

Herpes Simplex Virus Dendritic Epithelial Keratitis

AN EXECUTIVE SUMMARY AND TIPS FOR TREATING THIS COMMON FORM OF HSV

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Dendritic epithelial keratitis, the most common form of ocular infection caused by herpes simplex virus (HSV),¹ is characterized by branching lesions that can merge to form geographic ulcers.² Patients typically report eye tearing, redness, and foreign body sensation.² Diagnosis is made from a detailed medical history and the presence of hallmark findings on slit-lamp examination.³ Punctate or linear epithelial lesions may precede dendritic lesions.

While HSV dendritic keratitis usually resolves without treatment in 2 weeks, early diagnosis and prompt initiation of antiviral therapy can alleviate symptoms, reduce disease severity, hasten recovery, and reduce the risk of sight-threatening corneal complications.²⁻⁴ Recurrences are not uncommon, as HSV infection is a lifelong condition that can be reactivated by various triggers, such as fever, stress, ocular surgery/trauma, exposure to ultraviolet radiation, and hormonal changes.¹

The following are the authors' insights for treating HSV dendritic keratitis.

TREATMENT OPTIONS

All of the topical antiviral agents, often considered a first-line therapy for HSV dendritic keratitis, are efficacious, but differences in their antiviral activity and potential side effects, as well as in form, preservatives, dosing regimens, cost, and availability are noteworthy.

Trifluridine ophthalmic solution 1%, approved by the U.S. Food and Drug Administration (FDA) in 1980, is a nonselective agent that interferes with DNA synthesis in both the virus and mammalian cells.⁵ The dosing regimen is 1 drop every 2 hours while awake for a maximum of 9 drops per day until the ulcer has healed, and then 1 drop every 4 hours for a minimum of 5 drops per day for an additional 7 days.⁵ Trifluridine solution has a pH range from 5.5 to 6.0 and is preserved with thimerosal.⁵⁻⁷ The medication must be refrigerated.⁵

Ganciclovir ophthalmic gel 0.15% was approved by the FDA in 2009 to treat HSV dendritic keratitis. It is

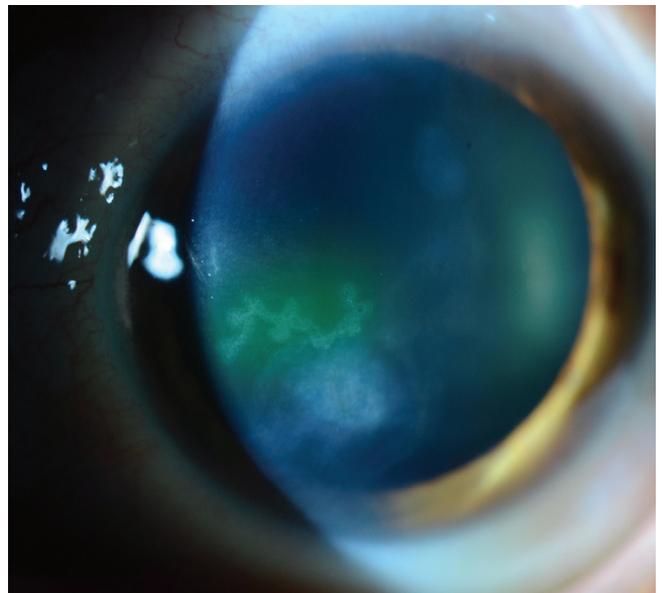


FIGURE 1A. Active HSV dendrite in central cornea. Note the branching pattern. There is moderate old inactive corneal stromal scarring inferiorly and mild stromal scarring centrally and superiorly from prior episodes of HSV keratitis.

indicated for topical ophthalmic use only. In contrast to trifluridine, the effects of ganciclovir are limited to HSV-infected cells, resulting in less potential host toxicity.^{8,9} Ganciclovir gel is applied every 3 hours while awake (about 5 times a day) until the ulcer is healed, and then 1 drop 3 times a day for 7 days. It has a pH range of 7.2 to 7.6 and contains a low concentration of benzalkonium chloride as a preservative. The most common side effect is blurred vision, with eye irritation (20%), punctate keratitis (5%), and conjunctival hyperemia (5%) also being reported. Ganciclovir can be stored at room temperature. Patients should not wear contact lenses if they have signs or symptoms of herpetic keratitis or during the course of therapy with this formulation.¹⁰

