Medical Therapy

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Introduction

Uveitis is not a disease; rather, it is the ultimate phenotypic expression of an immunologic abnormality that may be idiopathic or associated with a recognized systemic illness. The exact genetic, cellular, and cytokine/chemokine spectrum of specific forms of uveitis is currently being delineated. Therapeutic studies and data are frequently flawed based on patient populations studied, trial design, and outcome measures. In the absence of absolute data, treatment is to some extent empiric. The therapeutic approach to uveitis requires consideration of etiology, anatomic site involved, chronicity, prior medication failure and potential ophthalmic and systemic risks of the underlying disease and proposed therapy.

As primary systemic illnesses can be identified in a significant number of patients with uveitis, it is rational, in this population, to optimally treat the underlying systemic disease first. It is important to employ a team approach in treating patients with recalcitrant uveitis as particularly in patients with systemic diseases there are medical subspecialists (Rheumatologists, Immunologists, Dermatologists, Gastroenterologists, Pulmonologists, Hematologists, Neurologists, and Internists) that can contribute greatly to the outcomes of these patients. It is critical that the autoimmune ophthalmologist lead this team. This review will focus on the medical therapy of patients with recalcitrant uveitis. Therapies for specific underlying diseases will be covered independently in individual chapters.

Corticosteroids

Patients with a single or infrequent episode of anterior uveitis generally respond well to topical corticosteroids, cycloplegic, and/or mydriatic agents. It is the patient with chronic disease, intermediate, posterior, or panuveitis that requires aggressive therapy. Systemic steroids are generally the first therapeutic intervention. The recommended initial therapy is usually prednisone at doses of 40–80 mg per day. It is interesting that in rheumatic diseases the concept of a "window of opportunity" for treating patients with Rheumatoid Arthritis (RA) has been accepted as standard of care therapy [1]. This strategy employs the use of potent immunomodulators such as methotrexate (MTX) or leflunomide in the treatment of RA at the time of diagnosis. This concept has not yet

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been fully accepted or integrated in the treatment of autoimmune ophthalmic diseases, though it has clearly been entertained [2, 3].

Antimetabolites

MTX and Mycophenolate (MMF) are frequently the first agents utilized when an acceptable steroid dose is deemed ineffective and/or toxic. Methotrexate is an antimetabolite that inhibits dihydrofolate reductase, an enzyme that participates in tetrahydrofolate synthesis. It is used in the treatment of cancer, autoimmune diseases, and for the induction of abortions. MTX acts by inhibiting the metabolism of folic acid which is needed for the de novo synthesis of thymidine, required for DNA synthesis. Folate is essential for purine and pyrimidine base biosynthesis. This impediment leads to the accumulation of adenosine with subsequent inhibition of T cell activation.

The first descriptions of MTX use in uveitis were in a 2 small cohorts of patients in 1969 [4, 5]. There is an established literature on the use of MTX both in adults with a variety of autoimmune ophthalmic diseases [2, 3, 6–14] and in Juvenile Idiopathic Arthritis (JIA) associated uveitis [15–21]. Interestingly, in one study, early use of MTX in children with JIA who did not have uveitis resulted in a lower probability of developing uveitis [22], perhaps exemplifying the operational concept of a "window of opportunity" to prevent the occurrence of uveitis in an at risk group. Therapy with MTX requires dosages between 15 and 25 mg weekly, administered either orally or parenterally [2, 14]. Twenty milligrams per week is both the mean and median dose of MTX used by ophthalmologists queried from the American Uveitis Society [14].

In a retrospective, non-comparative interventional case series that evaluated 160 patients with chronic noninfectious uveitis unresponsive to conventional anti-inflammatory therapy who were treated with MTX, control of inflammation was achieved in 76.2 % of patients, a steroid-sparing effect was achieved in 56 % and visual acuity was maintained or improved in 90 %. Side effects requiring discontinuation of MTX occurred in 18 % of patients and serious adverse events occurred in 8.1 % [10]. In a smaller study of 14 steroid resistant patients with active chronic uveitis two different MTX therapeutic paradigms were evaluated. In 8 patients, a dose of 40 mg was given intravenously once weekly for 4 weeks followed by 15 mg/week given orally whereas 6 subjects were treated with only 15 mg/week orally. During a follow-up period of 3–24 months, intraocular inflammation improved in all patients as did visual acuity in 11 patients [6, 13]. In a large cohort of 257 patients with inflammatory eye disease seen at a single center 90 patients with inflammatory eye disease were treated with MTX. Sixty-seven percent of these patients had uveitis and the median time to treatment success was 6.5 months for MTX treatment group [11]. Intraocular MTX is infrequently used to treat uveitis but has been studied in two case series. In patients with uveitis and uveitic cystoid macular edema (CME), intravitreal MTX improves visual acuity and reduces CME. Recurrence of inflammation is not uncommon in these cohorts; however, patients respond to reinjection [23, 24].

