Topics in OCULAR ANTIINFLAMMATORIES

A CONTINUING MEDICAL EDUCATION PUBLICATION

ISSUE 7

Are We Doing Enough? Comprehensive Management of Ocular Herpetic Disease Includes Preventing Recurrences

ELISABETH J. COHEN, MD **Managing the inflammatory consequences of ocular herpetic infection requires skillful and strategic use of corticosteroids. But maximizing patient outcomes requires taking steps to prevent inflammatory events in the first place.**

Ocular disease related to herpes simplex virus (HSV) or varicella zoster virus (VZV) can manifest as vision-threatening inflammation in the form of stromal keratitis and uveitis. Corneal stromal inflammation can produce edema, corneal opacity, and neovascularization; and recurrent bouts of stromal inflammation can lead to corneal scarring and blindness.[1] Uveal inflammation can elevate intraocular pressure (IOP) and damage the optic nerve, causing irreversible vision loss. It is therefore important to use every means available for preventing and treating these cyclically recurrent and potentially devastating infections.

EPIDEMIOLOGIC TRENDS

The data available indicate that the incidence of herpes simplex keratitis (HSK) is relatively stable at approximately 11.8 cases per 100,000 per year, which equates to approximately 35,000 new cases each year in the US.[1-3] Many patients with initial ocular disease experience recurrences over the ensuing months or years, and approximately one- third to one-half of recurrences involve the stroma.

By contrast, the incidence of herpes zoster (HZ)—and ocular complications related to VZV—appears to be increasing, as evidenced by multiple studies.[4,5] Recent estimates suggest that approximately 1 million new cases of shingles, or VZV infection, occur each year in the US, with between

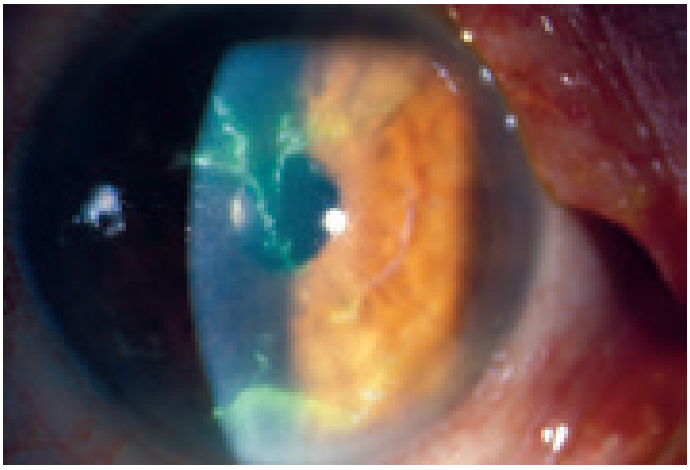

FIGURE 1 HZO dendriform epithelial keratitis. These delayed lesions are PCR positive for VZV and show that chronic active infection occurs in some HZO patients. *(Photo courtesy of the author.)*

See INSIDE for:
Strategies for Inflammation Control in Known Corticosteroid Responders *by Nick Mamalis, MD*

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. Integrate preventive tools into management of herpetic eye disease.
2. Employ strategies that reduce the risks associated with use of corticosteroids in known corticosteroid responders.

EDITORS

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10% and 20% of these cases involving the eye.[6] In a study of veterans, Rimland and Moanna found the annual incidence of herpes zoster in men and women over age 40 increased from 3.10 episodes per 1,000 in 2000 to 5.22 in 2007 ($P < .001$).[7] As is typical for HZ, nearly all cases involved immunocompetent individuals, even though risk and severity of HZ is much higher in immunosuppressed persons.[4]

Due to better management within the community, corneal specialists today see proportionally fewer cases of ocular HSV but increasing numbers of ocular HZ, or herpes zoster ophthalmicus (HZO). Increasing rates of zoster may be due at least in part to the natural waning of cell-mediated immunity that accompanies age coupled with the present shift toward an older population.[6] However, other epidemiologic trends related to HZ disease remain unexplained.