Acyclovir ophthalmic ointment 3% is the first-line topical treatment for HSV dendritic keratitis in Europe and other regions outside the United States.¹¹ Although it was approved by the U.S. FDA in 2019, it is not currently available here. The dosing regimen for acyclovir

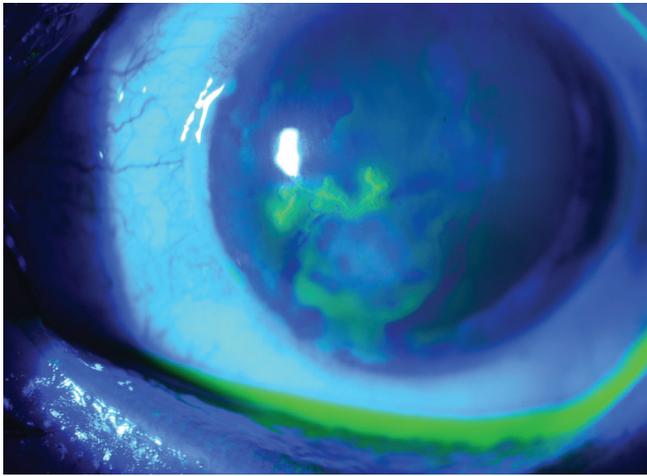


FIGURE 1B. Active HSV dendrite in central cornea with fluorescein dye staining in eye seen in Figure 1A. The edges of the dendrite are slightly elevated and stain poorly while the central core stains well with the fluorescein.

ointment is the same as for ganciclovir, and both agents selectively inhibit viral DNA synthesis in virus-infected cells. Acyclovir ointment is nonpreserved and can be stored at room temperature.¹² The ointment can cause some discomfort and blurred vision.¹¹

Owing to its safety, efficacy, and tolerability, ganciclovir gel is our preferred first-line topical medication for HSV dendritic keratitis in the United States.¹¹

TREATMENT INSIGHTS

For an initial episode of primary HSV dendritic keratitis without significant scarring or nodules, treatment is straightforward: topical monotherapy with ganciclovir ophthalmic gel 0.15% 5 times a day until the ulcer heals. If the ulcer is healed at the first follow-up visit, the dosing regimen can be decreased to 3 times a day for 1 week, and then treatment is stopped. In a clinical study of ganciclovir, up to 77% of dendritic ulcers resolved at Day 7, and by Day 14, 86% of ulcers had resolved. The results were non-inferior to acyclovir.^{10,13}

There are two important caveats to remember before initiating topical antiviral therapy for HSV dendritic keratitis:

- 1) Topical corticosteroids should be avoided while treating this infectious process. Advise patients who are already using steroids to quickly taper and stop them.¹⁰
- 2) Contact lens wear is contraindicated for patients who have signs or symptoms of herpetic keratitis or are being treated with ganciclovir.¹⁰

Colleagues often ask what should be done if the

disease does not resolve upon completion of the initial course of therapy. In the trifluridine days, toxicity was likely the reason an ulcer did not heal, and we would stop the medication. We know toxicity is not likely with ganciclovir and—assuming compliance is good—we have to think about a differential diagnosis and the possibility of a masquerader. For instance, a contact lens wearer who is newly diagnosed with HSV dendritic keratitis but not responding to seemingly appropriate therapy may actually have *Acanthamoeba* keratitis, a potentially devastating parasitic infection. (See also **“Differential Diagnosis of HSV Dendritic Keratitis”** for a list of other potential masqueraders.)

We may opt to obtain corneal culture if a patient's condition is worsening to confirm the original diagnosis and identify the possibility of another infection, such as with a bacterium or fungus.

Among the more challenging patients to manage—and who may warrant referral to a cornea specialist—are those who have dermal involvement or very large geographic ulcers, who are immunocompromised, or who have had multiple episodes of HSV dendritic keratitis. In these cases, some clinicians add an oral antiviral, such as acyclovir, famciclovir, or valacyclovir, to the patient's topical antiviral regimen. If recurrences continue, a low dose of an oral antiviral may be prescribed prophylactically over the long term—sometimes months to years at a time—to suppress

DIFFERENTIAL DIAGNOSES OF HSV DENDRITIC KERATITIS

Nonresponse to appropriate therapy for HSV dendritic keratitis could indicate a confounder or masquerader.

