

Glaucoma Associated With Herpes Simplex Virus

Evidence-based treatment allows for the successful management of this condition.

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Two thousand five hundred years ago, Hippocrates used the word *herpes* (after the Greek verb *to creep* or *to crawl*) to describe spreading cutaneous lesions. Two strains, herpes simplex 1 (HSV-1) and varicella-zoster virus (VZV) have been associated with uveitis and glaucoma.

HSV and VZV are the most commonly associated infectious causes of anterior uveitis.¹ HSV-1 keratouveitis is typically unilateral, with granulomatous keratic precipitates found inferiorly or in Arlt's triangle. The uveitis tends to have an acute, recurrent course.² Small and medium-sized keratic precipitates have also been observed.³ Iris atrophy is sectoral and may be associated with pupillary dilation.^{4,5} HSV-1 typically presents with corneal disease, although laboratory analysis has confirmed the diagnosis of HSV-1 in eyes with no prior keratitis.

Patients are generally young, lack a dermatomal vesicular lesion at presentation, and have a decreased prevalence of vitritis compared with those suffering from VZV ocular disease. Patients with HSV tend to have a greater inflammatory response with posterior synechiae, a lower incidence of cataract at presentation, and a lack of chorioretinal scars compared with those who have rubella-associated uveitis.⁶

ASSOCIATION WITH GLAUCOMA

The IOP of patients with HSV-related keratouveitis is usually normal on initial presentation. Falcon and Williams conducted a retrospective study of 50 patients who had elevated IOP associated with HSV keratouveitis. All had recurrent HSV disease prior to presenting with elevated IOP, and none had increased pressure on initial presentation of ocular herpetic disease. Patients who presented with elevated IOP had either stromal keratitis disease (96%) or a metaherpetic ulcer (4%). None of them presented with a dendritic or amoeboid ulcer. The patients whose IOPs rose were more

likely to have concomitant uveitis than those who did not develop high IOP. In a study by Sungur et al of patients with HSV and VZV stromal keratitis, the total incidence of ocular hypertension was 47% during the period of active uveitis, and there was a 13% incidence of persistently elevated IOP during the remission period (secondary glaucoma).⁷

There are many possible etiologies for the development of glaucoma associated with HSV keratouveitis. Although secondary angle closure may occur due to pupillary block by posterior synechiae, one study found that all patients who developed glaucoma had open angles.⁸ IOP is thought to rise due to an increase in aqueous viscosity from elevated aqueous proteins, fibrin, and inflammatory cells.⁹⁻¹¹ Damage to the cells within the trabecular meshwork by HSV-1 infection has also been implicated as a possible cause of elevated IOP with HSV-associated uveitis.¹² Severe alterations in the anterior segment after HSV infection have been noted.¹¹ Clinical observations of elevated IOP during periods of increased uveitis have been confirmed in animal models of herpetic keratouveitis.¹³

TREATMENT

The management of HSV-associated glaucoma requires the treatment and prevention of HSV ocular disease and the control of elevated IOP as needed. Although the Herpetic Eye Disease Study (HEDS) did not directly examine the management of glaucoma, it did specify treatment protocols for the management of HSV-associated ocular disease.¹⁴ The findings of HEDS may be summarized as follows:

- Acyclovir had no significant beneficial effect for treating HSV stromal keratitis in patients taking topical trifluoridine and topical steroids.¹⁵
- Treatment with topical steroids was better than placebo at reducing the risk of persistent or progressive stromal keratouveitis.¹⁶

TABLE. CHARACTERISTICS OF ORAL ANTIVIRAL AGENTS FOR THE TREATMENT OF HERPES SIMPLEX VIRUS

Drug (Brand Name)	Dose	Doses/Day (Active/ Suppressive Therapy)	Estimated Cost Per Year ^a
Acyclovir—generic	400 mg	5/2	\$509.36
Acyclovir (Zovirax)	400 mg	5/2	\$4,886.33
Valacyclovir (Valtrex)	• 500 mg • 1,000 mg	2/1	• \$2,663.52 for 500 mg daily suppressive therapy • \$4,657.07 for 1 g daily suppressive therapy
Famciclovir (Famvir)	250 mg	2/2	\$6,173.64

