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Immunosuppression for the Uveitides

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Abstract

The uveitides are a collection of over 30 diseases, characterized by intraocular inflammation. Many cases of juvenile idiopathic arthritis-associated uveitis, many cases of intermediate uveitis, and most cases of posterior and panuveitides needing treatment are treated with corticosteroids and immunosuppression. Disease-specific, time-updated modelling of clinical data for several uveitides suggests superior prevention of ocular complications and of visual outcomes with immunosuppression. These studies also suggest that oral corticosteroids at doses low enough for safe long-term therapy (i.e. ≤ 7.5 mg/day) are ineffective, implying that immunosuppression should be part of the initial regimen. The Multicenter Uveitis Steroid Treatment (MUST) Trial and Follow-up Study was a randomized comparative effectiveness trial comparing systemic therapy with oral corticosteroids and immunosuppression to regional corticosteroid treatment. It demonstrated that, when used properly, oral corticosteroids and immunosuppression can be given safely for up to 7 years with no evident increased risk of systemic side effects compared to regional corticosteroid therapy, except for greater antibiotic use for infections. The Systemic Treatment for Eye Diseases (SITE) Cohort Study suggested long-term safety for this approach, when the immunosuppressive agents were either antimetabolites or calcineurin inhibitors. Hence, oral corticosteroids and immunosuppression may be a preferred initial therapy for many non-infectious, intermediate, posterior, and panuveitides. Non-alkylating-agent immunosuppression has a low rate of sustained, drug-free remissions, <10%/year. Non-alkylating-agent immunosuppression for ≥3 years with control of the inflammation for ≥2 years is associated with a decreased risk of relapse after discontinuing immunosuppression. Alkylating agents can induce sustained drug-free remissions but likely increase the lifetime risk of cancer. Biologics, which target specific cytokines and pathways, hold promise for the future. Monoclonal antibodies directed against tumor necrosis factor (TNF)-α, have been studied most often, and one, adalimumab, is United States Food and Drug Administration approved for the treatment of non-infectious, intermediate, posterior, and panuveitides.

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Off label drug use

azathioprine; methotrexate; mycophenolate; cyclosporine; tacrolimus; cyclophosphamide; chlorambucil; infliximab; abatacept; tocilizumab; rituximab

The uveitides are a collection of >30 diseases characterized by intraocular inflammation.[1] The prevalence of the uveitides in the United States is estimated to be as high as 115–133 per 100,000;[2–5] collectively they are the fifth or sixth leading cause of blindness.[6–8] Because the uveitides affect persons of all ages, including children, they potentially have substantially greater years of vision lost than age-related diseases. The cost of treating the uveitides is estimated to be similar to that of treating diabetic retinopathy.[9] Patients with uveitis have greater medical resource use and need for prescription drugs, more work loss days and more disability days than patients without uveitis.[10] Hence, proper management of the uveitides is critical to maximizing vision and minimizing the impact of the disease on patients' lives.

The uveitides are categorized as a matrix of diseases characterized by the anatomic class, and whether they are infectious, associated with a systemic disease, or eye-limited and presumably immune-mediated (table 1).[1,11] Uveitides not classifiable as a specific disease are characterized as undifferentiated with the course and anatomic class (e.g. undifferentiated chronic anterior uveitis).[1,11] Treatment of non-infectious uveitides is guided by the anatomic class, course, and natural history. Some diseases are self-limited and spontaneously-remitting with a good visual prognosis (e.g. acute posterior placoid multifocal choroidopathy and multiple evanescent white dot syndrome); these diseases typically do not need treatment. Acute monophasic and recurrent acute uveitides (e.g. spondylitis/HLA-B27-associated uveitis) typically need treatment only of the acute attacks. Conversely, most chronic, non-infectious uveitides need chronic treatment to suppress the inflammation.[1,12,13] For non-infectious uveitides, which comprise over 90% of the cases of uveitis in the United States,[3,4] the anatomic class guides the initial treatment approach. Anterior uveitides are treated with topical corticosteroids; intermediate uveitides with regional corticosteroid injections (either periocular or intravitreal) or oral corticosteroids and, when needed, immunosuppression; and posterior and panuveitides typically with oral corticosteroids and immunosuppression.[12,13]

