Review of Systemic Immunosuppression for Autoimmune Uveitis

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REVIEW

Review of Systemic Immunosuppression for Autoimmune Uveitis

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ABSTRACT

The purpose of this review is to comprehensively examine the various therapeutic agents available to treat autoimmune eye disease, their indications, clinical safety and recent developments. The stepladder approach is reviewed, including corticosteroid administration of various forms, classic immunomodulators, and newer biologic response modifiers. The authors present that corticosteroid monotherapy is almost never curative and carries significant side effects, while immunomodulatory therapy, when used appropriately as way to induce steroid-free remission, carries far less risk of causing long-term complications and provides greater potential of altering the immune system to induce a durable remission.

Keywords: Corticosteroid; Immunomodulatory therapy; Inflammation; Ophthalmology; Uveitis

INTRODUCTION

Uveitis is the third leading cause of preventable blindness in the United States. Vision loss from uveitis can be secondary to cystoid macular edema, glaucoma, cataract, retinal vasculature abnormalities, corneal opacities, optic nerve atrophy, retinal and macular lesions. New modalities and effective therapies to control ocular inflammatory disease have been developed. The goal of therapy is to suppress the immune inflammatory response in order to preserve the integrity of the eye and therefore preserve visual function. The choice of agent is based on the patient's underlying disease, age, sex, medical conditions, and risk factors. The patient is monitored closely to assess the response and to screen for adverse effects. Therapy is continued with the mission to

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achieve quiescence of inflammation for a period of 2 years prior to considering tapering or discontinuation. This review will focus on the various therapeutic agents available to treat autoimmune eye disease, its indications, clinical safety and recent developments.

DISCUSSION

Corticosteroids

Corticosteroids therapy has been used extensively in the treatment of non-infectious uveitis. It can be administered in the form of topical drops, intravitreal and periocular injections, intravitreal implants and systemically which will be described [1].

Corticosteroids (mineralocorticoids and glucocorticoids) are naturally produced in response to adrenocorticotropic hormone (ACTH)-induced conversion of cholesterol to pregnolone in the adrenal cortex. Glucocorticoids regulate gluconeogenesis and inhibit the inflammatory response. On the other hand, mineralocorticoids regulate the body's ion balance by controlling inorganic ion reabsorption by the kidney. Corticosteroids are composed of 21 carbon molecules consisting of three hexane rings, one pentane ring and cyclopentanoperhydrophenanthrene nucleus [2]. Changes in this basic structure gives rise to different compounds with different biologic properties such as anti-inflammatory activity, duration of action, trans-corneal penetration, sodium retaining activity, efficacy and side effect profile [2].

The mechanism of corticosteroids has a direct impact on protein synthesis at the cellular level by switching gene transcription on and off. Corticosteroid receptors have been isolated in the ciliary body, corneoscleral tissue and iris. Glucocorticoids inhibit vascular permeability and vasodilation thereby affecting leukocyte migration to sites of inflammation and leukocyte distribution and survival. In addition, the distribution and maturation of lymphocytes in the thymus is also affected leading to lymphocytopenia. Long-term high doses may affect B lymphocytes and antibody production while small and moderate doses have an impact on T lymphocytes [2]. The production of neutrophils, as well as their adhesion to the vascular endothelium and their migration to sites of inflammation from the intravascular space, is affected. There is a reduction of circulating monocytes and eosinophils and a decrease in macrophage recruitment and their ability to act as antigen presenting cells. Corticosteroids stabilize the membranes of basophils and mast cells thereby inhibiting degranulation and the release of inflammatory mediators. Corticosteroids inhibit phospholipase A2, thereby affecting the conversion of phospholipid to arachidonic acid. The end result is inhibition of prostaglandin production through the cyclooxygenase pathway and inhibition in production of leukotrienes through the lipooxygenase pathway [2].

Topical Corticosteroids

Topical corticosteroids are frequently employed as the initial therapy for uveitis, specifically for anterior uveitis. The drops can be easily administered by the patient and frequency of dosing can be modified and tapered based on the degree of inflammation. There is wide variety of topical steroids available in the market with a range of anti-inflammatory activity. The most commonly prescribed is prednisolone acetate 1%, which is adequate for most cases of uncomplicated anterior

uveitis. Less potent options include loteprednol and rimexolone that can be used when there is a concern about elevated intraocular pressure [3]. However, these agents may not be adequate for severe anterior uveitis. Recent studies have demonstrated the efficacy of difluprednate ophthalmic solution 0.05% in the treatment of anterior uveitis requiring less frequent administration when compared to prednisolone acetate 1% [4].

Topical steroid use should be monitored closely and long-term use should be limited since corticosteroids can cause cataract and glaucoma. Topical steroids should be used with caution in patients with a history of intraocular infection and compromised corneal surface to avoid recurrence or onset of infectious processes such as herpetic keratitis. Topical therapy should be aggressive in the beginning with frequent dosing in order to halt the inflammation and then be tapered to avoid rebound inflammation [1, 2].

Periocular Corticosteroid

In cases of intermediate and posterior uveitis where topical therapy is not sufficient, transseptal, sub-Tenon's space or subconjunctival injection can offer an alternative. The most common agent used in these injections is triamcinolone acetate. These injections offer the benefit of local therapy and extended effect, whilst limiting systemic side effects. The patient needs to demonstrate cooperation in order to receive these injections. The drawbacks include eliciting steroid response and close monitoring of intraocular pressure. Patients should also be counseled about possible orbital fat atrophy or prolapse, ptosis or proptosis after repeated injections that may alter their cosmetic appearance.