HZ CHANGING

In stark contrast to the perception that shingles is a disease of old age, younger people are increasingly affected by HZ and its sequelae. In Australia, a study of diagnosis and prescribing trends revealed an increase in HZV-related illness among patients over 60 years but also among patients aged 20 through 59—in fact, half the patients were under 60.[5] A review of all patients seen by the cornea service at Wills Eye Institute in 2008 found that first-time HZO was seen most often among patients in their 50s.[8] Disease manifestations were different in older vs younger patients, with problems related to neurotrophic keratitis, including corneal ulcers and perforations, significantly more common in older onset patients.

A broader look at HZ beyond the eye finds that shingles recurrences may also be increasing. Further analysis of the previously mentioned Olmsted County population data found that 6.2% of patients with shingles had a recurrence within 8 years of the initial episode.[9] This is a higher rate of recurrent shingles than has been noted in earlier studies, although the historic data on the subject is not extensive.

With respect to HZO specifically,

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STATEMENT OF NEED

The indications for topical ophthalmic antiinflammatory drugs (both steroidal and nonsteroidal) are evolving rapidly, as new agents and new applications emerge. Many of these are novel—eg, the perioperative use of nonsteroidal antiinflammatory drugs (NSAIDs) to prevent cystoid macular edema—and/or fly in the face of older thinking—eg, the use of steroids to calm inflammation and reduce the risk of melting or scarring from infection. Neither of these important applications is on-label.

In addition, new steroidal and nonsteroidal agents continue to come to market, expanding the utility of both classes. Antiinflammatory drugs are now used for: the treatment of ocular surface disease and allergic conjunctivitis; prevention of perioperative pain and inflammation in ocular surgery; infection management; cystoid macular edema prophylaxis following cataract surgery; haze prevention in PRK; and much more.

What has regrettably not followed this expansion of indications, formulations, and new molecular entities are protocols for drug selection and use.[1] These are vital because significant differences in safety, tolerability, and efficacy exist between and within both antiinflammatory drug classes. C-20 ester steroids, for example, have a demonstrated lower risk of intraocular pressure (IOP) elevation than ketone steroids.[2,3] Since a range of steroid formulations and concentrations is available, clinicians need up-to-date information about the indications and optimum uses for each.[3]

Although topical NSAID formulations have been associated with significant adverse events (keratopathy ranging from superficial punctate keratitis to corneal melt), recent work shows these to be uncommon and less severe with newer formulations.[4] Indeed, novel NSAIDs make use of lower concentrations and less frequent dosing, potentially impacting safety profiles and reducing risk from long-term use.[5]

Although both are "antiinflammatory," steroids and NSAIDs act at different points in the inflammatory cascade, and thus offer opportunities for physicians to fine-tune their drug selection. And although they are frequently used together, whether or not the two drug classes can act synergistically is controversial. In the context of recent clinical data, a clear mechanistic understanding of each drug class generally—and of newer formulations specifically—will equip clinicians to make effective, evidence-based prescribing decisions across the many situations that call for ocular inflammation control.

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among Olmsted County patients who experienced HZO between 1980 and 2007 recurrences of keratitis (6.9%) and iritis/uveitis (7.4%) were common.[10] Most patients with recurrent HZO recovered vision, however, six patients developed serious permanent vision loss (20/200 or worse), and two required corneal transplantation. One patient was reportedly suicidal from the severity of her pain.

CHRONIC HZO

Cases of chronic HZO may also be increasingly prevalent; and it may prove impossible to wean these individuals from low dose corticosteroids (Figure 1). In 2010 a survey of 100 eye care providers in community and academic practices (85 corneal specialists, 14 other ophthalmologists, and 1 optometrist) revealed that almost all (87%) had seen at least one case of recurrent or chronic HZO in the year prior. Many had seen six or more cases (41% of respondents); 19% of these doctors had seen between 11 and 19 cases; and 4% had seen more than 20 cases.[11] A study by David Sackel and coworkers presented at the Cornea Society Fall Educational Meeting (New Orleans, November 2013) found that 37 centers reported having treated more than 50 patients with HZO in 2012.