Treatment target

The decision to treat an individual patient and the choice of therapy always represent risk-benefit decisions. Not every case of uveitis needs treatment. In Fuchs uveitis syndrome (also known as Fuchs heterochromic iridocyclitis), treatment appears not to have beneficial effects and typically is not given. Twenty-five to 35% of patients with pars planitis have mild disease, no macular edema or other complications, good vision, and do not need treatment; these patients maintain good vision with up to 10 years of follow-up.[14,15] However, when treatment is needed, the goal is complete suppression of the inflammation (i.e. to "grade 0" inflammation).[11] For anterior and intermediate uveitides, semi-quantitative grading scales of cells and haze are used; studies have shown good inter-observer agreement for the Standardization of Uveitis Nomenclature (SUN) scales.[11,16] For chorioretinal disease,

multimodal imaging may be required, and for many (but not all all) posterior uveitides, fundus autofluorescence appears to correlate with active disease.[17–19]

Sophisticated, time-updated modelling in juvenile idiopathic arthritis (JIA)-associated chronic anterior uveitis demonstrates that any inflammation doubles the risk of visual impairment (worse than 20/40) and triples the risk of blindness (20/200 or worse);[20] increasing grades of inflammation are associated with greater risks of visual loss.[21] The Systemic Immunosuppressive Treatment for Eye Diseases (SITE) Cohort Study found similar results for Behçet disease, where active uveitis increased the risk of visual impairment 2.5-fold and blindness 2.7-fold.[22] Although approximately 25–33% of patients with intermediate uveitis can be managed successfully with intermittent regional therapy,[14,15] the remainder of the chronic uveitides benefit from sustained suppression of the inflammation. In birdshot chorioretinitis, intermittent treatment can control the macular edema but does not prevent progressive retinal damage measured by loss of visual field and electroretinogram.[23] Immunosuppression reverses visual field loss and normalizes the retinal damage seen on optical coherence tomography.[24,25] In the SITE Cohort Study, complete suppression of inflammation halved the risk of choroidal neovascularization versus active uveitis, whereas minimally active uveitis was no different from active active.[26] In the Multicenter Uveitis Steroid Treatment (MUST) Trial and Follow-up Study, at 7 years of follow-up, regional therapy with the fluocinolone acetonide implant was associated with an 81% excess risk in the odds of blindness versus systemic therapy with oral corticosteroids and immunosuppression.[27] This difference appeared to be due to retinal damage from relapse of the uveitis prior to reimplantation.[27] A problem with regional therapies, particularly short-acting regional therapies, is the variable duration of effect; re-injection or re-implantation is performed after relapse. Each relapse prior to re-injection or re-implantation results in cumulative damage; although typically there is some recovery after re-injection or re-implantation, the long-term result is poorer visual outcomes, a phenomenon sometimes termed the “saw-tooth decline”. Scheduled replacement or re-injection prior to relapse might improve the results with regional therapies, but given the variable duration of action, the timing of scheduled replacement is difficult and, in practice, not typically done.

Oral corticosteroids

Oral corticosteroids are critical for the initial control of ocular inflammation, even when immunosuppression is used. Studies of patients with sarcoid uveitis have shown that oral corticosteroid therapy is associated with a 93% reduction in the odds of visual impairment.[28] The initial dose of prednisone should be 1 mg/kg/day up to a maximum of 60 mg/day.[12,13] Doses above 60 mg/day are associated with an increased risk of ischemic necrosis of bone and should be avoided.[29] After 2 to 4 weeks, prednisone should be tapered; for chronic diseases, the target dose is ≤7.5 mg/day. A systematic review of randomized trials of prednisone 7.5 mg/day in rheumatoid arthritis showed no increased risk of corticosteroid side effects over the intermediate term (months to years).[30] Tapering should be done with successively smaller decrements (table 2) to decrease the risk of relapse and, in patients receiving long-term oral corticosteroid treatment, withdrawal.[13] Although daily doses of ≤7.5 mg are safe for the intermediate term, studies in rheumatoid arthritis suggest that there

