

HERPES SIMPLEX VIRUS DENDRITIC EPITHELIAL KERATITIS DIAGNOSIS AND MANAGEMENT

A WHITEPAPER DEVELOPED WITH **DR. MARGUERITE MCDONALD**

HERPES SIMPLEX VIRUS (HSV) is a common cause of ocular infections. Data published in 2010 estimated that HSV accounted for approximately 24,000 new cases of eye disease in the United States annually and 34,000 recurrent cases.¹ According to a more recent paper, the incidence of ocular HSV infection in developed countries may be increasing.²

HSV infection can occur throughout the eye and affect all layers of the cornea. HSV keratitis is the leading infectious cause of corneal blindness in the United States and globally is estimated to be the cause for approximately 40,000 new cases per year of severe visual impairment or blindness.² Dendritic epithelial keratitis (“dendritic keratitis”) is the most common form of HSV ocular infection.³

Infection with HSV can occur early in life, and other than in neonates, most ocular HSV disease is caused by HSV type 1. The virus is acquired through entry into epithelial cells following direct contact with infected body secretions or lesions. Primary ocular infection often causes no to minimal signs or symptoms and therefore goes unrecognized. However, HSV infection is a lifelong condition because the virus remains latent in sensory ganglia innervating the site of primary infection. Most cases of HSV dendritic keratitis represent reactivation of virus lying dormant in the trigeminal nerve ganglion.³

Various triggers, including fever, stress, surgery, exposure

to ultraviolet radiation, corticosteroid treatment, and hormonal changes, can reactivate the virus, causing it to replicate and travel back down the nerve to the cornea.⁴ The risk and frequency of recurrent ocular HSV episodes varies. Once an individual has an initial recurrence, the risk of further episodes is increased.¹ Repeated recurrences increases the risk of permanent corneal damage with loss of vision.¹

DIAGNOSIS

The diagnosis of HSV dendritic keratitis is primarily made clinically based on history and the presence of hallmark findings on slit-lamp examination without a need for laboratory tests. Patients with HSV dendritic keratitis present with redness, foreign body sensation, tearing, watery discharge, pain, blurred vision, and light sensitivity. Inflammation may also be present in the anterior chamber. The condition is usually unilateral; bilateral disease is more common in atopic and immunocompromised individuals.^{3,5}

Slit-lamp examination very early in the course of the disease may reveal pinpoint vesicles on the corneal surface caused by swelling of virus infected cells.³ Viral spread within the cornea occurs upon rupture of the swollen cells. This process leads to the development of a stellate erosion and then dendrite formation as viral spread follows the pattern of the subbasal plexus of corneal nerves.^{3,6} The dendritic lesions can

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coalesce, leading to the development of a geographic ulcer.

The pathognomonic lesion of HSV dendritic keratitis is characterized by linear branches with swollen epithelial borders and bulbs at the terminal ends along with central ulceration through the basement membrane.³ Staining with fluorescein dye will illuminate the damaged corneal epithelial cells at the ulcer base and edges (FIGURE 1).³

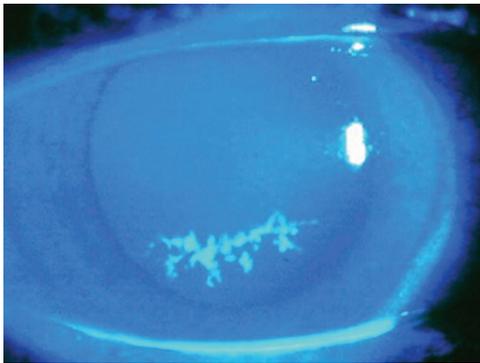


FIGURE 1. Staining with fluorescein shows an epithelial dendrite in an eye with HSV keratitis

Other conditions to consider in the differential diagnosis of HSV dendritic keratitis include abrasions, recurrent epithelial erosion, persistent epithelial defect, exposure keratopathy, and other infectious processes.⁵ Epidemic keratoconjunctivitis, is relatively common and shares some ocular signs and symptoms with HSV dendritic keratitis.⁷ Patients with an adenoviral infection, however, are more likely to present with bilateral ocular involvement and lymphadenopathy.⁷

