ACYCLOVIR FOR THE PREVENTION OF RECURRENT HERPES SIMPLEX VIRUS EYE DISEASE

THE HERPETIC EYE DISEASE STUDY GROUP*

ABSTRACT
Background Long-term treatment with antiviral agents has been shown to prevent recurrences of genital and orofacial herpes simplex virus (HSV) disease, but it is uncertain whether prophylactic treatment can prevent recurrences of ocular HSV disease.

Methods We randomly assigned 703 immunocompetent patients who had had ocular HSV disease within the preceding year to receive 400 mg of acyclovir or placebo orally twice daily. The study outcomes were the rates of development of ocular or nonocular HSV disease during a 12-month treatment period and a 6-month observation period.

Results The cumulative probability of a recurrence of any type of ocular HSV disease during the 12-month treatment period was 19 percent in the acyclovir group and 32 percent in the placebo group (P<0.001). Among the 337 patients with a history of stromal keratitis, the most common serious form of ocular HSV disease, the cumulative probability of recurrent stromal keratitis was 14 percent in the acyclovir group and 28 percent in the placebo group (P=0.005). The cumulative probability of a recurrence of nonocular (primarily orofacial) HSV disease was also lower in the acyclovir group than in the placebo group (19 percent vs. 36 percent, P<0.001). There was no rebound in the rate of HSV disease in the six months after treatment with acyclovir was stopped.

Conclusions After the resolution of ocular HSV disease, 12 months of treatment with acyclovir reduces the rate of recurrent ocular HSV disease and orofacial HSV disease. Long-term antiviral prophylaxis is most important for patients with a history of HSV stromal keratitis, since it can prevent additional episodes and potential loss of vision. (N Engl J Med 1998;339:300-6.)

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ERPETIC EYE DISEASE

HERPES simplex virus (HSV) is a leading cause of corneal opacification and infection-related visual loss. An estimated 400,000 Americans have had ocular HSV disease, and there are nearly 50,000 new and recurrent cases each year in the United States.1

After the initial exposure and primary, often asymptomatic infection, HSV establishes a latent infection in the trigeminal or other sensory ganglia. Recurrent viral shedding can lead to disease of one or both eyes. Superficial ocular infection can involve the eyelids (blepharitis), conjunctiva (conjunctivitis), or corneal surface (dendritic or epithelial keratitis). Deeper involvement of the cornea (stromal keratitis) or anterior uvea (iritis) represents a more serious form of the disease that can cause permanent visual loss. No treatment has been demonstrated to prevent recurrences of ocular HSV disease, and neither antiviral drugs nor other treatments are routinely prescribed after the resolution of acute HSV eye infections.

Acyclovir is a potent and specific antiviral agent that is effective in the treatment of and prophylaxis against nonocular HSV infection. Controlled trials have established that oral acyclovir significantly reduces the rate of recurrent genital1-3 and orofacial4 HSV infections in otherwise healthy persons. Some studies in animals have shown that systemic acyclovir can suppress experimental reactivation of ocular HSV disease,4 but others have not shown a benefit.7 Although preliminary reports have suggested that such an approach may help prevent ocular HSV disease in humans,8-10 clinical confirmation in a well-designed study has been lacking. Therefore, we conducted a randomized, placebo-controlled trial to determine whether treatment with 400 mg of oral acyclovir twice daily for one year would prevent ocular recurrences in immunocompetent persons who had had an episode of ocular HSV within the preceding year.

METHODS

The study was conducted at 74 clinical sites. The protocol and informed-consent forms were approved by the institutional review boards at the participating institutions, and all patients gave written informed consent. The study was overseen by an independent data and safety monitoring committee. Details of the protocol have been published previously11 and are summarized below.

Patients

Eligible patients were 12 years of age or older and had had an episode of ocular HSV disease (i.e., blepharitis, conjunctivitis, epithelial keratitis, stromal keratitis, or iritis) in one or both eyes within the preceding 12 months, but their disease had been inactive and untreated during the 30 days before the study began. Patients were excluded if they were receiving antiviral or immunosuppressive therapy or had a history of immune dysfunction, renal insufficiency, allergy or adverse reaction to acyclovir, or keratorefractive surgery of the involved eye. All sexually active patients...
of reproductive age agreed to use contraception during the one-year treatment period and for three months thereafter.