is an increased risk of cardiovascular disease and cardiovascular mortality with large cumulative doses of prednisone.[31] Calculations suggest that this risk is seen at doses of prednisone of 5 mg/day for 22 years or 7.5 mg/day for 15 years. When immediate control of the inflammation is needed, pulse intravenous corticosteroids (e.g. 1 gm methylprednisolone/day for 3 days) are effective initial therapy.[32] The Optic Neuritis Treatment Trial suggested that this treatment can be given safely.[33] For uveitis, pulse intravenous corticosteroids are followed by oral prednisone, often coupled with an immunosuppressive drug. Although oral corticosteroids can be given safely if these principles are followed (see below), surveys suggest that in general practice the daily doses of prednisone are too high for too long, and that not enough immunosuppression is used.[34]

Evidence for the effectiveness of immunosuppression

There are a limited number of randomized clinical trials demonstrating the efficacy of immunosuppression in the treatment of the uveitides. Azathioprine was shown to be effective for Behçet disease uveitis, but 22% of treated patients suffered uveitis relapses.[35] Cyclosporine was superior to colchicine (which is ineffective for uveitis) for Behçet disease, but only 48% of patients on cyclosporine had good control of the uveitis.[36] In a small single-center, randomized trial, cyclosporine was similarly effective to prednisolone for intermediate, posterior, and panuveitides, with inflammation control in ~50% of patients in each group.[37] A randomized trial of tacrolimus versus cyclosporine for intermediate, posterior, and panuveitides reported similar efficacy for both drugs with fewer side effects for tacrolimus.[38] A small randomized trial of methotrexate versus mycophenolate reported similar efficacy for the two drugs.[39]

Evidence for the effectiveness of immunosuppression comes from disease-specific, time-updated modelling of the effect of immunosuppression on outcomes. In birdshot chorioretinitis oral corticosteroids control macular edema, but it recurs at prednisone <15 mg/day, a dose too high for long-term use.[40] Immunosuppression results in an 83% reduction in the risk of macular edema.[40] Immunosuppression reverses (but does not always normalize) visual field loss, which otherwise is progressive.[24] In multifocal choroiditis, prednisone >10 mg/day reduced the risk of structural complications (e.g. macular edema, choroidal neovascularization, etc.), but doses ≤10 mg/day did not, indicating that a safe dose of oral corticosteroids alone was ineffective.[41] Immunosuppression reduced the risk of structural complications by 83% and blindness by 92%.[41] In late-stage Vogt-Koyanagi-Harada disease, immunosuppression prevented the occurrence of structural complications, and reduced the risks of visual impairment and blindness by 67% and 92%, respectively.[42] In two studies of JIA uveitis, immunosuppression (primarily methotrexate) reduced the risk of visual impairment by ~60%.[20,21] Taken together, these data strongly suggest superior results for immunosuppression for many uveitides.

Conventional immunosuppressive drugs

Conventional immunosuppressive drugs are classified as antimetabolites, calcineurin inhibitors, or alkylating agents (table 3).[13] The antimetabolites used most often are azathioprine (Imuran, Prometheus Labs, Inc., San Diego, CA), methotrexate (Rheumatrex,

Dava Pharmaceuticals, Inc. Newark, DE, and others), and mycophenolate (Cellcept, Genentech, Inc., San Francisco, CA). The calcineurin inhibitors are cyclosporine (Neoral, Novartis Pharmaceuticals Corp. New York, NY) and tacrolimus (Prograf, Astellas Pharma US, Inc. Northbrook, IL). The alkylating agents are cyclophosphamide (Cytoxan, Roxane laboratories, Inc. Columbus, OH) and chlorambucil (Leukeran, Aspen Global Pharma, Inc., Johannesburg, SA). This classification is useful therapeutically, as an antimetabolite and a calcineurin inhibitor often are combined when single-agent immunosuppression provides inadequate inflammation control. Because of their potency and toxicity, alkylating agents seldom are combined with another immunosuppressive drug.[13]