MANAGEMENT

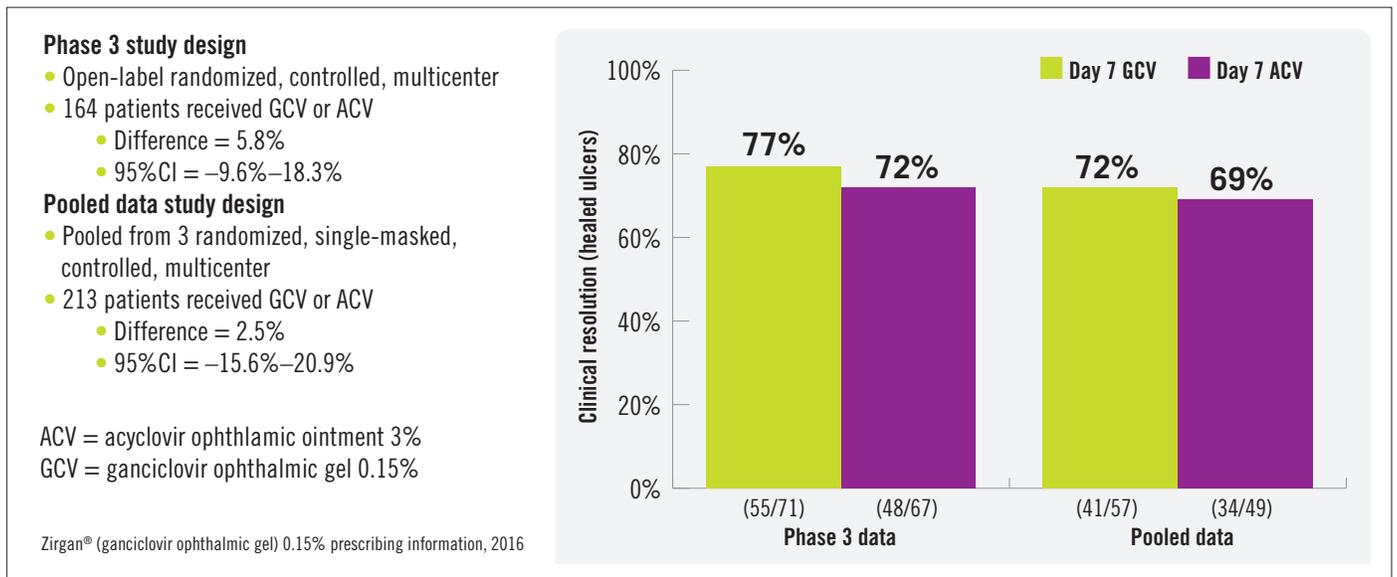
ANTIVIRAL TREATMENT

HSV dendritic keratitis may be self-limiting and resolve without causing permanent loss of vision. If treatment is delayed or withheld, however, the disease can progress, leading to the formation of larger and deeper lesions and the development of corneal scarring, thinning, neuropathy, and vascularization. Because the course of HSV dendritic keratitis in any individual is unpredictable, early diagnosis and treatment with an antiviral agent is recommended to reduce pain, discomfort, and the development of sight-threatening corneal complications.^{3,5}

Antiviral agents that have an FDA-approved indication for treatment of HSV dendritic keratitis include trifluridine ophthalmic solution 1%, ganciclovir ophthalmic gel 0.15%, and acyclovir ointment 3% ophthalmic ointment. Considering various features of the products as discussed below, ganciclovir gel is my drug of choice for treating HSV dendritic keratitis.

All of the topical antiviral agents are nucleoside analogs that act by inhibiting viral DNA synthesis, thereby terminating viral replication, and they are all prodrugs that must be converted to the active metabolite in a multi-step process by the action of thymidine kinases within infected cells. The conversion of ganciclovir and acyclovir requires action of an HSV-specific thymidine kinase and these two antiviral

FIGURE 2. In clinical trials, GCV was non-inferior to ACV in the primary endpoint analysis of % healed dendritic ulcers at day 7.



agents selectively inhibit viral DNA synthesis in viral infected cells. In contrast, trifluridine is a non-selective agent that interferes with DNA synthesis in both the virus and mammalian cells.⁸

Trifluridine solution must be stored under refrigeration, and its use involves a challenging administration regimen: trifluridine solution is recommended to be instilled every 2 hours while the patient is awake (up to 9 times a day) until the corneal ulcer is healed and then every 4 hours while the patient is awake for a minimum of 5 drops per day for an additional 7 days.