It is tempting to blame the uptick in VZV infections on the incorporation of the varicella vaccine into routine childhood immunization protocols, since, at least in theory, reducing wild-type varicella virus circulation in communities removes a potential "booster" effect against varicella virus reactivation in adults. But studies in various parts of the world that have attempted to correlate geographic coverage and vaccine timing with subsequent HZ development have not borne this out.[5,12-14] We still cannot be entirely sure why zoster appears to be starting younger and becoming more persistent.

PREVENTION

Since repeated bouts of infectious and inflammatory episodes can result in cumulative and permanent corneal damage, prevention of recurrences is arguably the most pressing need for physicians treating herpetic eye disease. There are currently two evidence-based tools for doing so and other tools that are potentially useful but unproven.

HSV AND ZOSTER PREVENTION

- For patients with recurrent ocular HSV: prescribe oral antiviral prophylaxis
- For healthy patients over 50 without impaired T cell-mediated immunity: recommend HZV vaccine
  - — Include patients who have already had an episode of HZV
  - — In all states, vaccine is available at pharmacies with a prescription; in many states, vaccine is available at pharmacies without prescription
  - — Patients between ages 50 and 59 may have to pay out of pocket
  - — Watch for changes in recommendations (eg, need for future booster, etc) as research and surveillance efforts continue

CORE CONCEPTS

- Risk for HZV starts around age 40 and increases over time; prevalence among individuals under 60 is increasing—half of affected individuals are under age 60.
- Complications of HZV are common at all ages
- Increasing rates of recurrent and chronic forms of HZO are being observed
- Oral antiviral prophylaxis is effective in suppressing ocular HSV recurrences; it remains underprescribed
  - — Atopy may increase patient risk for ocular HSV and HZO

One tool is prophylactic oral antiviral treatment for the prevention of HSV recurrences. In the landmark Herpetic Eye Disease Study (HEDS) prophylactic antiviral therapy reduced ocular HSV recurrences by nearly one half and was particularly effective among patients with a history of stromal involvement.[15,16] In addition, population studies have shown that prophylaxis markedly reduces recurrences of HSV-related blepharitis/conjunctivitis and epithelial and stromal keratitis and diminishes rates of poor outcomes of recurrences.[2]

So while there is clear evidence that patients who experience repeated episodes of ocular HSV benefit from oral antiviral prophylaxis, prophylaxis remains underutilized, even among corneal specialists.[2,17] In a survey of ocular HSV management practices, 38%, 40%, and 49% of eyecare providers (optometrists, ophthalmologists, and corneal specialists, respectively) reported practices inconsistent with HEDS findings, including that they would not prescribe prophylaxis for a patient experiencing repeated bouts of visually significant HSV stromal keratitis.[17] In HEDS, HSV was treated with oral acyclovir 400 mg five times a day; for prophylaxis the dose was 400 mg twice daily.

Per the package insert, valacyclovir is approved for treatment of initial episodes of genital HSV at a dose of 1 gram twice a day for 10 days; treatment of recurrent episodes of genital HSV: 500 mg twice a day for 3 days; and for suppressive therapy in immunocompetent people to prevent recurrent genital HSV: 1 gram a day (but 500mg a day for people for people with nine or few recurrences per year). Similar doses of 500 to 1000 mg daily are used for HSV ocular disease. Recommended treatment of herpes zoster includes valcyclovir1 gram three times a day for 7days, or famciclovir 500 mg three times a day, or acyclovir 800 mg five times a day. We have submitted grant to NEI to study suppressive treatment for zoster with valacyclovir 1000 mg daily for 1 year.

