Topics in OCULAR ANTIINFLAMMATORIES

A CONTINUING MEDICAL EDUCATION PUBLICATION

ISSUE 19

Steroid-sparing Therapies in the Management of Ocular Inflammation

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While very effective for managing ocular inflammation, corticosteroids are associated with undesirable side effects when used long-term. Many steroid-sparing therapies are a safe and effective alternative to corticosteroids for the treatment of chronic inflammatory ocular diseases.

Chronic ocular inflammation can affect any part of the eye, and in most cases, is noninfectious in origin. Noninfectious uveitis may take a host of different presentations and can arise from a wide variety of systemic diseases. On the ocular surface, long-term inflammation may be associated with conditions like dry eye disease, mucous membrane pemphigoid, or allergic keratoconjunctivitis.[1]

Corticosteroids have been a mainstay therapy for ocular inflammation since the 1950s. But particularly when administered over a long period of time, topical corticosteroids can have side effects such as elevated intraocular pressure and cataract formation; severe side effects of systemic corticosteroids can include hypertension, atherosclerosis, hyperglycemia, diabetes mellitus, osteoporosis, or aseptic necrosis of bone.[1] While useful to reduce acute inflammatory episodes, ideally, corticosteroids should be used for short periods and tapered.[1] Steroid-sparing therapies should be considered for patients with long-term or recurrent intraocular inflammation of any origin, particularly chronic conditions such as sympathetic ophthalmia, birdshot chorioretinitis, Vogt-Koyangi-Harada syndrome, or Behçet's disease.[1,3]

Ocular steroid-sparing treatments are frequently adapted from other specialties or clinical situations where immunosuppressants are indicated. Traditionally, such treatments have been used off label by ophthalmologists, but that is slowly changing, with recent FDA approvals for drugs such as adalimumab. The use of steroid-sparing therapy can improve patient lives significantly, offering the potential to consistently manage ocular inflammation while avoiding steroid-related side effects.

UVEITIS

Treatment options for uveitis can be categorized as corticosteroids, traditional (non-biologic) immunosuppressants, or biologics.[1] The three types of immunosuppressants typically used for uveitis are antimetabolites (such as azathioprine, methotrexate, and mycophenolate), T-cell inhibitors (which include cyclosporine), and alkylating agents (such as cyclophosphamide) (Table I).[1,2] While most of these drugs are not indicated by the FDA for the treatment of ocular inflammation, there is research to support them as effective treatments. For example, the rheumatoid arthritis therapy methotrexate has shown efficacy in managing chronic, noninfectious uveitis, both as primary therapy and as a steroid-sparing agent, due to its antiinflammatory properties.[4] Alkylating agents, while effective in controlling uveitis, are associated with myelosuppression and malignancies and are used sparingly.[1,2]

The biologics are the newest class of drugs to treat ocular inflammation in uveitis. The first agents in this class were the

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TARGET AUDIENCE This educational activity is intended for ophthalmologists and ophthalmologists in residency or fellowship training.

LEARNING OBJECTIVES Upon completion of this activity, participants will be able to:

1. Outline current and potential new steroid-sparing drugs for the treatment of ocular inflammation.
2. Apply knowledge of the different classifications and mechanisms of action of steroid-sparing therapies to treatment plans.
3. Identify the possible sources of ocular surface pain and inflammation, taking into account possible systemic or neuropathic origins.
4. Describe patient-tailored treatment options.

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tumor necrosis factor-α (TNF-α) antagonists, infliximab and adalimumab, which were used in rheumatology and shown to reduce T-cell mediated inflammation.[2] Infliximab has been used off label by ophthalmologists since 2006 after successful treatment of ocular inflammation in children with uveitis.[5] Adalimumab is now approved by the FDA for the treatment of uveitis.[6]

Tocilizumab and intravitreal sirolimus are two other potential nonsteroidal uveitis treatments that have been shown to decrease ocular inflammation in pilot studies and are now being investigated further in clinical trials. Tocilizumab, which is FDA approved for the treatment of rheumatoid arthritis, is an anti-interleukin-6 (IL-6) receptor monoclonal antibody that binds to soluble and membrane-bound IL-6 receptors and inhibits downstream inflammatory signaling.[7] The STOP-Uveitis study is a phase 2 clinical trial investigating the safety and efficacy of intravenous tocilizumab for the treatment of uveitis and has reported positive outcomes 6 months into the study.[8]