Ganciclovir gel and acyclovir ointment do not need to be refrigerated, and they are both recommended to be administered 5 times a day until the epithelial lesions heal and then continued 3 times a day for 7 days. Results from phase 2b and phase 3 clinical trials that directly compared ganciclovir gel and acyclovir ointment, however, showed that while the two medications were similarly effective as measured by rates of corneal ulcer healing (**FIGURE 2**), ganciclovir was better tolerated.⁹

The phase 3 study was an open-label trial that compared ganciclovir gel 0.15% with acyclovir ointment 3% in 164 patients.¹⁰ At day 7, clinical resolution, defined as healed ulcers, was achieved in 77% of 71 patients treated with ganciclovir (**FIGURE 3**) and 72% of 67 patients using acyclovir. Similar results were achieved pooling results from 3 randomized, single-masked multicenter trials that included 106 patients: clinical resolution was achieved by day 7 in 72% (41/57) patients using ganciclovir gel 0.15% and 69% (34/49) patients randomized to acyclovir ointment 3%.¹⁰

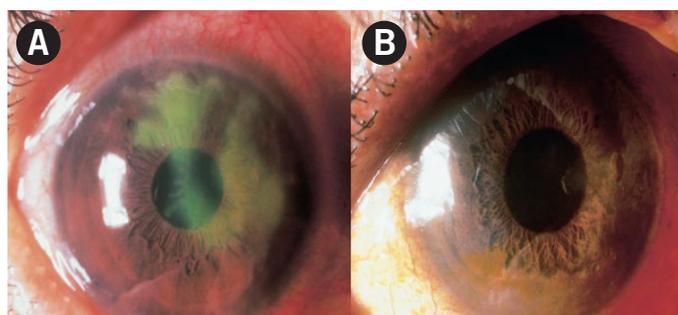


FIGURE 3. Dendritic ulceration from HSV keratitis (**A**) resolved after treatment with ganciclovir gel (**B**)

Analyses of safety data pooled from the comparative studies showed that compared with acyclovir ointment, ganciclovir gel was associated with lower rates of blurred vision (57.8% vs. 71.3%), eye irritation (25.6% vs. 46.2%), and punc-

tate keratitis (8.8% vs. 16%), and a nearly identical rate of conjunctival hyperemia (5.6% vs. 5%).¹¹ Consistent with the differences in adverse event rates, patient and investigator ratings of tolerability, which were collected in three studies, also favored ganciclovir gel over acyclovir ointment.⁹

Ganciclovir is formulated in an aqueous carbomer gel base that provides soothing comfort. The product has a non-irritating pH of 7.45 and contains a low concentration of benzalkonium chloride as a preservative (0.0075%). Although patients may notice slight blurring after instillation of the gel, the effect is very transient and disappears after just a few blinks. Patients should not wear contact lenses if they have signs or symptoms of herpetic keratitis or during the course of therapy with ganciclovir.

There is no definitive evidence that combining oral and topical antiviral therapy to treat HSV dendritic keratitis provides any benefit for accelerating healing or for preventing recurrence of dendritic keratitis or the development of the more sight-threatening stromal keratitis.^{5,12}

ADDITIONAL TREATMENT CONSIDERATIONS

I generally prescribe cycloplegic drops for patients with HSV dendritic keratitis only if they have associated anterior chamber inflammation. Despite its benefit for controlling inflammation, topical corticosteroid treatment is contraindicated in patients with HSV dendritic keratitis because it can worsen the infection if initiated in the setting of active viral replication.

FOLLOW-UP

HSV resistance to acyclovir has been reported and cross-resistance to ganciclovir is possible. The rate of HSV resistance to acyclovir appears to be low in immunocompetent individuals, but is higher in patients who have recurrent infections and immunocompromised patients.^{5,13} Once effective antiviral treatment is initiated, patients with HSV dendritic keratitis should expect to experience progressive improvement. A follow-up visit is scheduled after 5 to 7 days for immunocompetent patients and after 2 to 3 days for patients who are immunocompromised. All patients are instructed to call immediately for a return visit sooner if their condition fails to improve or seems to be worsening. The rate of HSV antiviral resistance has been reported to be higher in immunocompromised patients. Although culture is not necessary for initial diagnosis of suspected HSV dendritic keratitis, it may be performed in patients whose condition is worsening to confirm the original diagnosis and identify the possibility of a secondary infection.

PROPHYLAXIS

To reduce the risk of recurrent episodes, all patients are educated about warning signs and symptoms of HSV keratitis so that they will seek prompt attention from an eye care provider. In addition, they are counseled about preventive measures for mitigating potential triggers, such as protecting the eyes from sunlight when outdoors by wearing wraparound sunglasses and a hat with a wide brim.

CONCLUSION

HSV dendritic keratitis is a cause for significant morbidity. Early detection and appropriate treatment are important. Topical ganciclovir gel is my antiviral therapeutic agent of choice for the treatment of HSV dendritic keratitis because of its efficacy, safety, and tolerability.



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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.

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