ZOSTER VACCINE

A second powerful preventive tool in our current arsenal is varicella zoster vaccine for the prevention of shingles and its complications, including HZO. In the Shingles Prevention

Study the vaccine reduced zoster incidence by 51% overall, burden of illness by 61%, and postherpetic neuralgia by 66.5%.[18] Furthermore, HZO incidence was reduced by 49% among vaccine recipients; and most who developed HZO despite vaccination had far milder courses.[19]

A separate trial in the over-60 age group was similarly impressive: among those vaccinated there was a 55% reduction in the incidence of shingles (HR, 0.45; 95% CI, 0.42-0.48), a 63% reduction in ophthalmic involvement (HR 0.37, 95% CI, 0.23-0.61), and a 65% reduction in hospitalization (HR, 0.35; 95% CI, 0.24-0.51) with vaccination.[19]

The VZV vaccine (Zostavax®, Merck and Co, Inc.) is FDA approved for immunocompetent persons age 50 and older, including those with prior HZV or chronic illness.[20] Vaccine efficacy is highest among younger patients. Clinical trials demonstrated 70% zoster reduction among vaccine recipients 50 to 59 years old; 64% reduction among those 60 to 69 years old; a 41% reduction among individuals in their 70s; and an 18% reduction for those in their 80s.[20] The CDC, however, currently recommends waiting until age 60 to be immunized against HZV.[21] This gap in coverage combined with low utilization rates among those over 60 means that a large segment of the middle-aged adult population—indeed millions of individuals who would benefit from vaccination—remains vulnerable to HZV.[22]

IMMUNE DYSFUNCTION AND HERPETIC DISEASE

Sixty-eight percent of people in the US are exposed to varicella virus and HSV type 1 in their youth and harbor latent forms in their sensory nervous system throughout life. One of the great unsolved mysteries in virology is why some otherwise healthy individuals manifest herpetic disease, including ocular disease, and others never do. Some form of defect in cell-mediated immune regulation seems like a plausible explanation and is supported by studies that show higher rates of herpetic disease among patients with atopic disorders.

Borkar and coworkers at Kaiser Permanente Hawaii reviewed their database of over 200,000 patients and compared rates of ocular herpetic disease (HSV or HZO) among atopic (asthma, allergic rhinitis, or atopic dermatitis) and non-atopic individuals.[23] They found that patients with atopy had a 2.6-fold increased risk for HSV ocular infection and a 1.8-fold increased risk for HZO. In addition, patients with more than one atopic condition—signaling even greater T-cell dysregulation—had an 8.9-fold increased risk for ocular HSV and 2.9-fold increased risk for HZO.

Immune dysregulation or fluctuation might contribute to HSK flare-ups as well, although contradictions in our current knowledge base abound. On one hand, stromal keratitis is considered an inflammatory condition without an active infectious component and for which antiviral agents are generally ineffective. On the other hand, antiviral agents suppress recurrences according to HEDS, suggesting some element of viral involvement in stromal HSK. Some suggest that T-cells reacting to corneal viral antigens may be the root source of inflammation in HSK.[1]

TIPS FOR MANAGING STROMAL INFLAMMATION IN OCULAR HERPETIC DISEASES

- Consider start corticosteroids four times per day (rather than regimen of 8 times per day in HEDS trial)
- Cover with topical or oral antiviral prophylaxis
- Avoid topical NSAIDS
- Taper corticosteroids slowly to prevent rebound
  - — Very gradual taper especially important with HZV
  - — Once down to prednisolone acetate 1% once per day, continue taper by changing to a lower concentration (eg, prednisolone 0.125%) or mild or ester-based corticosteroid (eg, loteprednol etabonate), or to once every other day dosing
  - — Use least amount required to keep eye quiet; weak topical steroids less often than once every other day may be sufficient to control inflammation
- Clear patient communication is critical
  - — Educate about their condition, as appropriate, say "herpes simplex," or "shingles virus"
  - — Emphasize importance of never self-treating with corticosteroids
- Follow patients closely to ensure improvement on therapy—consider alternative diagnosis (eg Acanthamoeba keratitis) if not responding
- Monitor IOP at least every 3 months in patients on long-term corticosteroids
- Oral antivirals indicated for patients with recurrent HSV keratitis; further study needed to determine their efficacy in chronic HZO
  - — For HSV—yes!
  - — For HZV—strongly consider.

