Ganciclovir ophthalmic gel, 0.15%: a valuable tool for treating ocular herpes

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Abstract: Ocular herpes simplex virus (HSV) infection remains a major cause of corneal blindness. Several topical and oral antiviral medications have been used to treat herpetic keratitis. Advances in topical ophthalmic antivirals have been made over the past several decades. The first antivirals that were discovered were cytotoxic, while the antivirals developed more recently, such as acyclovir and ganciclovir, have exceeded these drugs in both efficacy and tolerability. Commercially available outside of the US since 1996, ganciclovir ophthalmic gel, 0.15% (GCV 0.15%, European tradename: Virgan®) is sold in more than 30 countries and has become the standard of care in treating acute herpetic keratitis. GCV 0.15% has been studied in animal models of ocular herpes, in healthy volunteers, and in several clinical studies. It has been found to be safe and effective at treating acute superficial herpetic keratitis. Previous preclinical studies of ganciclovir have shown activity against several common adenovirus strains and one recent clinical study demonstrated clinical effect against adenoviral conjunctivitis. This review is intended to provide a comprehensive overview of the GCV 0.15%, including a brief summary of the etiology and available treatments for ocular HSV, an explanation of GCV 0.15% mechanism of action, a compendium of preclinical and clinical GCV 0.15% studies, and an introduction into new areas of interest involving this drug.

Keywords: herpes simplex virus, antiviral, herpetic keratitis, ganciclovir, adenovirus

Introduction

Herpes simplex keratitis remains one of the leading causes of corneal blindness in the US (Biser 2007) and in the industrialized world. Herpes simplex virus (HSV) infections are very common, with nearly 60% of the US population showing evidence of infection by age 5 (Biser 2006). Approximately 1% of infected patients develop ocular outbreaks, and 20,000 new primary cases of ocular herpes are diagnosed in the US each year (Liesegang 1991; Pavan-Langston 1994). The Rochester study, which was conducted between 1950 and 1982, found the incidence to be 8.4 primary cases per 100,000/year in the US (Liesegang 1989; Liesegang et al 1989). One study conducted in Denmark found the incidence to be 12 cases per 100,000/year, while another study conducted in Denmark found the incidence to be 5.9 cases per 100,000/year (Norn 1970; Mortensen and Sjolie 1979). Possible reasons for these variations in reported incidence include completeness of recording, variations in diagnostic criteria, lack of data sharing among health care providers, and the inability to delineate the appropriate population base. A more recent epidemiologic study conducted in France from September 2002 to December 2002 found the incidence to be much higher. In this multicenter prospective study, Labetoulle et al (2005) concluded the overall incidence of herpetic keratitis to be 31.5 cases per 100,000/year. The incidence for new cases of herpetic keratitis was 13.2 per 100,000/year and for recurrent cases it was 18.3 per 100,000/year. A summary of the incidence of ocular HSV is included in Table 1.

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Table 1 Ocular herpes simplex virus incidence

Site	Study period	Incidence	Source
Rochester	1950–1982	8.4 primary cases per 100,000/year	Liesegang 1989; Liesegang et al 1989
Denmark	1970	12 primary cases per 100,000/year	Norn 1970
Denmark	1979	5.9 primary cases per 100,000/year	Mortensen and Sjolie 1979
France	September 2002 to December 2002	Overall incidence: 31.5 cases per 100,000/year Primary cases: 13.2 per 100,000/year Recurrent cases: 18.3 per 100,000/year	Labetoulle et al 2005

In the Herpes viridae family, 8 viruses are pathogenic for humans: herpes simplex virus type 1 (HSV1), herpes simplex virus type 2 (HSV2), varicella-zoster virus (VZV), cytomegalovirus (CMV), human herpesvirus type 6 (HHV6), human herpesvirus type 7 (HHV7), Epstein-Barr virus (EBV), and human herpesvirus type 8 (HHV8) (Ramel 1997). Of these 8 viruses, HSV1 is responsible for most ocular lesions. In fact, 98% of non-neonate ocular infections are due to HSV1 (Robinet-Combes and Colin 1993). In contrast, neonatal ocular infections are caused predominantly by HSV2, which is associated primarily with genital herpes that can be transmitted to the neonate during passage through the birth canal; these ocular infections are typically more severe than HSV1 infections.

HSV ocular infections are characterized by a primary outbreak and subsequent recurrences. The primary outbreak typically occurs during childhood, but is usually mild or subclinical. If symptomatic infections occur, it typically presents as acute follicular conjunctivitis associated with palpebral ulceration, vesicles, or corneal microdendrites and preauricular adenopathies.

After the primary infection, HSV typically becomes quiescent or latent in the trigeminal ganglion or the cornea and conditions such as stress, UV radiation, and hormonal changes can reactivate the virus. Lesions are also common in immunosuppressed individuals such as recent organ transplant patients or patients with HIV. These recurrent herpetic infections have a tendency to occur in the cornea and uvea and may cause dendritic (Figure 1) or geographic (Figure 2) corneal ulcers.

Initial recurrences of HSV keratitis typically present as epithelial disease, but subsequent recurrences may progress towards deeper layers resulting in stromal keratitis and/or anterior uveitis. Repeated outbreaks of herpes simplex viral infections involving the corneal stroma can ultimately lead to an alteration of the corneal transparency (Robinet-Combes and Colin 1993) (Figure 3).

The risk of blindness increases with the number and severity of recurrences, so prompt treatment of herpetic epithelial ulcers is imperative to limit scarring and other more serious complications that can lead to blindness.

Antiviral agents used to treat ocular herpes

While treatment of ocular HSV infection has advanced considerably during the past 15 years, problems related to the epithelial toxicity of some available antiviral agents remain, and this toxicity is responsible for the continued epithelial lesions and the poor tolerance of these treatments (Maudgal et al 1983; Naito et al 1987).