Adverse events from systemic MTX include alopecia, stomatitis, rashes, infections, nausea, abdominal pain, fatigue, fever, dizziness, acute pneumonitis, hepatic and pulmonary fibrosis, and kidney failure. Common adverse events include cytopenias and abnormal liver function tests. Malignancies including lymphoma have been described with use of this medication.

MMF has become an increasingly popular therapy to treat recalcitrant uveitis. MMF is a prodrug of mycophenolic acid that is used predominantly in transplant medicine. It is also used in the treatment of autoimmune diseases, such as systemic lupus erythematosus, Behçet's disease, and pemphigus vulgaris. It is a reversible inhibitor of inosine monophosphate dehydrogenase which is required in purine biosynthesis and is necessary for the development of T and B cells. Dosing generally requires 1–3 g/day in divided doses.

This medication has been used in JIA associated uveitis, systemic illnesses associated with

uveitis and in ocular immune mediated syndromes generally in the setting of steroid failure or toxicity [25–38]. In a relatively robust long-term study of 60 patients followed for at least 5 years that assessed the efficacy and tolerability of MMF in patients with chronic noninfectious uveitis, outcome measures evaluated included control of inflammation, corticosteroid-sparing potential, ability to stop or taper MMF and safety. Control of intraocular inflammation was achieved in 43 of 60 patients (72 %) after 1 year and in 45 of 55 patients (82 %) after 2 years. An improvement or stabilization of visual acuity was observed in 49 patients (82 %), and a worsening in 11 patients (18 %, 95 % CI: 10–30 %). At 5 years of therapy the probability of discontinuing corticosteroids was 40 %. Treatment was stopped because of inefficacy in 12 patients (rate: 0.05/PY) and because of side effects in four patients [33].

No definitive prospective, superiority, masked, head-to-head studies have been successfully completed comparing the different potentially steroid-sparing medications. There have been a number of retrospective studies comparing MTX and mycophenolate. In a series of 257 patients with inflammatory eye disease treated at one center, 90 patients with inflammatory eye disease were treated with methotrexate, 38 with azathioprine, and 129 with mycophenolate. Uveitis accounted for the majority of the diagnoses between 66 and 68 % in each group. The median time to treatment success was 4.0, 4.8, and 6.5 months for the MMF, azathioprine, and MTX treatment groups respectively ($P = 0.02$, log-rank test). These data suggest that the time to control of ocular inflammation is faster with mycophenolate than with MTX [11]. In a separate study of 80 patients with noninfectious intermediate, posterior, or panuveitis requiring corticosteroid-sparing therapy, patients were randomized to receive 25 mg weekly oral MTX or 1000 mg BID of MMF. Oral prednisone and topical corticosteroids were tapered. The primary outcome of treatment success was defined by: (1) ≤0.5+ anterior chamber cells, ≤0.5+ vitreous cells, ≤0.5+ vitreous haze and no active retinal/choroidal lesions in both eyes, (2) ≤10 mg of prednisone and ≤2 drops of prednisolone acetate 1 % a day, and (3) no declaration of treatment failure because of intolerability or safety. Additional outcomes included time to sustained corticosteroid-sparing control of inflammation, change in best spectacle-corrected visual acuity, resolution of macular edema and adverse events. Thirty five MTX treated patients and 32 MMF treated patients completed the study. Sixty-nine percent of patients achieved treatment success with MTX and 47 % with MMF ($P = 0.09$). There were no differences between treatment groups in time to corticosteroid-sparing control of inflammation ($P = 0.44$), change in best spectacle-corrected visual acuity ($P = 0.68$), or resolution of macular edema ($P = 0.31$). Treatment failure from adverse events or tolerability was not different by treatment arm ($P = 0.99$) [29]. There is currently a comparative MTX versus MMF effectiveness study ongoing entitled: First-line Antimetabolites as Steroid-sparing Treatment (clinicaltrials.gov).

