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Review article

Immunosuppressive therapy for eye diseases: Effectiveness, safety, side effects and their prevention

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ABSTRACT

Ocular inflammation is a significant cause of ocular morbidity and visual impairment. Topical, periocular, intraocular, and systemic corticosteroids are highly effective for treating appropriate forms of ocular inflammation. However, their use may be constrained by local and/or systemic side effects, especially if long-term therapy is required. As a result, immunosuppressive agents increasingly have been used to manage ocular inflammation alongside or in place of corticosteroids. The four categories of agents used today are antimetabolites [primarily methotrexate, mycophenolate mofetil (MMF), and azathioprine]; T-cell inhibitors (usually cyclosporine, less often tacrolimus or sirolimus); alkylating agents (cyclophosphamide and chlorambucil); and biologic agents [tumor necrosis factor (TNF) inhibitors, lymphocyte inhibitors, and interleukin inhibitors]. The primary goals of immunosuppressive therapy are (1) to control inflammation when corticosteroids fail to do so; (2) to prevent corticosteroid-induced toxicity when the necessary corticosteroid dosage exceeds the desired or safe level (corticosteroid sparing); and (3) to treat specific high-risk uveitis syndromes known to respond poorly to corticosteroids alone. Growing evidence shows the effectiveness of immunosuppressive drugs in achieving these goals, as well as improved visual function, prevention of ocular complications, and in some cases even disease remission. However, these agents also have side effects, which must be considered in each patient's management. In this report, we summarize the effectiveness and safety of immunosuppressive drug therapy utilized in the treatment of ocular inflammatory diseases.

1. Effectiveness of immunosuppressive agents

Ocular inflammation can produce considerable ocular morbidity and visual impairment. Although topical, periocular, intraocular, and systemic corticosteroids may be highly effective, their use may be limited in some patients due to ocular and/or systemic side effects. Thus, immunosuppressive agents are increasingly used to manage ocular inflammation alongside or in place of corticosteroids. The categories of immunosuppressive agents are antimetabolites (e.g., methotrexate, MMF, and azathioprine); T-cell inhibitors (e.g., cyclosporine and tacrolimus); alkylating agents (e.g., cyclophosphamide and chlorambucil); and biologic agents (e.g., TNF inhibitors, lymphocyte inhibitors, and interleukin inhibitors; Table 1).

Immunosuppressive therapy is primarily used in the following cases: (1) to control inflammation when corticosteroids fail to do so; (2) to prevent corticosteroid-induced toxicity (corticosteroid sparing); and (3) to treat high-risk uveitis syndromes unresponsive to corticosteroids alone. Growing evidence shows the effectiveness of immunosuppressive drugs in achieving these goals, as well as producing desirable clinical outcomes such as improved visual function, prevention of ocular complications, and in some cases even disease remission.

1.1. Effectiveness: Disease control, corticosteroid reduction, and treatment of specific diseases

Although the number of randomized clinical trials for uveitis treatments is increasing, the majority of data regarding the effectiveness of immunosuppressive drug therapy in treating ocular

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Table 1
Classes of immunosuppressive drugs used in ocular inflammation.

Class	Generic name	Trade name
Antimetabolites	Azathioprine	Imuran
	Methotrexate	Rheumatrex
	Mycophenolate mofetil	CellCept
T-cell/calcineurin inhibitors	Cyclosporine	Sandimmune
		Neoral
		Gengraf
	Tacrolimus	Prograf
	Voclosporin[a]	Luveniq[a]
Alkylating agents	Cyclophosphamide	Cytoxan
	Chlorambucil	Leukeran
Biologics		
TNF inhibitors	Etanercept	Enbrel
	Infliximab	REMICADE
	Adalimumab	Humira
Lymphocyte inhibitors	Rituximab	RITUXAN
	Abatacept	ORENCIA
Interferons	Interferon alpha-2a	Roferon-A
IL-1 antagonist	Anakinra	Kineret
IL-2 antagonist	Daclizumab [a]	Zenapax [a]

IL = interleukin; TNF = tumor necrosis factor.
[a] Not on the market.