Herpetic keratitis treatment is dependent on the manifestation and severity of the disease. Epithelial dendritic keratitis is most often treated with oral and/or topical antiviral therapy and corneal debridement, although the latter is becoming a less commonly used method. Five topically applied ophthalmic antivirals have been used in Europe and the United States. Four of these drugs include antiviral agents that target infected and healthy cells: idoxuridine (IDU), iododesoxycytidine (IDC), vidarabine (Ara-A), and trifluridine (TFT). More recently developed topical antivirals, such as acyclovir (ACV) and ganciclovir, are more selective and less toxic than their predecessors.

IDU, IDC, and Ara-A were found to be very toxic and have since been abandoned by clinicians in favor of less harmful agents.

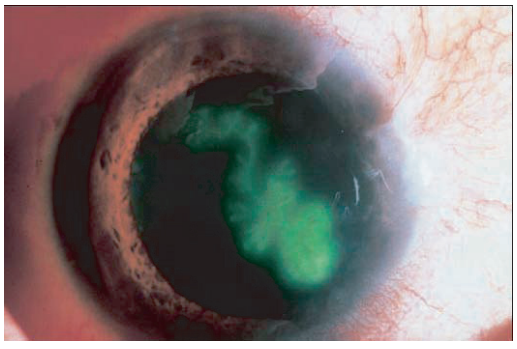

Figure 1 Dendritic corneal ulcer caused by herpes simplex virus keratitis.
All photographs have been obtained, and used with permission, from Yves Lackkar, Hôpital Saint-Joseph, 185 rue Raymond Losserand, 75014 Paris, France.

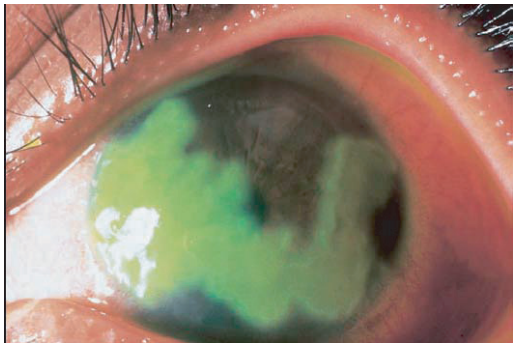

Figure 2 Geographic corneal ulcer caused by herpes simplex virus keratitis.

In the US, TFT (US tradename: Viroptic®) is the only antiviral agent currently available for topical ocular herpes treatment. TFT is a thymidine analogue which is activated by cell and viral thymidine kinase and is incorporated into the DNA of both the virus and host cells. It is effective for superficial herpetic keratitis, but because it is non-selective and affects healthy cells as well as infected cells, it results in epithelial toxicity that can lead to permanent damage of the cornea, as well as blepharitis, cannicular occlusion, and allergies. TFT is usually prescribed one drop every 2 hours during waking hours up to a maximum of nine times per day in the infected eye, and should not be administered for more than 21 days because of potential ocular toxicity. Additionally, ocular penetration is poor when the corneal epithelium is intact (Sugar et al 1980; Van Bijsterveld and Post 1980; La Lau et al 1982; Hovding 1989; Power et al 1991; Renard and Denis 1991; Robinet-Combes and Colin 1993). TFT is currently in use only in the US and Canada.

Outside the US, acyclovir ophthalmic ointment 3% (ACV 3%) and ganciclovir ophthalmic gel, 0.15% (GCV 15%) are used as first-line therapies for the treatment of acute superficial herpetic keratitis.

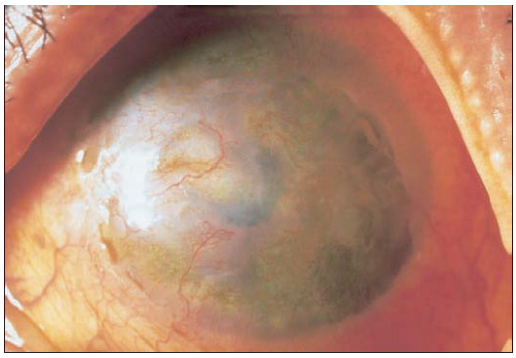

Figure 3 Stromal damage caused by herpes simplex virus keratitis.

Acyclovir and ganciclovir inhibit HSV infection and replication by similar pharmacologic mechanisms. Cellular and viral thymidine kinases convert ganciclovir and acyclovir into a triphosphate active derivative. This phosphorylation, or activation, is carried out primarily in infected cells. Once they are phosphorylated, acyclovir and ganciclovir inhibit the synthesis of viral DNA in two ways: competitive inhibition of viral DNA-polymerase and direct incorporation into the viral primer strand DNA, which results in viral DNA chain termination and prevention of viral replication (Hayden 2001). Intracellular ganciclovir triphosphate concentrations are 10-fold higher than those of acyclovir triphosphate and decline much more slowly with an intracellular half life exceeding 24 hours (Biron 1985).

The structure and in vitro activity of ganciclovir

Ganciclovir is a synthetic nucleoside analogue of 2′-deoxyguanosine. Its structure is 9-(1,3-dihydroxy-2-propoxymethyl) guanine, and its molecular weight is 255.23 (Figure 4).

Viral plaque reduction assays were used to test ganciclovir's antiviral activity in vitro, and ganciclovir was found to be a powerful inhibitor of viral replication for HSV1, HSV2, HZV, EBV, CMV, and HHV6 viruses. Ganciclovir has also been demonstrated to have an inhibitory effect on the replication of the hepatitis B virus (Locarnini et al 1989) and some adenovirus strains (Taylor et al 1988). The mean effective dose of ganciclovir in vitro for HSV1 and HSV2 in ocular clinical isolates is 0.23 µg/mL (Smee et al 1983; Smee et al 1985; Inoue et al 1989) and corresponds to a very low concentration of active substance illustrating ganciclovir in vitro potency. Based on this pharmacodynamic profile, topical formulations with low ganciclovir concentrations are assumed to be effective in ocular herpes. Such low concentrations are compatible with active substance solubilization in an aqueous vehicle, which is more convenient for patients than a greasy formulation.