Potential toxicities of MMF include hyperlipidemia, abnormal liver function tests, hypomagnesemia, hypocalcemia, hyperkalemia, and an increase in BUN. Leukopenia, anemia and thrombocytopenia have been described. Patients are at risk for infections and cases of progressive multifocal leukoencephalopathy have been described. Pulmonary toxicity including pleural effusions and pulmonary fibrosis have been noted. Malignancies including skin cancers, melanoma and lymphoma have occurred. Common and potentially troublesome side effects include rashes, headaches, fever and diarrhea.

Although azathioprine has been used to treat different forms of uveitis [39–43], a prominent role for this therapy is not established given the lack of large published studies. In one small study of 27 patients with various forms of uveitis (3 with anterior uveitis, 1 pars planitis, 4 idiopathic panuveitis, 8 Vogt-Koyonagi-Harada syndrome, 3 Behcet's disease, and 8 choroidoretinopathies), complete response was observed in 92 %. Eleven patients had well-tolerated minor side effects [40]. Azathioprine is a prodrug that is converted into 6-mercaptopurine which blocks purine metabolism and DNA synthesis suppressing leukocyte cellular proliferation. Significant adverse reactions can

include an increased risk of infection, bone marrow suppression, hepatotoxicity, pancreatitis, and increased risk of lymphoma. Common adverse reactions include nausea, vomiting, anorexia, and fever. The enzyme thiopurine S-methyltransferase (TPMT) deactivates 6-mercaptopurine. Patients who have low TMPT activity (<10 %) are at increased risk of drug induced bone marrow suppression.

T Cell Inhibitors

Cyclosporin [44–55] and tacrolimus [56–62] have been utilized in dosages of 2.5–5 mg/kg/day and 0.03–0.08 mg/kg/day respectively to treat recalcitrant uveitis. Cyclosporin is an immunosuppressant drug used in organ transplantation to prevent rejection. Its mode of action is thought to be due to the binding to the cytosolic protein cyclophilin of lymphocytes which inhibits calcineurin. This results in the inhibition of lymphokine production and interleukin release. Tacrolimus has similar indications and similar immunosuppressive properties to cyclosporine but is much more potent. It is a macrolide that binds to the immunophilin FK506 binding protein creating a complex that interacts with and inhibits calcineurin thus inhibiting both T lymphocyte signal transduction and IL-2 transcription.

In a prospective randomized study of 37 patients with posterior uveitis that required a second-line agent, the efficacy of tacrolimus and cyclosporine was assessed. The effect on peripheral blood CD4 (+) T-cell was also evaluated. The main outcomes were visual acuity, indirect ophthalmoscopy score, quality of life, and adverse events. Thirteen patients (68 %) taking tacrolimus and 12 patients (67 %) taking cyclosporine responded to treatment. No significant difference was detected with regard to effect on quality of life. Cyclosporine was associated with slightly greater toxicity with regards to blood pressure and serum cholesterol levels. No significant difference was detected with regard to effect on CD4 (+) T-cell phenotype [58]. In another retrospective study supporting the use of tacrolimus for the treatment of uveitis, 62 consecutive patients with noninfectious uveitis treated with tacrolimus at a single academic center successfully tapered prednisone to 10 mg daily at an average rate of 1.62 per patient-year (PY), with an 85 % probability of achieving ≤10 mg after 1 year 2 months of treatment. Tacrolimus was discontinued due to intolerance at a rate of 0.13/PY. This was predominantly due to non-cardiovascular adverse events. Creatinine rises of ≥30 % were uncommon (0.05/PY). It was felt by the investigators that tacrolimus's efficacy for the treatment of uveitis is maintained long term and that the cardiovascular risk profile is acceptable [61].

Potential side effects of cyclosporine include fever, vomiting, diarrhea, gingival hyperplasia, peptic ulcers, pancreatitis, seizures, confusion, hypercholesterolemia, dyspnea, paresthesia, pruritus, hypertension, hyperkalemia, kidney and liver dysfunction and an increased vulnerability to opportunistic fungal and viral infections. Potential adverse events from tacrolimus include infection, hypertension, electrolyte abnormalities, renal, pulmonary, cardiac and hepatic toxicity and several neurologic and psychiatric illnesses. Skin cancers and lymphoma have been reported.