inflammatory diseases are derived from retrospective studies. These include uncontrolled case series and cohort studies in which more robust statistical techniques such as longitudinal data analysis and time-to-event data (cumulative incidence data) may be used. For example, the Systemic Immunosuppressive Therapy for Eye Diseases Cohort Study (SITE) is a large retrospective cohort study of 7957 patients with noninfectious ocular inflammatory diseases treated at five tertiary-care centers from 1979 to 2005. This study provided data on the demographic characteristics, clinical course, treatment outcomes, side effects, discontinuation rates, and overall and cancer-associated mortality due to immunosuppressive therapy in these patients.[1]

Reported outcomes typically used for measuring treatment efficacy and effectiveness are disease control and reduction of corticosteroid dosage to desirable levels ("corticosteroid-sparing" effect).[2] Disease control in uveitis (inactive anterior uveitis) may be defined as rare cells or less in the anterior chamber; grade 0 vitreous cells (not including inactive cells seen in the formed vitreous) and grade 0 vitreous haze; and absence of active chorioretinal lesions, depending on the anatomic categorization of the uveitis.[2] Although there are some published studies describing specific parameters for disease control in other ocular inflammatory diseases,[3,4] many retrospective studies use the medical judgment of the physician to define disease control. Occasionally, reproducibility of disease control is required as part of the treatment-related outcome, as is the case in published SITE data in which disease control requires inactivity of inflammation spanning at least two visits spaced 28 days apart. The end point of corticosteroid-sparing success includes the control of the ocular inflammation disease coupled with the ability to taper the systemic corticosteroid to a level acceptable for long-term use. In the past, that level had been thought to be $\leq$ 10 mg of oral prednisone daily, although more recently a cutoff of $\leq$ 7.5 mg of prednisone daily is typically used in most cases. Table 2 summarizes the control of ocular inflammation and corticosteroid-sparing success for specific immunosuppressive drug therapies as reported by the SITE Cohort Study. These studies are summarized comparatively because the same end point was utilized in each report focusing on specific immunosuppressive drugs.

Regarding antimetabolites, azathioprine successfully controlled inflammatory disease in 62% of patients[5]; methotrexate in 66% of patients[6]; and MMF in 73% of patients.[7] The T-cell inhibitors cyclosporine and tacrolimus achieved disease control in 52% and 62% of patients, respectively[8]; and the alkylating agent cyclophosphamide controlled disease in 76% of patients.[9] Corticosteroid-sparing success was reported as 47%, 58%, and 55–82% for azathioprine, methotrexate, and MMF, respectively.[5–7,10] Corticosteroid-sparing success for mycophenolate was different in the Daniel et al[7] and Thorne et al[10] papers because in the case of the Thorne et al[10] article, success measured over two visits was not required. Although this article[10] and another from the Johns Hopkins cohort[11] suggest that corticosteroid-sparing success may occur more frequently[10] and more rapidly[11] with MMF than with the other antimetabolites, a multicenter, randomized, observer-masked clinical trial of 80 patients comparing methotrexate with mycophenolate therapy for uveitis failed to demonstrate a statistically significant difference between the two therapies.[12]

The corticosteroid-sparing success of cyclosporine was lower (36%) and that of cyclophosphamide was similar (61%) to the results observed with the antimetabolites in the SITE studies.[8,9] The biologics (specifically TNF inhibitors) achieved corticosteroid reduction in 75% of patients at 1 year, although this study only described treatment outcomes in children (Table 2).[13]

Immunosuppression also may be used in specific diseases in which high doses of corticosteroids are not adequate to control the disease (e.g., mucous membrane pemphigoid, Behçet retinal vasculitis) or in which clinical outcomes have been reported to improve with the use of these drugs (e.g., birdshot chorioretinopathy). For example, immunosuppression achieved disease control in 50–89% of patients with Behçet's disease,[5,14–16] and disease remission in 75% of patients with serpiginous choroidopathy.[17] For mucous membrane pemphigoid, immunosuppressive medications achieved disease control in 83% of patients by 6 months, and disease remission in 91% of patients by 2 years (Table 3).[3]

Table 2
Effectiveness: Percentage of patients achieving disease control, corticosteroid-sparing success, both, or remission.

