Steroid-sparing Therapies in the Management of Ocular Inflammation

DAVID S. CHU, MD  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. 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 opthalmologists, 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 antimitabolites (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
Improvements in ocular inflammation and Uveitis Treatment has reported im-
limus study Assessing double-masked phase 3 clinical trial SAKURA (Siro-
Adalimumab is now approved by the FDA for the treatment of uveitis.6

Tocilizumab and intravitreal sirolimus are two other potential non-
steroidal uveitis treatments that have been shown to decrease ocular inflam-
ination 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
involving safety and efficacy of intravenous tocilizumab for the treat-
ment of uveitis and has reported positive outcomes 6 months into the study.7

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.8 More recently, the phase 3 clinical trial SAKURA (Siro-
limus study Assessing double-masked Uveitis (Re)Atment) has reported im-
provements in ocular inflammation and preservation of visual acuity.9

Many other potential steroid-sparing treatments reduce ocular inflam-
ination, 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 dis-
eases with ophthalmic manifestations, as well as birdshot chorioretinopathy.10
IVIG appears to be well tolerated, but its antiinflammatory efficacy is relatively transient.10

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

TOPICS IN OCULAR ANTINFLAMMATORIES, ISSUE 19

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 poste-
rior segment conditions. Use of antiinflammatory agents is also common in cases of uveitis occurring 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.12 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 antiinflam-
matory drugs (NSAIDs) have been the mainstays of the
ocular antiinflammatory armamentarium, a number of new
agents with novel mechanisms of action (and new ocular
cure drug delivery systems) have come to market or are
being made ready for market.

As indications expand and change, and as new drugs,
formulations, and delivery systems become available, clinicians require up-to-date protocols for drug selec-
tion 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 these classes.

By putting the latest published evidence into the context of current clinical practice, Topics in Ocular Antiinflam-
matories equips ophthalmologists to maintain competen-
cies 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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management of dry eye disease: results of the OPUS-1
etabonate gel 0.5% for postoperative pain and inflam-
ation after cataract surgery: results of a multicenter
in clinical practice: our experience vs. a meta-analysis

OFF-LABEL USE STATEMENT
This work may discuss off-label uses of medications.

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flammation response (eg, rituximab and daclizumab), 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

**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.14 Two such therapies are safe and efficacious with FDA-indicated drugs available for uveitis and dry eye disease.

**TABLE I** Systemic corticosteroid-sparing agents

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

ophthalmic emulsion 0.05%, which improves tear production by reducing ocular surface inflammation and, more recently, lifitrgast 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 (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.

REFERENCES

Management of Ocular Surface Pain

ANAT GALOR, MD, MSPH  Ocular surface pain can have many possible causes, including systemic or neuropathic conditions. Treatment should be tailored to suit the needs of the patient, and topical, systemic, and non-medical treatments may all have a place in management.

The term “pain” encompasses a spectrum of sensations, defined by the International Association for the Study of Pain (IASP) as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage.” In the clinic, it is common to see patients complaining of dryness, irritation, itchiness, burning, or foreign body sensation—symptoms which may not always be considered explicitly painful, but often constitute an unpleasant sensory and emotional experience for the patient.

There is a close connection between inflammation and pain throughout the body. On the ocular surface, confocal microscopy reveals the density of neurons and immune cells in the cornea, and shows that both display specific abnormalities associated with disease. Nerve cells, like immune cells, express receptors for inflammatory mediators, enabling them to detect and respond to inflammatory signals. Neurogenic inflammation can occur when peripheral nerves respond to inflammatory signals by releasing additional mediators and furthering a cycle of inflammation. Inflammation can also contribute to chronic pain. Prolonged activation of nerves caused by inflammation associated with disease, surgery, environmental factors, or changes in nerve function and morphology, can all result in neuropathic pain.

DIAGNOSING OCULAR PAIN

When presented with a patient who is experiencing ocular pain, it is important to take a thorough history and conduct a systematic anatomical examination to locate the source of the pain. The eyelids are a good starting point. Pain and inflammation can be caused by many problems with the eyelids, including lagophthalmos, entropion or ektropion, or meibomian gland dysfunction. It is important to examine the bulbar conjunctiva for signs of inflammation, which could be due to allergies or infection. Vital dye staining of the cornea can reveal epithelial defects or infiltrates, and help assess tear film coverage. The source of apparent ocular surface pain may also be an internal inflammatory condition, such as iritis.

In some cases, the pain may be neuronal in origin. For example, pain in and around the eye could be due to a viral infection, like herpes zoster ophthalmicus, but the typical vesicular rash may be absent or have already resolved. Without a thorough patient history, this possibility could be missed.