Virgan® ophthalmic gel, containing GCV 0.15% as the active moiety, was developed to produce an ophthalmic form of ganciclovir that would meet all of the following criteria:

- Good tolerance,
- Viscous form ensuring a prolonged period of retention,
- Similar tonicity to tears,
- pH adjusted to a physiological value,
- Sterilizable (autoclavable),
- Long and stable shelf life,
- Antimicrobial protection in conformity with European regulations.

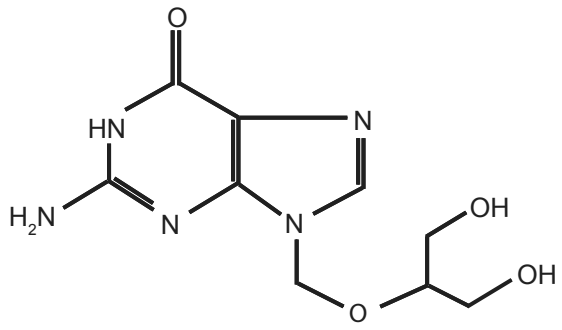

Figure 4 Structure of ganciclovir.

The aqueous gel formulation of Virgan® allows homogeneous distribution of the ganciclovir preparation and clinically has shown better tolerability (eg, visual disturbances and stinging or burning sensations were lower than acyclovir) when compared to other topical ophthalmic herpetic ointments. The GCV 0.15% strength was adopted on the basis of preclinical studies in experimental animal models of herpetic keratitis, preclinical and clinical pharmacokinetic distribution studies, and controlled clinical trials.

Virgan® is supplied in a polyfoil 5 g tube with a dropper fitting. The gel formulation allows for more prolonged contact time with the eye than an oil-based formulation. Because of its solubility, the aqueous gel allows for a GCV concentration of 0.15%, which has demonstrated good tolerability and efficacy in the local treatment of superficial acute herpetic keratitis. Its pH is 7.45 and its osmolarity is 300 mOsmol, and both were adjusted to values close to normal physiologic values.

Preclinical studies with ganciclovir

Ganciclovir ophthalmic gel, 0.15% (Virgan®; Laboratoires Théa) is a potent drug and has been found to be effective in animal herpetic keratitis models at much lower concentrations (0.15%) than effective doses achieved with acyclovir ointment (3%). When administered topically 5 times per day for 6 weeks, it is well tolerated in animals, and was found to penetrate rapidly and maintain effective antiviral concentrations in the anterior segment of the eye.

Preclinical efficacy studies

In an experimental model of herpetic keratitis in rabbits (Trousdale et al 1984), ganciclovir ointment demonstrated antiviral activity at a concentration of 0.1% with no positive ocular viral samples after 5 times a day treatment at 12 days and at 14 days when applied 3 times a day. Using this same model, Castela et al (1994) showed that ganciclovir gel at concentrations of 0.2%, 0.05%, and 0.0125% applied 4 times a day for 12 days, starting on day 3 after infection, effectively treated herpetic keratitis. Ocular isolates showed no positive viral samples on day 12 with GCV 0.2% and 0.05%, and on day 14 with GCV 0.0125%.

Additionally, Shiota and colleagues (1987) found that, after topical application in rabbits, ganciclovir ointment at concentrations ranging from 0.03% to 1% was capable of preventing herpetic keratitis. Treatment began 1 hour after bilateral inoculation of the HSV1 virus and continued 5 times a day for 2 days.

When ganciclovir solution and ointment were compared in mice infected with ocular HSV (Inoue et al 1989), solutions of 0.3% and 0.03% were shown to be as effective as the ointments with the same concentrations.

Preclinical tolerance studies

The tolerance of GCV gel when applied topically to the eye has also been evaluated in animals. In the rabbit, GCV gel 0.15% preserved with either benzalkonium chloride 0.0075% or sodium mercurothiolate 0.006% did not cause ocular irritation (Iris-Pharma 1992a) or any local anesthetic effects (Iris-Pharma 1992b). After 5 daily applications for 8–10 days in rabbits, GCV gel did not alter the rate of corneal re-epithelialization. Additionally, a 6-week tolerance study (Bio-Tox 1990) in rabbits also established the ocular tolerance of GCV gel.

Preclinical distribution studies

After topical application of GCV 0.15% ganciclovir was found to be rapidly distributed through the anterior segment disease-targeted ocular tissues in male rabbits at concentrations higher than the ED50 concentrations measured in vitro in HSV1 and HSV2 (Iris-Pharma 1990; Iris-Pharma 1991).

Clinical studies with ganciclovir

Pharmacokinetic studies in healthy volunteers

GCV ophthalmic gel was well tolerated by healthy volunteers (Clirophta 1994a). In a randomized, double-masked study of 10 subjects, the local tolerance of GCV 0.15% (preserved with benzalkonium chloride) was compared with its vehicle after repeated administrations. GCV 0.15% was administered to one eye and the vehicle gel was administered to the other. Both were applied 5 times daily for 7 days.

Assessment criteria included both subjective measures and ophthalmologic examination at the preinclusion visit, on the day of inclusion (before the first administration and 30 minutes after the first administration), and on the second and seventh day of treatment. Additionally, a standard general purpose examination was conducted at the preinclusion visit and after 7 days of treatment.

All 10 enrolled volunteers completed the trial. Overall, tolerance was good, with only mild anomalies (no clinical consequences) reported. No changes were observed in the physical examination between the preinclusion visit and the final study visit, and systemic absorption of GCV was minimal.