Medication	% Disease control	% Corticosteroid sparing	% of both achieved at 1 y	Percentage or rate of remission
Methotrexate	66 [6]	58 [6]	58 [6]	8% at 1 y [6]
Azathioprine	62 [5]		47 [5]	0.09/PY [5]
Mycophenolate mofetil	73% by 1 y [7]	55–82 [7,10]	55 [7]	
Cyclosporine	50 [8]	36 [8]		
Tacrolimus	62 [8]			
Cyclophosphamide	76% by 1 y [9]	61% by 1 y [9]		0.32/PY [9]
				0.50/PY [24]
				63% by 2 y [9]
				75% by 3 y [9]
				91% by 2 y (MMP only) [9]
Chlorambucil				77% by 4 y [26]
TNF inhibitors			75 [13]	

MMP = mucous membrane pemphigoid; PY = person-year.

Table 3
Effectiveness: Outcomes of immunosuppressive therapy for specific diseases.

Disease	% of patients with disease control	% of patients in remission	% decrease in number of patients with vision loss to ≤20/200	% decrease in incidence of complications
Behçet's disease	50–89% [5,14–16]			
Serpiginous choroidopathy		75% [17]		
Birdshot chorioretinopathy				82% decrease in CME [18] 100% with reversal of VF loss [19]
MFCPU			90% [20]	83% decrease in overall complications [20] 100% decrease in new CNV or optic neuropathy [21]
Chronic VKH			92% [22]	
MMP	83% by 6 mo [3]	91% by 2 y [3]		

CME = cystoid macular edema; CNV = choroidal neovascularization; MFCPU = multifocal choroiditis and panuveitis; MMP = mucous membrane pemphigoid; VF = visual field; VKH = Vogt–Koyanagi–Harada syndrome.

1.2. Effectiveness: Improved clinical outcomes

In addition to disease control and corticosteroid-sparing effects, immunosuppressive medications may improve a variety of clinical outcomes. For example, immunosuppression significantly reduced new-onset cystoid macular edema [relative risk (RR) = 0.17; 95% confidence interval (CI) 0.05–0.64; $p = 0.009$],[18] and reversed visual field loss[19] in patients with Birdshot chorioretinitis. For patients with multifocal choroiditis and panuveitis (MFCPU), use of immunosuppressive agents reduced the risk of posterior segment complications by 83%, prevented risk of visual loss to the 20/200 or worse threshold by 90%; and prevented new cases of optic neuropathy and choroidal neovascularization (CNV) in contralateral eyes of patients with unilateral optic neuropathy or CNV due to MFCPU.[20,21] In the case of chronic Vogt–Koyanagi–Harada syndrome (VKH), use of immunosuppressive drug therapy was associated with a 67% reduction of vision loss to the 20/50 threshold or worse, and a 92% reduction of vision loss to the 20/200 threshold or worse.[22] For patients with acute VKH uveitis, addition of immunosuppressive medication (specifically MMF) to corticosteroids as first-line therapy led to a 15% reduction in disease recurrence, a 35% reduction in overall complications, a 36% increase in achievement of 20/20 visual acuity, and 100% prevention of late-stage retinal findings (sunset glow fundus).[23]

In comparison to corticosteroids, immunosuppressant agents are capable of inducing medication-free remission (as opposed to suppression). For the antimetabolites, remission rates typically were 0.09/person-year (PY; 95% CI 0.07–0.12/PY)[6] for methotrexate and 0.09/PY (95% CI 0.06–0.14/PY) for azathioprine.[5] For the alkylating agent cyclophosphamide, remission rates have been reported to be between 0.32/PY and 0.50/PY annually[9,24]; 63% of patients achieved remission within 2 years, and 75% of patients achieved remission within 3 years.[9] Similarly, chlorambucil has a reported remission rate of 43% in patients with Behçet's disease uveitis over 1.5 years,[25] and 77% in patients with all types of ocular inflammation within 4 years.[26] Among patients with mucous membrane pemphigoid, the rate of remission appeared even higher for cyclophosphamide with a cumulative incidence of remission of 91% at 2 years after initiation of therapy (Table 3).[3]

2. Short-term toxicities of immunosuppressive agents

Despite a growing literature supporting the effectiveness of immunosuppressive drug therapy in the treatment of ocular inflammatory disease, side effects of such therapy remain a concern. Fortunately, recent data from both prospective and retrospective studies of ocular inflammation patients support the relative safety of immunosuppressive medications, particularly in terms of short-term safety and tolerability. In the Multicenter Uveitis Steroid Treatment (MUST) trial, for example, systemic adverse events typically associated with immunosuppression were no more common in the group randomized to systemic therapy (in which 86% received immunosuppression) than in the group randomized to fluocinolone acetonide implant therapy, with the exception that an increased risk of infections required antibiotics; however, this risk was low in both groups.[27] The immunosuppressant-specific risks requiring surveillance are summarized in Table 4.