Although several case series have been published with each drug, the best single-immunosuppressive-agent effectiveness data come from the SITE Cohort Study, a large retrospective study, which used trained coordinators to enter medication use and activity of the disease at every visit. It evaluated each drug in a standardized fashion, to estimate the effectiveness of these agents in clinical practice.[43–46,48] For non-alkylating agent therapy, control of the inflammation was accomplished by 12 months in 52 to 73% of patients, depending on the specific drug (table 4).[43–46] Control of the inflammation while tapering of prednisone to ≤10 mg/day was less successful, occurring in 36 to 58% of patients.[43–46] Cyclosporine appeared to be least effective with a 36% success rate for uveitis control and corticosteroid-sparing.[46] Azathioprine and methotrexate appeared to be less well tolerated with higher rates of discontinuation for side effects (0.16/person-year [PY] and 0.13/PY, respectively) than mycophenolate (0.08/PY).[43–46] Tacrolimus was used too infrequently in the SITE cohort to evaluate its effectiveness, but one small, randomized trial suggested efficacy similar to that of cyclosporine,[38] and one standardized-outcome, retrospective study suggested efficacy similar to that of mycophenolate.[47] Tacrolimus is used differently than other agents for uveitis; it employs dose-escalation until a therapeutic blood level is reached.[38]

There are limited comparative effectiveness data on the antimetabolites. The Johns Hopkins study of 257 patients receiving antimetabolites suggested that mycophenolate and azathioprine were similarly effective for uveitis control and corticosteroid-sparing at 6 months but that methotrexate was less effective (42% versus 70% for mycophenolate). Methotrexate and mycophenolate were discontinued at similar rates for side effects (0.09/PY), but azathioprine was discontinued at a significantly greater rate (0.24/PY).[49] One small, randomized trial of 80 patients reported similar efficacy for methotrexate and mycophenolate; however, the trial used the highest oral dose of methotrexate and the lower dose of mycophenolate.[39] The Mount Sinai study of posterior uveitis treatment with mycophenolate achieved uveitis control and prednisone <10 mg/day in 95% of patients at 2 years of follow-up.[50] However, 77% of patients needed dose escalation of the mycophenolate to >2 gm/day, and 21% of patients needed a second immunosuppressive drug. Although the mean prednisone dose at 2 years was 5.7 mg/day, only 11% of patients were able to discontinue prednisone.[50]

The alkylating agents, cyclophosphamide and chlorambucil, appear to be the most effective conventional agents but also the most toxic.[48] Cyclophosphamide is begun at 2 mg/kg/day, and the dose adjusted to achieve a white blood count in the 3000 to 4000 cells/μL range

when the patient is off prednisone. Treatment is continued for one year and then tapered to determine if a remission has been induced.[51,52] Oral daily cyclophosphamide appears superior to pulse intravenous cyclophosphamide for sustained remission induction.[53] Because of the risk of *Pneumocystis carinii* pneumonia with cyclophosphamide, many clinicians use antibiotic prophylaxis, such as trimethoprim-sulfamethoxazole.[53] Chlorambucil can be used in a similar fashion, starting at a dose of 0.1 mg/kg/day; however, the response to dose escalation appears less predictable than that of cyclophosphamide.[13] An alternative method of using chlorambucil is termed "high-dose, short-term" therapy; chlorambucil is started at 2 mg/day and escalated weekly until uveitis control is achieved or bone marrow suppression occurs, and treatment is discontinued; the mean maximum dose with this approach is 20 mg/day.[54] This approach's goal is remission induction.

Remission induction

The SITE Cohort Study suggested that sustained, drug-free remissions (i.e. inactive disease off all treatment) were uncommon with non-alkylating agent immunosuppression. In intermediate uveitis, the incidence of a sustained, drug-free remission was 0.089/PY.[55] For non-alkylating agent conventional immunosuppressive drugs estimated remission incidence was <0.10/PY for each drug.[43–46] In JIA uveitis, the median time to a drug-free remission is ~10 years for mild disease; with severe disease <25% of patients enter a remission over 20 years.[56] In JIA uveitis, 3 years of methotrexate treatment and 2 years of inactive disease are associated with a decreased risk of relapse after discontinuation of methotrexate.[57] Taken together, these data suggest that sustained, drug-free remissions are difficult to achieve with non-alkylating agent therapy, and provide a paradigm for attempting remission induction. Patients treated with non-alkylating agent immunosuppressive drugs should be treated for 2 years after discontinuing oral corticosteroids, while maintaining inactive disease; after that, an attempt can be made to taper and discontinue immunosuppression to determine if a remission has been achieved. Even after a remission has been achieved, monitoring for relapse is needed.

