Ganciclovir Gel—A New Topical Treatment for Herpetic Keratitis

a report by
C Stephen Foster, MD

Clinical Professor of Ophthalmology, Harvard Medical School *DOI: 10.17925/USOR.2007.03.00.52*

Herpes simplex virus (HSV) infection of the eye is a major cause of corneal opacity in the US[1] and other developed countries.[2] Infection with either HSV-1 or HSV-2 is common. Data from the US National Health and Nutrition Examination Survey (NHANES) suggest an overall 58% seroprevalence rate for HSV-1—the predominant cause of herpes simplex keratitis[2] (HSK)—with rates in individual ethnic groups as high as 89%.[3] A three-month prospective epidemiological study conducted in France put the incidence of HSK at 31.5 cases per 100,000 per person-year.[4] Of these, 13.2 cases represented primary infections and 18.3 were recurrences. HSV infection is lifelong and recurrent, with the virus becoming latent in sensory nerves after the original outbreak. Estimates in the US indicate approximately 20,000 new cases of HSK each year with another 28,000 cases of recurrent disease.[5] The only currently available topical treatment for HSK in the US is trifluridine (TFT), a drug whose toxic effects highlight the need for more effective and less harmful treatments. This article will summarize HSV ocular infection and review current treatments approved both in the US and worldwide. It will also focus on efficacy and safety findings for ganciclovir 0.15% gel, an antiviral ophthalmic preparation available outside the US to treat HSK that is a promising new drug for the US market.

Pathophysiology of Herpes Simplex Virus Keratitis

Ocular HSV infection comprises several potentially vision-impairing conditions. In approximately 72% of cases, infection involves the cornea; in 41% of cases, there is lid or conjunctival involvement.[6] Conjunctival infection with herpes is commonly not diagnosed because physicians are frequently unaware of this possible expression of herpes infection; this is also the case with herpes episcleritis and herpes scleritis.

At presentation, corneal herpes infection typically manifests as a cluster of small, clear vesicles in the corneal epithelium. The infected cells coalesce within 24 hours to form branching epithelial defects ('dendrites'), which stain with fluorescein. The resulting dendritic keratitis is associated with corneal scarring and decreased corneal sensation.[7] Each recurrence of HSK is associated with increased irregular scarring of the cornea and decreased corneal sensitivity. Dendritic ulcers occur in approximately 15% of initial episodes of ocular HSV, with disciform stromal keratitis in 2% of initial cases.[8] Dendrites can progress to geographic ulcers, a type of large (amoeboid) epithelial defect with fimbriated edges. Geographic ulcers may also arise in response to corticosteroid therapy, most likely as a consequence of the immunosuppressive effect of these agents.[1,9] The situation can worsen with stromal ulceration, and can progress to descemetocel or even frank perforation of the cornea, endophthalmitis, and loss of the eye. HSK is not a trivial matter, and early, effective therapy is the key to prevention of vision loss as a consequence of the infection. Additional strategies are appropriate for prevention of recurrences.

C Stephen Foster, MD, is a Clinical Professor of Ophthalmology at Harvard Medical School and a Fellow of both the American College of Rheumatology (ACR) and the American College of Surgery (ACS). He is Founder and President of the Massachusetts Eye Research and Surgery Institution (MERSI) and the Ocular Immunology and Uveitis Foundation, a research and education foundation devoted to the study of eye surgery, inflammation, and infections. Dr Foster created the ocular immunology service at the Massachusetts Eye and Ear Infirmary (MEEI) in 1980, and began the Uveitis and Ocular Immunology Fellowship in 1984.