2.1. Short-term toxicities: Antimetabolites

The majority of data on the use of antimetabolites suggest a favorable safety profile, including decades of experience in non-ocular fields (such as for methotrexate and azathioprine). Most side effects are detectable by following established monitoring guidelines, are reversible with dose reduction or cessation, and only infrequently require discontinuation of drug (Table 4).[5] One significant irreversible effect of the antimetabolites is teratogenicity; therefore, withdrawal of therapy before planned pregnancy and use of contraception during therapy is mandatory.[7]

Adverse effects of methotrexate monotherapy include gastrointestinal intolerance, oral ulcers, hepatotoxicity, cytopenias, and interstitial pneumonia. The SITE study reported discontinuation due to these side effects at a rate of 0.13/PY (95% CI 0.10–0.17/PY).[6] For MMF monotherapy, the SITE study reported cessation due to side effects at a rate of 0.10/PY (95% CI 0.06–0.14/PY),[7] similar to two retrospective case series reporting discontinuation due to side effects at rates of 0.08/PY (95% CI 0.03–0.16/PY)[10] and 0.09/PY[28] over 6 years of follow-up, respectively. Enteric-coated mycophenolate sodium is available to help minimize gastrointestinal side effects (the most common treatment-limiting toxicity of antimetabolites[7]) while maintaining similar immunosuppressive benefits.[29]

For azathioprine monotherapy, gastrointestinal symptoms caused discontinuation at a rate of 0.06/PY (95% CI 0.03–0.10/PY) during 2 years of follow-up.[5] This was followed in frequency by bone marrow suppression (0.03/PY; 95% CI 0.01–0.07/PY), elevated liver enzymes (0.03/PY; 95% CI 0.01–0.06/PY), and allergic reaction (0.01/PY; 95% CI 0.001–0.03/PY), with an overall toxicity-related discontinuation rate of 0.16/PY (95% CI 0.11–0.22/PY).[5] Rarely, a homozygous deficiency of thiopurine methyltransferase (TPMT) can result in severe decreases in leukocytes, red blood cells, and platelets; thus, many clinicians recommend testing for TPMT activity prior to initiating azathioprine therapy, as dose-adjustment guidelines are available.[30]

2.2. Short-term toxicities: T-cell inhibitors

Of the T-cell inhibitors, cyclosporine has been the most widely used and studied for ocular inflammatory diseases, although tacrolimus and sirolimus also may be used. In the SITE study,

Table 4
Short-term side effects of immunosuppressive medications.

Medication	More common side effects	Rare side effects
Antimetabolites (methotrexate, mycophenolate mofetil, azathioprine)	Gastrointestinal upset Bone marrow suppression	Hepatotoxicity Malaise, myalgia, fatigue Headache Rash Alopecia Teratogenicity
T-cell inhibitors (cyclosporine, tacrolimus)	Renal toxicity Hypertension Neurologic symptoms Gastrointestinal symptoms (tacrolimus) Hyperglycemia (tacrolimus)	Hepatotoxicity Hirsutism Gingival hyperplasia Hypomagnesemia
Alkylating agents (cyclophosphamide, chlorambucil)	Bone marrow suppression Cystitis, hematuria (cyclophosphamide)	Ovarian suppression Testicular atrophy azoospermia, male sterility Alopecia Nausea, vomiting
TNF inhibitors (infliximab, adalimumab, etanercept)	Infusion/hypersensitivity reactions Autoantibody formation	
Interferons	Flu-like symptoms (almost universal) Mild leukopenia	Psychological disturbances Arthralgia, myalgia Thrombocytopenia Fever, nausea, headache Thyroiditis Alopecia Hepatotoxicity
Lymphocyte inhibitors (rituximab, abatacept)	Infusion/hypersensitivity reactions	Leukopenia Granulocytopenia Gamma-globulin decrease

TNF = tumor necrosis factor.