Alkylating agents are remission-inducing. For safety concerns, the total duration of alkylating agent therapy is kept below 18–24 months,[58] and the goal is 1 year of inactive disease off oral corticosteroids, before tapering and discontinuing alkylating agents.[13] The best data on cyclophosphamide remission induction are in ocular mucous membrane pemphigoid; 91% of patients treated with cyclophosphamide achieved a sustained drug-free remission by 2 years; the relapse rate after stopping cyclophosphamide was 0.03/PY.[52] These results contrasted with non-alkylating agent therapy, where the remission rate was 67% at 2 years, and the relapse rate was 0.23/PY.[52] A small case series of patients with serpiginous choroiditis suggested that alkylating agent therapy induced remissions in ~77% of patients.[51] In the SITE Cohort Study, cyclophosphamide therapy resulted in remissions in 64% of patients by 2 years of follow-up.[48] In a study of 53 patients with various uveitides, "high-dose, short-term" chlorambucil therapy induced remissions in 77% of patients, with a relapse rate of ~0.05/PY.[54] Taken together, these data suggest that alkylating agent therapy is capable of remission induction; however, there is a cost in terms of safety (see below).

Safety of immunosuppression

The MUST Trial and Follow-up Study evaluated the safety of systemic therapy for the uveitides.[27,58–61] The Trial randomized patients with non-infectious, intermediate, posterior, and panuveitides to treatment with either the fluocinolone acetonide implant (Retisert, Bausch & Lomb, Rochester, NY) or systemic therapy with oral corticosteroids and immunosuppression. The fluocinolone acetonide implant is surgically placed in the eye and releases corticosteroids over a period of 2.5 to 3 years.[62,63] Hence, this trial compared a "local" treatment paradigm to a "systemic" treatment paradigm. Immunosuppressive drugs were used by 88% of patients in the systemic group; 93% of these patients used non-alkylating agent, conventional immunosuppression as the initial agent. Throughout 7 years of follow-up there was no increased risk of systemic side effects in the systemic group, except for a greater use of antibiotics for infections (72% versus 57%). There were little weight gain and no significant difference between the two groups.[27,59–61] A key factor in this comparatively safe use of systemic medications was the adherence to the principles discussed above, especially maintenance prednisone doses ≤7.5 mg/day.[27] These data suggest that oral corticosteroids and immunosuppression can be administered relatively safely for at least 7 years. Nevertheless, the MUST Trial was not powered to identify differences in rare adverse events.

In the MUST Trial and Follow-up Study, both treatment approaches controlled the inflammation in the large majority of patients, but the implant was slightly better for the first 5 years, after which they were similar with uveitis control in 87% of patients at 7 years. The better control of inflammation with the implant suggests utility in patients with inflammation poorly controlled by systemic therapy. However, the implant's superior control came with a cost: higher rates of cataract, nearly universal need for cataract surgery, higher rates of ocular hypertension and glaucoma surgery, and a nearly 3-fold greater risk of glaucoma.[27,59–61]

Although systemic therapy was effective for managing the uveitis, ancillary treatment with 1 or 2 regional corticosteroid injections was needed in nearly two-thirds of patients with macular edema on systemic therapy in order to resolve the edema, demonstrating the value of selective use of adjunctive regional corticosteroids.[64]

The long-tem safety of immunosuppression was addressed by the SITE Cohort Study, which evaluated 9250 ocular inflammation patients with up to 30 years of follow-up.[66] A systematic review suggested no increased malignancy risk with antimetabolites or calcineurin inhibitors in patients without an inherent increased risk (e.g. patients with uveitis). Alkylating agents appeared to have an increased cancer risk.[67] Long-term follow-up of the cohort showed no increased risk of mortality or cancer mortality with non-alkylating agent immunosuppression.[68] Alkylating agents did not have a significantly increased risk of overall mortality but had a borderline significant increased risk of cancer-related mortality, driven more by chlorambucil, but the sample size for chlorambucil was small.[68] A follow-up study of "high-dose, short-term" chlorambucil therapy suggested no increase risk of malignancy, but the sample size and follow-up may not be adequate to detect an increased risk.[69] In rheumatoid arthritis, cyclophosphamide's increased cancer risk is not seen until 5–

