Comparative Antiviral Efficacies of Cidofovir, Trifluridine, and Acyclovir in the HSV-1 Rabbit Keratitis Model

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PURPOSE. To determine the relative antiviral inhibitory activity of topical 1% and 0.5% cidofovir, topical trifluridine (Viroptic; Burroughs-Wellcome, Research Triangle Park, NC), and topical acyclovir (Zovirax; The Wellcome Foundation, London, UK) during a 7-day period for the treatment of herpes simplex virus type 1 (HSV-1) keratitis and HSV-1 replication in the New Zealand rabbit ocular model.

METHODS. In a series of four experiments using a two-eye design, a total of 80 New Zealand rabbits were inoculated in both eyes with HSV-1 McKrae after epithelial scarring. Forty-eight hours after inoculation, the rabbits were randomly assigned to a treatment group. Five treatment groups (16 rabbits/group) were evaluated: I, 1% cidofovir, twice daily for 7 days; II, 0.5% cidofovir, twice daily for 7 days; III, 3% acyclovir ointment, five times daily for 7 days; IV, 1% trifluridine, nine times daily for 3 days, then 4 times daily for 4 days; and V, control vehicle twice daily for 7 days. HSV-1 dendritic keratitis was graded in a masked fashion by slit-lamp examination on days 2, 3, 5, 7, 9, 11, and 14. Ocular viral cultures were obtained after slit-lamp examination on days 1, 3, 5, 7, 9, 11, and 14.

RESULTS. Compared with the control group, all four treatment groups demonstrated significantly lower viral titers, fewer HSV-1-positive eyes/total during the treatment period, lower keratitis scores, fewer eyes with keratitis/total, and a shorter time to resolution of keratitis. Within the treatment groups, the 1% and 0.5% cidofovir treatments were significantly more effective than acyclovir and trifluridine as measured by the previous viral and keratitis parameters.

CONCLUSIONS. Topical 1% and 0.5% cidofovir both appeared to be significantly more efficacious than topical trifluridine and acyclovir, during a 7-day course, in the treatment of experimental HSV-1 ocular disease in the New Zealand rabbit keratitis model. (Invest Ophthalmol Vis Sci. 1999;40:378-384)

Herpes simplex virus type 1 (HSV-1) is the leading cause of infectious corneal blindness in industrialized nations. There are approximately 400,000 cases of herpes simplex ocular disease in the United States each year.¹ There are several antiviral agents available today for the treatment of HSV-1 keratitis. These antivirals include trifluridine (F3T, Viroptic; Burroughs-Wellcome, Research Triangle Park, NC), acyclovir (acycloguanosine, Zovirax; The Wellcome Foundation, London, UK), idoxuridine GDU; Herplex Liquifilm; Allergan Inc., Irvine, CA), and vidarabine (Ara-A, Vira-A; Parke-Davis, Morris Plains, NJ). IDU and trifluridine are nucleoside analogues. These agents are incorporated into the viral DNA and disrupt viral DNA synthesis. Ara-A inhibits viral DNA polymerase and acts as a viral DNA chain terminator.² Acyclovir is specifically activated by viral thymidine kinase and then is modified by cellular enzymes to form acyclovir triphosphate, which binds preferentially to HSV-1 DNA polymerase and blocks viral replication.