A separate study conducted on healthy volunteers evaluated the kinetics of ganciclovir in tears after repeated instillations of GCV 0.15% (Clirophta 1994b). In this phase I study, 6 healthy male volunteers instilled one dose of GCV 0.15% ophthalmic gel into each eye at 3-hour intervals for 12 hours (total of 4 instillations). This dosing frequency was chosen based on the usual dosing frequency for the initial treatment of superficial herpetic keratitis.

Before the first instillation, and 2 hours and 45 minutes after the four instillations, the tears of each eye were collected using a technique similar to Schirmer's test. Paper strips were used to collect approximately 10 mm of tears. High-performance liquid chromatography was used to measure the concentration of ganciclovir in the tears. The detection limit was 4 ng/strip, with a maximum limit of 200 ng/strip. All analyses were masked. Additionally, ophthalmic examinations were performed at the preinclusion visit and before and after each tear sampling. None of the study participants experienced significant discomfort. The mean application time of the paper strips was 72 seconds, with a minimum of 8 seconds and a maximum of 376 seconds.

In this study, there was a wide range of inter-individual and intra-individual variations in the ganciclovir concentration in the tears. This is most likely due in part to the difficulty of collecting tears with the strips, which may have induced reflex tearing. The mean concentration of ganciclovir ranged from 0.92 to 6.86 μg/mL. These concentrations are greater than the inhibitory concentrations for the HSV1.

Overall tolerance to ganciclovir was good. The inherent irritation of obtaining samples with Schirmer's strips led to mild conjunctival hyperemia in 5 study participants.

Safety and efficacy trials in patients with herpetic keratitis – the results of four clinical trials

Virgan® was developed for the treatment of acute superficial herpetic keratitis as a replacement for earlier and less effective or less well tolerated antivirals, such as idoxuridine, vidarabine, and trifluridine. Virgan® was first approved in France in 1995, and in clinical trials, it was compared to ACV 3%, which was the standard of care at that time in Europe. However, Virgan® is available as a gel and ACV is available as an ointment, so it is impossible to conduct a double-masked study with these two formulations. No clinical trials have been conducted that compare Virgan® to TFT, which is the current standard of care for herpetic keratitis in the US.

Four clinical trials have been conducted to assess the efficacy and safety of ganciclovir ophthalmic gel (listed as Studies A, B, C, and D below). Inclusion criteria were the same for all four studies. Patients had to have a dendritic or geographic ulcer, but no virologic confirmation was necessary for inclusion. Dendritic ulcers are pathognomonic of a corneal HSV infection and can be distinguished from dendrites occurring with herpes zoster or pseudodendrites observed with amebic keratitis. Geographic ulcers are generally not difficult to diagnose because of their distinctive form. Additionally, most virologic techniques for detecting HSV are relatively insensitive and are often a source of false-negative results.

Patients were excluded if they had used an antiviral treatment in the previous 14 days, if they had severe stromal disease, if they had keratouveitis, if they had previous keratoplasties of the affected eye, if they had corneal or conjunctival bacterial secondary infection, if they had recent ocular trauma (except phototrauma), or if the visual acuity of the contralateral eye was less than 2/10.

Other general exclusion criteria included a known hypersensitivity to ganciclovir or acyclovir, leukopenia, known anemia or thrombocytopenia, pregnancy or breast feeding, known HIV infection, known immune deficiency, or previous tissue transplantation.

Study A

The first study included 67 eyes in 66 patients who were treated in four centers (Tunis, Dakar, Sousse, and Bamako) in Africa from April 1990 through May 1992 (Transphyto 1993a; Colin et al 1997). Patients were treated with GCV 0.15%, GCV 0.05%, or ACV 3% 5 times daily until healing of the ulcer and then 3 times daily for 1 week. Patients were excluded from the study if their ulcer had been present for more than 14 days or if they were younger than 12 years of age. The 67 eyes were divided into three groups. Twenty-three eyes received GCV 0.15%, 22 eyes received ACV 3% ointment, and 22 eyes received GCV 0.05%.

All eyes were included in the intention-to-treat (ITT) analysis. Eight eyes were excluded from the per protocol (PP) analysis because the observations violated the study protocol (typically missed treatments). The PP analysis included 59 eyes (20 in the GCV 0.15% group, 18 in the ACV group, and 21 in the GCV 0.05% group).

The results of the ITT and PP analyses were similar. The patient groups were comparable demographically and ophthalmologically at the time of inclusion in the study.

In the ITT analysis, the rate of healing was 82.6% for the GCV 0.15% group, 77.3% for the GCV 0.05% group, and 72.7% for the ACV group. Additionally, the median healing time was 7 days in the GCV 0.15% and GCV 0.05% groups and 8 days in the ACV group, and the number of relapses was 1 in the GCV 0.15% and GCV 0.05% groups and 3 in the ACV group (Table 2).

The rate of study withdrawals was 13% in the GCV 0.15% group, 27.3% in the GCV 0.05% group, and 31.8% in the ACV 3% group, most likely due to tolerance issues. Investigators were asked to assess the efficacy of the 3 treatments on Day 14: 71.43% assessed the efficacy of GCV 0.15% as very satisfactory, compared to 66.67% for GCV 0.05% and 52.63% for ACV 3%. In the ITT analyses, a tendency emerges in favor of GCV 0.15% in comparison with GCV 0.05% and a slightly superior efficacy of GCV 0.05% compared with ACV 3%. During this clinical trial, a viral kinetic study of repeated conjunctival samples seemed to indicate an identical rate of disappearance of the virus in GCV 0.15% and ACV 3%, while that of GCV 0.05% appears less efficacious.

GCV 0.15% and 0.05% were well tolerated, and stinging and burning sensations appeared to be less common compared with ACV 3%. Additionally, the rates of toxic superficial punctate keratitis were comparable (Table 3).