E: fosters@uveitis.org

Current Treatments for Herpes Simplex Virus Keratitis

Trifluridine

Currently, TFT is the only drug marketed in the US for superficial herpetic keratitis. It is a thymidine analog activated by cell and viral thymidine kinase (TK) that is incorporated into both virus and host DNA. Although efficacious against superficial keratitis,[9] TFT affects healthy and infected cells alike. This lack of selectivity contributes to its epithelial toxicity, leading to superficial punctate keratitis (SPK) or filamentous keratitis, blepharitis, and cannicular punctal occlusion. In fact, prolonged TFT use (>21 days) is discouraged because it can lead to corneal epithelial dysplasia (considered a pre-cancerous condition),[10] conjunctival scarring,[11] and, potentially, anterior ocular ischemia.[12] Contact dermatitis has been reported in up to 10% of patients who use TFT.[13] Formulated as a 1% eye drop, TFT must be instilled nine times daily because of its short duration of action. Furthermore, penetration of the intact cornea is poor,[14] suggesting that treatment of deeper stromal herpetic disease may not be possible with TFT.

Acyclovir

Acyclovir, a purine nucleoside, acts specifically against HSV by integrating itself into viral DNA, forming an irreversible complex with DNA polymerase that terminates the DNA chain. As the topical formulation of the drug is activated only in infected cells, normal tissues are spared and toxicity is less of a problem compared with TFT.

Mutations in the viral TK enzyme may cause resistance to acyclovir. With resistance reported in 10% of HSV strains,[15] cross-resistance with other agents activated by viral TK is a concern. While acyclovir resistance is rare, it is particularly problematic in immunocompromised patients undergoing

long-term therapy.[16] Topical acyclovir 3% ointment is more effective and better tolerated than idoxuridine, vidarabine, and trifluridine;[17–19] it is commonly used in Europe for the treatment of HSK. Although acyclovir can be prescribed in the US for oral and dermatological administration, no ophthalmic preparation is available. Oral acyclovir, taken daily as prophylaxis, has revolutionized the care of patients with life-altering recurrent herpes outbreaks.

Ganciclovir

Ganciclovir is a nucleoside analog of guanosine that, similar to acyclovir, is a broad-spectrum virustatic agent (see *Figure 1*). It is active against several herpesviruses, including HSV-1, HSV-2, human herpesvirus 6, cytomegalovirus (CMV), Epstein–Barr virus (EBV), and varicella zoster virus (VZV), as well as hepatitis B virus[20] and some strains of adenovirus.[21] Ganciclovir is activated only in infected cells, where it is phosphorylated first to a monophosphate by viral TK, and then, via cellular enzymes, to ganciclovir triphosphate. This inhibits viral DNA synthesis by slowing the viral DNA chain.[22] The affinity of ganciclovir for viral TK renders it more specific in its action than TFT and, consequently, less toxic to normal cells and more tolerable to patients.

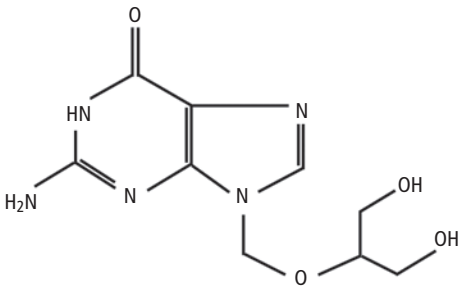
Although ganciclovir and acyclovir bear some similarities in their mechanisms of action, intracellular concentrations of ganciclovir triphosphate exceed those of acyclovir triphosphate 10-fold and also decline more slowly, with about 40% of the drug still detectable after 24 hours.[23] As its high potency permits an extremely low drug concentration, ganciclovir can be solubilized in an aqueous vehicle, such as a gel, which is appealing for patients, unlike oil-based, vision-blurring ointments.[24] Furthermore, viral resistance to ganciclovir is low—comparable to that of acyclovir, to which it is closely related.

The efficacy of topical ganciclovir in herpetic keratitis was first demonstrated in experimental studies comparing various concentrations (0.03–0.1%; 1%) with acyclovir 3% and idoxiuridine 0.5% in live rabbits.[25–27] In these studies, ganciclovir was at least as effective as acyclovir and more effective than idoxiuridine in resolving the signs and symptoms of herpetic keratitis. Importantly, ganciclovir neither altered the rate of corneal re-epithelialization nor produced irritation or local anesthetic effects.[27] Following four international multicenter clinical trials against acyclovir 3%, ganciclovir 0.15% aqueous gel was approved for use in most European countries, Argentina, and some Asian and African nations. The gel formulation distributes the active drug more evenly, prolongs contact with the cornea better than an ointment, and provides more efficacy at a concentration of only 0.15%. Pharmacokinetic studies indicate that corneal penetration occurs whether or not the epithelium is intact, while systemic absorption is low (see *Table 1*). The pH (7.45) and osmolarity (300 osmoles) of ganciclovir gel 0.15% are close to normal physiological values, which promotes good tolerability.