CORE CONCEPTS

✦ A number of adverse sensations on the ocular surface may be considered under the umbrella of “pain.”
✦ Pain and inflammation are closely connected.
✦ A thorough and systematic exam is required to identify the source of ocular pain.
✦ Systemic conditions may manifest in the eye as pain and inflammation.
✦ Ocular pain may have a neuropathic component in some cases, and may be chronic.
✦ Treatment may include topical, systemic, and non-medical options.

SYSTEMIC CONDITIONS THAT CAN CAUSE OCULAR PAIN

When confronting ocular pain, it is important to investigate possible systemic causes. An example is Sjögren’s Syndrome, an autoimmune condition characterized by inflammation of the exocrine glands that results in dryness primarily of the mouth and eyes. Sjögren’s can be present as either a primary or secondary condition associated with another underlying autoimmune disease. Often associated with fatigue, depression, and anxiety, symptoms are variable and diagnosis can be difficult.

Hyperthyroidism is another systemic condition with the potential to cause ocular pain. Symptoms of thyroid eye disease (also called Graves’ ophthalmopathy) are also highly variable, and often encompass nonspecific dry eye complaints. Not uncommonly, it is a careful ophthalmologist who pieces together the diagnostic picture of autoimmune- or endocrine-mediated eye disease, and this is crucial for Sjögren’s Syndrome in particular, as time to diagnosis can be protracted.

NEUROPATHIC OCULAR PAIN

Conditions such as dry eye disease can be associated with both nociceptive and neuropathic pain (Table I). Whereas nociceptive pain usually results from tissue damage and inflammation and is often transient, neuropathic pain is more likely to be chronic. In addition to typical symptoms of dryness, irritation, and foreign body sensation, patients with dry eye may also report symptoms that are associated with neuropathy, including pain that is spontaneous, exaggerated (hyperlgesia), or occurs in response to normally non-painful stimuli (allodynia).

Though the diagnosis of dry eye disease can be complicated by a lack of concordance between patient-reported symptoms and clinical signs, in cases where this disconnect is particularly pronounced (eg, severe dry eye symptoms but an absence of signs and a poor response to initial therapy), a neuropathic component may be considered.
Neuropathic pain needs to be managed as a chronic condition with a multidisciplinary approach. Ophthalmologists often form good connections with rheumatologists and dermatologists because autoimmune and dermatological diseases have traditionally been managed in a multidisciplinary way. To manage neuropathic disorders, ophthalmologists will need to work with pain specialists and consider managing pain with local and systemic therapies. Chronic pain also has an emotional component, so cognitive behavioral therapy and the development of coping mechanisms can be an important part of managing the condition.

**TREATING PAIN AND INFLAMMATION**

In general, the recommended approach to ocular pain management is to find and address any underlying anatomical reason(s) for the pain, which often means local inflammation control. Topical corticosteroids are a mainstay of treatment for acute inflammation from a wide variety of causes, including postoperatively, or for dry eye disease flares. In addition, cyclosporine ophthalmic emulsion 0.05% and lifitragast ophthalmic suspension 5% each target different aspects of the inflammatory pathway in dry eye disease.\(^\text{16,17}\) For severe dry eye cases, autologous serum tears can be another helpful option, though more randomized, controlled trials are needed to assess their benefit in dry eye.\(^\text{18}\)

The use of corticosteroids in infection is controversial. For bacterial keratitis, topical corticosteroids are shown to be beneficial after initiating antibiotic treatment for at least 48 hours.\(^\text{19}\) One exception is *Nocardia* infection, for which steroids are associated with poorer outcomes.\(^\text{19,20}\) Corticosteroids can also promote proliferation of herpetic, fungal, or *Acanthamoeba* infections and are generally not recommended in these cases.\(^\text{21}\)

For neuropathic pain, topical therapies can have a role in improving the condition of the ocular surface and reducing the irritation that may have been the initial cause of the symptoms. One study showed that autologous serum tears improve nerve morphology and symptoms in patients with neuropathic photoallodynia.\(^\text{22}\) Amniotic membrane preparations are available for use on the ocular surface and can help speed healing of corneal infection or injury, or in cases of limbal stem cell deficiency, though more research is needed to determine their effects on corneal nerve regeneration.\(^\text{23}\)

Neuropathic pain can involve sensitization of somatosensory nerves of the peripheral or central nervous system (Figure 1).\(^\text{15}\) Treatments for neuropathic ocular pain must therefore be aimed at decreasing the excitability of peripheral and central nerves throughout the pathway. Anticonvulsant drugs such as the alpha-2 delta ligand antiepileptics gabapentin and pregabalin are well-tolerated for the treatment of neuropathic pain outside the eye and are good first-line medications for ocular neuropathy.\(^\text{5}\) Serotonin–norepinephrine reuptake inhibitor antidepressants such as duloxetine are also effective for patients with concomitant depression.\(^\text{5}\)

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**TABLE I Nociceptive versus neuropathic symptoms in dry eye disease.**