These antiviral agents are quite effective in the treatment of herpetic keratitis, demonstrating cure rates of 76% to 95%.³ However, there are adverse effects associated with all these drugs. Long-term use of IDU, Ara-A, and trifluridine has been associated with ocular toxicity (irritation, superficial punctate keratitis, lacrimal punctal occlusion, follicular conjunctivitis, and contact dermatitis).⁴ There are additional practical factors to consider when using these drugs. The formulation of the antiviral is one such factor. Patients complain about ointments such as acyclovir, Ara-A, or IDU because they blur vision. Frequency of administration is another important factor. Patient compliance usually decreases as the frequency of doses increases. The recommended treatment regimen for trifluridine drops is nine times a day until dendrites heal, then four times a day for 14 days. Similarly, IDU drops are administered every hour during the day and every other hour at night (18-20 doses/d) until the dendrites heal, then four times a day for 14 days. The antiviral ointments are administered five times a day for 14 days. The development of a long-acting, effective, nontoxic antiviral drop that requires less frequent daily adminis-
Cidofovir (S-HPMPC) is a promising broad-spectrum long-lasting antiviral with significant inhibitory activity against a number of DNA viruses (human cytomegalovirus, HSV-1, HSV-2, varicella-zoster virus, and adenoviruses). Cidofovir is a nucleoside analogue of cytosine that is actively transported across cell membranes. Once inside the cell, cellular kinases convert cidofovir to its active form, cidofovir-diphosphate. The antiviral effect of cidofovir-diphosphate is the result of a selective interaction with the viral DNA polymerase after which it acts as both a competitive inhibitor and as a chain terminator during DNA synthesis. The long intracellular half-life of cidofovir is probably attributed to the accumulation of the metabolite cidofovir monophosphate-choline, which may act as a reservoir for cidofovir-diphosphate.

We previously demonstrated in prevention and treatment studies that topical administration of cidofovir significantly reduced ocular viral titers and the duration of viral shedding in the Ad5 McEwen—New Zealand rabbit ocular model. Maudgal and De Clercq first demonstrated that frequent daily dosing with topical 0.2% cidofovir was effective in reducing herpetic keratitis. Subsequently, our group demonstrated that frequent dosing with 0.2% cidofovir (nine times a day × 4 days, then four times a day × 6 days) was as effective as trifluridine in reducing HSV-1 dendritic keratitis, lowering ocular viral titers, and shortening the duration of HSV-1 shedding in the tear film. Recently, Kaufman et al. also demonstrated that cidofovir was as effective as trifluridine in the treatment of experimental herpetic keratitis in rabbits.

The goal of the present study was to determine whether twice daily dosing with higher concentrations of cidofovir (1% and 0.5%) would be as effective as topical 1% trifluridine (Virotic) and 3% acyclovir (Zovirax), the current standards of care worldwide, in the treatment of experimental HSV-1 ocular disease in the New Zealand rabbit keratitis model.

### METHODS

**HSV-1 Virus Strain and Cells**

HSV-1 McKrae strain is a well-characterized neurovirulent laboratory strain that produces typical dendritic keratitis when inoculated ocularly. A stock of HSV-1 McKrae was grown in Vero cell monolayers at 37°C in a 5% CO₂-water vapor atmosphere, harvested, aliquoted, and frozen at −70°C. Before use, the stock HSV-1 McKrae was titrated using a standard plaque assay.

Vero cells, a cell line derived from African Green monkey kidneys (American Type Culture Collection [ATCC], Rockville, MD) and A549 cells, an epithelial-like cell derived from human lung carcinoma (ATCC), were grown and maintained in Eagle’s minimum essential medium with Earle’s salts (Sigma Cell Culture Reagents, St. Louis, MO), supplemented with 6% fetal bovine serum (Harlan Bioproducts for Science, Indianapolis, IN), 2.5 μg/ml amphotericin B, 100 U/ml penicillin G, and 0.1 mg/ml streptomycin (Sigma).

**Experimental Drugs**

The synthesis of cidofovir (S-HPMPC [(S)-9-(3-hydroxy-2-phosphonylmethoxypropyl)-cytosine]) was originally described by Holy et al. and was made available to us by Storz Ophthalmics (Pearl River, NY). A topical ocular formulation was prepared as 1% and 0.5% solutions. Control eye drops for cidofovir consisted of the vehicle alone.

Two antivirals used clinically for the treatment of HSV-1 keratitis, 1% trifluridine (Virotic Ophthalmic Solution) in the United States and 3% acyclovir (Zovirax Ophthalmic Ointment) worldwide were used as the standard of therapy controls.

**Animals**

Six-week-old, 1.5-kg, female New Zealand albino rabbits obtained from either Green Meadows Rabbity or Myrtle’s Rabbity were used. All animal studies conformed to the ARVO Statement on the Use of Animals in Ophthalmic and Vision Research. Institutional approval was obtained, and institutional guidelines regarding animal experimentation were followed.