Review of the patients after randomization revealed that 15 did not fulfill all the eligibility criteria: 8 had insufficient documentation of their most recent episode of ocular HSV disease or had not had active disease within the 12 months before enrollment, 6 had either had active ocular HSV disease or received topical antiviral or corticosteroid treatment within 30 days before enrollment, and 1 had been given a misdiagnosis.

**Treatment Assignment and Monitoring**

A permuted-block design, with a separate sequence of computer-generated random numbers for each of eight geographic regions, was used to assign patients in approximately equal numbers to the two treatment groups. One group received 400 mg of acyclovir (Zovirax, Glaxo Wellcome, Research Triangle Park, N.C.) orally twice daily for 12 months (administered as two capsules, each containing 200 mg of acyclovir, 162 mg of lactose, cornstarch, magnesium stearate, and sodium lauryl sulfate). The other group received two placebo capsules (Glaxo Wellcome) twice daily that contained 218 mg of lactose and were identical in appearance and taste to the capsules containing active drug. Treatment (acyclovir or placebo) was continued for the full 12 months regardless of whether there was a recurrence. In the event of a recurrence of ocular HSV disease, the use of topical treatment was left to the discretion of the investigator. Patients and clinic personnel were unaware of the patients’ treatment assignments; the data analysts and monitoring committee were not masked.

We assessed compliance with the treatment protocol by counting the number of capsules remaining in each bottle when it was returned. If a bottle was not returned by the patient, compliance was estimated from the patient’s report and from medication cards used by the patient to record when medication was taken.

At each study visit, patients were asked whether any adverse events had occurred since the last visit and were asked to call and report any adverse events that occurred between visits.

**Outcomes**

Whether patients had a recurrence of active ocular HSV disease was assessed by an experienced ophthalmologist using slit-lamp biomicroscopy. Examinations were performed after 1, 3, 6, 9, and 12 months of treatment; during the post-treatment observation period, after months 13, 15, and 18; and at any time new ocular symptoms developed. Recurrences were classified as infections of the ocular surface (blepharitis, conjunctivitis, or epithelial keratitis), stromal keratitis (corneal stromal inflammatory infiltrate or corneal edema associated with endothelial inflammatory precipitates), or iritis. Nonocular HSV infections were recorded solely on the basis of patients’ reports and were classified as orofacial or genital or as affecting some other cutaneous site.

**Statistical Analysis**

We estimated that a total of 696 patients were required for the study to detect with a power of 80 percent a treatment effect of 50 percent, with a probability of a type I error of 5 percent (two-tailed), given a projected rate of recurrence of 15 percent at one year in the placebo group. The calculation was adjusted to account for the possibility that 10 percent of the enrolled patients had not actually had previous ocular HSV disease and that 10 percent of the patients would be lost to follow-up. Primary analyses included all randomized patients and followed the intention-to-treat principle. All reported P values are two-tailed. Interim analyses were performed at six prespecified intervals according to the method of Lan and DeMets.12

The primary outcome was the recurrence of any type of ocular HSV disease during the 12-month treatment period. Analyses were also performed with development of stromal keratitis as the outcome variable, since this is the form of the disease that is most likely to cause permanent loss of vision. The cumulative probability of a recurrence was calculated for each treatment group with the Kaplan–Meier product-limit method, and values in the two groups were compared with the Mantel log-rank test.13 Data on patients who were withdrawn from the trial or were lost to follow-up before having a recurrence were censored at the time of the last completed examination. Unadjusted and adjusted rate ratios were determined from a proportional-hazards model.14 The assumption of proportional hazards was tested for the treatment groups with a time-dependent covariate and found to be appropriate.

Comparisons of categorical variables were made with Fisher’s exact test or a chi-square test, and continuous variables were assessed with either a t-test or the Wilcoxon rank-sum test, as appropriate.

**RESULTS**

Between September 1992 and December 1996, 703 patients entered the trial, with 357 assigned to the acyclovir group and 346 to the placebo group. The baseline characteristics of the two groups were similar (Table 1).