Alkylating Agents

Cyclophosphamide [63–66] and chlorambucil [67–73] have been used to treat recalcitrant uveitis but only in circumstances where all other therapy has failed. With the current availability of biologic therapies these two medications are only rarely used to treat uveitis. Cyclophosphamide and chlorambucil are alkylating agents which covalently bind and crosslink a variety of macromolecules including deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and proteins. DNA crosslinking impairs DNA replication and transcription, ultimately leading either to cell death or to altered cellular function [74]. The degree of immune suppression is dose and duration of treatment dependent. Toxicities include risk of infection, bone marrow

suppression, gonadal dysfunction/sterility, increased risk of secondary malignancies (including lymphoma and lymphoma). Cyclophosphamide also carries the additional risk of potentially inducing hemorrhagic cystitis and bladder cancer.

Biologic Agents

Biologic therapies have been introduced for the therapy of recalcitrant uveitis over the last two decades. These compounds are defined as bioengineered chimeric and monoclonal antibodies, cytokine receptors, Fab fragments and agents such as interferons that influence the expression of cells and pro- and anti-inflammatory constituents of the immune system.

Biologic therapies were initially introduced to treat more common autoimmune illnesses such as Crohn's disease, rheumatoid arthritis, organ transplant rejection and malignancies. As the use of these therapies has evolved, they have become increasingly employed in the management to treat both idiopathic ocular inflammatory disease and uveitis associated with known underlying systemic illnesses. Recognized difficulty in interpreting published data is due to the lack of prospective, double masked, randomized trials and a deficiency of more strict definitions of the autoimmune ophthalmic disease being studied. Therefore, the published literature is comprised of predominantly case series. Biological therapies used to date include a broad range of agents: anti-TNF, anti-IL1, anti-IL2 receptor, anti-IL6 receptor, anti-IL17, co-stimulatory blockade, interferon, and CD-20 B cell-directed therapy. It is of important note that every one of these therapies were developed for the treatment of conditions other than uveitis.

There are currently five anti-TNF agents approved for the treatment of autoimmune diseases and although most of these have been used in autoimmune ophthalmic diseases none of these therapies are yet approved for the treatment of uveitis. Adalimumab was recently granted "orphan drug status" by the FDA for the treatment of noninfectious intermediate, posterior, or panuveitis, or chronic noninfectious anterior uveitis. For the most part, anti-TNF therapies have been studied in a retrospective manner although some prospective studies have been successfully completed. There are a number of studies that target one underlying systemic disease or form of uveitis; however, most reports combine different underlying systemic diseases and include idiopathic uveitis.

Infliximab

Based on published literature, infliximab appears to be the most frequently used biological therapy to treat recalcitrant uveitis. It is a chimeric mouse/human monoclonal antibody with a murine variable region that binds to the soluble and transmembrane forms of TNF-α. In the United States it is approved for Crohn's disease (in both adults and children), rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis and ulcerative colitis (in both children and adults). It is not approved in JIA. In Japan, infliximab is approved for the treatment of Behçet's associated uveitis.

Infliximab is unique in that it is approved for different systemic diseases with or without MTX and in a wide range of doses and thus, provides dosing flexibility that can range from 3 mg/kg every eight weeks to 10 mg/kg every four weeks. Given the potential impediment of the blood ocular barrier and the need for high-dose medications to treat ocular inflammatory disease, this appears to be a significant advantage over other biologics. It must be recognized however, that at a higher dose infliximab does incur a higher risk of serious infections [75].

There are a number of conditions for which infliximab is approved that have a significance incidence of uveitis. Foremost amongst these are Ankylosing Spondylitis [76, 77], Psoriatic Arthritis and Crohn's disease [78, 79]. It has additionally been used in uveitis associated with JIA [80–87], sarcoidosis [85, 88] and Behçet's Disease.

In one of the few prospective studies on the use of infliximab in recalcitrant uveitis, 31 patients

with various underlying etiologies were enrolled and 78 % of patients met criteria for clinical success at week 10 as judged by a composite clinical end point of visual acuity, control of intraocular inflammation, ability to taper concomitant therapy, and improvement of fluorescein angiography and/or ocular coherence tomography. This study was unique however as there were an inordinate number of serious adverse events that were potentially related to infliximab. These included: lupus-like reaction in two patients, pulmonary embolus, congestive heart failure, and vitreous hemorrhage in two patients. Although infliximab was effective, the number of potential toxicities in this study was dramatically different than any other study published across all indications for this medication. In a 2-year follow-up a 60 % retention rate for maintenance of infliximab therapy was observed [89].

