Oral Acyclovir After Penetrating Keratoplasty for Herpes Simplex Keratitis

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Objective: To determine the efficacy of systemic acyclovir in decreasing complications and improving the outcome of penetrating keratoplasty for herpes simplex virus (HSV) keratitis.

Methods: Retrospective study of 53 primary penetrating keratoplasties for HSV keratitis at an eye hospital from January 1, 1989, through December 31, 1996. Medical records were analyzed for history of HSV keratitis, preoperative neovascularization, and disease activity. Postoperative use of acyclovir, recurrence of HSV keratitis, rejection, uveitis or edema, and graft failure were evaluated.

Results: Twenty-four patients (mean ± SD follow-up, 44.7 ± 32.6 months) received no acyclovir and were compared with 20 patients, (mean ± SD follow-up, 28.8 ± 16.7 months), who received 400 mg acyclovir twice a day for at least 1 year. No patient in the acyclovir group had a recurrence of dendritic keratitis in the first year compared with 5 (21%) of the patients who did not receive acyclovir (P = .03). No patient had graft failure in the acyclovir group compared with 4 (17%) in the group without acyclovir after 1 year of follow-up (P = .06).

Conclusion: Postoperative systemic acyclovir therapy after penetrating keratoplasty for HSV keratitis is associated with a reduced rate of recurrent HSV dendritic keratitis and possible graft failure at 1 year of follow-up.


Ocular herpes simplex virus (HSV) is a prevalent disease worldwide. It is estimated that 400,000 to 500,000 people are affected in the United States.1,2 Recurrent epithelial disease, stromal keratitis, and iritis can cause scarring and loss of vision that may require penetrating keratoplasty for visual rehabilitation. Approximately 3.6% of all corneal grafts performed at Wills Eye Hospital, Philadelphia, Pa, from January 1, 1989, through December 31, 1995, were for viral keratitis (herpes simplex and herpes zoster).3 After the corneal transplant, there remains the risk for recurrent HSV keratitis contributing to corneal scarring and graft failure. In addition, herpes simplex keratitis may be associated with increased risk for allograft rejection, contributing to a poor outcome.

The use of topical antiviral agents has been associated with decreased recurrent herpetic keratitis during treatment of allograft rejection episodes.4,5 Prophylactic use after corneal transplantation causes toxic effects without evidence of benefit.6,7 The Acyclovir Prevention Trial of the Herpetic Eye Disease Study (HEDS) evaluated the efficacy of long-term oral acyclovir therapy in reducing recurrent episodes of HSV in patients with a history of HSV keratitis but who have not undergone corneal transplantation. We evaluated the effect of oral acyclovir therapy for at least 1 year on recurrent HSV dendritic keratitis, graft rejection, graft failure, and episodes of corneal edema or uveitis 1 and 2 years after penetrating keratoplasty and compared these outcomes with those of patients who did not receive postoperative acyclovir.

RESULTS

The mean age of the 53 patients was 56.5 ± 18.9 years. The study population included 20 women and 33 men. The average follow-up was 37.9 ± 25.5 months.

Of the 53 patients, the 24 in group 1 were observed for 44.7 ± 30.6 months. The 20 patients in group 2 were observed for 28.8 ± 16.7 months. Twelve (60%) of the 20 received 12 months of acyclovir; 4 (20%), 18 to 24 months; and 4 (20%), 30 months or longer. Follow-up was significantly shorter in patients treated with acyclovir than those who were not (P = .04), due to increasing use of acyclovir during the study period. The 9 patients in group 3 were observed for an average of 40.3 ± 20.9 months. Due to the small num-
PATIENTS AND METHODS