Intravitreal Corticosteroids

Intraocular injections can be an alternative if the inflammation is unilateral, mild to moderate in nature or in situations where it is recalcitrant to periocular and systemic administration. The effects can be transient with duration of about 3 months therefore requiring repeated injections. Agents such as triamcinolone have been employed with success and can be quite useful in reducing macular edema and improving visual acuity [2]. Water-soluble steroids have a shorter duration and may not be sufficient in controlling cystoid macular edema. The risks include frequent injections that can increase the risk of endophthalmitis and retinal detachment. The injections also carry the same side effect profile of elevated intraocular pressure and cataracts [5].

Intravitreal Implants

In order to address the need for frequent intraocular steroid administration, sustained-release delivery vehicles have been developed such as Retisert® (Bausch + Lomb, Bridgewater, NJ, USA) and Ozurdex® (Allergan, Irvine, CA, USA).

Retisert® was approved in April 2005 in the United States for the treatment of chronic, non-infectious uveitis affecting the posterior segment of the eye. It is a non-biodegradable sustained delivery fluocinolone acetonide intravitreal implant that is surgically implanted in the posterior segment [5].

It releases fluocinolone acetonide, a synthetic corticosteroid, 0.6 μg/day during the first month and then 0.3–0.4 μg/day at a stable rate over the next 30 months. Systemic absorption has been shown to be minimal. Clinical studies have demonstrated improvement of visual acuity of more than three lines after 34 weeks of having the implant placed in about 19–21% of patients. About 15–17% of Retisert recipients who noted an

improvement in vision at the 34-week mark were able to maintain the improvement. The Retisert implant has been shown to reduce uveitis recurrences, improve visual acuity, and decrease the need for adjunctive therapy [6]. Nevertheless, Retisert recipients have been shown to develop cataracts and glaucoma often necessitating additional cataract and glaucoma filtering surgery. In studies comparing Retisert and standard systemic therapy, there was an increased incidence of cataracts and glaucoma where cataract formation was noted in 88–93% in patients with Retisert and 21–40% of patients required glaucoma surgery [7, 8].

Ozurdex® is Food and Drug Administration (FDA) approved to treat adults with macular edema after a branch or central retinal vein occlusion or adults with non-infectious posterior uveitis. It is a 0.7 mg dexamethasone biodegradable drug delivery system that is inserted into the vitreous in an outpatient setting. The implant lasts about 3 months and has been found to be effective with better side effect profile when compared with intravitreal triamcinolone injections and Retisert. It was originally approved in 2009 for the treatment of macular edema. It offers an alternative for patients who may need repeated intravitreal injections, but are not yet ready to proceed with surgical Retisert implantation.

In a study comparing Ozurdex and Retisert implants, no eyes in the Ozurdex group needed additional glaucoma medications, surgery or laser, compared to 44% of eyes in the Retisert group. Eyes with the Retisert implant had a statistically higher rate of having more glaucoma medications and surgery. With regard to cataracts, in the Ozurdex group, 50% of phakic eyes at baseline had cataract progression and subsequent surgery compared with 100% of Retisert phakic eyes. Eyes with the Retisert implant were 4.7 times more at risk of cataract progression [9].

Systemic Steroids

In the situation of refractory uveitis and the need for immediate control, systemic steroids can be employed in the oral or intravenous route. High doses of oral steroids may be necessary to quell the inflammation initially, followed by a taper. The typical dose can be 1 mg/kg daily. If disease control requires more than 10 mg of prednisone daily, immunosuppressive therapy should be discussed. The patient needs to be advised about the importance of tapering the steroids appropriately to avoid recurrence of inflammation and an adrenal crisis. Patients should also be aware that the hypothalamic-pituitary axis may not return to baseline 6–12 months after chronic oral steroid therapy has been discontinued [10].

Pulse intravenous steroids are used if immediate control is required or if the patient does not tolerate high doses of oral steroids. A regimen of intravenous methylprednisolone 1 g/day for 3 days with transition to oral steroids can be used. It should be administered over a period of 30 min or longer [1, 10].

The side effect profile is significant with notable mention of osteoporosis even with doses as low as 7.5 mg per day. Prolonged steroid use warrants close bone density monitoring and bone preservation therapy. It is important to counsel patients about possible weight gain, mood changes, insomnia, hyperglycemia, easy bruising, skin atrophy and striae, and susceptibility to infection. Less common, but more severe adverse effects include aseptic bone necrosis, pancreatitis, myopathy and psychosis. Patients on corticosteroids and non-steroidal anti-inflammatory should be monitored for the

onset of gastrointestinal symptoms and prompt therapy should be started if they occur. Ocular side effects also include cataract formation and elevation of intraocular pressure [1, 10].

Immunomodulatory Drugs

Patients with chronic ocular inflammation often benefit from long-term management with steroid-sparing therapy. Immunomodulators can be considered in patients with systemic disease affecting multiple organ systems such as in the case of patient with sarcoidosis, rheumatoid arthritis and juvenile idiopathic arthritis (JIA) among others. Other scenarios include steroid intolerance or cases of uveitis such as Behcet's disease, sympathetic ophthalmia, Vogt–Koyanagi–Harada syndrome and rheumatoid scleritis that warrants immediate use of immunomodulators. Prior to starting therapy the patients age, type and severity of inflammation, associated medical conditions and type of family planning must be assessed carefully [2, 11].