**Experimental Protocol**

In a series of four experiments using a two-eye design, a total of 80 New Zealand rabbits were inoculated in both eyes after topical anesthesia with 1% proparacaine eye drops and epithelial scarification (three interlocking circles of a 7.5-mm trephine) with 50 μl (3.2 × 10⁵ plaque-forming units/eye) of HSV-1 McKrae. Forty-eight hours after inoculation, the rabbits were randomly assigned to a treatment group. The rabbits were treated with either 1% cidofovir, 0.5% cidofovir, 3% acyclovir, or vehicle control. The treatments were administered twice daily for 7 days; group IV, 1% trifluridine, nine times daily for 3 days, then four times daily for 4 days. Each frozen HSV-1 ocular sample to be titered was thawed and diluted serially (1:10) for three dilutions. Each dilution (0.1 ml) was then inoculated onto A549 cells in duplicate wells of a 24-well plate. The virus was adsorbed for 1 hour at 37°C in a 5% CO₂-water vapor atmosphere. After adsorption, 0.1 ml outgrowth media and 0.5% methylcellulose was added to each well, and the plates were incubated at 37°C in a 5% CO₂-water vapor atmosphere. The wells were examined daily for progressive cytopathic effect, samples were stained with 0.5% gentian violet after 4 days, and the number of plaques per well was counted under a dissecting microscope (25×). The ocular HSV-1 titer was then calculated and expressed as plaque-forming units per milliliter.

**Determination of HSV-1 Ocular Titters**

Each frozen HSV-1 ocular sample to be titered was thawed and diluted serially (1:10) for three dilutions. Each dilution (0.1 ml/well) was then inoculated onto A549 cells in duplicate wells of a 24-well plate. The virus was adsorbed for 1 hour at 37°C in a 5% CO₂-water vapor atmosphere. After adsorption, 1 ml outgrowth media plus 0.5% methylcellulose was added to each well, and the plates were incubated at 37°C in a 5% CO₂-water vapor atmosphere. The wells were examined daily for progressive cytopathic effect, samples were stained with 0.5% gentian violet after 4 days, and the number of plaques per well was counted under a dissecting microscope (25×). The ocular HSV-1 titer was then calculated and expressed as plaque-forming units per milliliter.

**Statistical Analysis**

After the completion of all experiments, the data from each experiment were analyzed statistically. Because comparable results were obtained in each experiment, the data were then pooled to obtain a larger subject number and analyzed using the appropriate statistical test (analysis of variance [ANOVA],
TABLE 1. Assessment of HSV-1 Replication in the HSV-1 New Zealand Rabbit Keratitis Model

<table>
<thead>
<tr>
<th></th>
<th>1% Cidofovir</th>
<th>0.5% Cidofovir</th>
<th>3% Acyclovir</th>
<th>1% Trifluridine</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ocular titer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(day 7), pfu/ml§</td>
<td>0.5 ± 2.7 × 10^2*</td>
<td>2.5 ± 9.3 × 10^2*</td>
<td>2.3 ± 6.4 × 10^2*</td>
<td>1.5 ± 4.0 × 10^2*</td>
<td>1.4 ± 2.3 × 10^5</td>
</tr>
<tr>
<td>HSV-1-positive eyes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>per total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days 3-14 (overall)</td>
<td>48/174 (28)†</td>
<td>65/180 (36)†</td>
<td>104/174 (60)†</td>
<td>134/176 (77)</td>
<td>127/178 (71)</td>
</tr>
<tr>
<td></td>
<td>48/91 (53)†</td>
<td>65/96 (68)†</td>
<td>69/92 (75)†</td>
<td>84/96 (88)*</td>
<td>91/91 (100)</td>
</tr>
<tr>
<td>Days 9-14 (after Rx)</td>
<td>0/83 (0)†</td>
<td>0/84 (0)†</td>
<td>35/82 (43)</td>
<td>50/80 (63)*</td>
<td>36/87 (41)</td>
</tr>
<tr>
<td>Mean duration of HSV-1 shedding (days)$§</td>
<td>4.1 ± 1.5†</td>
<td>5.1 ± 0.9†</td>
<td>8.2 ± 4.3‡</td>
<td>9.7 ± 3.9</td>
<td>9.6 ± 1.9</td>
</tr>
</tbody>
</table>