cyclosporine side effects resulted in a discontinuation rate of 0.07/PY (95% CI 0.05–0.09/PY).[8] Renal toxicity and hypertension were the most frequent side effects, occurring at rates of 0.02/PY (95% CI 0.01–0.04/PY) and 0.02/PY (95% CI 0.009–0.03/PY), respectively.[8] Discontinuation of cyclosporine was statistically significantly associated with increasing age; compared with patients aged 18–39 years, discontinuation for toxicity was 3.25 times more common in patients aged 55–64 years, and was 5.66 times more common in patients aged > 65 years (overall $p = 0.0005$).[8] Although no data on treatment with cyclosporine for ocular inflammatory diseases during pregnancy are available, in a transplant pregnancy cohort, no excess malformations were observed in women receiving cyclosporine during pregnancy.[31]

A previous retrospective case series evaluating tacrolimus for ocular inflammation also found a low discontinuation rate due to toxicity (0.13/PY), predominantly due to noncardiovascular and nonrenal effects such as neurologic symptoms (e.g., tremor, paresthesias), gastrointestinal symptoms, hyperglycemia, insomnia, and headache.[32] Rarely, tacrolimus causes irreversible toxicity to pancreatic beta cells leading to type 1 diabetes mellitus. Sirolimus has been associated with cytopenias, hypercholesterolemia, arthralgias, extremity edema, and impaired wound healing.[33]

2.3. Short-term toxicities: Alkylating agents

The alkylating agents cyclophosphamide and chlorambucil typically are used for very severe inflammatory disease due to the high-toxicity risk associated with these drugs. For example, the SITE study reported discontinuation of cyclophosphamide therapy at an overall rate of 0.39/PY (95% CI 0.31–0.49/PY),[9] substantially higher than rates of antimetabolites or T-cell inhibitors observed in the same cohort. The most commonly reported side effects were leukopenia (0.20/PY; 95% CI 0.14–0.27/PY), thrombocytopenia (0.016/PY; 95% CI 0.003–0.046/PY), anemia (0.04/PY; 95% CI 0.015–0.075/PY), and cystitis/blood in the urine (0.07/PY; 95% CI 0.04–0.12/PY).[9] Other studies have shown the bone marrow suppression of cyclophosphamide to be dose dependent and reversible, with older individuals being more susceptible.[34,40]

The adverse effects of chlorambucil therapy are similar to those of cyclophosphamide, with bone marrow suppression being the most common toxicity.[34] Both cyclophosphamide and chlorambucil can cause alopecia, sterility, and embryotoxicity.[26,33] Bladder toxicity is not associated with chlorambucil therapy.

2.4. Short-term toxicities: Biologics

Many of the side effects of TNF-alpha inhibitors are sufficiently mild to not require discontinuation. These include autoantibody formation[16,34]; limited treatment in volume-sensitive individuals (such as those with low cardiac output), due to intravenous administration of the medication; and infusion reactions such as local erythema at the injection site, atopic dermatitis, flushing, rash, hypertension, fever, and fatigue.[16] Subcutaneously delivered biologics may be associated with injection site pain as well. These effects generally do not lead to discontinuation of therapy. Some of these agents appear to be safe to use during pregnancy.[35]

Rituximab has side effects, which are usually mild, transient, and do not result in discontinuation of therapy. Hypersensitivity reactions including hypotension, local erythema, cough, laryngeal edema, and infusion-related rigors occur occasionally.[36] A meta-analysis of patients with lymphoma taking rituximab showed increased risk of severe leukopenia (RR = 1.24; 95% CI 1.12–1.37) and granulocytopenia (RR = 1.07; 95% CI 1.02–1.12), although this did not result in higher infection risk.[37]

Dose-dependent flu-like symptoms from interferon-alpha treatment are expected, but usually do not require discontinuation. In a retrospective study of interferon-alpha treatment in patients with severe uveitis due to Behçet's disease, discontinuation due to toxicity occurred in 9.4% of patients during nearly 5 years of follow-up.[14] In addition to flu-like symptoms, mild leukopenia (>

2000/μL) was seen in all patients, but caused discontinuation in none.[14] Uncommon findings during treatment included fibromyalgia, depression, hair loss, thrombocytopenia, headache, mild hepatotoxicity, thyroiditis, fever, and nausea.

