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Review article

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

Dana M. Hornbeak, Jennifer E. Thorne*

Division of Ocular Immunology, The Wilmer Eye Institute, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

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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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* Corresponding author. Division of Ocular Immunology, The Wilmer Eye Institute, Johns Hopkins School of Medicine, 600 North Wolfe Street, Woods Building, Room 476, Baltimore, MD 21287-9217, USA.
E-mail address: jthorne@jhmi.edu (J.E. Thorne).

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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.

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