Rx, treatment.
* P < 0.05 when compared with control.
† P < 0.05 when compared with acyclovir and trifluridine.
‡ P < 0.05 when compared with trifluridine.
§ Analysis of variances, Duncan multiple comparison test.
|| Chi-square analysis. Values in parentheses are percentages.

Kruskal–Wallis ANOVA, Duncan multiple comparisons test for ANOVA and Kruskal–Wallis ANOVA, Monte Carlo Randomization Test, Fisher exact test, and chi-square analysis). Significance was established at the P ≤ 0.05 confidence level.

RESULTS

Efficacy of Cidofovir, Trifluridine, and Acyclovir Treatment on HSV-1 Replication: Serial HSV-1 Ocular Titers

The mean HSV-1 ocular titers for all groups were determined by calculating the mean of all HSV-1 cultures per group per day. These results are demonstrated in Table 1 (day 7) and graphically in Figure 1. All antivirals tested demonstrated lower mean HSV-1 titers compared with the control group (ANOVA, Duncan multiple comparisons test, P < 0.0005), with no differences among the treatment groups, on days 3, 5, 7, and 9. The trifluridine (day 11) and acyclovir (day 14) groups demonstrated a significant increase in mean viral titers (rebound) compared with the control and 1%, and 0.5% cidofovir groups (P ≤ 0.02), after the cessation of treatment. In contrast, eyes treated with either 1% or 0.5% cidofovir demonstrated no rebound of viral titers after the cessation of treatment.

HSV-1-Positive Eyes per Total

The number of HSV-1 positive eyes per total was determined for each group by ascertaining the number of eye swabs that demonstrated a positive HSV-1 culture per total number of cultures. Table 1 summarizes these results. Overall from days 3 to 14, 1% and 0.5% cidofovir and acyclovir demonstrated fewer HSV-1-positive eyes than the control and trifluridine groups (chi-square analysis, Fisher exact test, P < 0.000001, P < 0.000001, P < 0.03, respectively). Trifluridine demonstrated no difference compared with the control. There was no difference between 1% and 0.5% cidofovir, and both had fewer HSV-1-positive eyes than the acyclovir group (P < 0.00002).

From days 9 to 14, after the cessation of treatment, 1% and 0.5% cidofovir groups demonstrated complete clearance of virus from all eyes. In contrast, the acyclovir and trifluridine groups maintained more HSV-1-positive eyes than both cidofovir groups (P < 0.000001). Acyclovir demonstrated a com-

FIGURE 1. Demonstration of the mean HSV-1 ocular titers over time for 0.5% cidofovir (O), 1% cidofovir (D), trifluridine (Δ), acyclovir (V), and control (C) groups. Asterisks denote the days on which all antiviral treatments demonstrated significantly lower mean HSV-1 ocular titers than the control group. The y axis is a log scale.
parable number of HSV-1-positive eyes from days 9 to 14 to that of the control group but fewer than the trifluridine group ($P < 0.02$). The trifluridine group also demonstrated more ($P = 0.01$) than the control group. The number of HSV-1-positive eyes per group are different (Table 1) because the HSV-1 inoculation of several of the rabbit eyes was unsuccessful, and some of the rabbits died before the end of the study due to viral encephalitis.