Systemically, no hematologic effects were observed. A plasma sample was evaluated on day 14 in 11 patients in the GCV 0.15% group and in 13 patients in the GCV 0.05% group both 30 minutes and 1 hour after the last instillation. The mean cumulative level of exposure to treatment was 2968.6 µg in the GCV 0.15% group and 1015 µg in the GCV 0.05% group. The sensitivity threshold of the method was 5 ng/mL. The mean plasma ganciclovir level values were 12.7 ± 3.7 ng/mL in the GCV 0.15% group and 22.6 ± 10.4 ng/ml in the GCV 0.05% group. For both of these groups, the plasma ganciclovir concentrations found after 2 weeks of treatment were approximately 100-fold less than the typical residual plasma concentrations observed in patients treated with intravenous ganciclovir (Cytovene®-IV; Vidal 2000), which corresponds to concentrations 600-fold lower than the maximum concentration.

Study B

A second clinical trial was conducted at 4 study centers located in France (Brest, Clermont-Ferrand), Switzerland (Lausanne), and the United Kingdom (Bristol) from December 1990 through May 1992 (Transphyto 1993b; Colin et al 1997). The study included 37 patients: 19 patients were treated with GCV 0.15% gel and 18 patients were treated with ACV 3% ointment. Patients were given either GCV or ACV 5 times daily until healing of the ulcer and then 3 times daily for 1 week. Patients were excluded from the study if their ulcer had been present for more than 14 days or if they were younger than 18 years of age.

The GCV 0.15% and ACV 3% groups were comparable at the time of inclusion in the study. A total of 37 subjects were enrolled in Study B; 19 subjects receiving GCV 0.15% and 18 subjects receiving ACV 3%. Out of these subjects, there was 1 subject in each group who was treated but found to be misdiagnosed as having a herpetic ulcer. Therefore, the efficacy analysis included all patients except for the 2 included in error (n = 18 and n = 17, respectively). However, the investigators considered all of the enrolled subjects (n = 19 and n = 18, respectively) in the tolerance analysis.

Table 2 Summary of efficacy results (Study A)

Efficacy measure	GCV 0.15%		GCV 0.05%		ACV 3%		p value *
No. of subjects	ITT	PP	ITT	PP	ITT	PP	
	N = 23	N = 20	N = 22	N = 21	N = 22	N = 18	
Recovery at Day 14 (%)	19 (82.6)	17 (85)	17 (77.3)	17 (81)	16 (72.7)	13 (72.2)	ns
Relapses by Day 14 (%)	1 (4.3)	1 (5.0)	1 (1.45)	1 (4.76)	3 (13.6)	2 (11.1)	ns
Withdrawals due to worsening condition or complications (%)	3 (13)	3 (15)	6 (27.3)	5 (23.8)	7 (31.8)	6 (33.3)	ns
Time to healing (median days)	7	7	7	7	8	10	ns

*Statistical significance was evaluated for between-group differences.
Abbreviations: ACV, acyclovir; GCV, ganciclovir; ITT, intention to treat; ns, not significant; PP, per protocol.

Table 3 Summary of tolerance results, ITT population (Study A)

Tolerance measure no. of subjects	GCV 0.15% N = 23	GCV 0.05% N = 22	ACV 3% N = 23	p value
Blurred vision	3	3	3	ns
Blurred vision >5 min.	0	0	0	ns
Stinging and burning	4	5	10	p = 0.10*
Toxic superficial punctate keratitis related to treatment at Day 14	3	0	2	ns

*Chi squared test.
Abbreviations: ACV, acyclovir; GCV, ganciclovir; ITT, intention to treat; ns, not significant.

This study found that GCV 0.15% was at least as effective as ACV 3% in healing the ulcers (Table 4). The rate of healing in the GCV 0.15% group was 83.3%, and the rate of healing in the ACV 3% group was 70.6%. The median time of healing was 6 days for GCV 0.15% and 7 days for ACV 3%. There were no recurrences for GCV 0.15% and 1 for ACV 3%. Additionally, 11.1% of GCV 0.15% patients and 41.2% of ACV patients withdrew from the study due to worsening of the ulcer or complications. While only 35 patients were included in the efficacy analysis, all 37 patients receiving the test agents were included in the tolerance analysis. Local tolerance was significantly better in the GCV 0.15% group. In the GCV 0.15% group, 38.5% of patients experienced blurred vision lasting longer than 5 minutes after instillation compared with 76.9% of patients in the ACV group. Additionally, 16.7% of GCV 0.15% patients and 50% of ACV patients experienced burning or stinging sensations. According to the investigators' observations, there were no cases of superficial punctate keratitis that were found to be toxic. Investigators and study subjects were asked to assess the tolerance of the study drug during the trial. In the GCV 0.15% group, 100% of investigators and 100% of patients rated the general tolerance of GCV 0.15% to be "excellent". In the ACV 3% group, these percentages were 75 and 67, respectively.

Study C

In the third study, which included 109 patients and was conducted from May 1991 to October 1992 at one study center in Karachi, Pakistan, GCV 0.15% was found to be at least as effective as ACV 3% (Transphyto 1993c). Patients were divided into 3 groups: 36 patients were treated with GCV 0.15%, 38 patients were treated with ACV 3%, and 35 patients were treated with GCV 0.05%. Patients were treated 5 times daily for 10 days. Patients were excluded if their ulcer had been present for more than 7 days or if they were younger than 5 years of age.

In the ITT population, the healing rate was 86.1% with GCV 0.15%, 80.0% with GCV 0.05%, and 71.05% with ACV. The median time to healing was 7 days with ACV, 6 days with GCV 0.15%, and 4 days with GCV 0.05%. There were 3 relapses with ACV, compared to 0 with GCV 0.15% and 2 with GCV 0.05%. Additionally, 21.05% of ACV patients, 11.4% of GCV 0.05% patients, and 5.6% of GCV 0.15% patients withdrew from the study due to complications (Table 5). The withdrawals were all treatment failure-related, primarily due to worsening condition (eg, stromal damage, hypopyon) or to problems of therapeutic efficacy (ie, increase in ulcer size, lack of healing, relapse). Stromal damage was found in 62.5% of the acyclovir withdrawals, compared to only 50% in both the GCV 0.15% and GCV 0.05% withdrawals.