**Follow-up**

During the 18-month study, 88 percent of protocol-specified visits were completed by patients in the acyclovir group and 86 percent by those in the placebo group. Among the 486 patients who did not have a recurrence of ocular HSV disease during the trial, follow-up was incomplete for 64 (13 percent). Five patients died during the course of the study of causes unrelated to study participation (in the acyclovir group, one died of colon cancer and one of emphysema; in the placebo group, one died of prostate cancer, liver cancer, and non-Hodgkin’s lymphoma).

Patients with incomplete follow-up data were more likely to be black than patients with complete follow-up data (17 percent vs. 8 percent, P=0.03) and were younger (mean [±SD] age, 44±18 vs. 49±18 years; P=0.02).

**Compliance and Adverse Effects**

No serious adverse effects were attributable to treatment group; however, 32 patients (15 in the acyclovir group and 17 in the placebo group) discontinued treatment because of side effects (Table 2). The treatment assignment was unmasked for one of these patients, who was in the acyclovir group, after erythema nodosum developed.

Among the 575 patients (82 percent of the 703 patients) who completed the full 12-month course of treatment, 89 percent of patients in the acyclovir group and 87 percent of patients in the placebo group were at least 80 percent compliant in taking the oral study medication; 72 percent and 68 percent, respectively, were at least 90 percent compliant. In the acyclovir group, the compliance rate was similar for the patients who had a recurrence of ocular HSV disease during the 12-month treatment period and for those who did not: 90 percent and 89 percent, respectively, were at least 80 percent compliant.
Recurrences of Ocular HSV Disease

Treatment Period

The cumulative probability of a recurrence of ocular HSV disease during the 12-month treatment period was significantly lower in the acyclovir group than in the placebo group (19 percent vs. 32 percent; rate ratio, 0.55; 95 percent confidence interval, 0.41 to 0.75; P<0.001) (Fig. 1 and Table 3). Adjustment for base-line covariates did not substantially change the results. The results were similar when the data were analyzed according to whether the patients were enrolled at a university-affiliated or community-based clinical center (data not shown). In both treatment groups, the number of past episodes of ocular HSV disease was strongly associated with the likelihood of a recurrence (P=0.04 in the acyclovir group and P=0.006 in the placebo group). The magnitude of the relative treatment effect was similar irrespective of the number of past episodes of ocular HSV disease (Table 3). Sixteen patients in the acyclovir group (4 percent) and 30 in the placebo group (9 percent) had more than one recurrence during the 12-month treatment period.

Stromal keratitis was the initial recurrence during the 12-month treatment period. The cumulative probability of a recurrence of ocular HSV disease (Table 3). Sixteen patients in the acyclovir group (4 percent) and 30 in the placebo group (9 percent) had more than one recurrence during the 12-month treatment period.
The cumulative probability of a recurrence of ocular HSV disease was 19 percent in the acyclovir group and 32 percent in the placebo group during the 12-month treatment period (P<0.001 by the Mantel log-rank test) and 28 percent and 38 percent, respectively, during the full 18 months of the study (P=0.005 by the Mantel log-rank test). Two patients in the acyclovir group and 3 patients in the placebo group had their last study visit in month 17, rather than month 18. The numbers of patients at risk are the numbers who had not had a recurrence of ocular HSV disease at the beginning of each month. Data on patients who did not have a recurrence were censored at the time of the last study visit.

**Figure 1.** Kaplan–Meier Estimates of the Cumulative Probability of a Recurrence of Ocular HSV Disease, According to Treatment.