In a large retrospective analysis of 88 patients with resistant uveitis from a single center treated with infliximab, 81.8 % of the patients achieved clinical remission but 58.3 % required additional immunomodulatory medications. In this study 36.4 % of the patients experienced at least one side effect and 19.3 % discontinued treatment due to toxicity. Interestingly, even in this study in contrast to the Suhler study [90], potential serious adverse events were not common and included only one case of autoimmune hepatitis, two of chronic infections and one of drug-induced lupus [91].

Although not approved for JIA, infliximab has been frequently used to treat uveitis in children [80–87]. In an interesting retrospective study stressing the importance of aggressive therapy to control recalcitrant uveitis in children, seventeen children with chronic uveitis were administered high-dose infliximab (10–20 mg/kg/dose). All 17 patients demonstrated a dramatic, rapid response, with no observed inflammation in 13 patients after the second infusion. Four patients required three to seven infusions to achieve disease control [80]. This therapeutic dose is not approved as a starting therapy for any condition and is very uncommonly used to treat any autoimmune disease. In a more traditionally dosed retrospective review of infliximab use in JIA in six patients with both ocular and musculoskeletal involvement, five of whom had been treated with other anti-TNF agents, drug induced remission occurred in three patients, with improvement of ocular inflammation in two more patients. Resolution of joint involvement occurred in five of six patients [84].

Adalimumab

Adalimumab, a recombinant human Ig G 1 monoclonal antibody targeting TNF approved for the therapy of many autoimmune diseases, has also been used to treat recalcitrant uveitis [85, 87, 92–120]. It is currently approved for RA, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, psoriasis and JIA. The medication is used at a dosage of 40 mg every two weeks for RA with or without methotrexate. The dose can be increased to 40 mg per week. It has been demonstrated that in RA combination therapy of adalimumab and methotrexate is superior to monotherapy with adalimumab alone [121].

In a prospective, multicenter, open-label trial to assess the effectiveness and safety of adalimumab in treating refractory uveitis patients with multiple underlying systemic conditions, 68 % of patients were responders at ten weeks and 39 % exhibited durable response at 50 weeks. No patients experienced treatment-limiting toxicity [96]. In a large study comprising of 1250 patients with ankylosing spondylitis treated with adalimumab the rates of anterior uveitis flares per 100 patient years (PYs) reported during the year before adalimumab treatment were compared to rates during adalimumab treatment. Flare rates before adalimumab treatment were 15/100 PYs in all patients. During adalimumab treatment, the rate was reduced by 51 %. Additionally, flares during adalimumab treatment were predominantly mild. Two patients with periods of high ankylosing spondylitis disease activity had new-onset anterior uveitis during the treatment period.

In the largest retrospective series of JIA patients with uveitis treated with adalimumab

studied to date, composed of 54 patients, 66 % achieved good clinical control. There was, however, worsening of disease activity in 13 % of patients [109]. A current prospective randomized controlled trial of the clinical effectiveness, safety, and cost-effectiveness of adalimumab in combination with methotrexate to treat JIA associated uveitis is ongoing [102].

In an interesting study, comparing infliximab to adalimumab, a greater benefit for adalimumab was demonstrated; however, caution needs to be exercised in interpretation of this study given the trial design and small numbers of patients [87]. There is currently an ongoing prospective sponsored trial entitled Efficacy and Safety of Adalimumab in Subjects with Active Uveitis (VISUAL l) that is enrolling patients (ClinicalTrials.gov).

Golimumab

Golimumab, a fully human anti-TNF IgG1 monoclonal antibody, has been used to treat autoimmune uveitis in small studies [122–127]. It is available as a subcutaneous preparation dosed at 50 mg per month and as an intravenous preparation dosed at 2 mg/kg every 2 months. The medication is approved for a number of autoimmune diseases. As a subcutaneous medication it is approved both with and without methotrexate depending on the indication (RA, ankylosing spondylitis psoriatic arthritis, and ulcerative colitis). As an intravenous medication it is only approved for RA with MTX.