The tolerability was acceptable for all 3 treatment groups. Mild stinging or burning were reported from 1 subject in the GCV 0.15% group, 5 subjects in the GCV 0.05% group, and 3 subjects in the ACV 3% group. The number of superficial punctate keratitis cases that appeared or were exacerbated while receiving treatment was similar across the treatment groups. Finally, no hematological effects were observed.

Study D

The fourth clinical study took place in Europe from September 1992 through September 1994 and included 164 patients at 28

Table 4 Summary of efficacy results, PP population (Study B)

Efficacy measure no. of subjects	GCV 0.15% N = 18	ACV 3% N = 17	p value
Recovery at Day 14 (%)	15 (83.3)	12 (70.6)	ns
Relapses by Day 14 (%)	0	1 (5.9)	ns
Withdrawals due to worsening condition or complications (%)	2 (11.1)	7 (41.2)	0.06†
Time to healing (median days)	6	7	0.056*

†Fisher's exact test; *Logrank test; ns = not significant.
Abbreviations: ACV, acyclovir GCV, ganciclovir; ns, not significant; PP, per protocol.

Table 5 Summary of efficacy results (Study C)

Efficacy measure	GCV 0.15%		GCV 0.05%		ACV 3%		p value
No. of subjects	ITT	PP	ITT	PP	ITT	PP	
	N = 36	N = 23	N = 35	N = 21	N = 38	N = 17	
Recovery at Day 14 , n (%)	31 (86.1)	21 (91.3)	28 (80)	19 (90.5)	27 (71.1)	15 (88.2)	ns
Relapses, %	0	0	5.7	4.8	7.9	11.8	ns
Withdrawals due to worsening condition or complications, %	5.56	0	11.4	4.8	21.1	23.5	p = 0.02*
Time to healing, median days	6	6	4	4	7	6	ns

*PP group only.
Abbreviations: ACV, acyclovir; GCV, ganciclovir; ITT, intention to treat; ns, not significant; PP, per protocol.

study centers in the following locations: Aulnay-Sous-Bois, Bamako, Birmingham, Bobigny, Bordeaux (2 centers), Brest, Bristol, Chambery, Chateaulin, Clermont-Ferrand (5 sites), Cournon, Dublin, Le Golfe Juan, Lesneven, London, Marseille, Palaiseau, Paris (2 sites), Sousse, Tananarivo, Thiers, and Toulon (Transphyto 1994; Hoh et al 1996). Patients were given either GCV 0.15% or ACV 3% 5 times daily until healing of the ulcer and then 3 times daily for 1 week. Patients were excluded if their ulcer had been present for more than 7 days or if they were younger than 18 years.

The data relating to dendritic and geographic ulcers were analyzed separately. A breakdown of study population by ulcer type and treatment group is provided in Table 6. Overall, 138 patients presented with dendritic ulcers: 67 in the ACV 3% group and 71 in the GCV 0.15% group. The number of observations was 62 for ACV 3% and 64 for GCV 0.15%. The treatment groups were homogenous in terms of demographic characteristics, prognostic factors, and distribution of protocol violations.

The clinical study results showed that GCV 0.15% was as at least as effective as ACV 3% for the treatment of acute herpetic keratitis (Table 7). The efficacy results for dendritic ulcers of the ITT and PP analyses were similar. Because so few patients had geographic ulcers, a statistical comparison was not conducted.

In the ITT dendritic ulcer groups, the percent healed on Day 14 were 88.7% in the GCV 0.15% group and 91% in the ACV 3% group, and in the PP group, the percent healed were 92.2% and 93.6%. The median time to healing was 7 days for the ITT analysis for both treatment groups, and 6 days and 7 days for the PP analysis for the GCV 0.15% and ACV 3% groups, respectively. None of these results were statistically significant.

GCV 0.15% showed similar rates of withdrawals due to exacerbation or complications compared to the ACV 3% group. There were 2 subjects with dendritic ulcers that relapsed in each treatment group.

The local tolerance results in this study for subjects in the GCV 0.15% group proved to be better than for those in the ACV 3% group (Table 8). There were fewer subjects treated with GCV 0.15% reporting blurring, which was significant at all time points for the subjects with dendritic ulcers, and the average duration of blurring was significantly shorter at all of the evaluation time points except for Day 14 for the GCV 0.15% group. There were fewer subjects reporting a stinging or burning sensation in the GCV 0.15% group (p = 0.03) at Day 14. Also, the frequency of toxic superficial punctate keratitis was reduced by half in the GCV 0.15% group compared with the ACV group, and the proportion of cases where the investigator judged the tolerance to the product as excellent was significantly higher in the GCV 0.15% group compared with the ACV group. Similarly, patients reported that the overall tolerance with GCV 0.15% was more frequently considered excellent compared with ACV.

Table 6 Subject population by ulcer type and treatment (Study D)

Treatment groups	Dendritic ulcers – number of subjects		Geographic ulcers – number of subjects
	ITT	PP	
GCV 0.15% (N = 84)	71	64	13
ACV 3% (N = 80)	67	62	13
Total	138	126	26

Abbreviations: ACV, acyclovir; GCV, ganciclovir; ITT, intention to treat; PP, per protocol.