The pathophysiologic mechanisms at play in recurrent HZ are even more poorly understood, and randomized trials comparable to HEDS are lacking. Absent that data, it remains conceivable that recurrent VZV stromal keratitis may also be suppressed by antiviral prophylaxis, and many doctors are applying that logic.[11] Our group at New York University School of Medicine, in collaboration with cornea leaders and community-based practices across the US, has submitted a grant request to the National Eye Institute for a multicenter, placebo-controlled, randomized trial of suppressive valacyclovir to reduce the complications of chronic HZO, including ocular disease and postherpetic neuralgia, which, if approved, will provide important evidence to guide the treatment of HZO.

MANAGING INFLAMMATION

Patients with stromal keratitis warrant a course of treatment with topical corticosteroids with or without adjunctive antivirals for coverage. My recommendation is to initiate corticosteroid therapy with four times daily dosing of an agent such as prednisolone acetate; in my view, the eight times daily protocol followed in HEDS is unnecessary for most patients. Also,

in contrast to the approach taken in HEDS, which used a slow taper to once-a-day dosing with low dose prednisolone and then stopping, I suggest that switching to a weaker steroid and dosing less than daily may allow for a longer period of tapering.

Stromal keratitis is not the result of inappropriate treatment of epithelial HSV with corticosteroids, although such treatment can make the epithelial keratitis worse. Patients with epithelial keratitis should be treated with topical and/or oral antivirals. Corticosteroid treatment for concomitant stromal keratitis should be withheld until the epithelial keratitis has healed, usually within 1 week; and the antiviral treatment should be continued when corticosteroids are added.

Corticosteroids should be tapered and discontinued in patients who develop HSV epithelial keratitis while on topical steroids.

When topical steroids are needed perioperatively for patients with a history of HSV keratitis, the recommend antiviral prophylaxis is valacyclovir 1000 mg daily, or acyclovir 400 mg twice a day, or famciclovir 250 mg twice a day (the dose approved to suppress genital HSV).

For the safety of the patient, I recommend avoiding NSAIDs whenever treating ocular herpetic disease as these drugs may contribute to neurotropic complications. Lastly, it is important to take the time to communicate with patients. Make sure they understand their condition, its name, and that it is serious. Patients who are stable should know how to recognize signs and symptoms of a recurrence and to call the clinic immediately. While it is generally acceptable for patients to self-medicate with an antiviral if they must, they should never self-medicate with a corticosteroid.

CONCLUSION

Management of herpetic ocular disease must include treating acute episodes as well as, to the extent possible, preventing recurrences. Risk of HZO begins around age 40 and increases with each decade, although better use of the zoster vaccine among eligible patients can reduce HZO incidence. Oral antiviral prophylaxis for patients with HSV keratitis reduces recurrences and is also underutilized. Better clinical data around management of chronic or recurrent HZO is needed.

Elisabeth J. Cohen, MD, is a professor of ophthalmology at New York University Langone Medical Center, New York, NY. Dr. Cohen reports that she has received research support from Merck. Medical writer Noelle Lake, MD, assisted in the preparation of this article.

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Strategies for Inflammation Control in Known Corticosteroid Responders

NICK MAMALIS, MD **Currently available corticosteroid options for the treatment of ocular inflammation offer excellent efficacy. While these agents do have dangerous side effects, a thoughtful approach to patient management can almost always enable clinicians to take advantage of corticosteroids' therapeutic effect, even in patients with a known tendency to corticosteroid-induced ocular hypertension.**

CORE CONCEPTS

- A topically applied potent corticosteroid can induce significant IOP increases (15 mm Hg or more) in about 4% to 6% of individuals.
- Patients previously identified as corticosteroid responders are likely to develop a hypertensive response when retreated with corticosteroid therapy.
- The likelihood and the magnitude of pressure elevation are related to the corticosteroid's dosage and potency and to the duration of the therapy.
- Topical ophthalmic corticosteroids differ in their propensity to induce IOP increases.
- Modification of the corticosteroid dose or change to a different corticosteroid can reduce the risk of IOP elevation.
- Patients on corticosteroid therapy should be frequently monitored to enable early intervention in the event of an IOP spike or other complication.

For decades topical corticosteroids have been an essential component of antiinflammatory treatment in ophthalmology. Affecting multiple signaling pathways, corticosteroids are the most effective of all available antiinflammatory agents, this therapeutic efficacy makes them a common first choice in treating acute and chronic ocular inflammation.