The cumulative probability of a recurrence of ocular HSV disease was 19 percent in the acyclovir group and 32 percent in the placebo group during the 12-month treatment period (P<0.001 by the Mantel log-rank test) and 28 percent and 38 percent, respectively, during the full 18 months of the study (P=0.005 by the Mantel log-rank test). Two patients in the acyclovir group and 3 patients in the placebo group during the 12-month treatment period (P<0.001 by the Mantel log-rank test) and 28 percent and 38 percent, respectively, during the full 18 months of the study (P=0.005 by the Mantel log-rank test). Two patients in the acyclovir group and 3 patients in the placebo group (13 percent) (Table 4). Acyclovir reduced the risk of stromal keratitis only among the 337 patients who had had at least one prior episode of stromal keratitis (Table 3). Among such patients, the cumulative probability of a recurrence of HSV stromal keratitis during the 12-month treatment period was 14 percent in the acyclovir group and 28 percent in the placebo group (rate ratio, 0.48; 95 percent confidence interval, 0.29 to 0.80; P=0.005), whereas among patients with no history of stromal keratitis, the cumulative probability of stromal keratitis was 4 percent in the acyclovir group and 3 percent in the placebo group. In no subgroup of patients without a history of stromal keratitis (on the basis of the base-line characteristics given in Table 1) was acyclovir effective in preventing stromal keratitis.

**Observation Period**

During the 6-month observation period after the 12-month treatment period, there were no significant differences between groups in the frequency of recurrences of ocular HSV disease. Among the patients who were followed up for at least 12 months, 45 of the 335 acyclovir-treated patients (13 percent) had a recurrence during the 6-month observation period.
Recurrences of Nonocular HSV Disease

The orofacial region was by far the most common location of nonocular HSV infection. During the 12-month treatment period, at least one nonocular HSV infection occurred in 71 patients (20 percent) in the acyclovir group (62 orofacial, 3 genital, 1 at another site, and 5 at more than one site) and 122 patients (35 percent) in the placebo group (111 orofacial, 4 genital, and 7 at more than one site). The cumulative probability of a nonocular recurrence during the 12-month treatment period was 19 percent in the acyclovir group and 36 percent in the placebo group (rate ratio, 0.51; 95 percent confidence interval, 0.38 to 0.69; P<0.001). Among patients with no such history, the cumulative probability of orofacial infection was 11 percent among 187 patients in the acyclovir group and 21 percent among 169 patients in the placebo group (rate ratio, 0.48; 95 percent confidence interval, 0.37 to 0.74; P<0.001). Among patients with no such history, the cumulative probability of orofacial infection was 11 percent among 187 patients in the acyclovir group and 21 percent among 169 patients in the placebo group (rate ratio, 0.48; 95 percent confidence interval, 0.37 to 0.74; P<0.001). Among patients with no such history, the cumulative probability of orofacial infection was 11 percent among 187 patients in the acyclovir group and 21 percent among 169 patients in the placebo group (rate ratio, 0.48; 95 percent confidence interval, 0.37 to 0.74; P<0.001). Among patients with no such history, the cumulative probability of orofacial infection was 11 percent among 187 patients in the acyclovir group and 21 percent among 169 patients in the placebo group (rate ratio, 0.48; 95 percent confidence interval, 0.37 to 0.74; P<0.001). Among patients with no such history, the cumulative probability of orofacial infection was 11 percent among 187 patients in the acyclovir group and 21 percent among 169 patients in the placebo group (rate ratio, 0.48; 95 percent confidence interval, 0.37 to 0.74; P<0.001). Among patients with no such history, the cumulative probability of orofacial infection was 11 percent among 187 patients in the acyclovir group and 21 percent among 169 patients in the placebo group (rate ratio, 0.48; 95 percent confidence interval, 0.37 to 0.74; P<0.001). Among patients with no such history, the cumulative probability of orofacial infection was 11 percent among 187 patients in the acyclovir group and 21 percent among 169 patients in the placebo group (rate ratio, 0.48; 95 percent confidence interval, 0.37 to 0.74; P<0.001). Among patients with no such history, the cumulative probability of orofacial infection was 11 percent among 187 patients in the acyclovir group and 21 percent among 169 patients in the placebo group (rate ratio, 0.48; 95 percent confidence interval, 0.37 to 0.74; P<0.001). Among patients with no such history, the cumulative probability of orofacial infection was 11 percent among 187 patients in the acyclovir group and 21 percent among 169 patients in the placebo group (rate ratio, 0.48; 95 percent confidence interval, 0.37 to 0.74; P<0.001). Among patients with no such history, the cumulative probability of orofacial infection was 11 percent among 187 patients in the acyclovir group and 21 percent among 169 patients in the placebo group (rate ratio, 0.48; 95 percent confidence interval, 0.37 to 0.74; P<0.001). Among patients with no such history, the cumulative probability of orofacial infection was 11 percent among 187 patients in the acyclovir group and 21 percent among 169 patients in the placebo group (rate ratio, 0.48; 95 percent confidence interval, 0.37 to 0.74; P<0.001). Among patients with no such history, the cumulative probability of orofacial infection was 11 percent among 187 patients in the acyclovir group and 21 percent among 169 patients in the placebo group (rate ratio, 0.48; 95 percent confidence interval, 0.37 to 0.74; P<0.001). Among patients with no such history, the cumulative probability of orofacial infection was 11 percent among 187 patients in the acyclovir group and 21 percent among 169 patients in the placebo group (rate ratio, 0.48; 95 percent confidence interval, 0.37 to 0.74; P<0.001). Among patients with no such history, the cumulative probability of orofacial infection was 11 percent among 187 patients in the acyclovir group and 21 percent among 169 patients in the placebo group (rate ratio, 0.48; 95 percent confidence interval, 0.37 to 0.74; P<0.001). Among patients with no such history, the cumulative probability of orofacial infection was 11 percent among 187 patients in the acyclovir group and 21 percent among 169 patients in the placebo group (rate ratio, 0.48; 95 percent confidence interval, 0.37 to 0.74; P<0.001).