In discussing immunomodulatory therapy with patients, compliance with medication, office visits and laboratory testing, birth control methods to be used while the patient is taking immunomodulators and in-depth counseling with regard to the medication side effects and possible off-label use need to be assessed. The need to receive killed vaccines such as the influenza vaccines and never receive live vaccines, the need to conduct baseline laboratory testing such as complete blood count (CBC), liver function tests (LFT), and renal function tests and patient understanding to stop immunomodulator therapy in the setting of infection should also be assessed. Finally, the patient should be made aware of the teamwork approach with their primary care doctor, pediatrician or rheumatologist.

Antimetabolites

Methotrexate

The pharmacology involves inhibition of DNA replication by using a folate analog that interferes with DNA synthesis. It reduces cellular and humoral immune responses by affecting proliferation, inducing T-cell apoptosis, altering B-cell response, inhibiting cytokine production and also with antiangiogenic properties. The most common indication for its use is a patient who is steroid intolerant and needs more long-term management such as in the case of chronic uveitis or scleritis. The Systemic Immunosuppressive Therapy for Eye Diseases (SITE) multi-center retrospective cohort study of 384 patients treated with methotrexate as the only immunosuppressant for ocular inflammation showed that 66% of patients were able to achieve quiescence of their ocular inflammation within a year, also permitting a taper of systemic steroids [5]. Methotrexate was employed in controlling anterior uveitis, posterior uveitis, panuveitis and mucous membrane pemphigoid. Therapy success was most commonly achieved in patients with anterior uveitis and scleritis. Methotrexate has a long track record and has been safely and efficiently used in the adult as well as in the pediatric population. It is available in the oral, subcutaneous and intravenous administration. It is provided in doses of 7.5 mg and up to 25 mg once a week. Folic acid (1 mg) daily is also employed to limit side effects due to folate deficiency. It takes about 3–6 weeks for methotrexate to become effective. Side effects may include bone marrow suppression, elevated liver enzymes, fatigue, malaise, gastrointestinal discomfort. These side effects are typically reversible with dose reduction or by stopping the medication. The subcutaneous route can be

more effective in the same doses without affecting its tolerability. Therapy is continued for 2 years after quiescence is achieved to be able to obtain durable remission. If no adequate control is achieved, the dose can be increased by 5 mg per week. If no improvement is noted another agent can be added or methotrexate needs to be replaced. Important laboratory testing to follow include complete blood counts (CBC), liver enzymes (LFT) and creatinine at 6-week intervals to assess for any kind of toxicity [5].

Mycophenolate Mofetil

Mycophenolate mofetil (MMF) inhibits inosine monophosphate dehydrogenase causing a reduction of nucleotides required for purine synthesis, DNA synthesis and for B- and T-cell proliferation. It also interferes with cell adhesion on vascular endothelium, lymphocytic chemotaxis and decreases antibody synthesis [5].

Mycophenolate has been successfully employed as monotherapy or in conjunction with steroids, cyclosporine, azathioprine and methotrexate to treat ocular inflammation [12]. It can also be the next agent to be employed if a patient does not tolerate methotrexate. In the SITE cohort study which included 236 patients with ocular inflammatory disease, 73% of them were able to achieve inflammation control within 1 year, while 55% of patients were able to experience a steroid-sparing effect at the 1 year mark [13].

Side effects led to the discontinuation of MMF in 12% of patients during the first year. The SITE study also showed no increase in overall or cancer-related mortality in patients who were treated with MMF when compared to untreated controls [11, 14].

The starting dose of MMF is 500 mg twice a day by oral route on an empty stomach, 1 h prior to eating or 2 h after meals while assessing for side effects. If the patient is tolerating the medication well, the dose can be increased to 1 g twice a day with a maximum dose of 3 g a day. The most common side effect is gastrointestinal irritability, followed by bone marrow suppression and elevated liver function tests. Baseline laboratory testing such as CBC with differential, liver function tests are done at the onset of therapy and then monitored every 4–6 weeks. Duration of therapy is usually 2 years in order to achieve steroid-free remission.

Azathioprine

Azathioprine is a prodrug that it is metabolized in the liver to the active form, 6-mercaptopurine, that is then converted to thioinosine 5-phosphate, that serves as a purine analog that interferes with RNA and DNA synthesis [2]. It has been shown to inhibit T-lymphocyte function, interferes with targeting of circulating T cells, decreases the development of monocyte precursors, suppresses type IV hypersensitivity reaction, and interferes with the participation of natural killer (NK) cells in the antibody-dependent cytotoxic reactions [11]. The SITE study included 145 patients treated with azathioprine for ocular inflammatory conditions and 62% of these patients were able to achieve quiescence of inflammation and 47% were able to experience a steroid-sparing effect. Inflammation control with azathioprine was most commonly achieved in patients with intermediate uveitis [11]. During a median follow-up of 230 days, 24% of patients stopped therapy due to side effects including gastrointestinal discomfort, bone marrow suppression, altered liver functions, infections

and allergic reactions. Fourteen percent of patients achieved remission and were able to stop therapy. The SITE study showed no increased risk of mortality or cancer in patients taking azathioprine when compared to controls who never took the therapy [14, 15].

It is typically given at an initial dose of 2–3 mg/kg/day orally and the dose is then adjusted based on clinical response and side effect profile. Baseline testing at the beginning of therapy should include a CBC with differential, LFT and quantitative testing for thiopurine methyltransferase enzyme activity. It should not be given to patients who have low or absent enzyme activity. If a patient is also taking allopurinol, the azathioprine dose should be reduced by 25%. Follow-up CBC and liver function tests should be done at 4- to 6-week intervals. Therapy should be maintained typically for 2 years with the goal of durable steroid-free remission.