^aCost is per year based on data from a single pharmacy (Walgreens) in Chicago. Data adapted from www.goodrx.com. Manufacturing information: Zovirax, Valeant Pharmaceuticals International, Inc.; Valtrex, GlaxoSmithKline; Famvir, Novartis Pharmaceuticals Corporation.

- The benefit of oral acyclovir for the treatment of HSV iridocyclitis was not statistically significant.¹⁷
- Oral acyclovir had no apparent benefit for the prevention of stromal keratitis and iritis in patients with HSV epithelial keratitis.¹⁸
- Long-term prophylaxis with acyclovir helped to reduce the recurrence of HSV ocular disease.¹⁹

Ganciclovir ophthalmic gel (Zirgan; Bausch + Lomb) has advantages over the use of topical trifluridine for the treatment of HSV dendritic keratitis, including less corneal toxicity and less frequent dosing.²⁰ Topical ganciclovir, however, has not demonstrated any benefit for the treatment of other HSV-associated ocular disease. Valacyclovir and famciclovir are relatively new oral antiviral agents used for the treatment of HSV infection. The former has been shown to be as effective as acyclovir at reducing the recurrence of HSV ocular disease.²¹ All three oral agents are associated with infrequent systemic side effects, the most common of which are nausea, headache, sore throat, flu-like symptoms, and diarrhea. The table presents estimates of the cost of yearly therapy with these drugs.

Together with antiviral treatment, topical steroids have a beneficial effect on the treatment of intraocular inflammation, which often initially reduces IOP.²² If the IOP remains high despite the control of intraocular inflammation, topical and oral IOP-lowering medications (including β -blockers, oral and topical carbonic anhydrase inhibitors, and topical α -agonists) can be considered. There has been some concern about the use of topical prostaglandin analogues in the treatment of glaucoma associated with uveitis, although a recent study demonstrated a benefit with minimal side effects.²³ In addition, there have been anecdotal reports of reactivation of HSV with the use of topical hypotensive medications such as β -blockers, prostaglandins, and prostamides.²⁴⁻²⁸ Whether or not this association differs from what is prevalent in the general population, however, is a subject of controversy.²⁹ Because IOP may rise prior to or after topical steroid therapy, physicians must exercise caution when

prescribing these agents. If a patient's IOP remains high on maximally tolerated medical therapy, surgical options may be considered. Filtration surgery is infrequently required to control IOP in patients with HSV-related glaucoma.⁸

For uveitic glaucoma in general, trabeculectomy tends to be more successful with the use of an antimetabolite Z (50%-67%) than without it (30%).³⁰⁻³² The use of mitomycin C shows no demonstrable benefit over the use of 5-fluorouracil.³²⁻³⁴ Glaucoma drainage device surgery is currently the procedure of choice in this population, given its higher postoperative success rate at controlling IOP (1- to 2-year success rate over 90%).^{35,36} We have found that postoperative hypotony is greatly reduced after a drainage device procedure using a valved rather than a nonvalved implant. Preoperative topical and systemic corticosteroid treatment may help to manage ocular inflammation and to minimize postoperative fibrosis. Cyclodestructive procedures such as diode laser therapy have proven effective but have a higher rate of hypotony than in eyes with nonuveitic glaucoma, possibly due to the chronic decrease in aqueous production associated with uveitis.³⁷

CONCLUSION

Ocular hypertension and glaucoma may be associated with HSV. These patients' IOPs are typically elevated during periods of increased uveitis and may be persistently high during remission. Topical IOP-lowering agents can successfully manage increased IOP, although surgical intervention may be necessary in recalcitrant cases. ■

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