The more concerning side effects reported with biologic therapy such as increased risk of infections (including tuberculosis) and the potential risk of cancer with use of these agents are discussed in the following sections.

3. Infection risk with immunosuppressive agents

Increased infection risk is a frequent concern when using immunosuppressive medications for ocular inflammation, and data regarding this risk are summarized in Table 5. In the MUST trial, a higher risk of infections requiring a drug prescription was observed in the systemic therapy group (systemic corticosteroids plus immunosuppression in 86% of patients) than in the implant group (0.60/PY vs. 0.36/PY, $p = 0.034$). However, these typically were mild infections and as such, it is unclear to what extent the difference reflected an increased likelihood of prescribing drugs for mild infections in patients known to be taking immunosuppressive drugs (as both participants and clinicians were unmasked) rather than a true difference in infection incidence.[27]

Existing data from the SITE Cohort Study reported no observed opportunistic infections in patients treated with MMF, methotrexate, or azathioprine monotherapy (with or without systemic corticosteroids).[5–7] This confirmed previous evidence showing no increase in infection risk associated with MMF monotherapy.[27] The SITE study also showed no increased infection risk associated with T-cell inhibitors,[38] consistent with previous studies reporting no association of cyclosporine or tacrolimus monotherapy with increased risk of serious infections.[34]

These results for monotherapy are reassuring, but patients sometimes require multiagent therapy. The combination of an antimetabolite with a T-cell inhibitor such as cyclosporine is a common approach, because the drugs have different toxicity profiles and have been used together for other conditions such as transplantation.[34] In some transplant cohorts, the combination of MMF with cyclosporine (with or without corticosteroids) has been associated with a nonsignificant increase in opportunistic infections compared with either agent alone (Table 5)[39]; however, infection risk was substantially lower in an ocular inflammation cohort in which only two patients developed major infections while taking MMF–cyclosporine combination therapy.

In contrast to antimetabolites and T-cell inhibitors, cyclophosphamide has been associated with opportunistic infections in ocular inflammation patients, leading to discontinuation in 3.0% (95% CI 1.2–7.1%) of patients in the 1st year, at a rate of 0.03/PY over 3 years of follow-up (95% CI 0.0084–0.061).[9] Infections included *Pneumocystis jirovecii* pneumonia leading to death in one (0.5%) patient, who had been managed according to standard guidelines but had not taken the recommended *Pneumocystis* prophylaxis with trimethoprim/sulfamethoxazole. These findings are consistent with (but less extreme than) results of a previous randomized controlled clinical trial of 50 patients with Wegener's granulomatosis, which reported infections in 70% of patients receiving cyclophosphamide, including 30% who developed *P. jirovecii* pneumonia.[40] Substantial granulocytopenia (absolute neutrophil count < 1000 cells/μL) associated with cyclophosphamide can increase the risk of bacterial infections, particularly sepsis. To decrease the risk of infections and sepsis, many clinicians temporarily discontinue cyclophosphamide for white blood counts below 2500 cells/μL, followed by downward dose adjustment.[34] This practice may explain the lower risk of infection observed in the ocular inflammation cohort.[9]

The most common infection sites in patients taking biologics are the respiratory tract, skin and soft tissues, and urinary tract.[41] Anti-TNF therapy is associated with increased risk of infection with intracellular pathogens, such as *Mycobacterium tuberculosis*, *Listeria monocytogenes,* and *Legionella pneumophila*.[42] A meta-analysis of TNF inhibitors in 369 patients with Behçet's disease reported tuberculosis reactivation in four patients, and opportunistic infections in 10 patients (including *P. jirovecii* pneumonia, *L. pneumophila* pneumonia, cryptococcal meningitis, varicella zoster infection, cytomegalovirus colitis, forearm cellulitis, and bacterial endocarditis).[16] A meta-analysis of adults with rheumatoid arthritis taking infliximab or adalimumab reported a statistically significant higher risk [odds ratio (OR) = 2.0; 95% CI 1.3–3.1) of serious infections during 22–54 weeks of follow-up, but the absolute risk was low (0.036% with anti-TNF therapy vs. 0.017% with placebo).[43] Such a low absolute risk probably does not represent a clinically important constraint on the use of these agents for ocular inflammation, but clinicians should bear in mind that significant infection does occur occasionally.