Sirolimus, which is FDA approved for the prevention of transplant rejection, can be administered by intravitreal injection, thus limiting its systemic side effects. It has been well tolerated and effective at reducing inflammation in uveitis pilot trials.[9] More recently, the phase 3 clinical trial SAKURA (Sirolimus study Assessing double-masKed Uveitis tReAtment) has reported improvements in ocular inflammation and preservation of visual acuity.[10]

Many other potential steroid-sparing treatments reduce ocular inflammation, but have not been investigated in large clinical trials. Intravenous immunoglobulins (IVIG), prepared from pooled healthy human plasma, are an emerging potential treatment for a number of autoimmune or inflammatory diseases with ophthalmic manifestations, as well as birdshot chorioretinopathy.[11] IVIG appears to be well tolerated, but its antiinflammatory efficacy is relatively transient.[11]

There are other monoclonal antibodies that act similarly to tocilizumab, by targeting specific parts of the in-

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STATEMENT OF NEED

The control of ocular inflammation is a critical aspect of medical and surgical ophthalmic practice. Despite their side effects, antiinflammatory drugs are used to treat a very wide range of conditions throughout the eye, from ocular surface disease and allergic conjunctivitis to posterior segment conditions. Use of antiinflammatory agents is also critical in ocular surgery, contributing greatly to patient comfort and positive outcomes.

The ocular antiinflammatory landscape is changing as research reveals more about the role of inflammation in a range of ocular conditions and as new antiinflammatory agents enter the market.[1,2] Twenty years ago, for example, the idea of using a topical corticosteroid to treat dry eye and/or allergic conjunctivitis was viewed with alarm; today, it is accepted practice.

Although corticosteroids and nonsteroidal antiinflammatory drugs (NSAIDs) have been the mainstays of the ocular anti-inflammatory armamentarium, a number of new agents with novel mechanisms of action (and new ocular drug delivery systems) have come to market or are being made ready for market.[3,4]

As indications expand and change, and as new drugs, formulations, and delivery systems become available, clinicians require up-to-date protocols for drug selection and use. Such protocols are also needed for routine (but nevertheless off-label) uses of corticosteroids and NSAIDs because important differences in efficacy, safety, and tolerability exist between these classes and among formulations within each of these classes.[5,6]

By putting the latest published evidence into the context of current clinical practice, *Topics in Ocular Antiinflammatories* equips ophthalmologists to maintain competencies and narrow gaps between their actual and optimal inflammation management practices, across the range of clinical situations in which current and novel ocular antiinflammatories may be used.

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flammation response (eg, rituximab and daclizamab), or by inhibiting other inflammatory interleukins (eg, anakinra).[11,12]

Adrenocorticotropic hormone (ACTH) therapy was approved by the FDA in 1950s for a range of inflammatory conditions, including uveitis, but has been rarely used due to a lack of strong supporting clinical data. However, in a recent case study, a patient with uveitis was successfully treated with twice-weekly subcutaneous injections of an ACTH gel. These results have motivated the researchers to pursue a phase 2 clinical trial of subcutaneous ACTH for uveitis.[13]

CORE CONCEPTS

- Corticosteroids should be avoided for long-term management of ocular inflammation.
- Immunosuppressant and biologic steroid-sparing therapies are suitable alternatives to corticosteroids for uveitis treatment.
- Alternative antiinflammatory / immunomodulatory drugs are available to treat ocular surface inflammation.
- Steroid-sparing therapies are safe and efficacious with FDA-indicated drugs available for uveitis and dry eye disease.

OCULAR SURFACE INFLAMMATION

Topical corticosteroids are among the first line of treatment for inflammatory ocular surface diseases, but for chronic conditions, steroid-sparing therapies may be required, much like uveitis and other intraocular inflammatory diseases. Local management of ocular surface inflammation is most often achievable with topical therapies, limiting systemic side effects.