<table>
<thead>
<tr>
<th>NOCICEPTIVE SYMPTOMS</th>
<th>NEUROPATHIC SYMPTOMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiological responses to noxious stimuli</td>
<td>Represent nervous system dysfunction at some level</td>
</tr>
<tr>
<td>Associated with tissue damage</td>
<td>Not necessarily associated with tissue damage</td>
</tr>
<tr>
<td>Proportional to the stimulus</td>
<td>May involve peripheral or central sensitization</td>
</tr>
<tr>
<td>More likely to be associated with clinical signs and respond to standard treatments</td>
<td>Despite being described as “dry eye-related,” they may not involve tear dysfunction</td>
</tr>
</tbody>
</table>


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Many patients with chronic eye pain report other types of chronic pain, and this could be related to a central pain processing disorder.\(^24\) In these cases, an ophthalmologist can work with a pain specialist to titrate medications and address all aspects of the patient’s pain. Clinical experience has shown that cognitive behavioral therapy with a pain psychologist can be beneficial, as can adjunctive therapies, including acupuncture, massage, meditation, and transcutaneous electrical nerve stimulation.

**TAILORING TREATMENT TO THE PATIENT**

It is vital to get the best possible diagnosis of the underlying cause of pain and use a targeted therapy that suits the patient. Acute conditions such as iritis or corneal abrasion can generally be managed with short-term treatments. For patients with dry eye symptoms, an underlying cause such as conjunctivochalasis (excess conjunctiva that blocks tear flow) can be treated effectively and relatively quickly. If the cause is a chronic, systemic condition like Sjögren’s Syndrome, treatment options may be discussed with the patient and a rheumatologist or other care provider. Finally, it is important to bear in mind that there will be a subset of patients with chronic pain that is likely to be neuropathic.

Some patients are more comfortable with topical therapy than oral medication. Some are more comfortable with non-medical therapies than others. For some patients with photophobia, FL-41-tinted glasses, which have been shown to be beneficial for people with photophobia,\(^25\) might be sufficient to filter out the specific light frequencies that affect them without the need for additional medical treatment.

**THE FUTURE OF CHRONIC PAIN TREATMENT**

The current focus of chronic pain research is on diagnosis and treatment, but evidence for the effectiveness of interventions for neuropathic pain is frequently low-quality or lacking.\(^26\) In addition, research into strategies for prevention of chronic and neuropathic pain is an important direction. To this end, a small, randomized study is currently underway to test whether perioperative pregabalin will decrease chronic dry eye symptoms at six months after LASIK surgery. If this is shown to be beneficial, prevention of chronic pain following other eye surgeries could perhaps be approached in a similar manner.

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**REFERENCES**

1. Dry eye disease may result in:
   A. Solely neuropathic pain symptoms
   B. Solely nociceptive pain symptoms
   C. Symptoms of neuropathic and nociceptive pain
   D. Dry eye symptoms do not fall under the definition of pain

2. What immunosuppressant drugs are used to treat uveitis?
   A. Antimetabolites
   B. T-cell inhibitors
   C. TNF-α inhibitors
   D. All of the above

3. Infliximab and adalimumab are:
   A. Corticosteroids
   B. IL-6 inhibitors
   C. TNF-α antagonists
   D. Immunosuppressants

4. Which sensations could fall under the IASP definition of pain?
   A. Burning
   B. Irritation
   C. Foreign body sensation
   D. Any of the above, if an unpleasant sensory and emotional experience

5. Ocular surface inflammation in dry eye disease:
   A. Is not necessary to treat
   B. May be treated by the FDA approved drugs cyclosporine and liftegrast
   C. Is well managed by tocilizumab and sirolimus
   D. Can only be treated by prescribing infliximab and adalimumab

6. Which of these statements is correct?
   A. Immune cells are not present in the cornea
   B. Nerve cells and immune cells are present in the cornea and communicate with each other
   C. Nerve cells and immune cells in the cornea do not communicate with each other
   D. There are few nerve cells in the cornea

7. Appropriate steroid-sparing therapy for ocular inflammation depends on:
   A. Length of required treatment time to resolve the condition
   B. The overall health of the patient
   C. Evidence and efficacy of that treatment for the specific condition
   D. All of the above

8. Corticosteroids for the treatment of uveitis should be:
   A. Considered to reduce initial inflammation then tapered off and discontinued
   B. The only treatment choice for uveitis
   C. Administered long term
   D. Avoided altogether

9. Nerve-based pain could be associated with herpes zoster infection:
   A. Even if no rash is visible
   B. Only when there is a vesicular rash
   C. Only when a rash is present on and around the eye
   D. Ocular nerve pain is not associated with herpes zoster

10. Corticosteroids may be beneficial for treating associated inflammation in which of these cases?
    A. Acanthamoeba keratitis
    B. Nocardia keratitis
    C. Candida keratitis
    D. None of the above