DISCUSSION

This study of 703 patients who had had an episode of ocular HSV disease during the year preceding the trial demonstrated that oral acyclovir reduced the incidence of ocular recurrences during a 12-month treatment period by nearly half. A reduction of similar magnitude in the rate of orofacial HSV recurrences

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<tr>
<th>TYPE OF OUTCOME AND PATIENT GROUP</th>
<th>ACYCLOVIR GROUP</th>
<th>PLACEBO GROUP</th>
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*The cumulative probability of a recurrence of ocular HSV disease during the 12-month treatment period was calculated with the Kaplan–Meier product-limit method.
†The rate ratio was derived from the proportional-hazards model, in which the acyclovir group was compared with the placebo group in each stratum. CI denotes confidence interval.
‡To be eligible for the study, patients had to have had at least one prior episode of ocular HSV disease.
§For 73 of the 81 patients in whom stromal keratitis developed in the first 12 months, this was the first recurrence of ocular HSV disease during the trial; before the episode of stromal keratitis, 6 patients had had an episode of epithelial keratitis (3 in each group), 1 patient in the placebo group had had an episode of blepharoconjunctivitis, and 1 patient in the acyclovir group had had an episode of iritis.
in the trial of patients at both university-affiliated and community-based clinical centers, since the results were similar for both subgroups of patients.

Our finding that prophylactic treatment with oral acyclovir resulted in a 45 percent decrease in the rate of recurrence of ocular HSV disease as compared with placebo is similar to the reported reductions of 50 to 78 percent in the rate of orofacial recurrences\(^4\) and of 80 percent in the rate of genital recurrences\(^6\) with acyclovir prophylaxis. At the time the trial was initiated, acyclovir was the only commercially available oral antiviral medication. The treatment regimen was empirically selected on the basis of previous trials of prophylaxis against nonocular HSV disease. It is not known whether a shorter treatment period, a different dose of acyclovir, or another antiviral agent would provide similar benefit.

In summary, our results show that long-term treatment with acyclovir helps prevent recurrences of ocular HSV disease and orofacial HSV infections in patients with a history of ocular HSV disease. Since the form that a recurrence of ocular HSV disease takes is strongly associated with the form of previous episodes, prolonged acyclovir therapy should provide the greatest clinical benefit for patients with a history of stromal keratitis because it should reduce the likelihood of the corneal scarring and loss of vision that can result from recurrent episodes of stromal keratitis. The role of prophylaxis is less clear for patients who have had only superficial forms of ocular HSV disease (epithelial keratitis, conjunctivitis, and blepharitis), since these forms generally resolve with short-term topical antiviral therapy and cause little permanent damage.\(^7\) In general, our results should apply to patients who have had an episode of ocular HSV disease within the year before treatment but not necessarily to those who are immunosuppressed.

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### APPENDIX

REFERENCES