Cyclosporine

Cyclosporine (CsA) is a fungal anti-metabolite primarily used in solid organ transplantation. It is postulated that CsA reversibly inhibits T-cell mediated alloimmune and autoimmune responses. Its mechanism of action is not fully understood, but it has been shown that CsA disrupts the transmission of signals from the T cell receptor to genes that encode multiple lymphokines needed for activation of resting T cells such as T helper-inducer and cytotoxic subsets, while leaving T suppressor cells unaffected [2, 11]. The SITE study evaluated 373 patients with ocular inflammation treated with CsA in which 52% of them were able to achieve inflammation control and tapering of systemic steroids was achieved in 36% of patients at the 1-year time point. About 10.7% of patients stopped therapy within a year due to toxicity. About 55 patients discontinued CsA after 1 year of therapy start due to achieving remission.

CsA has been effective in patients with Behcet's disease, Vogt–Koyanagi–Harada and sarcoidosis [16]. It can be used as monotherapy or in conjunction with steroids or other immunomodulators such as with mycophenolate mofetil in the setting of birdshot chorioretinopathy. The most common side effects noted were hypertension and renal toxicity, both being dose-dependent. According to the SITE study, CsA did not show an increased risk of mortality of cancer [14]. Additional side effects include gingival hyperplasia, hypertrichosis, normochromic normocytic anemia, paresthesias, temperature hypersensitivity, nausea, vomiting, neurotoxicity manifested by fine hand tremor and reversible myopathy [2].

It is administered in oral form at starting doses of 2.5 mg/kg/daily to a maximum dose of 5 mg/kg/day, adjusted to the clinical response [11]. The topical ophthalmic formulation of CsA known as Restasis® (Allergan, Irvine, CA, USA) is not useful in the therapy of uveitis and should be used for its approved use of dry eyes therapy.

Before starting treatment, baseline CBC with differential, serum creatinine, creatinine clearance, urinalysis, blood urea nitrogen (BUN), liver function tests, fasting lipid profile and blood pressure measurements should be done. While the dosage is being adjusted, blood pressure, serum creatinine and BUN should be checked every 2 weeks and once the dose has been stabilized then the testing should be done every 4–6 weeks. Fasting lipid profiles should be monitored at 3-month intervals. Therapy is continued for 2 years once inflammation control has been achieved.

Tacrolimus

Tacrolimus is a macrolide antibiotic derivative from *Streptomyces tsukubaensis*. It interferes with the calcineurin phosphatase pathway that regulates T-cell-based immune responses [1]. Comparison between tacrolimus and CsA showed comparable efficacy with a lower incidence of tacrolimus-induced systemic hypertension and lipid abnormalities [17]. Tacrolimus monotherapy was also shown to allow oral prednisone tapering to less than 10 mg per day after 14 months in patients with anterior, intermediate, posterior uveitis, panuveitis and demonstrated a more favorable side effect profile [11, 18]. It is dosed 0.05 mg/kg/day. Possible side effects with tacrolimus include nephrotoxicity and hypertension with rare occurrences of headaches, neuropathy and seizures, all of which are reversible with therapy cessation [1, 10].

Sirolimus

Sirolimus, also known as rapamycin, is a macrolide antibiotic derived from *Streptomyces hygroscopicus*. It binds to FK Binding Protein (BP) 12 inhibiting the mTOR pathway and activation of p70 kinase, stopping the cell cycle between G1 and S phases which prevents the activation and proliferation of T lymphocytes [1, 11]. It has also been shown to block the growth factor proliferation signaling and activation of hypoxia inducible factor (HIF)-1α.

Sirolimus was shown to be an effective strategy in reducing inflammation [19]. It has a long history of use in drug-eluting stents in cardiology and in solid organ transplants. Side effects include recurrent chest infections, gastrointestinal and dermatologic problems [1]. The typical dose is 2 mg daily. A recent trial evaluating the intravitreal and subconjunctival administration of sirolimus in patients with non-infectious uveitis showed that it is safe and tolerable with no systemic adverse side effects. It was noted to have immunomodulatory and steroid-sparing effects and led to a reduction in vitreous haze and cells and improvement of visual acuity were noted [20].

Voclosporin

Voclosporin, also known as luveniq, is a novel calcineurin inhibitor that affects T helper cells (TH) 1 and TH17-mediated responses. It was developed by modifying the functional group of cyclosporine thereby becoming a more potent inhibitor and having a more predictable pharmacokinetic profile [1, 21]. The Lux Uveitis Multicenter Investigation of a New Approach to Treatment (LUMINATE) trial demonstrated superiority to placebo in reducing vitreous haze and a 50% decrease in the recurrence rate of inflammation at 6 months with tolerable side effects [11, 22]. Voclosporin was dosed orally at 0.4 mg/kg twice a day. However, the primary endpoint for the phase 3 clinical trials to show reduction in vitreous haze at week 12 or at the time of treatment failure was not achieved and Lux Biosciences Inc. (NJ, USA) ended its plans to proceed with the drug development for uveitis.

Alkylating Agents

Alkylating agents interfere with DNA replication by transferring alkyl groups, cross-linking nucleic acids, causing abnormal base pairing, DNA strand breakage and termination of the cell cycle. It has a cytotoxic effect on rapidly proliferating cells [1, 2, 11]. Cyclophosphamide and chlorambucil fall in this category.