Clinical Trial Data

As mentioned above, four international trials have compared the safety and efficacy of ganciclovir 0.15% gel with acyclovir 3% in patients with HSK: three phase IIb trials conducted in Africa (study 1),[28,29] Europe (study 2), and Pakistan (study 3); and a phase III trial that stratified patients by dendritic or geographic ulcers (study 4) carried out in four European and African centers. The trials employed similar multicenter randomized designs, inclusion and exclusion criteria, dosing regimens, and end-points (study 3 was conducted at different sites within a single center). Enrollment was contingent on a clinical diagnosis of dendritic or geographic ulcer, without virological confirmation. Exclusion

Figure 1: Structure of Ganciclovir



The ganciclovir molecule is a 9-(1,3-dihydroxy-2-propoxymethyl) guanine with a weight of 255.23u.

Table 1: Intraocular Penetration of Ganciclovir 0.15% in Rabbits

ED50 *In Vitro* Against Herpes Simplex Virus-1 <0.5µg/ml

	Normal Eyes			De-epithelialized Cornea Eyes		
	C_{max} µgEq/g	T_{max} (h)	AUC (0–24h) (h-µgEq/g)	C_{max} µgEq/g	T_{max} (h)	AUC (0–24h) (h-µgEq/g)
Tears	143.4	0.5	153.3	346.6	1	425.4
Conjunctiva	160	0.5	128.9	44	0.5	33.5
Cornea	17.3	0.5	43.4	190.1	0.5	185.1
Aqueous humor	0.9	1	5.6	32.1	0.5	52.8
Iris–ciliary body	3.9	0.5	6.9	29.4	0.5	49.4
Lens	0.2	0.5	0.4	0.4	0.5	2.6
Vitreous humor	0.2	0.5	0.15	0.2	0.5	0.4
Retina	1.1	0.5	1.3	1.8	0.5	1.9
Choroid	6.3	0.5	8.5	6.1	0.5	9.1
Plasma	0.005	1	0.065	0.02	0.5	0.2
Total blood	0.004	1	0.057	0.02	0.5	0.1

ED50 = effective dose in 50% of patients; C_{max} = rate of absorption; T_{max} = time of rate of absorption; AUC = area under the curve; h = hours.

criteria included antiviral treatment in the previous 14 days, severe stromal disease, keratouveitis, previous keratoplasties (in the affected eye), a secondary bacterial infection of the cornea or conjunctiva, recent ocular trauma, visual acuity <2/10 in the unaffected eye, or known sensitivity to treatment. Although age criteria varied by study (≥18 years in studies 2 and 4, <12 years in study 1, <5 years in study 3), all groups within a study exhibited comparable demographic and ophthalmological characteristics at inclusion.[24]

Each of the four studies used the same dosing regimen, with patients randomized to five daily drops of ganciclovir gel or five applications of acyclovir 3% ointment until the ulcers were completely healed. Post-healing, the protocol required three daily doses of the specified treatment for one week in studies 1, 3, and 4 and five daily doses for 10 days in study 2. Maximum duration of treatment was set at 21 days for dendritic ulcers and 35 days for geographic ulcers. In studies 1 and 3, patients were randomized to one of two ganciclovir strengths: 0.15 or 0.05%. However, double-masking was impossible because ganciclovir is an aqueous gel and acyclovir is an ointment.

All four studies had the same primary objective: time to recovery, as ascertained by fluorescein staining. Secondary objectives included recovery rate, relapse rate, and local tolerability. Of the 376 patients included in the data analysis, 162 received ganciclovir 0.15% gel, the licensed strength in countries outside the US and the focus of this article.