Table 7 Summary of efficacy results by ulcer type (Study D)

Efficacy measure	Dendritic ulcers		Geographic ulcers	p value
No. of subjects	ITT	PP		
Recovery at Day 14- (%)				
GCV 0.15%	63 (88.7)	59 (92.2)	11 (84.6)	ns
ACV 3%	61 (91)	58 (93.6)	12 (92.3)	
Withdrawals due to exacerbation or complication (%)				
GCV 0.15%	9 (12.37)	6 (9.37)	2 (15.38)	ns
ACV 3%	7 (10.45)	6 (9.67)	2 (15.38)	
Time to healing (median days)				
GCV 0.15%	7	6	9	ns
ACV 3%	7	7	7	

Abbreviations: ACV, acyclovir; GCV, ganciclovir; ITT, intention to treat; ns, not significant; PP, per protocol.

The original statistical analysis conducted for Study D was based on a superiority hypothesis with a 20% improvement in recovery rate expected for GCV 0.15% compared to ACV 3%. At the time the study was conducted, methodology for non-inferiority analyses was not understood as well as it is today. The sample size for the study was based upon a superiority analysis. Since the results showed comparable efficacy between GCV 0.15% and ACV 3%, the study failed to meet the superiority margin required.

Table 8 Summary of local tolerance results by ulcer type (Study D)

	GCV 0.15% (N = 70)*	ACV 3% (N = 66)*	p Value†
Blurring: % subjects; range across visits through Day 14			
Dendritic ulcers	28.1– 45.7	50.9–63.6	$p < 0.02$ at all time points, except
Geographic ulcers	0–30	14.3–53.9	Day 10 where $p = 0.056$
Stinging/burning: % subjects; range across visits through Day 14			
Dendritic ulcers	9.3–21.43	14.3–26.42	$p = 0.03$ at Day 14
Geographic ulcers	20–25	38.5–50	
Duration of blurring (sec): range across visits through Day 14			
Dendritic ulcers	164–301	474–972	$p < 0.04$ at all time points, except
Geographic ulcers	20–120	120–644.28	Day 14 where $p = 0.056$
Duration of stinging/burning (sec): range across visits through Day 14			
Dendritic ulcers	100–223	148–745	ns
Geographic ulcers	10–260	55–150	
Toxic SPK: % subjects; range across visits through D14			
Dendritic ulcers	3.7–7.9	6.1–16.98	$p = 0.03$ at Day 10
Geographic ulcers	0	15–43	
Investigator assessment of tolerance, excellent, at Day 14 (%):			
Dendritic ulcers	56 (78.87)	29/66 = 43.94	$p = 0.00006$ at all time points
Geographic ulcers	12 (92.31)	6 (46.15)	
Subject assessment of tolerance, excellent, at Day 14 (%)			
Dendritic ulcers	52/69 = (75.36)	28/66 = (42.42)	$p = 0.0002$ at all time points
Geographic ulcers	10 (90.91)	4 (30.77)	

*Number of patients included for assessment of tolerance (investigatory and subject) and for adverse events.
Abbreviations: ACV, acyclovir; GCV, ganciclovir; ns, not significant; SPK, superficial punctate keratitis.

Recently, a non-inferiority analysis was conducted using the original data obtained (data on file). A non-inferiority margin of 18.5% was selected based upon an analysis of published studies. The non-inferiority analysis conducted on Study D showed that the lower 95% confidence interval around the difference in proportions between GCV 0.15% and ACV 3% was no greater than the non-inferiority margin, and hence the non-inferiority of ganciclovir to acyclovir in Study D, across ulcer types and time points, was established.

Antiviral resistance

The risk of emergence of viral strains resistant to ganciclovir is low and has been found to be similar to acyclovir (Goldschmidt et al 1994). These antiviral drugs are structurally closely related and have similar mechanisms of action, so there is cross-resistance to these two drugs. Both in vitro and in vivo, and under selective pressure with idoxuridine, it is possible to obtain strains of HSV1 and HSV2 that are resistant to acyclovir, and in most cases, these strains show cross-resistance to ganciclovir. Viral strains can eliminate or alter the kinase so that the drug is not phosphorylated, but most of these mutant strains are relatively avirulent. They can also alter the DNA polymerase so the drug does not bind, but these mutants are very rare. There are no data in the literature that suggests an inherent risk of the emergence of new strains of HSV resistant to ganciclovir and not resistant to acyclovir.

Acyclovir and ganciclovir have been widely used for more than 25 years, and HSV resistance to these antivirals is sporadic and is generally isolated to immunocompromised populations in the US (Levin et al 2004) and in other countries (Greco et al 2007; Morfin and Thouvenot 2003). In fact, in immunocompetent patients in the US, only 0.1% to 0.7% of clinical ocular isolates show resistance in vitro (Levin et al 2004).

Prophylatic treatment of recurrent ocular herpes

Oral acyclovir

The Herpetic Eye Disease Study (HEDS), a large clinical study funded by the US National Eye Institute, changed and refined treatment and management protocols for herpetic eye disease (HEDS 2000). HEDS was undertaken to discover several things, including the assessment of low-dose oral acyclovir for prevention of recurrent HSV ocular infections in patients with previous episodes of herpetic eye disease.

HEDS results showed that long-term suppressive therapy with an oral antiviral agent (acyclovir 400 mg bid) reduced the recurrence of HSV epithelial keratitis and stromal keratitis, produced a 45% decrease in the rate of recurrence of all forms of ocular complications, produced a 50% reduction in the rate of recurrence of HSV stromal keratitis, and demonstrated that the benefit was greatest among patients with prior HSV stromal keratitis.

HEDS also showed that long-term acyclovir therapy was not effective in preventing HSV stromal keratitis or iritis in patients with HSV epithelial keratitis.

While these results offered advances to ophthalmologists treating herpetic eye disease, oral acyclovir still continues to be used more as an adjunct to therapy, rather than a stand alone treatment.

