the use of rituximab has been advocated for the treatment of primary intraocular lymphoma recurrences, vigilant central nervous system surveillance, management, and treatment with a neuro-oncologist for systemic chemotherapy are highly recommended. Finally, **abatacept** (fusion protein that binds the co stimulatory factor B7,thereby inhibiting T-cell activation),and **tocilizumab** (humanized monoclonal antibody against IL-6) have been found to have some efficacy against rheumatoid arthritis, and therefore may be under future consideration for patients with ocular inflammatory disease who fail with other biologic agents.

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