Table 2: Results of Four Trials Comparing Ganciclovir and Acyclovir Topical Formulations in Patients with Herpetic Keratitis[a]

	Phase IIb Studies								Phase III Study			
									Study 4 (Europe and Africa)			
	Study 1 (Africa)			Study 2 (Europe)		Study 3 (Pakistan)			Dendritic Ulcer		Geographic Ulcer	
	GCV 0.15%	ACV 3%	GCV 0.05%	GCV 0.15%	ACV 3%	GCV 0.15%	ACV 3%	GCV 0.05%	GCV 0.15%	ACV 3%	GCV 0.15%	ACV 3%
Number of Patients	(n=23)	(n=22)	(n=22)	(n=19[b]	(n=18)[b]	(n=36)	(n=38)	(n=35)	(n=71)	(n=67)	(n=13)	(n=13)
Dosing and applications	5 times/day till healing, then 3 times/day for 7 days			5 times/day till healing, then 5 times/day for 10 days		5 times/day till healing, then 3 times/day for 7 days			5 times/day till healing, then 3 times/day for 7 days			
Efficacy												
Healing at day 14 (%)	83	73	77	83	71	86	71	80	89	91	85	92
Median time to healing[d]	7	8	7	6	7	6	7	4	7	7	9	7
Withdrawals (%)[c]	13	32	27	11	41	6	21	11	12	10	15	15
Relapses by day 14 (%)	4	14	2	0	6	0	8	6	3	3	0	0
Tolerability												
Visual disturbances (%)	13	14	14	61–82[d]	72–91[d]	ND	ND	ND	28–46[d]*	51–64[d]	0–30[d]*	14–54[d]
Tingling or burning (%)	17	45	23	6–17[d]	10–50[d]	6	8	3	9–21[d]*	14–26[d]	20–25[d]*	38–50[d]
Toxic SPK by day 14 (%)	13	9	0	0	0	ND	ND	ND	4–8[d]*	6–17[d]	0*	15–43[d]
Local Tolerability Judged Excellent												
By patient (%)	76	58	90	61*	19	ND	ND	ND	75[e†]	42[e]	92[e†]	46[e]
By investigator (%)	86	68	90	82[†]	19	ND	ND	ND	79[e†]	44[e]	91[e†]	31[e]

*ND = no data; SPK = superficial punctate keratitis; * p<0.05; † p<0.001; a. Data reported for the intent-to-treat population in each study; b. One patient was removed from the efficacy evaluation because of misdiagnosis; c. Due to worsening condition or complications; d. Range across visits; e. Assessment at day 14.*

Efficacy

Efficacy findings across the four studies were largely consistent. While both antiviral agents exhibited comparable efficacy, ganciclovir 0.15% was associated with a lower relapse rate (see *Table 2*). Across all studies, median time to healing with ganciclovir was six to seven days, and nine days in the study that stratified patients with geographic ulcers versus seven to eight days with acyclovir. Healing rates ranged from 83 to 89% with ganciclovir and from 71 to 92% with acyclovir, with no statistical difference between the groups. Relapse rates ranged from 0 to 4% and from 0 to 14%, respectively. Investigator-assessed efficacy was deemed highly satisfactory in 66.8% of ganciclovir subjects (range 58.8–73.6%) versus 54.9% of acyclovir subjects (range 31.3–72.7%). Although the percentage of patients discontinuing drug therapy because of disease exacerbations or complications was considerably lower with ganciclovir (6–15%) compared with acyclovir (10–41%), the difference was not statistically significant. Statistical significance between treatments could not be computed in studies 1, 2, and 3, owing to the limited enrollment in each trial (higher recruitment goals had been planned but not met). However, a pooled analysis of intent-to-treat patients in the three studies revealed a statistically significant difference in treatment success (ulcer resolution at end-point) between ganciclovir 0.15% (85%) and acyclovir 3% (71%) (p=0.04).