Ganciclovir ophthalmic gel, 0.15%

A recent prospective interventional case series studied the use of topical ganciclovir gel 0.15% for both the treatment and prophylaxis of herpetic epithelial keratitis (Tabbara 2005). The study evaluated the effects of GCV 0.15% for the treatment of herpetic keratitis among 16 consecutive cases and for the prophylaxis of herpetic keratitis among 6 of these patients, 3 of whom had a corneal graft. Ten cases had epithelial dendritic ulcers and 6 cases had recurrent geographic epithelial herpetic corneal ulcers. Topical GCV 0.15% gel was given to all patients once every 6 hours for 2 weeks. Complete resolution of herpetic keratitis was noted in all patients. During the follow-up observation period, none of the 6 patients on prophylactic ganciclovir developed a recurrence of herpetic keratitis. Three (30%) of the 10 patients without prophylaxis developed recurrences of their herpetic infection. No ocular side effects from topical use of ganciclovir gel were noted. Topical ganciclovir may be helpful in the treatment of herpetic epithelial keratitis and in the prophylaxis of patients with herpetic keratitis, but larger well-controlled trials are needed to validate this finding.

The treatment and prevention of herpetic eye disease is expensive (Lairson et al 2003). In fact, approximately US$17.7 million is spent annually to treat new and recurrent cases in the US. Chronic suppressive oral acyclovir costs US$8,532 per ocular HSV episode avoided. This study also found that if a more effective antiviral prophylaxis was available, the incremental cost per infection avoided would decrease by up to 51%.

Antiviral treatment of keratoconjunctivitis caused by adenovirus

Conjunctivitis and keratoconjunctivitis caused by adenoviruses are common and highly contagious. There are

more than 50 different serotypes of adenoviruses and they are considered a major public health risk because of their ability to generate epidemics. In both the United States and Europe, they are considered the infectious agents most commonly involved in external ocular infections. Adenoviruses usually affect both eyes and patients with adenoviruses usually report a clear discharge. These patients may also have palpable and painful preauricular adenopathy. In children, adenoviral conjunctivitis is often accompanied by a fever and sore throat. Adults typically experience acute follicular inflammatory conjunctivitis with occasional hemorrhage. They usually have a red painful tearful eye with palpebral edema and foreign body sensation. While there is no licensed antiviral product available to treat this condition, antiviral agents such as ganciclovir may be possible treatments (Duggan et al 1997; Tabbara et al 2001; Bruno et al 2003; Naesens et al 2005; Kinchington et al 2005).

To limit contamination of the environment, meticulous hand hygiene as well as time off from work or school are required. These viruses are highly contagious due to the non-enveloped structure of the virion. They are resistant to body temperatures higher and lower than normal, as well as to changes in osmolarity, pH, and dehydration. Infections are transmitted directly by direct contact, in swimming pools, and by exposure to droplet nuclei. They are also transmitted indirectly through contact with handkerchiefs, utensils, and other objects contaminated with body secretions from the infected person.

Drugs active against adenoviral infections include the nucleoside analogues, which are prodrugs that required activation by a viral or cell enzyme to exercise the antiviral effect. Examples include 5-iodo-2′-desoxyuridine, trifluridine, zalcitabin, stampidine, cidofovir, and ganciclovir.

Acyclovir is inactive against adenoviruses, while ganciclovir is active, but at concentrations higher than those usually used for herpes virus inhibition (Table 9).

Tabbara and colleagues (2001) conducted a study that examined the comparative effects of ganciclovir ophthalmic gel, 0.15%, with the instillation of preservative-free artificial tears in 18 patients with adenoviral keratoconjunctivitis. Nine patients received ganciclovir and nine patients received artificial tears. In this study, the group treated with ganciclovir had a mean recovery time of 7.7 days (range: 7–12 days) compared with 18.5 days for the patients treated with artificial tears (range: 7–30 days). Two patients treated with ganciclovir and 7 patients treated with artificial tears developed subepithelial opacities. The authors of this study concluded that GCV 0.15% topical gel is safe and effective for the treatment of adenoviral keratoconjunctivitis. Early treatment with ganciclovir would reduce ocular morbidity and prevent or modify the severity of subepithelial corneal opacities.

Table 9 Inhibitory activity of ganciclovir on adenovirus

Adenovirus serotype	ED50
1	19.5 μM
2	5.4 μM
4	8.1 μM
6	9.7 μM
8	15.0 μM
10	11.0 μM
19	7.2 μM
22	5.4 μM
28	13.8 μM

Conclusions

Ocular HSV infections are a major cause of corneal blindness in the developed world. Ganciclovir ophthalmic gel, 0.15% is an effective and well tolerated antiviral treatment for superficial acute herpetic keratitis and it represents an advance in the treatment of this condition. Randomized, multicenter, comparative clinical trials that compared GCV 0.15% with ACV 3% ointment found that ganciclovir is as effective as acyclovir. Additionally, these clinical trials showed that the local tolerance of ganciclovir was better than that with acyclovir, particularly with regard to blurring and stinging or burning sensations assessed after instillation. Since ganciclovir is delivered in the form of an aqueous gel, it allows for prolonged contact time with the corneal surface. This may explain its ability to maintain comparable efficacy and better tolerance when compared with oil-based ointments.

Commercially available since 1996, GCV 0.15% ophthalmic gel is currently marketed as Virgan® by Laboratoires Théa in over 30 countries within Europe, Asia, Africa, and South America. In January 2007, Sirion Therapeutics, an ophthalmic biopharmaceutical company based in Tampa, FL, licensed the US rights to this drug. On April 16, 2007, ganciclovir ophthalmic gel, 0.15% received orphan drug designation for the treatment of acute herpetic keratitis from the US Food and Drug Administration (FDA). Sirion plans to submit a New Drug Application to the FDA in 2008. If this agent is approved for use in the US, it may provide patients with a more tolerable, convenient, and effective treatment. Based upon its proven safety and efficacy, the

introduction of a topical antiviral agent with less toxicity and a more convenient dosage regimen such as ganciclovir would clearly be a valuable tool for US clinicians who treat herpetic keratitis.

Disclosures

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