Cyclophosphamide (Cytoxan)

It is commonly used in cancer chemotherapy and in autoimmune disorders. Its action is

similar to that of nitrogen mustards that cause a cytotoxic effect to proliferating cells, such as immunocompetent lymphocytes undergoing cell division, by alkylating nucleophilic groups on DNA bases leading to linking of DNA bases, irregular base pairing and breaks in DNA strands [1, 11].

Cyclophosphamide has been effective in treating scleritis caused by underlying systemic disorders such as granulomatosis with polyangiitis (GPA), rheumatoid arthritis, polyarteritis nodosa and relapsing polychondritis [23–26]. In the SITE cohort study, 215 patients receiving cyclophosphamide for ocular inflammation were studied and 76% of them achieved inflammation control at 1 year. A steroid-sparing effect was noted in 61% of patients. Similar outcomes in time to control inflammation were noted in those patients receiving intravenous and oral therapy, but the patients taking the oral cyclophosphamide had a higher rate of control. Therapy was discontinued by 33.5% of patients within a year due to side effects and in 10.8% for unknown reasons. Low white blood cell count, cystitis, and hematuria were the most common toxicities noted that led to discontinuation of therapy in 3% of patients during the first year. Opportunistic infections caused therapy cessation in 3% of patients during the first year, including *Pneumocystis carinii* pneumonia, that lead to the death of one patient, managed using the commonly accepted guidelines, but who did not take the pneumocystis prophylaxis. In 9.7% of patients, therapy was discontinued due to inadequate inflammation control [11, 27]. The SITE study showed no significant increase in overall mortality. The data suggested a possible increased risk of cancer mortality with cyclophosphamide use, but additional data are required since the results were not conclusive [14].

Oral cyclophosphamide is dosed at 1–3 mg/kg/day. Intravenous pulsed therapy dosing and timing is titrated to achieve a white blood cell count of 3,000–4,500 with an absolute neutrophil count ≥1,000. Infusions can occur every 2–4 weeks and double strength sulfamethoxazole/trimethoprim (Bactrim DS ®; AR Scientific, Brampton, Canada) three times a day is given for phencyclidine (PCP) prophylaxis. The most toxic potential side effects occur less frequently with the intravenous dosing. Monitoring is of utmost importance and CBC and urinalysis should be done every 2 weeks. Bladder toxicity from acrolein, one of the metabolites, and the risk of bladder cancer is minimized by intermittent pulsed intravenous (IV) therapy, adequate hydration, and premedication with 2-mercapto-ethane sulfonate (mesna) [1, 11].

A recent study showed that pulsed IV cyclophosphamide results in high rate of sustained complete remission in patients with recalcitrant and fulminant, vision-threatening ocular inflammatory disease. Its side effect profile was excellent under the management of experienced clinicians and its use allowed tapering and discontinuation of corticosteroids [28].

Chlorambucil

Chlorambucil is nitrogen mustard that replaces hydrogen ions with alkyl groups on DNA bases. It causes intra-strand cross-linking and DNA to protein cross-linking, disrupting DNA replication, transcription and function. The SITE study showed no significant increase in overall mortality in patients treated with alkylating agents. A non-significant increase in cancer-related mortality was observed.

Chlorambucil has not been as extensively studied as cyclophosphamide. It was studied in Behcet's disease where high-dose, short-term therapy was effective in preventing recurrence after 6–24 months of use [1, 29]. It has also been used effectively in non-infectious uveitis related to human leukocyte antigen (HLA)-B27, JIA, pars planitis, sympathetic ophthalmia, and Crohn's disease.

Baseline CBC with differential and liver function tests are obtained prior to starting therapy. Close monitoring for side effects and myelosuppression should be done. Treatment parameters of white blood cell count of 3,000–4,500 with an absolute neutrophil count $\geq$1,000 should guide therapy. It can be started at an oral dose of 0.1 mg/kg/day, titrating the dose to clinical response and tolerance every 3 weeks with a maximum daily dose of 6–12 mg/day followed by a progressive reduction of the dose over the next 3–6 months. Treatment is continued for 1 year of disease quiescence to induce durable remission [11]. An alternate approach is short-term and high-dose therapy for 3–6 months. The initial dose is of 2 mg a day for 1 week, followed by an increase of 2 mg/day each week until inflammation is completely resolved or until the leukocyte count decreases to below 2,400 cells/μl or platelet count is below 100,000 cells/μl. CBC with differential is done weekly as the dose is being adjusted. Therapy is discontinued if bone marrow toxicity occurs [11]. A combination of the two approaches can be employed.

Biologic Response Modifiers

These agents specifically target cytokines or their inflammatory signaling pathways. They have revolutionized the treatment of inflammatory disease and offer novel options in the management of uveitis.

Etanercept

Etanercept is a soluble, bivalent receptor for tumor necrosis factor alpha (TNF-α). It competitively binds TNF-α and TNF-β inhibiting the immune activities that rely on these cytokines for signal transduction such as expression of adhesion molecules responsible for leukocyte migration and decreased synthesis of pro-inflammatory cytokines and matrix metalloproteinase (MMP). Etanercept has been effective in the treatment of arthritis, but its effect in uveitis is debatable [11, 30]. In a study, etanercept showed no significant efficacy over placebo in uveitis relapses in patients being tapered off methotrexate [31]. While other studies showed some improvement with etanercept in Behcet's associated uveitis and pediatric patients [32]. The SITE study, showed an increased risk of mortality and cancer-related mortality in patients taking TNF inhibitors, including etanercept [14].