Corticosteroid therapy is, however, also associated with significant side effects, including elevated intraocular pressure (IOP), especially in long term use. In addition, some patients have a significantly higher risk of a hypertensive response to corticosteroids, putting them at increased risk of glaucomatous optic nerve damage and visual field loss. These patients are referred to as corticosteroid responders.

Historically, the fear of this complication has driven clinicians to limit corticosteroid use despite its efficacy. As our experience with topical corticosteroids has grown, we have learned better how to manage their side effects, and it is now standard practice to use in them in cases where we might previously have employed an alternative. In this paper, we will discuss strategies for reducing inflammation and the risk of IOP spikes in the corticosteroid treatment of known responders.

THE CORTICOSTEROID RESPONSE

Soon after corticosteroids were discovered to be potent antiinflammatory agents and were introduced to ophthalmology, it was found that corticosteroids, whether systemic or topical, could cause IOP elevation and development of glaucoma. The response to corticosteroids varies from individual to individual in the normal population, and that variability was characterized in the landmark clinical studies from 1960s.[1,2]

In these studies, the researchers examined the IOP response in clinically normal eyes treated with a potent topical corticosteroid. It was found that there are three distinct levels of corticosteroid responsiveness in the normal population. At 4 to 6 weeks, the IOP of a majority of subjects remained below 20 mm Hg, with an increase less than 6 mm Hg. Meanwhile, the IOP rose to between 20 and 31 mm Hg (an increase of 6 to 15 mm Hg above baseline) in about 30% of the normal eyes and to over 31 mm Hg (an increase greater than 15 mm Hg above baseline) in about 4% to 6%.

The latter 4% to 6% who have IOP increases of 15 mm Hg or more in response to corticosteroid therapy are what we commonly call corticosteroid responders. It is in these patients that ocular hypertension is of greatest concern with use of corticosteroids.

Ultrastructural changes in the trabecular meshwork of patients treated with corticosteroids show accumulation of abnormal extracellular material.[3] These changes may be related to the duration of corticosteroid therapy as these histologic changes have not been noted in patients treated for less than two months.

ACUTE VS CHRONIC TREATMENT

The degree of corticosteroid- induced hypertensive response is a function of, among other things, the duration of treatment. For this reason, the type of inflammation being treated and the length of required treatment matter in calculating the risk of corticosteroid-induced hypertension.[4]

For postoperative inflammation—eg, inflammation after routine cataract surgery—corticosteroids are typically used for a period of 2 to 4 weeks and then rapidly tapered. Pressure elevation is a much smaller concern in this relatively brief

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and limited exposure than in it is in the treatment of patients with chronic uveitis or corneal transplant, who require continuous, long-term antiinflammatory treatment. In this latter group the potential for corticosteroid induced IOP elevation is significantly higher.

It was long ago shown that the corticosteroid response is a fairly stable trait—that is, patients who have a history of corticosteroid response will likely develop ocular hypertension again with repeated corticosteroid exposure.[5] The quandary in treating these individuals is what to do when inflammation poses a serious threat to the patient's vision. Rather than avoid corticosteroid use entirely, the clinician can choose to use a corticosteroid and employ strategies to a) minimize the risk of pressure elevation and b) manage the increased pressure, if it should occur.

MINIMIZING RISK

Ophthalmic corticosteroids differ in their propensity to cause pressure elevation, and this difference is related to their potency.[4] One common approach to inflammation control to "hit hard and early" by using a potent corticosteroid with frequent dosing initially and then quickly tapering, hopefully after the inflammation has begun to subside and before significant IOP rise takes place. Once the inflammation has been reduced, the strong corticosteroid can be replaced by a safer corticosteroid, if maintenance therapy is necessary.

Two older corticosteroids, dexamethasone and prednisolone acetate, are potent agents whose propensity to elevate IOP is well known. Another newer and even stronger agent is difluprednate, which can induce IOP spikes in an unpredictable manner. These potent corticosteroids all contain a ketone moiety at the carbon-20 of their core structure and are sometimes classified as C20 ketone steroids.