Percentage of HSV-1-positive eyes per day is demonstrated graphically in Figure 2. There were no differences among the treatment groups and the control group on days 1 and 3. On day 5, the 1% cidofovir group demonstrated fewer HSV-1-positive eyes than all other groups (Monte Carlo Randomization Test, $P < 0.001$). By day 7, all treatment groups had fewer HSV-1-positive eyes than the control group ($P < 0.03$). Both cidofovir groups and the acyclovir group demonstrated fewer positive eyes than the trifluridine group ($P < 0.002$). On days 9 and 11 the 1% and 0.5% cidofovir groups demonstrated fewer HSV-1-positive eyes than the control, trifluridine, and acyclovir groups and on day 14 fewer than the trifluridine and acyclovir groups ($P < 0.0008$). The acyclovir group had fewer HSV-1-positive eyes than the control group on day 9 ($P < 0.002$) and fewer than the trifluridine group on day 11 ($P = 0.05$). However, on days 11 and 14 for the trifluridine group and day 14 for the acyclovir group, these groups had more HSV-1-positive eyes than the control group ($P < 0.05$) due to the rebound of viral replication.

### Duration of Shedding

The duration of HSV-1 shedding was ascertained for each eye by determining the final day on which a positive HSV-1 culture was detected and calculating the mean for each treatment group. These results are presented in Table 1. The 1% and 0.5% cidofovir groups demonstrated a significant reduction in the mean duration of shedding (3 to 5 days) compared with the control, trifluridine, and acyclovir groups (ANOVA, Duncan multiple comparisons, $P < 0.00004$). There were no differences between the cidofovir groups, between the trifluridine and control groups, and between the acyclovir and control groups. However, the acyclovir group did demonstrate a significant decrease in mean duration of shedding compared with the trifluridine group ($P < 0.04$).

### Efficacy of Cidofovir, Trifluridine, and Acyclovir Treatments on HSV-1 Keratitis: Serial Keratitis Scores

The mean epithelial keratitis scores were determined by calculating the mean keratitis scores of all eyes per group per day. These results are presented in Table 2 (day 7) and graphically in Figure 3. On days 3 to 11, all antiviral treatment groups demonstrated lower keratitis scores than the control group (Kruskal–Wallis ANOVA, Duncan multiple comparisons, $P < 0.01$) except for trifluridine on day 11, which was no different from the control group. From days 5 to 14, 1% and 0.5% cidofovir groups had lower keratitis scores than trifluridine and acyclovir groups ($P < 0.01$), whereas there were no differences between the 1% cidofovir group and the 0.5% cidofovir group. During this period, acyclovir-treated eyes demonstrated lower keratitis scores than the trifluridine group ($P < 0.01$). On day 14, a rebound in keratitis scores was demonstrated in the acyclovir and trifluridine groups that correlated to an increase in viral titers, with the result that their scores were greater

### Table 2. Assessment of HSV-1 Keratitis in the HSV-1 New Zealand Rabbit Keratitis Model

<table>
<thead>
<tr>
<th></th>
<th>1% Cidofovir</th>
<th>0.5% Cidofovir</th>
<th>3% Acyclovir</th>
<th>1% Trifluridine</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean keratitis score (day 7)</td>
<td>$0^*$</td>
<td>$0.3 \pm 0.1^*$</td>
<td>$0.3 \pm 0.3^*$</td>
<td>$0.7 \pm 0.5^*$</td>
<td>$2.3 \pm 0.5$</td>
</tr>
<tr>
<td>Eyes with keratitis per total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days 3–14 (overall)</td>
<td>$26/174 (15)^*$</td>
<td>$41/180 (23)^*$</td>
<td>$75/174 (43)^*$</td>
<td>$134/176 (76)^*$</td>
<td>$116/178 (65)^*$</td>
</tr>
<tr>
<td>Days 3–7 (Rx period)</td>
<td>$24/91 (26)^*$</td>
<td>$36/96 (38)^*$</td>
<td>$56/92 (61)^*$</td>
<td>$81/96 (84)^*$</td>
<td>$91/91 (100)^*$</td>
</tr>
<tr>
<td>Days 9–14 (after Rx)</td>
<td>$2/85 (2)^*$</td>
<td>$7/84 (8)^*$</td>
<td>$53/82 (40)^*$</td>
<td>$53/80 (66)^*$</td>
<td>$54/87 (62)^*$</td>
</tr>
<tr>
<td>Mean time to resolution of keratitis (days)$^*$</td>
<td>$4.5 \pm 0.9^*$</td>
<td>$5.3 \pm 1.1^*$</td>
<td>$7.0 \pm 2.8^*$</td>
<td>$7.9 \pm 4.1^*$</td>
<td>$13.2 \pm 1.3^*$</td>
</tr>
</tbody>
</table>

$^*$ Rx, treatment; ANOVA, analysis of variance.