10 years of follow-up.[53] The duration of therapy is associated with cancer risk; patients without cancer had on average 2 years of cyclophosphamide, leading to the recommendation that alkylating agent therapy be limited to no more than 18–24 months duration.[53]

Although the SITE Cohort Study suggested long-term safety for non-alkylating agent immunosuppression, an Australian study reported an increased risk of skin cancer and possibly lymphoma among patients with ocular inflammation treated with immunosuppression.[70] This study did not detail the individual immunosuppressive drugs used and lumped together non-alkylating agent and alkylating agent therapy, leaving uncertain the risk of non-alkylating agent therapy. Furthermore, skin cancer is epidemic in Australia, so that the immunosuppression may be potentiating an already increased risk.[71] Nevertheless, it seems prudent to advise appropriate sunscreen use and annual skin exams for patients on long-term immunosuppression. Furthermore, given the role of the immune system in the management of patients with metastatic melanoma, it also appears prudent to avoid the use of immunosuppression (when possible) in patients with malignant melanoma.

Biologics for the uveitides

Biologics have transformed the field of rheumatology and are widely used. In uveitis, most of the data on biologics are on the use of agents directed against tumor necrosis factor (TNF)-α and involve either infliximab (Remicade, Janssen Biotech, Inc., Titusville, NJ), a chimeric monoclonal antibody to TNF-α given as an intravenous infusion, or adalimumab (Humira, AbbVie, Inc. North Chicago, IL), a fully human monoclonal antibody, given every other week as a subcutaneous injection.[72–76] Infliximab is approved for rheumatic diseases with a wide dose range, but it appears that doses ≥5 mg/kg monthly are required to treat uveitis.[72,76] Although both monoclonal antibodies appear effective for several of the uveitides, etanercept (Enbrel, Amgen, Thousand Oaks, CA), a soluble receptor-Fc fragment fusion protein, was not very effective in pilot studies and is not recommended for uveitis.[72] Uveitides for which anti-TNF-α antibodies appear particularly effective include Behçet disease, spondylitis/HLA-B27-associated uveitis, and JIA-associated uveitis.[72–74] One long-term study of Behçet disease suggested substantially superior visual outcomes with the use of anti-TNF-α therapy (i.e. 70–80% reductions in visual loss over 5 to 10 years).[74] A systematic review by an Expert Panel of the American Uveitis Society recommended infliximab or adalimumab as a first-line therapy for Behçet disease and as a second-line therapy for JIA uveitis.[72] In uncontrolled studies, infliximab was used in birdshot chorioretinitis and other non-infectious uveitides with apparent success.[75,76] Over 80% of patients achieved inactive uveitis with successful corticosteroid sparing. Relapse was common with discontinuation of therapy, suggesting that remissions were uncommon; the discontinuation rate for side effects was 0.19/PY.[75,76] In patients with Crohn’s disease (but apparently not in patients with spondylitis), use of a second immunosuppressive drug decreases the formation of anti-infliximab antibodies, prolongs the effect of infusions, and decreases the rate of infusion reactions.[77] Hence, some clinicians recommend that a conventional immunosuppressive drug, such as methotrexate or mycophenolate, be given with infliximab. Anti-TNF-α therapy also may be effective for uveitic macular edema.[78] In June 2016, adalimumab was approved by the United States (US) Food and Drug Administration (FDA) for the treatment in adults of non-infectious intermediate, posterior,

and panuveitides, based on two randomized, placebo-controlled clinical trials.[79,80] These trials, one of patients with active uveitis and one of patients with suppressed uveitis, demonstrated an ~50% reduction in the relapse rate (prolongation of the time to relapse) with adalimumab in the face of a rapid oral corticosteroid taper.[79,80] Adalimumab was demonstrated to be an effective addition to methotrexate in a placebo-controlled, randomized trial of patients with JIA-associated uveitis.[81] A retrospective observational study of 160 patients from France suggested that infliximab and adalimumab had similar effectiveness for uveitides.[82] How well anti-TNF-α therapy compares to conventional immunosuppression awaits comparative effectiveness trials.