Five surgeons at Wills Eye Hospital performed 58 primary penetrating keratoplasties for HSV keratitis during the study. We retrospectively reviewed the medical records of 53 patients who were observed for a minimum of 1 year after the operation (records of 5 patients who had surgery in 1989 were missing). The diagnosis of HSV keratitis was based on the clinical history documented in the medical record. The following information was recorded for each patient: age, sex, number of past recurrences, activity of the disease, and preoperative visual acuity. The extent of preoperative neovascularization was graded as 1 for avascular; 2, mild (superficial vessels only); 3, moderate (superficial and deep vessels in 1 to 3 quadrants); or 4, severe (superficial and deep vessels in 4 quadrants). Surgical technique, surgeon experience, and postoperative management were similar in all cases. All patients received postoperative topical steroids. Topical antivirals were used for recurrent dendritic keratitis and prophylaxis during high-dose topical steroid therapy for episodes of graft rejection, uveitis, or new onset of corneal edema. Trifluridine was used routinely 8 times a day to treat dendritic keratitis and 4 times a day for prophylaxis. Occasionally, an additional 400 mg of acyclovir was used 5 times a day for dendritic or geographic ulcers.

The use of prophylactic oral acyclovir started in 1992 and was routine by 1993. Group 1 consisted of 24 patients who did not receive postoperative acyclovir. Group 2 consisted of 20 patients who received postoperative oral acyclovir, 400 mg twice a day for at least 12 months. Group 3 included 9 patients who received postoperative oral acyclovir for 1 to 11 months. Use of acyclovir, 400 mg twice a day for 1 year or more, was analyzed for effect on complications and outcome, including graft failure, recurrent dendritic keratitis, rejection episodes, and development of uveitis or corneal edema. In our study, the diagnosis of a rejection episode required a new endothelial rejection line, subepithelial infiltrates, and/or an epithelial rejection line. New onset of keratic precipitates, uveitis, and/or corneal edema could represent rejection or recurrent HSV keratouveitis and was analyzed separately from graft rejection.

The results were analyzed using the $\chi^2$ test for independence, Kaplan-Meier survival curves, and the log rank test. Unless otherwise indicated, data are given as mean ± SD.

Table 1. Penetrating Keratoplasty for Active HSV Keratitis*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Preoperative Condition</th>
<th>Use of Oral Acyclovir†</th>
<th>HSV Recurrence</th>
<th>Outcome</th>
<th>Length of Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Descemetocoele</td>
<td>Group 2</td>
<td>No</td>
<td>Clear</td>
<td>3 y</td>
</tr>
<tr>
<td>2</td>
<td>Descemetocoele</td>
<td>Group 1</td>
<td>Yes</td>
<td>Failed</td>
<td>9 mo</td>
</tr>
<tr>
<td>3</td>
<td>Neurotrophic ulcer</td>
<td>Group 1</td>
<td>Chronic ulcer</td>
<td>Failed</td>
<td>8 mo</td>
</tr>
<tr>
<td>4</td>
<td>Necrotizing keratitis</td>
<td>Group 3</td>
<td>Edema</td>
<td>Failed</td>
<td>29 mo</td>
</tr>
<tr>
<td>5</td>
<td>Necrotizing keratitis</td>
<td>Group 3</td>
<td>Edema</td>
<td>Failed</td>
<td>3 mo</td>
</tr>
</tbody>
</table>

*HSV indicates herpes simplex virus.
†Groups are described in the “Patients and Methods” section.

Of the 53 patients, only 5 (9%) had active disease at the time of the surgery (Table 1). There were no statistically significant differences in disease activity between groups 1 and 2. The small number of patients with active disease who had grafts reflects improved medical management of HSV keratitis and the strong preference to delay surgery until disease is inactive whenever possible. There was no statistically significant difference between groups 1 and 2 regarding severity of preoperative corneal neovascularization (Table 2). There was a slight tendency for patients receiving acyclovir to have a preoperative history of more frequent episodes of recurrent HSV keratitis ($P = .15$).