Safety and Tolerability

Overall, local tolerability was better with ganciclovir 0.15% than with acyclovir 3% in each study (see *Table 2*), although for some measures similar rates were evident across the studies (SPK: ganciclovir, 16–42%; acyclovir, 18–44%). In study 1, the two treatment groups exhibited similar rates of visual disturbances and toxic SPK, but the incidence of stinging/burning was much lower with ganciclovir (17 versus 45%). In study 2, ganciclovir recipients had a lower incidence of prolonged visual disturbance (p=0.047 at day seven) and tingling/burning (p=0.045 at day two at all time-points). Tolerability measures were mostly comparable in study 3, with similar rates of treatment-emergent SPK in each group. In study 4, ganciclovir showed greater local tolerability compared with acyclovir. Significantly fewer patients with dendritic ulcers reported visual disturbances at all time-points except day 14. Duration of discomfort after dosing was also significantly shorter with ganciclovir than acyclovir at day 14 (p=0.03), while the incidence of toxic SPK was nearly double with acyclovir. Finally, the percentage of patients and investigators rating tolerability as excellent was significantly higher for ganciclovir.

Non-inferiority Analysis

Study 4 efficacy data were re-analyzed using a non-inferiority hypothesis, with a therapeutic response measured by recovery rate in the intent-to-treat population for dendritic and geographic ulcers separately and together at days seven, 10, 14, and 21, and both dendritic and geographic ulcers together at any point within the study period (see *Table 3*). A positive value for the difference in proportions implies an advantage for ganciclovir (dendritic ulcers at day seven, geographic ulcers at days seven and 10, both at day seven), whereas a negative value implies an advantage for acyclovir. Results for all analyses were within the non-inferiority margin of acyclovir.

Conclusions

The development of more effective antiviral treatments has dramatically improved the prognosis for patients with HSK; however, ocular HSV infection remains a major cause of corneal blindness and public health concern. There are few topical ophthalmic treatment options in the US. Most of the antiviral medications initially developed are no longer marketed because of their cytotoxicity and poor tolerability. TFT is the only approved and marketed treatment, but its toxicity presents major concerns. Topical acyclovir—a commonly used treatment in Europe—is effective and well tolerated, but not approved for ophthalmic use in the US. More effective and better tolerated treatments are needed. Ganciclovir is a broad-spectrum virustatic agent with a similar structure to acyclovir. Marketed as Virgan, ganciclovir ophthalmic gel 0.15% is commercially available in Europe, Argentina, and some Asian countries, packaged in a 5g polyfoil tube with a dropper fitting and screw cap.

Table 3: Non-inferiority Analysis of Proportion of Ulcers Healed in Study 4 Intent-to-treat Population

Type	Day	GCV 0.15%	Number	ACV 3%	Number	Difference in Proportion[a]	Standard Error	Lower 95% Confidence Limit	Upper 95% Confidence Limit
Dendritic ulcer	7	78.87	71	74.63	67	4.25	7.19	-9.87	18.42
only (%)	10	80.28	71	80.60	67	-0.32	6.76	-13.61	13.10
	14	85.92	71	86.57	67	-0.65	5.87	-12.33	11.15
	21	85.92	71	88.06	67	-2.14	5.72	-13.59	9.37
Geographic ulcer	7	53.85	13	53.85	13	0.00	–	–	–
only (%)	10	69.23	13	69.23	13	0.00	–	–	–
	14	84.62	13	92.31	13	-7.69	12.44	-34.99	18.79
	21	92.31	13	92.31	13	-0.00	–	–	–
Dendritic and	7	75.00	84	71.25	80	3.75	6.92	-9.82	17.33
geographic	10	78.57	84	78.75	80	-0.18	6.40	-12.74	12.47
ulcer (%)	14	85.71	84	87.50	80	-1.79	5.31	-12.38	8.85
	21	86.90	84	88.75	80	-1.85	5.10	-12.06	8.40
	Healed any time	86.90	84	88.75	80	-1.85	5.10	-12.06	8.40

GCV = ganciclovir; ACV = acyclovir; a. Calculated as ganciclovir 0.15% minus acyclovir 3%; b. Lower 95% confidence limits that are greater than the non-inferiority limit support the conclusion of non-inferiority.