It is typically administered via a subcutaneous injection of 25 mg twice a week for a period of 2 years. The most common side effect is pain at the site of injection. Anti-TNF therapy is not recommended for patients with active systemic infection. All patients are tested for latent tuberculosis by tuberculin skin testing or serum quantiferon testing. Serologic hepatitis B testing including antibody to hepatitis B core antigen (anti-HBc) and hepatitis B surface antigen (HBsAg) was done.

Patients with severe heart failure are excluded from using this therapy. A baseline CBC and liver function tests are done prior to therapy initiation and repeated at 4–6 week intervals. Sustained remission seems to occur less commonly after therapy cessation even after a period of 2 years.

Adalimumab

Adalimumab is a fully human immunoglobulin (Ig) G1 monoclonal anti-TNFα antibody. It is

indicated for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, juvenile idiopathic arthritis, ankylosing spondylitis and psoriasis.

It has been shown to be effective in treatment-resistant uveitis, reducing flares of uveitis in the pediatric populations and in patients with juvenile idiopathic arthritis, and in patients with spondyloarthropathy-associated uveitis [33–37]. Overall malignancy and mortality rates were comparable to those in the general population as shown by Burmester et al. [38]. Further studies are needed to assess the long-term safety of adalimumab in treating uveitis and if it follows the similar long-term effects of etanercept and infliximab.

It is administered via pre-packaged subcutaneous injection in doses of 40 mg and it is typically given at 2-week intervals. However, the interval can be decreased to 1 week if additional control is necessary. It can be used in conjunction with other immunomodulator agents such as methotrexate and mycophenolate mofetil in order to achieve remission. The common side effects include pain at the site of injection, upper respiratory, sinus and urinary tract infections, gastrointestinal discomfort, elevated cholesterol and high blood pressure. Baseline CBC and liver function tests are done prior to starting therapy and repeated at 3-month intervals while the patient is taking the medication. Therapy duration should be 2 years in order to be able to achieve sustainable remission.

Infliximab

Infliximab is a chimeric IgG monoclonal antibody directed at soluble and transmembrane forms of TNF-α. It has been used in treating autoimmune disorders such as psoriasis, rheumatoid arthritis, Crohn's disease. It is only effective against TNF-α. Studies have revealed efficacy in treating ocular complications of Behcet's disease not controlled with other agents and success has also been noted in treating refractory uveitis in patients with juvenile idiopathic arthritis and ankylosing spondylitis [39–41].

TNF-α is involved in host defense against infections with pathogens such as *Mycobacterium*, *Aspergillus*, *Histoplasma*, *Toxoplasma* and *Candida* and could make patients susceptible to reactivation with tuberculosis [42]. Infliximab has been associated anaphylactic reactions, demyelinating disease and heart failure and should be used with caution in patients with a known past medical history that may be affected by potential side effects [43]. The SITE cohort showed infliximab group to have a greater risk of cancer and overall mortality; however, it is proposed that TNF inhibitors do not initiate cancer but exacerbate pre-existing malignancies that are undetected [11, 14]. A study evaluating the effects of infliximab in patients with Behcet's disease uveoretinitis showed that it was well tolerated with no serious adverse effects occurring in about half of the patients. At the 1-year endpoint, the uveoretinitis had improved in 92% of patients. No flare-ups were seen during the 1 year period in 44% of patients and improvement in visual acuity was noted [44].

Infliximab is administered as an intravenous infusion at 5 mg/kg at week 0 and 2 as loading doses followed by infusions at 4-week intervals. For refractory cases, the doses can be as high as 10 mg/kg. The dosing can be increased or tapered and the dosing intervals can be adjusted based on clinical response and state of inflammation. Based on the authors experience within the Massachusetts Eye Research and Surgery Institution (MERSI), infliximab is the most efficacious amongst the targeting antibodies for the treatment of ocular inflammatory disease, but its use may be limited by the need for monthly infusions.

Baseline tuberculin skin test is required and repeated annually during the duration of therapy, and a baseline CBC and LFT is done and repeated at 4- to 6-week intervals [1].

Daclizumab

Daclizumab is a humanized monoclonal antibody against the interleukin (IL)-2 receptor of activated lymphocytes. It binds to the cluster differentiation (CD) 25 portion of the IL-2 receptor; thereby, inhibiting the IL-2 mediated cytokine response.

It affects the T-lymphocyte response and does not have an impact on the humoral immune pathways.

It showed effectiveness in treating childhood uveitis, non-infectious intermediate and posterior uveitis and refractory inflammatory disease. Efficacy was also demonstrated in treating birdshot retinochoroidopathy [11, 45–49]. The dose is 1–4 mg/kg given intravenously every 14 days. It is generally well tolerated with side effects ranging from headaches, nausea, lymphadenopathy and skin reactions. Daclizumab was not examined in the SITE cohort study; however, studies done on patients receiving it for transplants did not show an increased risk of malignancy or mortality [50]. Unfortunately, daclizumab was withdrawn from the market in January 2010 due to its projected revenue when compared to alternative medications in the renal transplant field [11].