The risk of severe infection due to rituximab therapy also appears low.[36,37,44] Although a randomized, double-blind, placebo-controlled, dose-ranging trial of rituximab reported serious infection that was 0.015/PY higher than in the placebo group, the absolute rates for both groups were low (0.052/PY vs. 0.037/PY, respectively) and no tuberculosis or opportunistic infections occurred in either group.[36] Furthermore, two meta-analyses of patients with lymphoma treated with rituximab showed no statistically significant increases in the risk of severe infection (defined as life threatening, or requiring hospitalization or intravenous antibiotics).[37,44]

Infection risk with interferon treatment has also been reported to be low, with no increased risk of opportunistic infections for either interferon-alpha[29] or interferon-gamma.[45]

Table 5
Infection and malignancy risk of immunosuppressive medications for ocular inflammatory disease.

Medication	Increased infection risk with medication, with or without corticosteroids (evidence grade)	Increased cancer risk with medication (evidence grade)
Antimetabolites	None (2++)	None (2+ to 2++)
T-cell inhibitors	None (2++)	None [a] (2− to 2++)
Combined therapy (antimetabolite and T-cell inhibitor)	Mild increase (2+)	
Alkylating agents	Increase (2++)	Increase [a] (2++ to 3)
Biologics		
TNF inhibitors	Mild increase (1++)	None (2+)
Interferons	None (2++)	None (2−)
Rituximab	None (1++)	None (2−)

TNF = tumor necrosis factor.
[a] Medication may interact with other factors to increase cancer risk.

4. Cancer risk with immunosuppressive agents

Immunosuppression has been thought to increase the risk of skin, mucosal, and lymphoproliferative cancers. Proposed mechanisms include susceptibility to infection with oncogenic infectious agents, interrupted immune surveillance of malignant cells, and damage to DNA (alkylating agents) or to DNA metabolism (antimetabolites).[46] However, most of these observations are from transplant studies, and may not apply to ocular inflammation patients. Incidences of cancer associated with immunosuppressive drugs used in ocular inflammatory disease are summarized in Table 5.

Antimetabolites appear to have a relatively low risk of clinically important carcinogenicity. Azathioprine has been studied in patients with rheumatoid arthritis, inflammatory bowel disease, and multiple sclerosis, and consistently has shown no increased risk of malignancy except for sporadic reports of post-transplant lymphoproliferative disorder (PTLD)-like cases,[46] which do not occur more often in treated than in nontreated patients (RR = 1.27, 95% CI 0.03–8.20).[47] Methotrexate also has shown no increased cancer risk in several cohorts with a variety of diseases.[46] Although rare PTLD-like cases have been reported, a large observational study following 19,591 rheumatoid arthritis patients over 89,710 PY found no increased lymphoma risk with methotrexate therapy,[48] suggesting that PTLD-like cases are rare in nontransplant patients. Observational studies of MMF in the post-transplant setting have found a significantly reduced risk of PTLD, improved survival of patients with PTLD, and a lower cancer risk when MMF is compared with alternative regimens,[46] which has contributed to a preference for this drug over alternatives in transplant patients.

Studies of T-cell inhibitors, derived from transplant cohorts, show the increased malignancy risk typical of those cohorts. However, this risk is not necessarily applicable to nontransplant cohorts.[46,49] For example, a cohort of rheumatoid arthritis patients showed no increased malignancy risk due to cyclosporine treatment.[50] Thus, in the absence of these treatments or of an organ transplant, such as in uveitis patients, cyclosporine likely would not confer a higher cancer risk.[46]

By contrast, alkylating agents are associated with higher malignancy risk. Several studies have shown that cyclophosphamide increases incidence of leukemia, lymphoma, and skin malignancies, as well as bladder cancer due to the accumulation of acrolein (a carcinogenic metabolite) in urine.[46] Bladder cancer risk appears to be dose and/or duration dependent, is higher in smokers, and can be mitigated by intravenous or oral hydration to prevent acrolein buildup.[51] Chlorambucil has been linked to development of cutaneous malignancies, lymphoma, and leukemia, but not with bladder cancer.[46]