Other biologic agents have fewer data, typically consisting of small case series. Abatacept (Orencia, Bristol Myers, Squibb, New York, NY), a co-stimulation inhibitor was used in JIA uveitis with mixed results: one 17-patient study suggested 14% sustained inflammation control, whereas another 35-patient study suggested a 49% success rate over 1 year of follow-up.[83,84] Tocilizumab (Actemra, Genentech), an interleukin (IL)-6-receptor antagonist, was studied in JIA uveitis: one 17-patient study reported suppressed inflammation in 41%; another 25-patient study suggested inflammation suppression in 75% over 1 year of follow-up.[85,86] Rituximab, a monoclonal antibody to CD20 on B cells, is used to treat B-cell lymphomas and rheumatoid arthritis, and has similar efficacy to cyclophosphamide for ANCA-associated vasculitides.[87] Small case series of JIA uveitis suggest good efficacy with infusions every 6 months, including one with follow-up for >3.5 years.[88,89]

There have been failures. Secukimunab (Cosentyx, Novartis Pharmaceuticals), a monoclonal antibody to IL-17A, with good efficacy for psoriasis, psoriatic arthritis, and ankylosing spondylitis, failed in 3 separate trials of Behçet disease and of other uveitides.[90] The results were surprising as the Th17 pathway is involved in autoimmunity and animal models of uveitis.

In uncontrolled case series, interferon-α-2a reportedly was successful in Behçet disease and other uveitides. In a case series of 53 patients with Behçet disease, 89% entered drug-free remissions with a relapse rate of 0.07/PY. The drug appeared better at treating uveitis than non-ocular features. Use in the United States has been limited, perhaps due to the “flu-like illness” side effect in seen in 100% of patients.[91,92]

Anti-TNF-α therapy is associated with an increased risk of infections, particularly invasive fungal infections and tuberculosis.[93] Prior to initiating anti-TNF-α therapy, patients should be tested for tuberculosis and treated appropriately. In patients with rheumatoid arthritis, the infection rate appears greater in the first 90 days after starting anti-TNF-α therapy than with other disease modifying anti-rheumatic drugs, but not long-term, perhaps due to their more rapid onset of action.[93] Anti-TNF-α therapy can worsen multiple sclerosis. Patients with multiple sclerosis should not be treated with anti-TNF-α therapy; those with intermediate uveitis, who are at an increased multiple sclerosis risk,[14,15] should undergo magnetic resonance imaging of the brain prior to initiating anti-TNF-α therapy, in order to identify subclinical multiple sclerosis.

There is concern about anti-TNF-α therapy and an increased risk of malignancy. In the SITE Cohort Study, there was a suggestion that anti-TNF-α treatment was associated with an increased risk of cancer-related death.[68] However, the number of patients was small, the follow-up short, and the sensitivity analyses unstable, prompting the authors to consider these pilot data. Large, 13,000- to 19,000-patient, registries of rheumatoid arthritis suggest only an increased risk of non-melanoma skin cancer and not of other tumors.[94,95] Similarly a meta-analysis of clinical trials of biologic agents in rheumatology did not demonstrate any significantly increased risk of cancer with biologics.[96] However, the sample sizes and follow-up of many of the studies were small and short, respectively, so that they may not be fully adequate to detect an increased risk.

Summary

Many non-infectious uveitides, particularly intermediate, posterior, and panuveitides are chronic diseases, requiring chronic suppressive therapy. Oral corticosteroids, though part of the initial regimen, alone typically are inadequate to control the inflammation at safe doses. Immunosuppression results in superior outcomes, and permits tapering of prednisone to safe doses. Used correctly, systemic treatments can be given relatively safely with little increased systemic side effect risk versus local therapies. Biologics hold promise, and adalimumab has been US FDA-approved for the treatment of non-infectious intermediate, posterior, and pan-uveitides.