Rituximab

Rituximab is a murine/human chimeric monoclonal IgG antibody against the CD20 antigen in B lymphocytes, thereby serving as a strong immune suppressant of the humoral arm of the immune system. The CD 20 marker is essential in B lymphocyte activation and differentiation [1]. It also inhibits T-cell activation through a reduction of antigen presentation by B cells and by inducing lysis of peripheral B lymphocytes. It has been employed in the therapy of lymphoma, leukemia, multiple myeloma, rheumatoid arthritis and uveitis [1]. Rituximab has been useful in treating chronic anterior uveitis refractive to steroids and other steroid agents [51], inducing remission in a patient with relapsing necrotizing scleritis associated with granulomatosis with polyangiitis (Wegener's) (GPA) [52], and inducing remission of retinal vasculitis in a patient with Behcet's disease [53]. In MERSI, good results have been observed in inducing remission with rituximab in patients with refractory uveitis and treatment-resistant ocular cicatricial pemphigoid [1].

Rituximab is administered as an intravenous infusion, 375 mg/m^2, every week for 4 weeks. Possible side effects include flu-like symptoms, headache, nausea, fatigue and rash. A baseline CBC should be obtained and monitored during therapy for evidence of neutropenia that could render patients vulnerable to infection. Rituximab can also be given in conjunction with intravenous immunoglobulin (IVIG) in patients with recalcitrant ocular cicatricial pemphigoid. It is infused at 375 mg/m^2, once weekly for 8 weeks and then infused monthly for 4 months, for a total of 6 months of therapy [54]. IVIG is infused 1 month prior to starting rituximab therapy, and then monthly until B-cell levels decrease to within normal limits. Afterwards, IVIG is given at 6, 8, 10, 12, 14, and 16 weeks. CBC and peripheral blood B-cell levels (CD20+ cells) testing via flow cytometry are done prior to every infusion [11].

Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIG) treats autoimmune disease without suppressing the immune system.

Its mechanism is thought to be a possible interaction with Fc receptors or cross-linking of antibodies [55]. It is an effective therapy in the situation of refractory inflammation or in patients with medication intolerance [56–58]. It is administered via intravenous infusion at 2 g/kg spaced over a 2- to 3-day period. Side effects include aseptic meningitis that usually occurs within the 24 h of infusion completion and may last for about 5 days. The infusions can be administered over an 8-h period and can be given on an every other day basis to minimize this effect. The patient may also be pre-medicated and may be given post-infusion pain control [59]. Additional serious reactions include acute renal failure, thromboembolic events and anaphylaxis. IVIG can be used in conjunction to rituximab in patients with recalcitrant ocular cicatricial pemphigoid [54].

Interferon

Interferons (IFNS) are a group of cytokines produced by diverse cell populations with immunomodulatory, antiproliferative and antiviral qualities. Type 1 IFNs are the most clinically important in the setting of ocular inflammation and include IFN-β and IFNα. These two subtypes increase the expression of the major histocompatibility class (MHC) 1 surface molecules and activate NK cells and macrophages [52]. IFN-α_{2a} and IFN-α_{2b} are used in the therapy of hepatitis C and IFN-β_{1a} and IFN-β_{1b} are employed in multiple sclerosis [60].

It has been used in patients with ocular manifestations of Behcet's disease since 1994 and was effective in causing a response rate of 92% with significant improvement in ocular inflammation and visual acuity [61, 62]. Patients with multiple sclerosis-associated uveitis were treated with IFN-β_{1a} in case series and experienced improvements in ocular inflammation, macular edema and visual acuity [63].

Side effects included fatigue, flu-like syndromes, mood changes such as depression and medication-induced SLE. IFNα_{2a} is given at dose of 3–6 million IU daily to three times a week [63]. Liver function tests, CBC and thyroid function tests are done prior to therapy initiation and then at 4- to 6-week intervals. Treatment is continued with a goal of achieving inflammation control for 2 years prior to stopping therapy.

Tocilizumab

Tocilizumab is a humanized antibody to IL-6 which is an important cytokine involved in B and T cell activation and differentiation. It is currently approved for treatment of patients with moderate to severe rheumatoid arthritis or patients who have not had a favorable response to TNF-α agents [64, 65]. Currently, there are studies evaluating its efficacy in treating ocular inflammation.

It is administered intravenously at 4–8 mg/kg at 4-week intervals. Potential side effects include elevated liver enzymes, thrombocytopenia, neutropenia, increased lipid values and therefore CBC and liver function tests should be done at 4- to 6-week intervals [11, 66]. Since Tocilizumab does not affect granulomatous inflammation, reactivation of latent tuberculosis does not pose a risk to patients.

Anakinra

Anakinra is an IL-1 receptor antagonist, IgG monoclonal antibody currently approved for rheumatoid arthritis [67]. IL-1 is a cytokine involved in the stimulation of inflammation and recruitment of inflammatory cells to a particular tissue [68]. A multi-center trial showed efficacy of Anakinra as first-line

therapy for JIA [69]. It is administered as a subcutaneous injection 100 mg daily.

Pregnancy and Uveitis Management

Appropriate contraception should be used during the use of immunosuppressive therapy.

Prednisone seems to be the most widely used systemic anti-inflammatory agent, safest and best tolerated during pregnancy. Its use does not appear to adversely affect fertility. Animal studies noted developmental defects with topical corticosteroids such as cleft lip and palate. No studies have been conducted on the nursing infant or if there are detectable levels in breast milk. However, human studies of corticosteroid-treated pregnant patients with asthma receiving a mean dose of 8 mg of prednisone daily did not show an increase in the incidence of birth defects when compared to the normal population [2, 10, 70, 71]. The American Association of Pediatrics has declared prednisone and prednisolone safe and compatible with breastfeeding.