In a small series combining patients with JIA and HLA B-27 associated uveitis (13 patients with JIA, 4 with HLA-B27) who had failed other biologics, of 17 patients treated, response at last visit was noted in 12 patients [123]. There are ongoing studies on this agent [124].

Etanercept

Etanercept a fusion protein produced by recombinant DNA technique that expresses the p75 TNF receptors attached to an IgG1 Fc. It can be administered as a once a week 50 mg dose or 25 mg twice a week. It is approved for RA, psoriatic arthritis, psoriasis, ankylosing spondylitis, and JIA both with and without MTX. Although etanercept was first thought to have a potential role in treating resistant uveitis [76, 128–130], further studies have not substantiated a definitive benefit in uveitis [131, 132]. A controversial area that requires clarification and further study is the potential paradoxical role of anti-TNF agents as a cause of uveitis. Uveitis has not been the only potential paradoxical reaction to anti-TNF therapy; indeed, psoriasis, inflammatory bowel disease, scleritis, and sarcoidosis have been reported in case studies as potential consequence of anti-TNF therapy. A pivotal study on this subject clarifies the potential causative role of anti-TNF therapies on the development of uveitis by demonstrating that while the incidence of uveitis is higher in etanercept-treated patients than those treated with infliximab or adalimumab, the overall incidence of new-onset uveitis with the first three anti-TNF agents approved is very low, and if indeed there was an association between any one of these agents and uveitis, the incidence of uveitis should have been much higher [133].

A difficult question that remains however is whether to use etanercept in patients with underlying diseases that in and of themselves have a risk for the development of uveitis. It is well accepted that uveitis can occur in 20–40 % of patients with any of the HLA B-27 associated inflammatory conditions [134]. In the published literature it has been found that in the ankylosing spondylitis trials in which etanercept was used, there was no observation of a higher incidence of uveitis [135].

A recent expert panel has published recommendations for the use of anti-TNF agents in ocular inflammatory diseases with a focus on infliximab and adalimumab. Both of these agents can be considered as first line for the treatment of ocular manifestations of Behçet's disease. Additionally, these medications can be considered as second line for the treatment of uveitis associated with JIA and for severe ocular inflammatory conditions including posterior uveitis, panuveitis,

severe uveitis associated with seronegative spondyloarthropathy, and scleritis in patients who have failed or who are not candidates for antimetabolite or calcineurin inhibitor immunomodulation [136].

There are overlapping but not completely identical potential side effects of anti-TNF therapies. These include increased susceptibility to routine and opportunistic infections (Tuberculosis, Listeria Mycosis, Histoplasmosis, Coccidiomycosis, reactivation of Hepatitis B), other autoimmune diseases such as paradoxical psoriasis, uveitis is listed as one of the potential risks in patients treated with etanercept, congestive heart failure, neurological complications (particularly multiple sclerosis), skin cancers, lymphoma, and malignancies in general. Adalimumab and infliximab have also had a number of cases reported of hepatosplenic T-cell lymphoma—an uncommon malignancy reported in patients with inflammatory bowel disease and concomitant therapy with purine inhibitors

Interleukin Blockers

Daclizumab, a humanized monoclonal antibody of IgG1 subtype that binds to the Tac epitope on the interleukin-2 receptor α-chain55k subunit has been used for the prevention of organ transplant rejection, multiple sclerosis and HTLV-1 associated lymphoma [137]. It is available as both an intravenous and as subcutaneous formulation and administered at 2 mg/kg every 2 weeks for two doses then 1 mg/kg every 2 weeks or intravenously at 1 mg/kg every 4 weeks [138, 139] Initial reports on the use of this agent in patients with uveitis were published in 1999 [140] with subsequent supporting efficacy data [141].

One of the largest published retrospective studies on the use of daclizumab included 39 patients with an average follow-up of 40 months. Different formulations and dosages were evaluated. Twenty-nine patients underwent intravenous administration with the standard regimen, five patients received a high-dose intravenous regimen and five patients received subcutaneous administration. Visual acuity improved by two lines or more in seven patients and worsened by two lines or more in six patients. The mean number of flares was 0.62 per patient-year. The mean number of other immunosuppressant therapies decreased from 1.89 per patient at baseline to 1.17 medications [142].