We observed recurrent HSV dendritic keratitis in 5 (9%) of 53 patients during the first year and an additional 1 (3%) of 35 during the second year. During the first year, there was a statistically significant difference between groups 1 and 2 when comparing the recurrence rate of HSV keratitis ($P = .03$; Table 3). No patient in group 2 had a recurrence of HSV compared with 5 patients (21%) in group 1. One patient in group 1 had 2 episodes of dendritic keratitis during the first year. During the second year, there was 1 additional failure in 1 patient (6%) in group 1, compared with none in group 2 patients ($P = .41$).
The overall graft survival curve shows 90% survival at 12 months and 82% at 36 to 60 months (Figure 2). In group 1, the survival was 83% at 12 months and 72% at 36 to 60 months, compared with 100% at 48 months in group 2 (P = .03). Overall, 9 grafts failed. Graft failure followed epithelial recurrence in 2 patients (22%), endothelial rejection in 1 patient (11%), and uveitis or edema in 6 patients (67%). Two of these 6 patients also had recurrent HSV epithelial keratitis before the failure. Among the 9 patients with failed grafts, 3 (33%) had glaucoma diagnosed previously or after the surgery, compared with 6 (14%) among the 44 patients without graft failure (P = .15).

We grouped together epithelial rejection, subepithelial infiltrates, and endothelial rejection lines with or without graft edema for analysis of the effect of acyclovir on graft rejection episodes. Overall, 9 patients (17%) experienced rejection episodes during the first year of follow-up and 3 (9%) during the second year of follow-up (Table 3). During the first year of follow-up, rejection episodes occurred in 3 (12%) of 24 patients in group 1 and 3 (15%) of 20 patients in group 2 (P = .81). During the second year, 1 additional patient (6%) experienced rejection in group 1 and 2 additional patients (18%) in group 2 (P = .30). No statistical significance was found in rejection episodes between groups (P = .61).

The overall survival curve shows 82% rejection-free survival at 12 months, 67% at 36 months, and 63% at 48 to 60 months. Group 1 had a rejection-free survival of 86% at 12 months, 66% at 36 to 48 months, and 61% at 60 months, compared with 85% at 12 months, 61% at 36 months, and 54% at 48 months in group 2.

Patients in whom new-onset graft edema or uveitis developed without an endothelial rejection line underwent separate analysis because these signs could represent graft rejection or recurrent herpes simplex kerato-uveitis. Overall, during the first year of follow-up, 10 patients (19%) had episodes of uveitis or edema, 5 (21%) in group 1 and 3 (15%) in group 2 (P = .62). Overall during the second year, 9 patients (26%) had episodes of uveitis or edema, including 6 patients (35%) in group 1 and 3 (27%) in group 2 (P = .66). Uveitis or edema developed after more than 2 years of follow-up in 9 patients.

The overall uveitis- and edema-free survival was 83% at 12 months, 65% at 36 months, and 58% at 60 months. In group 1, 82% of the patients were free of uveitis or edema episodes at 12 months, 58% at 36 months, and 48% at 60 months, compared with 90% at 12 months and 68% at 36 months in group 2. There was no statistical significance between groups 1 and 2 with regard to the development of graft edema or uveitis (P = .31).

We calculated the rates of complications when patients were receiving and not receiving oral acyclovir regardless of previous acyclovir use. Patients not receiving acyclovir had a 17% chance per year of recurrent HSV dendritic keratitis developing vs 0% while receiving acyclovir (P = .05). They had an 18% chance per year of experiencing a rejection episode, with no difference if they were or were not receiving acyclovir. Finally, if patients were receiving acyclovir, their chance of having uveitis or edema was 22% per year vs 40% when they were not.

Best corrected visual acuity was 20/100 or better at 1 year of follow-up in 15 (62%) of the 24 patients in group 1 compared with 16 (80%) of 20 in group 2 (Table 4).
of the 24 patients in group 1, 4 (16%) had visual acuity of counting fingers to light perception, all of them with failed grafts, compared with no patient with this outcome in group 2 (P = .25) (Table 4). During the second year of follow-up, 10 (59%) of the patients in group 1 achieved visual acuity of 20/100 or better, compared with 8 (73%) in group 1. The 2 patients with poor visual acuity (light perception and hand motions) were in group 1 (Table 4).