Not all ketone corticosteroids have such prominent IOP-increasing effect; fluorometholone and rimexolone, two ketone corticosteroids with weaker ocular penetration, are associated with lower risk of elevated IOP. The downside is that lower penetration also leads to a reduction in their antiinflammatory strength.

Loteprednol etabonate, a relatively recent entrant among the topical ophthalmic corticosteroids, is a potent agent with efficacy similar to traditional ketone corticosteroids.[6] It is, however, associated with fewer adverse events than would be expected based on its potency, and it has been demonstrated to produce less IOP elevation than other topical corticosteroids, even in known corticosteroid responders.[7-10] This difference is attributable to the presence of an ester at C20, which causes the corticosteroid to be quickly converted into inactive metabolites by endogenous esterases. Like the weaker corticosteroids, loteprednol can a useful agent for antiinflammatory treatment in known corticosteroid responders.

Depot steroids such as sub-tenons injections or intravitreal injections/implants should be avoided or used with great caution in steroid responders.

NSAIDS: AN ALTERNATIVE

Nonsteroidal antiinflammatory drugs (NSAIDs) can reduce or prevent some antiinflammatory effects without causing elevated IOP. Corticosteroids, which act upstream in the arachidonic acid pathway and block both prostaglandin and leukotriene production, have multiple antiinflammatory effects. NSAIDs' antiinflammatory effect comes largely from their ability to block the cyclooxygenase pathway and inhibit prostaglandin formation, giving them a narrower spectrum of action than corticosteroids.

Although NSAIDs are not as potent or as broadly active as corticosteroids, they are efficacious against certain forms of ocular inflammation. Topical ophthalmic NSAIDs are now commonly used following cataract surgery to prevent and manage inflammation and cystoid macular edema (off-label), typically in combination with corticosteroids. The aggressive suppression of acute inflammation with a strong corticosteroid is beneficial in the early postoperative period, but then the corticosteroid can be removed from the regimen to prevent IOP spikes, as the NSAID therapy provides an effective, alternative for managing chronic inflammation without the risk of IOP elevation.

IOP MONITORING

Like all patients undergoing corticosteroid therapy, patients at known risk for pressure spikes must be monitored frequently to enable early intervention in the event of a pressure spike. Often, the IOP response can be mitigated by reducing the dose of the corticosteroid or switching the patient to a corticosteroid with a better safety profile such as loteprednol etabonate, rimexolone, or fluorometholone. But when the inflammation is severe and requires intensive corticosteroid therapy, a better strategy may be to stay on the strong steroid and add an antihypertensive glaucoma medication.

There are a number of ocular antihypertensive drug classes to choose from, including beta-blockers, alpha-2 agonists, carbonic anhydrase inhibitors, and various combination products. The only glaucoma medications that require special precautions in this situation are the prostaglandin analogs. While prostaglandin analogs are widely used as first-line therapy in glaucoma, natural prostaglandins play a pivotal role in promoting the inflammatory response. Because of this association between prostaglandin and inflammation, the prostaglandin analogs should be avoided in managing corticosteroid induced pressure elevation.

CONCLUSION

Known corticosteroid responders are at increased risk for significant pressure elevation when receiving corticosteroid therapy, particularly long-term therapy for chronic inflammatory control. It is often the case, however, that clinicians can continue use of their most powerful weapon against inflammation. Strategies for minimizing the side effect of corticosteroids include modifying the dosage or strength of

the medication, selecting a safer agent such as loteprednol or a weaker steroid such as fluorometholone, and, when necessary, adding a glaucoma medication reduce the pressure. Frequent IOP monitoring is required throughout the period of steroid treatment.

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Medical writer Ying Guo, MBBS, PhD, assisted in the preparation of this article.