Daclizumab is generally very well tolerated with the most common adverse event being a cutaneous reaction. Other reported side effects include infections, elevated liver function tests, transient leukopenia, neuralgia, edema, palpitations, lymphadenopathy and cramping. In a retrospective review by Wroblewski, 4 cases of malignancy were reported in 39 patients studied and one patient with Behçet's disease treated with daclizumab who terminated the medication acutely, developed cerebellar herniation [142]. The drug was voluntarily removed from the United States market in 2009 (although still available in Europe) and currently undergoing clinical trials in the treatment of relapsing, remitting multiple sclerosis.

Il-17 has recently been demonstrated to be a critical cytokine in autoimmune dysregulation. A number of biologic therapies are currently in development that target IL-17 for a number of autoimmune diseases. Upregulation of IL-23 and IL-17A occurs in patients with various forms of uveitis [143]. Secukinumab a fully human monoclonal antibody that targets interleukin-17A has been studied in three independent studies to evaluate efficacy and safety. 118 patients with Behçet's uveitis (SHIELD study); 31 noninfectious, active non-Behçet's uveitis (INSURE study); and 125 patients with quiescent, noninfectious, non-Behçet's uveitis (ENDURE study) were studied. Reductions of uveitis recurrence or vitreous haze score during withdrawal of concomitant immunosuppressive medication were the main outcomes studied. The primary efficacy end points of the three studies were not met [144]. The safety profile for this agent has not yet been fully delineated, but there does appear to be a slightly greater risk of infections [145]. Other therapies targeting IL-17 remain as potential therapeutic agents for the treatment of recalcitrant uveitis.

IL-1 is a potent inflammatory cytokine that plays an important role in a number of

autoimmune diseases and has been a successful target in conditions such as Still's disease [146]. In uveitis it has been found that this is one of the cytokines that is expressed in the vitreous fluid of patients with active uveitis [147]. Two therapies that target IL-1 have been published for the treatment of uveitis. Anakinra, a glycosylated version of human IL-1 receptor antagonist has been studied in only a small number of patients with uveitis and therefore definitive statements about efficacy are difficult to determine at this time [148, 149]. It is used at a dose of 100 mg daily by subcutaneous injection or 1–2 mg/kg daily in children. Potential significant risks of Anakinra include injection site reactions and infections.

Gevokizumab, a recombinant, humanized IgG2 monoclonal antibody that binds IL-1β, is a modulating antibody that reduces the affinity for IL-1RI, IL-1RAcP signaling, and thus downregulates IL-1β activity. In 2012 it was granted Orphan Drug Designation for the treatment of noninfectious intermediate, posterior and panuveitis, or chronic noninfectious anterior uveitis. Seven patients with acute posterior or panuveitis, and/or retinal vasculitis resistant to azathioprine and/or cyclosporine were enrolled. Immunosuppressive agents were discontinued at baseline and patients received a single infusion of gevokizumab. All patients responded and no serious adverse events were reported [150]. Larger multicenter studies are currently enrolling patients (ClinicalTrials.gov).

IL-6 has been identified as one of the cytokines overexpressed in patients with uveitis [151]. Tocilizumab, a recombinant humanized anti-human IgG1 IL-6 receptor monoclonal antibody with approved indications in RA, polyarticular JIA and systemic onset JIA has been reported as an effective therapy to treat uveitis in a small number of patients. It is available as both and IV preparation dosed at 4 mg or 8 mg/kg monthly or as a subcutaneous medication dosed at 162 mg every 2 weeks or weekly. It can be given with or without MTX. Patients with uveitis and various underlying illnesses previously treated with remittive medications, anti-TNF agents and abatacept have been successfully treated with tocilizumab. In a series of patients with JIA, Adan published five patients with uveitis refractory to conventional therapy including at least 1 biologic agent [152]. The patients received tocilizumab 8 mg/kg every 4 weeks. At mean follow-up of 8.4 months, 50 % of the affected eyes studied had improvement in visual acuity and 25 % of affected eyes remained stable. All patients sustained uveitis remission for the 6-month follow-up period. Most of the studies did not find toxicity with Tocilizumab administration, although neutropenia has been described. The most common adverse effects observed in clinical trials have been upper respiratory tract infections, headache, and high blood pressure. Abnormal liver function tests and elevations in cholesterol levels were common. Among the less common side effects dizziness, various infections, as well as reactions of the skin and mucosae like mild rashes, gastritis, and mouth ulcers. Rare but severe reactions of gastrointestinal perforations and anaphylaxis have been described.