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The use of acyclovir as a prophylactic agent was first studied for herpetic genital and labial infections and more recently for ocular infections. In patients with recurrent genital HSV, several studies revealed that oral acyclovir diminished the frequency and severity of HSV recurrences. Others have reported that prophylactic oral acyclovir therapy suppresses recurrent orolabial or genital HSV infection in patients receiving immunosuppressive drugs while undergoing bone marrow or organ transplants. Short-term oral acyclovir therapy has been reported to be effective in treating herpes simplex ocular infections. Simon and Pavan-Langston studied 13 patients with a history of frequently recurring HSV keratitis who, during long-term systemic acyclovir therapy, had a decrease in the number of recurrences per month from 0.15 to 0.03 and a decrease in the average duration of relapses from 12.6 to 7.8 days.

The HEDS Epithelial Keratitis Trial found that a 3-week course of acyclovir, 400 mg 5 times a day, did not prevent the development of herpetic stromal keratitis or uveitis in patients with trifluridine-treated dendritic keratitis. The HEDS Acyclovir Prevention Trial demonstrated the efficacy of acyclovir in reducing recurrent HSV keratitis in patients without grafts during 1 year of treatment with acyclovir, 400 mg twice a day.

Acyclovir has also been evaluated for use in patients with HSV who have undergone penetrating keratoplasty. Barney and Foster reported that there were no recurrences of herpes simplex keratitis after penetrating keratoplasty in a small series of patients receiving oral acyclovir (14 patients) compared with recurrence in 4 (44%) of 9 patients not receiving acyclovir (P<.01). Graft failure occurred in 2 (14%) of 14 acyclovir-treated patients compared with 5 (56%) of 9 patients not receiving acyclovir. Beyer et al observed that oral acyclovir in a rabbit autograft penetrating keratoplasty model significantly lowered the incidence of HSV ocular shedding (0% vs 82%), geographic ulceration (10% vs 82%), and stromal keratitis (12% vs 56%).

The incidence of HSV keratitis after penetrating keratoplasty depends on length of follow-up. The recurrence rate is highest during the first year of follow-up after penetrating keratoplasty, perhaps due to the use of frequent topical corticosteroids, which enhances infection during episodes of viral shedding. However, patients remain at risk for recurrent dendritic keratitis indefinitely. In a previous report reviewing the results of corneal transplantations performed for HSV keratitis from 1970 to 1979 at our institution, Cohen et al found a recurrence of HSV keratitis in 11 (10.3%) of 107 patients during the first year of follow-up and 20 (18.7%) of 107 after a median follow-up of 3 years. Other studies have reported recurrent herpes dendritic keratitis in 10% to 25% of patients during the first year of follow-up and in 9% to 21.6% during 2 to 5 years of follow-up. In patients treated for rejection with frequent topical corticosteroids without prophylactic antivirals, the rates are higher, with 15% to 28% of patients having recurrences during the first year and 18% to 45% during the second through the fifth years. We observed a statistically significant reduction in dendritic keratitis from 10% to 0% in patients treated with acyclovir for 1 year (P = .03).

The graft survival rate at 2 to 5 years varies from 60.4% to 80%, depending on the length of follow-up and use of antivirals when high-dose steroids are prescribed. In a previous report, an overall graft clarity in 86 (80.4%) of 107 patients was found after a mean follow-up of 3 years. In this series, our overall surgical rate was 82% at 5 years. We observed a failure rate of 10% during the first year of follow-up and 3% during the second year. Again, 4 failures occurred in group 1, with no failures in group 2 for at least 1 year. The reduction in graft failure rate at 1 year approached significance (P = .06).

Due to the difficulty in differentiating allograft rejection and herpetic keratouveitis after keratoplasty, a patient with known herpes, we decided to categorize only patients who developed a new endothelial rejection line, epithelial rejection line, and/or subepithelial infiltrates as having rejection episodes. Not surprisingly, systemic acyclovir did not reduce the rejection rate. The rejection rate was somewhat higher, but not significantly so, in group 2, perhaps because initially acyclovir was given to patients who were thought to have a worse prognosis. Episodes of uveitis or edema were less frequent in group 2, but not significantly so. Acyclovir may reduce uveitis or edema caused by recurrent HSV but not graft rejection.