The more common differential diagnoses include:

- **Varicella-zoster virus**
- **Healing corneal abrasion, eg, after trauma or recurrent erosions**
- **Drug-related toxicity (topical aminoglycosides and other antibiotics; topical antivirals such as trifluridine; glaucoma medications, such as prostaglandin analogues, beta-blockers, etc)**
- **Neurotrophic epitheliopathy**

Less common differential diagnoses include *Acanthamoeba* keratitis (particularly in soft contact lens wearers) and Thygeson superficial punctate keratitis.

A thorough review of the patient's history and demographics, along with a careful slit-lamp examination of both eyes and comprehensive workup, will help identify masqueraders.

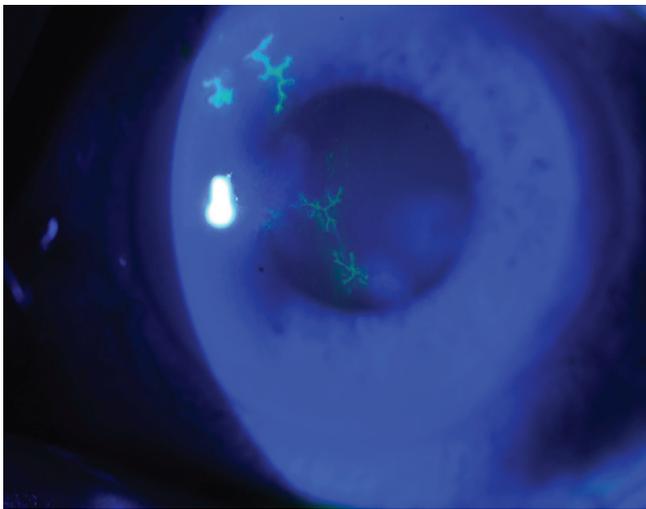


FIGURE 2. Multiple active HSV dendrites are present in this eye, highlighted by fluorescein dye. The central dendrites have smaller central staining cores, while the superior dendrites have larger staining cores and are beginning to become geographic dendrites.

those episodes and avoid permanent corneal scarring.

Compared to adults with HSV keratitis, children tend to have more severe disease, more recurrences, and more secondary corneal scarring and astigmatism, leading to greater reduction of vision.³ Children are also more likely than adults to have bilateral disease, particularly when associated with atopy. Oral antiviral agents are often recommended for the pediatric population, as children tend to tear or cry when eye drops are instilled, which can dilute the medication and possibly reduce its effectiveness.¹⁴ Also, some topical agents, such as ganciclovir ophthalmic gel 0.15%, are indicated for use in children ages 2 and older.¹⁰ Dosages must be adjusted for a child's weight and whether the medication is intended to treat active infection or to suppress recurrences.

CONCLUSION

HSV dendritic keratitis is a fairly common and potentially sight-threatening disease, requiring prompt, accurate diagnosis and treatment. With its proven efficacy, safety, and tolerability, ganciclovir gel is our topical antiviral therapy of choice. ■

Dr. Rapuano and Dr. Shovlin are paid consultants of Bausch + Lomb.

INDICATION AND IMPORTANT SAFETY INFORMATION FOR ZIRGAN®

INDICATION

ZIRGAN® (ganciclovir ophthalmic gel) 0.15% is a topical ophthalmic antiviral that is indicated for the treatment of acute herpetic keratitis (dendritic ulcers).

IMPORTANT SAFETY INFORMATION

- ZIRGAN® is indicated for topical ophthalmic use only.
- Patients should not wear contact lenses if they have signs or symptoms of herpetic keratitis or during the course of therapy with ZIRGAN®.
- Most common adverse reactions reported in patients were blurred vision (60%), eye irritation (20%), punctate keratitis (5%), and conjunctival hyperemia (5%).
- Safety and efficacy in pediatric patients below the age of 2 years have not been established.

[Click here](#) for full Prescribing Information for ZIRGAN®.

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