Interferon Blockers

Interferons (IFN) have a number of immune regulatory functions including the capacity to increase regulatory T cells. There are numerous published series and reports that define a beneficial role for IFN-α in the treatment of Behçet's disease and other types of uveitis. In a small prospective study of 12 patients with sight-threatening uveitis that failed to respond to one or more immunosuppressive therapies, human IFN-alpha-2b was administered subcutaneously daily. After a mean observational period of 11 months a favorable clinical response was observed in 83 % of patients [153]. Potential side effects of interferon include infections, neuropsychiatric illnesses, cardiovascular events, and other autoimmune disorders. Injection site reactions and a flu-like syndrome are also frequently noted.

Other Targets

Other biologic agents have been utilized to treat uveitis, include abatacept [154], and rituximab [155, 156].

In selected cases, abatacept, an agent that blocks the costimulatory signaling that normally leads to T cell activation, has been used to treat autoimmune uveitis. It is a fusion protein composed of the Fc region of the immunoglobulin IgG1 fused to the extracellular domain of CTLA-4. It binds to CD80. This agent is currently approved for the treatment of rheumatoid arthritis as both an intravenous and subcutaneous medication.

In the largest published series of seven patients with JIA and uveitis, abatacept was found to be efficacious in maintaining clinical remission in six of the seven patients during a period 9.2 months [157]. The patients were found to have decreased uveitis flares after 6 months of therapy. One patient, however, relapsed after 12 months with both arthritis and uveitis, and two patients required continued methotrexate. There have been other smaller series of reports using abatacept to treat uveitis and interestingly this medication has been effective in a few patients who have failed or been intolerant of anti-TNF agents [154, 158, 159]. Side effects have been reported, with a case of oral mycosis [157] and interestingly arthritis flare [154]. Given the small sample size of the study, abatacept use needs to be investigated further. The most serious adverse reactions are serious infections and malignancies. The most commonly reported adverse events include headache, upper respiratory tract infection, nasopharyngitis, and nausea.

Although the role of B cells is unknown in uveitis, in a pathologic study of an enucleated eye of a patient with JIA associated uveitis, focal aggregates of CD20 positive cells with CD3 and CD8 positive cells were noted [160]. Therefore, there may be rationale for using anti-B cell therapy and rituximab has been reported as a successful treatment for noninfectious uveitis. In one study of eight patients with JIA associated uveitis, seven patients attained a response [155]. In another publication ten patients with JIA and severe uveitis with vision threatening complications resistant to traditional therapy, including anti-TNF agents, responded after one cycle of rituximab. Uveitis became inactive in seven patients for a mean period of 11 months. It then recurred in four patients, though retreatment with rituximab resulted in disease inactivity in three of the four patients [161]. Other case studies of rituximab use have been published [156, 162]. Listed side effects for rituximab include infusion reactions, mucocutaneous reactions, Hepatitis B reactivation, progressive multifocal leukoencephalopathy, tumor lysis syndrome, infections, and renal toxicity. The most common adverse reactions of Rituxan (incidence ≥25 %) observed in clinical trials of patients with NHL were infusion reactions, fever, lymphopenia, chills, infection, and asthenia.

Although approved for the therapy of severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as keratitis, iritis, iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis, and anterior segment inflammation, ACTHAR Gel, an adrenocorticotropic hormone (ACTH) analogue does not have any published data on use in uveitis.

Intravitreal infliximab and adalimumab have been studied in animal models and patients with uveitis [163–167]. In a study of seven patients with anterior and posterior uveitis that was unresponsive to conventional treatments, 1.5 mg of infliximab in 0.15 cc was injected intravitreally and patients were followed for six months. Interestingly this approach has not resulted in dramatic response and the authors concluded that infliximab probably improves vision and decreases macular edema but the observed effect is only temporary [166].

Conclusion

The therapeutic armamentarium to treat patients with autoimmune ophthalmic disease is diverse and includes medications in different classes with individually unique modes of action. These

include corticosteroids, antiproliferative therapies, and targeted biological agents. New classes of therapies including small molecules and perhaps medications that will alter the microbiome may in the future continue to expand the therapeutics available to treat this group of diseases. Challenges remain in terms of better understanding the immunology of autoimmune ophthalmic disease, defining the phenotype of individual disease entities, constructing prospective trials of comparative efficacy, developing genetic and biomarkers to provide guidance in choosing a specific therapy for a unique patient.

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