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EXAMINATION QUESTIONS TOPICS IN OCULAR ANTIINFLAMMATORIES | ISSUE 7

This CME program is sponsored by the University of Florida College of Medicine and supported by an unrestricted educational grant from Bausch + Lomb, Inc. **Directions:** Select the one best answer to each question in the exam (Questions 1–10) and in the evaluation (Questions 11–16) below by circling one letter for each answer. Participants must score at least 80% on the questions and complete the entire Evaluation section on the form below. The University of Florida College of Medicine designates this enduring material for a maximum of 1.0 *AMA PRA Category 1 Credit*™. There is no fee to participate in this activity. You can take the test online at **http://cme.ufl.edu/toai**.

1. Which of the following does Dr. Cohen recommended for the treatment of ocular herpetic infection?
   A. Tapering corticosteroids very slowly to prevent rebound
   B. Adjunctive NSAID to lower exposure to corticosteroids
   C. Slowly increasing the corticosteroids dose
   D. Following the treatment protocol exactly as put forth in the HEDS trial

2. Which class of pressure-lowing medications should be avoided when managing corticosteroid-induced pressure elevations?
   A. Beta-blockers
   B. Alpha-2 agonists
   C. Prostaglandin analogs
   D. Carbonic anhydrase inhibitors

3. Which of the following was demonstrated in clinical studies of the HZV vaccine?
   A. It was 70% effective at preventing shingles among 50-59 year olds
   B. It was effective at preventing herpes zoster ophthalmicus (HZO)
   C. Efficacy was greater in older age groups
   D. Both A and B are true

4. Studies have shown that half of zoster cases occur in
   A. Occur in immunocompromised patients
   B. Patients under age 60
   C. Individuals who had did not have chickenpox as youngsters
   D. Patients 80 years of age and older

5. Which of the following statements is NOT true of corticosteroid responders?
   A. Exposure to a potent topical corticosteroid can cause IOP to increase
   B. They make up less than half of the general population
   C. Once identified, they will most likely remain a responder
   D. Any corticosteroid use is contradicted in known responders

6. Which if the following is not a potential consequence of inflammation associated with herpetic ocular disease?
   A. Corneal thinning
   B. Corneal scarring
   C. Atopic dermatitis
   D. Blindness

7. Which of the following is associated with the least tendency to cause increased IOP?
   A. Dexamethasone
   B. Fluorometholone
   C. Prednisolone acetate
   D. Difluprednate

8. In the Herpetic Eye Disease Study (HEDS) oral acyclovir reduced ocular herpetic recurrences by:
   A. 15%
   B. 30%
   C. 45%
   D. Recurrences were not reduced

9. Approximately what percentage of the general population is susceptible to corticosteroid-induced IOP elevation > 15 mm HG?
   A. About 0.5%
   B. About 5%
   C. About 50%
   D. More than 50%

10. The propensity of corticosteroids to cause increased IOP is determined by the:
   A. Dosing regimen
   B. Potency of the particular drug
   C. Ocular penetration and metabolism of the particular drug
   D. All of the above

EXAMINATION ANSWER SHEET TOPICS IN OCULAR ANTIINFLAMMATORIES | ISSUE 7

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ANSWERS:

1.	A	B	C	D	**6.**	A	B	C	D
2.	A	B	C	D	**7.**	A	B	C	D
3.	A	B	C	D	**8.**	A	B	C	D
4.	A	B	C	D	**9.**	A	B	C	D
5.	A	B	C	D	**10.**	A	B	C	D

EVALUATION:

1=Poor 2=Fair 3=Satisfactory 4=Good 5=Outstanding

11. Extent to which the activity met the identified
    Objective 1: 1 2 3 4 5
    Objective 2: 1 2 3 4 5
12. Rate the overall effectiveness of how the activity:
    Related to my practice: 1 2 3 4 5
    Will influence how I practice: 1 2 3 4 5
    Will help me improve patient care: 1 2 3 4 5
    Stimulated my intellectual curiosity: 1 2 3 4 5
    Overall quality of material: 1 2 3 4 5
    Overall met my expectations: 1 2 3 4 5
    Avoided commercial bias/influence: 1 2 3 4 5
13. Will the information presented cause you to make any changes in your practice? Yes No
14. If yes, please describe: _____
15. How committed are you to making these changes? 1 2 3 4 5
16. Are future activities on this topic important to you? Yes No

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