† $P < 0.05$ when compared with control.

‡ $P < 0.05$ when compared with cidofovir and trifluridine.

§ Kruskal–Wallis ANOVA, Duncan multiple comparisons test.

‖ Chi-square analysis. Values in parentheses are percentages.

$^*$ ANOVA, Duncan multiple comparison test.
The number of eyes with epithelial keratitis per total (Table 2) was calculated for each group by determining the number of eyes that demonstrated at least a minimal keratitis score per total number of eyes examined. Overall from days 3 to 14, the 1% cidofovir, 0.5% cidofovir, and acyclovir groups all demonstrated significantly fewer eyes with keratitis than the control and trifluridine groups as demonstrated by chi-square analysis, Fisher exact test, and control (O), acyclovir (V), and trifluridine (A) groups. Days on which the 1% and 0.5% cidofovir groups demonstrated significantly fewer eyes with keratitis than the trifluridine and acyclovir groups, 0.5% cidofovir (O), 1% cidofovir ( ), trifluridine (A), acyclovir (V), and control (O) groups. Days on which the 1% and 0.5% cidofovir groups demonstrated fewer eyes with keratitis than the control group on days 5, 7, and 14 only (P < 0.000001) and from days 5 to 14 had fewer than the acyclovir and trifluridine groups (P ≤ 0.03). The 0.5% cidofovir group demonstrated several eyes with keratitis on days 9, 11, and 14, and the 1% cidofovir group had several eyes with keratitis on day 14, but this keratitis was not associated with any viral replication. The trifluridine group demonstrated fewer eyes with keratitis than the control group on days 5 and 9 only (P < 0.005) and the acyclovir group on days 5, 7, and 9 only (P < 0.000006). The acyclovir group had fewer eyes with keratitis than the trifluridine group on days 5, 7, and 14 (P ≤ 0.03).

Time to Resolution of Keratitis
The time to resolution of keratitis was ascertained for each eye by determining the first day on which a negative keratitis examination was detected after a previously positive examination and then calculating the mean time for each treatment group. These results are presented in Table 2. All antiviral treatment groups demonstrated a significant reduction in the mean time to resolution of keratitis compared with the control group (ANOVA, Duncan multiple comparisons test, P < 0.000001). In addition, the 1% and 0.5% cidofovir groups demonstrated a shorter mean time to resolution of keratitis than the acyclovir and trifluridine groups (P ≤ 0.009). There were no differences between the two cidofovir groups or between the trifluridine and acyclovir groups.

Discussion
Cidofovir is a promising broad-spectrum antiviral with significant in vitro inhibitory activity against a number of DNA viruses...
human cytomegalovirus, HSV-1, HSV-2, varicella-zoster virus, and adenoviruses). Cidofovir (Vistide; Gilead Sciences, Foster City, CA) is now available in the United States and Europe as an approved systemic therapy for cytomegalovirus retinitis in AIDS patients. It has been used experimentally both topically and systemically to treat AIDS patients with mucocutaneous infections due to acyclovir-resistant HSV. Maudgal and De Clercq first demonstrated that frequent daily dosing with topical 0.2% cidofovir was effective in reducing herpetic keratitis in rabbits. Subsequently, our group demonstrated that frequent daily dosing with 0.2% cidofovir was as effective as trifluridine in reducing HSV-1 keratitis and viral replication in the HSV-1-New Zealand rabbit keratitis model.