Alkylating agents are cytotoxic, teratogenic and can cause sterility and should be avoided during pregnancy. Effective contraception is mandatory and patients should consider sperm banking or ova cryopreservation prior to the initiation of therapy. Attempts at conception should be delayed until 3 months after stopping therapy. Cyclophosphamide has been shown to cause skeletal, palate and limb malformations in animal studies while chlorambucil can cause cardiac and urogenital abnormalities. Breastfeeding is contraindicated [2].

Azathioprine has been studied in pregnant renal transplant patients receiving azathioprine and prednisone and in pregnant patients with inflammatory bowel disease treated with azathioprine or 6-mercaptopurine. These studies showed no increase in pregnancy complications or congenital malformations. Risks including lower gestational age, birth weight and prematurity have been reported [2, 10, 72, 73]. The fetal liver does not have the enzyme to convert azathioprine to its active form and may be protected from its effects. It may be used during pregnancy in situations of severe sight-threatening uveitis at daily dose not exceeding 2 mg/kg/day and breastfeeding is not recommended.

Methotrexate is also teratogenic and at elevated doses may have abortifacient properties and is contraindicated during pregnancy. Congenital anomalies include neural tube defects, limb, palate and growth retardation and cranial ossification [2, 10]. Although methotrexate has not been shown to affect female fertility, there is a risk of sperm mutation in treated male patients. Therefore, it is recommended the methotrexate should be discontinued 4 months prior to conception. Breastfeeding is also contraindicated [2, 10].

Mycophenolate mofetil has been shown to cross the placenta, but no data are available on teratogenic effects. It is contraindicated in pregnancy and during breast feeding. Due to its long half-life and hepatic circulation, it should be discontinued 6 weeks prior to conception.

Tacrolimus and cyclosporine cross the placenta. A recent study reviewing cyclosporine therapy during pregnancy concluded that the prevalence of major malformation in this group did not vary substantially with that of the general population [2, 74]. Both agents may be maintained in pregnancy at the lowest effective dose. Breast feeding is not recommended.

The use of biologic response modifiers such as etanercept, adalimumab and infliximab is growing, but there is limited experience on their use during pregnancy and breastfeeding. As a result, these agents should be stopped once

pregnancy is recognized [2]. Case reports of the use of rituximab in pregnant patients with B-cell malignancies and autoimmune diseases have not revealed teratogenic or fetotoxic effects suggesting that this therapy may offer an alternative during pregnancy [2, 75].

Intravenous immunoglobulin has been safely used to prevent recurrent pregnancy loss in patients undergoing therapy for GPA and as preventive therapy for congenital heart block [2, 76, 77]. It has a safe side effect profile but the limiting factors include cost, long infusions during a 3-day period each month. Its use has allowed patients to conceive and carry their pregnancy to term while also controlling their uveitis. It is secreted in breast milk and may transfer protective antibodies to the neonate [2].

The use of IFN-α during pregnancy has been documented in treating patients with hepatitis C, chronic inflammatory demyelinating polyneuropathy and essential thrombocythemia [78–80].

Emerging Therapies

Recent developments in uveitis therapies have shifted focus to targeting inflammatory cytokines, T-cell activation, T-cell migration, downstream pathways by using small molecule inhibitors. Developments of antibodies generated against inflammatory cytokines involved in uveitis and other autoimmune diseases such as IL-17, IL-23, IL-22 and IL-6 have been under investigation and offer novel strategies. Small molecule inhibitors of Janus kinases and protein kinases may offer strategies to modulate the intracellular downstream signaling. Tofacitinib is FDA approved for rheumatoid arthritis and sotrastaurin currently studied in phase 2 trials in patients with macular edema associated with uveitis offer examples of this approach, respectively. Small interfering RNA (siRNA) and microRNA technology can also be utilized to inhibit the expression of inflammatory cytokines [81].

Improved local drug delivery methods are also being advanced. Lee et al. [82] demonstrated the effectiveness of topical tacrolimus ointment in controlling refractory inflammatory ocular surface disease, such as scleritis and Mooren ulcer, and reducing inflammation recurrence and reliance on steroid use. For the intravitreal route, trials of micro-particle injectables are being conducted. These can be in the form of drug-eluting micro-particles with sizes of 1–10 μm, suspended in a liquid carrier or microspheres with drug–polymer associations dispersed within a polymeric matrix [81]. For example, Tethadur™ (pSivida, MA, USA) is a porous silicone micro-particle designed to have sustained release of proteins, peptides, chemical molecules and therapeutic antibodies. Intravitreal injections of a viscous gel or liquid can be formulated to release monoclonal antibodies and small peptides, proteins and molecules as demonstrated by the Verisome® system (Icon Bioscience, Inc. CA, USA) [81, 83]

CONCLUSION

The advances in the understanding of the immune system and the mechanisms behind autoimmune disease and ocular inflammatory disease have permitted new insights and developments of diverse therapies. Further work is needed to further clarify long-term effects in the case of the biologic response modifiers and to assess which medication is best indicated for a particular disease.

Each patient presents a unique clinical scenario and therapy must be individualized. Long-term therapy may be needed with antimetabolites and T-cell inhibitors while therapy with alkylating agents may result in long-term, drug-free remission [10]. The strategy to use combination therapy gives the opportunity to modulate the various arms of the immune system leading to enhanced immunosuppression and limiting dose toxicity [10]. The understanding is that chronic corticosteroid therapy is almost never curative and carries significant side effects, while immunomodulatory therapy (IMT) when used appropriately as a way to induce steroid-free remission carries less risk of causing long-term complications. IMT provides greater potential of altering the immune system to induce remission and allow the patient to be cured of their ocular inflammatory disease and be able to discontinue medications without any further relapses [84].

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