Four international multicenter trials indicate that ganciclovir ophthalmic gel 0.15% is at least as effective—and safer—than acyclovir 3% ointment. Additionally, despite the high viscosity (50,000 millipascal seconds) of the gel, blurring occurs less often with ganciclovir 0.15% gel than with acyclovir ointment,[28] making it a more tolerable option for patients. In 2007, Sirion Therapeutics, a privately held ophthalmic biopharmaceutical company, received orphan drug designation from the US Food and Drug Administration (FDA) for ganciclovir ophthalmic gel, which is a special status for diseases or conditions that affect fewer than 200,000 patients in the US. In August 2008, the FDA accepted for filing a new drug application (NDA) for ganciclovir ophthalmic gel 0.15%, submitted by Sirion as a treatment for acute herpetic keratitis. Sirion Therapeutics has an exclusive licensing agreement with Laboratoires Théa of France for the US rights to develop and market ganciclovir. With its excellent tolerability, safety, and efficacy profile, ganciclovir ophthalmic gel 0.15% has the potential to surpass TFT as the first-line treatment for HSK in the US. Its introduction to the US market as a new antiviral agent is eagerly awaited. ■

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Editor's Recommendations

Evidence-based Treatment of Herpes Simplex Virus Keratitis: A Systematic Review

Guess S, et al., Ocul Surf*, 2007;5(3):240–50.*

Herpes simplex virus (HSV) keratitis is a common cause of ocular and visual morbidity. In this article, we systematically review published randomized clinical trials (RCTs) for HSV epithelial and stromal keratitis in order to establish a rational evidence-based foundation for treatment of these disorders.

Articles for review were identified in the MEDLINE database from January 1, 1966 to May 30, 2006. Our review criteria stipulated that each study be performed in prospective, randomized, and double-blinded fashion, that it be controlled, and that it rely on specific clinical criteria for diagnosis and outcome. Of articles thus identified in the English-language press, 38 articles met our review criteria: 30 for HSV epithelial keratitis and eight (including seven RCTs) for HSV stromal keratitis.

From these studies, we concluded that the best evidence from treatment trials on HSV epithelial keratitis supports the use of topical trifluridine and topical or oral acyclovir, and suggests a possible additional benefit for topical interferon.

The best evidence from RCTs for HSV stromal keratitis supports the use of topical corticosteroids given together with a prophylactic antiviral to shorten the duration of active HSV stromal keratitis, and the use of long-term suppressive oral acyclovir therapy to reduce the incidence of recurrent HSV keratitis. ■

Trends in Herpes Simplex Virus Type 1 and Type 2 Seroprevalence in the United States

Xu F, et al., JAMA*, 2006;296(8):23–30.*

This study examined trends in herpes simplex virus (HSV)-1 and HSV-2 seroprevalence in the US in 1999–2004 compared with 1988–1994. Cross-sectional, nationally representative surveys were used to compare national seroprevalence estimates from 1999–2004 with those from 1988–1994, and changes in HSV-1 and HSV-2 seroprevalence since 1976–1980 were reviewed. Persons 14 to 49 years of age were included in these analyses.

The age-adjusted HSV-2 seroprevalence was 17.0% in 1999–2004 and 21.0% in 1988–1994, a relative decrease of 19.0%. Decreases in HSV-2 seroprevalence were especially concentrated in persons 14 to 19 years of age between 1988 and 2004. In adolescents 17 to 19 years of age and young adults, the decreases in HSV-2 seroprevalence were significant even after adjusting for changes in sexual behaviors.

Among those with HSV-2, the percentage who reported having been diagnosed with genital herpes was statistically different between 1988–1994 and 1999–2004, with a relative decrease of 6.9%. Among persons infected with HSV-1 but not HSV-2, a higher percentage reported having been diagnosed with genital herpes in 1999–2004 compared with 1988–1994. These data show declines in HSV-2 seroprevalence, suggesting that the trajectory of increasing HSV-2 seroprevalence in the US has reversed. The seroprevalence of HSV-1 has decreased, but the incidence of genital herpes caused by HSV-1 may be increasing. ■