In the present study, all the antiviral agents tested were effective in reducing HSV-1 ocular replication and keratitis compared with the control group. However, treatment with either 1% or 0.5% cidofovir twice daily was significantly more effective than trifluridine and acyclovir in their multidose regimens during the 7-day treatment period. After the cessation of treatment, there was total clearance of virus from all eyes in the 1% and 0.5% cidofovir groups, and there was no rebound of HSV-1 replication and keratitis such as demonstrated in the trifluridine and acyclovir groups. This study confirms and extends those previous reports by demonstrating that twice daily dosing with higher concentrations of cidofovir (1% and 0.5%) was more effective in reducing HSV-1 replication and keratitis than the current standards of care, over a 7-day treatment period, in the New Zealand rabbit keratitis model.

The present study also demonstrated that 3% acyclovir ointment was superior to 1% trifluridine drops in the treatment of experimental herpetic keratitis during the 7-day treatment period. These results differ from those obtained from two previous clinical trials that demonstrated no significant difference between trifluridine and acyclovir in the treatment of herpetic keratitis. However, those clinical studies compared 3% acyclovir ointment to 2% trifluridine ointment using the same treatment regimen (5 times per day until the dendrites healed or a maximum of 2 weeks). The differences between the vehicles (liquid drops versus ointment), concentrations of trifluridine (1% versus 0.2%), and the duration of treatment (7 days versus therapy until the dendrites healed or a maximum of 2 weeks) may explain the differences in results between the present study and previous studies.

This study was specifically designed to assess whether the long intracellular half-life of cidofovir observed in vitro would reflect as prolonged antiviral inhibitory activity compared with trifluridine and acyclovir in an in vivo herpetic eye model. Recommended clinical treatment for both antivirals calls for 14 days of continuous therapy. Consequently, the experimental design of this study does not reflect the antiviral efficacy of trifluridine and acyclovir therapy after 2 weeks of treatment. In the present study, if the therapy had not been abruptly terminated at 7 days, there would not have been a rebound of HSV-1 ocular titers and keratitis.

Treatment of patients with HSV-1 ocular disease using topical 1% or 0.5% cidofovir offers several potential advantages over the current standards of care. The advantages of cidofovir over trifluridine would include decreased frequency of dosing (twice daily for cidofovir versus nine times daily for trifluridine), decreased duration of treatment (7 days versus 14 days), decreased toxicity (topical 0.5% cidofovir twice daily for 7 days has been shown to be nontoxic to the corneas of healthy volunteers and topical administrations of as much as 2% cidofovir twice daily for 10 days have been demonstrated to be nontoxic to corneas of uninfected New Zealand rabbits), and, possibly, better antiviral efficacy. The advantages of cidofovir over acyclovir would include decreased frequency of dosing (twice daily for cidofovir versus five times daily for acyclovir), decreased duration of treatment (7 days versus 14 days), formulation (liquid drop versus ointment), and, possibly, better antiviral efficacy.

This study also demonstrated that 1% cidofovir was slightly more effective than 0.5% cidofovir in the rapid reduction of viral replication and keratitis. This is most likely because of a quicker achievement of therapeutic tissue levels of cidofovir with the more concentrated solution. This slight early advantage was quickly overcome by continued treatment with 0.5% cidofovir. Despite these findings, there were no major differences between 0.5% cidofovir and 1% cidofovir in the treatment of HSV-1 ocular disease in the New Zealand rabbit keratitis model. We therefore advocate topical 0.5% cidofovir twice daily for 7 days as the treatment for HSV-1 keratitis in patients. Phase 2 clinical trials are currently under way to determine the efficacy of this treatment regimen.

Topical trifluridine and acyclovir have been shown to be very effective in the treatment of HSV-1 ocular disease. In order for a new topical antiviral agent to be introduced for patient use, it must be as effective as or more effective than current antivirals. It should be formulated as a liquid, require infrequent daily dosing for fewer days, and be nontoxic to the eye. Cidofovir meets all these criteria in experimental and phase 1 clinical studies. If phase 2 and 3 clinical studies confirm these findings, then topical cidofovir would represent a significant improvement over current topical antiviral agents for the treatment of ocular herpes simplex infections.

References