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Table 1

Major Uveitic Diseases

Anatomic Class	Infectious	Systemic Disease	No Systemic Disease
Anterior	Cytomegalovirus anterior uveitis	Spondylitis/HLA-B27 associated anterior uveitis	Fuchs uveitis syndrome
	Herpes simplex anterior uveitis	Juvenile idiopathic arthritis-associated anterior uveitis	
	Herpes zoster anterior uveitis	Behçet disease	
	Syphilis	Sarcoidosis	
		Tubulointerstitial nephritis with uveitis	
Intermediate	Syphilis	Multiple sclerosis-associated uveitis	Pars planitis
	Lyme disease	Sarcoidosis	
Posterior	Acute retinal necrosis	Sarcoidosis	Acute posterior multifocal placoid pigment epitheliopathy
	Cytomegalovirus retinitis		Birdshot chorioretinitis
	Lyme disease		Multiple evanescent white dot syndrome
	Syphilis		Multifocal choroiditis with panuveitis
	Toxoplasmic retinitis		Punctate inner choroiditis
	Tuberculosis		Relentless placoid choroiditis
			Serpiginous choroiditis
Panuveitis	Syphilis	Behçet disease	Sympathetic ophthalmia
	Lyme disease	Vögt-Koyanagi-Harada disease	

Adapted from reference 1.

Table 2

Suggested Tapering Schedules for Prednisone

Prednisone dose (mg/day)	Decrement (mg/day)	Taper interval	
		Rapid	Standard
60 to 30	10	2 days	Weekly
30 to 15	5	2 days	Weekly
15 to 7.5	2.5	2 days	Weekly
<7.5	2.5 to 1	2 to 7 days	Weekly to monthly *

* For patients on long-standing prednisone (e.g. years) tapering rate may need to be as low as 1 mg every other day decrements monthly to avoid withdrawal. Adapted from reference 13.

Table 3

Conventional Immunosuppressive Drugs used for the Uveitides

Class	Generic name	Trade name	Suggested Initial dose	Typical Maximum dose	Most frequent potential side effects	Suggested monitoring*
Antimetabolite	Azathioprine	Imuran	2 mg/kg/day	3 mg/kg/day	Gastrointestinal upset, cytopenias†, hepatitis	CBC & chemistries q 4-6 weeks
	Methotrexate	Rheumatrex others	15 mg/week‡	25 mg/week	Hepatitis, cytopenias, fatigue/malaise, nausea	CBC & chemistries q 4-6 weeks
	Mycophenolate	Cellcept	1 gm BID	1.5 gm BID	Diarrhea, cytopenias, hepatitis	CBC & chemistries q 4-6 weeks
Calcineurin inhibitor	Cyclosporine	Neoral, others	2 mg/kg BID	2 mg/kg BID	Hypertension, nephrotoxicity, anemia, hirsutism	CBC & chemistries q 4-6 weeks; Blood pressure
	Tacrolimus	Prograf	1 mg BID	3 mg BID	Neurotoxicity (tremors), nephrotoxicity	CBC & chemistries q 4-6 weeks; Tacrolimus blood level until in therapeutic range
Alkylating agent	Chlorambucil	Leukeran	0.1 mg/kg/day	0.2 mg/kg/day	Cytopenias	CBC weekly
	Cyclophosphamide	Cytoxan	2 mg/kg/day	250 mg/day	Cytopenias, bladder toxicity	CBC & urine analysis weekly

*CBC = complete blood count; chemistries typically are run on multichannel analyzers and include creatinine & liver enzymes.

†Cytopenias include anemia, leukopenia, and thrombocytopenia.

‡May be given orally or subcutaneously; subcutaneously may have fewer gastrointestinal and fatigue/malaise side effects. Should be given with folate 1 mg/day to minimize side effects.

Table 4

Single Agent Success with Conventional Immunosuppressive Drugs

Drug	Number patients	Success (%)			Sustained drug-free remission rate (/PY[†])	Interruption or discontinuation for side effects rate (/PY)
		Uveitis Control				
		6-month	12-month	Corticosteroid-sparing[*]		
Azathioprine	145	41	62	47	0.09	0.16
Methotrexate	384	49	66	58	0.09	0.13
Mycophenolate	236	53	73	55	0.05	0.08
Cyclosporine	373	33	52	36	0.08	0.04
Cyclophosphamide	215	49	76	61	0.32	0.39

[*] Uveitis controlled and prednisone <10 mg/day.

[†] PY = person-year. Data derived from the Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study (data from references 43–46, 48).