Dry eye disease, now widely recognized as an inflammatory condition, is amenable to topical corticosteroid therapy in short bursts, but steroid-sparing agents are preferable for long-term use. Fortunately, many therapies with antiinflammatory mechanisms are available to treat dry eye.[11] Two such therapies FDA approved for this indication are cyclosporine

TABLE I Systemic corticosteroid-sparing agents

DRUG	MECHANISM	PRIMARY INDICATION(S)	SIDE EFFECTS
Methotrexate	Folic acid analog	Neoplastic disease, severe psoriasis, and adult rheumatoid arthritis	Stomatitis, bone marrow suppression, hepatotoxicity, nephrotoxicity
Azathioprine	Purine base analog	Prevention of renal transplant rejection, treatment of active rheumatoid arthritis	Bone marrow suppression, hepatotoxicity
Mycophenolate mofetil	Selective purine synthesis inhibitor	Prevention of renal, cardiac, and hepatic transplant rejection	Bone marrow suppression, hepatotoxicity
Cyclophosphamide	DNA alkylation	Neoplastic disease, typically in combination with other agents; pediatric minimal change nephrotic syndrome	Hemorrhagic cystitis, bone marrow suppression, gastrointestinal toxicity, bladder and hematologic malignancies
Chlorambucil	DNA alkylation	Neoplastic disease	Bone marrow suppression, gastrointestinal toxicity, hematologic malignancies
Cyclosporine	Calcineurin inhibitor	Prevention of renal, hepatic, and cardiac transplant rejection; treatment of rheumatoid arthritis and psoriasis	Hirsutism, gingival hyperplasia, nephrotoxicity, hypertension, hypercholesterolemia, convulsions
Tacrolimus	Calcineurin inhibitor	Prevention of renal, hepatic, and cardiac transplant rejection	ECG abnormalities, cardiomyopathy, chronic diarrhea, lymphoproliferative disease, infections
Infliximab	TNF-α antibody	Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis	Infusion reaction (fever, rash, dyspnea, hypotension), headaches, anaphylaxis, susceptibility to tuberculosis, demyelinating disease
Adalimumab	Fully humanized TNF-α antibody	Rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, plaque psoriasis, hidradenitis suppurtiva, uveitis	Headaches, rash, nausea, stomach upset, infections
Rituximab	Anti-CD20 antibody	Neoplastic disease, rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis	Infusion reaction, systemic infections
Interferon-α2a	Immunomodulatory cytokine	Neoplastic disease, hepatitis	Flu-like symptoms, leukopenia, central nervous system depression

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ophthalmic emulsion 0.05%, which improves tear production by reducing ocular surface inflammation[14] and, more recently, lifitegrast ophthalmic solution 5%, an integrin antagonist that inhibits T cells.[15]

Ophthalmic preparations of cyclosporine in higher concentrations (eg, 1%) have also been explored and demonstrated to decrease inflammation in chronic ocular surface conditions such as chronic follicular conjunctivitis and keratoconjunctivitis (including epidemic keratoconjunctivitis and vernal keratoconjunctivitis).[16,17]

CONSIDERATIONS FOR USING STEROID-SPARING THERAPY

In many cases, corticosteroid therapy has the apparent benefit of reduced cost compared to immunosuppressants and biologics. But at least one study has shown that corticosteroid therapy increases the comorbidity burden for patients with uveitis versus treatment with immunosuppressants and biologics.[18] Steroid-sparing therapies are not without risk, though the rates of complications are much lower than with long-term corticosteroids. Of course, a patient's overall health status should be assessed when steroid-sparing options are considered and, after a treatment regimen has been implemented, the patient should be monitored appropriately.

Some steroid-sparing therapies may be more effective for one condition over another, and there are issues to weigh with each. For a patient with birdshot chorioretinitis, for example, the chosen treatment may be cyclosporine and/or mycophenolate, whereas for a patient with scleritis, where the ocular inflammation is closely related to vasculitis and rheumatoid arthritis, one of the TNF-α antagonists, infliximab or adalimumab, may act more rapidly than other steroid sparing agents.[3,10]

On the other hand, TNF-α antagonists are not suitable for a patient with a history of tuberculosis or multiple sclerosis, and cyclosporine is potentially nephrotoxic. Methotrexate should be avoided in patients with liver conditions. Thus, in choosing an appropriate steroid-sparing therapy, ophthalmologists need to take into consideration not only the supporting evidence relating the drug's efficacy and safety, but also the patient's type of ocular inflammation and any comorbidities.

CONCLUSION

Steroid-sparing therapy offers an alternative to corticosteroids for the treatment of chronic inflammatory eye conditions. With many options currently available, and new therapies in development, there are many situations in which steroid-sparing therapy is worth considering in place of long-term corticosteroid therapy.

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