Adverse side effects of long-term acyclovir therapy include reversible renal damage caused by deposition of crystals in the renal tubules, reversible toxic effects on bone marrow, diarrhea, and potential mutagenicity. One patient in our population with mild renal insufficiency unknown to him required temporary dialysis following systemic acyclovir treatment. Although evaluation of renal function is not recommended before use of acyclovir, the drug should be avoided in patients with known renal disease, and people at risk for kidney problems

<table>
<thead>
<tr>
<th>Table 4. Visual Acuity at 1 and 2 Years of Follow-up*</th>
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<tr>
<td><strong>No. (%) of Patients, Length of Follow-up</strong></td>
</tr>
<tr>
<td><strong>Group 1</strong></td>
</tr>
<tr>
<td><strong>Group 2</strong></td>
</tr>
<tr>
<td>Visual Acuity</td>
</tr>
<tr>
<td>20/20-20/40</td>
</tr>
<tr>
<td>20/50-20/100</td>
</tr>
<tr>
<td>20/200-20/400</td>
</tr>
<tr>
<td>CF-LP</td>
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</tbody>
</table>

* CF indicates counting fingers; LP, light perception. Groups are described in the “Patients and Methods” section. For group 1 vs group 2, P = .25 at 1 year; P = .40 at 2 years.

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should be cleared by their physicians before using acyclovir. The HEDS protocol recommends that men and women discontinue acyclovir therapy 3 months before conception. Contraception should be discussed with patients before beginning oral acyclovir therapy. However, systemic acyclovir is used prophylactically late in pregnancy in patients with a history of genital HSV infection to reduce the likelihood of recurrent infection at the time of delivery and the need for caesarean section to prevent neonatal herpes.30

One important issue to be clarified is the dosing and duration of acyclovir prophylaxis after penetrating keratoplasty for herpes simplex keratitis. It is an expensive drug, with potential side effects. Our patients used oral acyclovir, 400 mg twice a day after surgery for at least 1 year, based on the dosage used in the HEDS Acyclovir Prevention Trial. We do not have data to support use beyond 1 year, given the duration of follow-up in patients in group 2 and variable use of acyclovir after 1 year. Some authors suggest a higher postoperative dose in recent penetrating keratoplasties, although 400 mg twice a day was found generally to be the minimal effective dose in preventing recurrences.31 One year may be a reasonable duration of treatment, since most herpetic recurrences occur within the first year, but the benefits can only be expected while the patient is receiving the drug.19,22,23

Our study design has limitations because it is retrospective and not randomized. There is the potential for subtle, unknown, or unrecognized changes in management between the historical control and acyclovir groups. The cost of acyclovir did not seem to influence who was prescribed or who received acyclovir. It is difficult to perform a prospective randomized study, because herpes simplex keratitis is an uncommon indication for penetrating keratoplasty.

The results of the HEDS Acyclovir Prevention Trial may be applicable to patients with grafts. However, patients with grafts differ from patients in the HEDS Acyclovir Prevention Trial, not only with regard to the presence of a corneal transplant but also with regard to the use of topical steroids before and after surgery. Patients with multiple recurrences of HSV keratitis require grafts due to scarring and loss of visual acuity and have the severe end of the spectrum ocular herpes. If acyclovir is beneficial for patients with less severe disease and fewer recurrences, it is likely to also benefit patients who require grafts. Given the efficacy of acyclovir in reducing recurrences demonstrated in the HEDS Acyclovir Prevention Trial, it would probably be ethically inappropriate to randomize patients undergoing penetrating keratoplasty to receive placebo vs acyclovir in a prospective study. The HEDS Acyclovir Prevention Trial did not answer the question of when to use acyclovir for longer than 1 year. Further studies are needed to evaluate the risks and benefits of long-term acyclovir prophylaxis.

At present, we recommend the use of oral acyclovir, 400 mg twice a day, in patients without contraindications for at least 1 year after penetrating keratoplasty for herpes simplex keratitis due to a significant reduction of recurrent dendritic keratitis and tendency toward improved graft survival observed in our patients.

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REFERENCES