The majority of reports on cancer risk with TNF inhibitors are favorable. Seven large observational studies of TNF inhibitors for rheumatoid arthritis, with nearly 100,000 PY of follow-up, showed no increased malignancy risk,[48,52–58] except for nonmelanotic skin cancer in one analysis (OR = 1.5 vs. no anti-TNF therapy).[59] Results in a Crohn's disease cohort also found no increased cancer risk.[60] Regarding lymphoma specifically, a large observational database of 19,591 patients (approximately 89,710 PY of follow-up) with rheumatoid arthritis showed no increased lymphoma risk with anti-TNF therapy[61]; in addition, a meta-review of lymphoma risk in patients with rheumatoid arthritis found no clear association between lymphoma and anti-TNF therapy.[62] By contrast, a meta-analysis of TNF inhibitors in 5014 patients with rheumatoid arthritis in clinical trials showed a 3.3-fold higher cancer risk over 22–54 weeks of follow-up, but this was theorized to be the result of accelerated diagnosis of pre-existing cancers given the short period during which the difference appeared.[43]

Published results from clinical trials have shown no increased risk of malignancy due to rituximab therapy (RR = 1.05, 95% CI 0.76–1.42).[63] These findings were similar to an observational cohort study of 186 rheumatoid arthritis patients reporting no increased cancer risk due to rituximab treatment.[64] For this reason, rituximab is sometimes considered the first choice in patients with current or previous history of cancer in whom anti-TNF is contraindicated.

Regarding interferon-alpha therapy, a retrospective study of patients with Behçet-associated uveitis found no increase in malignancy with interferon-alpha over nearly 8 years of follow-up,[65] as did a systematic literature review of 338 patients with ocular and systemic manifestations of Behçet's disease.[66]

5. Mortality risk with immunosuppressive agents

Data on mortality risk of immunosuppressive drugs for patients with ocular inflammatory disease were evaluated in the SITE Cohort Study.

Antimetabolites as a class were not associated with increased overall mortality [adjusted hazard ratio (aHR) = 1.08, 95% CI 0.86–1.37) or cancer-related mortality (aHR = 0.89, 95% CI 0.54–1.48). Azathioprine, methotrexate, and MMF individually were not associated with increased overall or cancer-related mortality. Similarly, T-cell inhibitors as a class—or cyclosporine individually—did not increase overall mortality (aHR = 0.81, 95% CI 0.59–1.11) or cancer-related mortality (aHR = 0.78, 95% CI 0.38–1.59). The latter observation was consistent with a retrospective cohort study showing no increased mortality risk in patients with rheumatoid arthritis treated with cyclosporine.[50]

Alkylating agents as a class were not associated with significantly increased overall mortality (aHR = 1.17, 95% CI 0.85–1.61) or cancer-related mortality. However, statistical power for the latter outcome was limited and available data did show a trend toward increased risk (aHR = 1.74, 95% CI 0.91–3.32), which was similar to the increased cancer risk observed in other cohorts and also consistent with previous reports showing a dose-dependent increase in cancer-related mortality due to cyclophosphamide.[24,67] These risks generally restrict the use of these agents to the most serious cases of ocular inflammatory disease.

Several well-powered rheumatologic cohort studies of TNF inhibitors have found no increased mortality risk.[49,52–54,56] By contrast, the SITE Cohort Study showed significant increases in overall mortality (fully aHR = 1.99, 95% CI 1.00–3.98) and cancer mortality (HR = 3.83, 95% CI 1.13–13.01) in association with TNF inhibitors. Individual risk ratios for etanercept and infliximab were similar in magnitude, but nonsignificant due to sample size and follow-up time.

Long-term data are more limited on rituximab. A recent analysis of 500 patients with pemphigus vulgaris treated with rituximab therapy showed no increase in mortality risk.[68] However, because B-cell depletion can last for $\geq$ 18 months after rituximab therapy, there is reasonable concern that future data will show an increase in infection-related mortality.[69] Further research is needed to determine the risk of mortality with interferon therapy for eye disease.

6. Conclusion

In summary, increasing evidence supports the effectiveness and safety of using immunosuppressive drug therapy as treatment for ocular inflammatory diseases. The antimetabolites and the biologics, in particular, appear to offer the best balance between effectiveness and safety and pose excellent alternatives to long-term high-dose corticosteroid therapy. Immunosuppressive

drugs should be used to control inflammation when corticosteroids fail to do so, to prevent corticosteroid-induced toxicity, and to treat high-risk uveitis syndromes unresponsive to corticosteroids alone.

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