

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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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 an-

terior 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 genital^{2,3} and orofacial^{4,5} HSV infections in otherwise healthy persons. Some studies in animals have shown that systemic acyclovir can suppress experimental reactivation of ocular HSV disease,⁶ 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 keratoplasty or keratorefractive surgery of the involved eye. All sexually active patients

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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 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 base-line 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 each 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 [\pm SD] age, 44 ± 18 vs. 49 ± 18 years; $P=0.02$).

Compliance and Adverse Effects

No serious adverse effects were attributable to treatment; 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.

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	ALL PATIENTS (N=703)	ACYCLOVIR GROUP (N=357)	PLACEBO GROUP (N=346)
Male sex — no. (%)	377 (54)	197 (55)	180 (52)
Age — yr	49±18	50±18	48±18
Race or ethnic group — no. (%)			
White	553 (79)	284 (80)	269 (78)
Black	65 (9)	36 (10)	29 (8)
Hispanic	56 (8)	22 (6)	34 (10)
Asian	20 (3)	10 (3)	10 (3)
Other	9 (1)	5 (1)	4 (1)
Past episodes of ocular HSV disease — no. (%)			
1	202 (29)	101 (28)	101 (29)
2–3	230 (33)	115 (32)	115 (33)
≥4	271 (39)	141 (39)	130 (38)
Types of prior ocular HSV involvement — no. (%)			
Blepharitis or conjunctivitis only	28 (4)	17 (5)	11 (3)
Epithelial keratitis and no stromal keratitis†	331 (47)	170 (48)	161 (47)
Stromal and epithelial keratitis†	223 (32)	109 (31)	114 (33)
Stromal keratitis and no epithelial keratitis†	114 (16)	56 (16)	58 (17)
Iritis alone	7 (1)	5 (1)	2 (1)
No. of days since resolution of most recent ocular HSV episode — median (interquartile range)	56 (36–162)	55 (36–154)	57 (38–167)
History of nonocular HSV disease — no. (%)	365 (52)	180 (50)	185 (53)
Orofacial‡	347 (49)	170 (48)	177 (51)
Genital	7 (1)	4 (1)	3 (1)
Other cutaneous site	11 (2)	6 (2)	5 (1)

*Values are means ±SD. Because of rounding, not all percentages total 100.

†Blepharitis, conjunctivitis, iritis, or a combination may also have been present.

‡This group includes 7 patients (2 in the acyclovir group and 5 in the placebo group) who also had a history of genital herpes infection and 12 patients (5 in the acyclovir group and 7 in the placebo group) who also had a history of infection at other cutaneous sites.

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

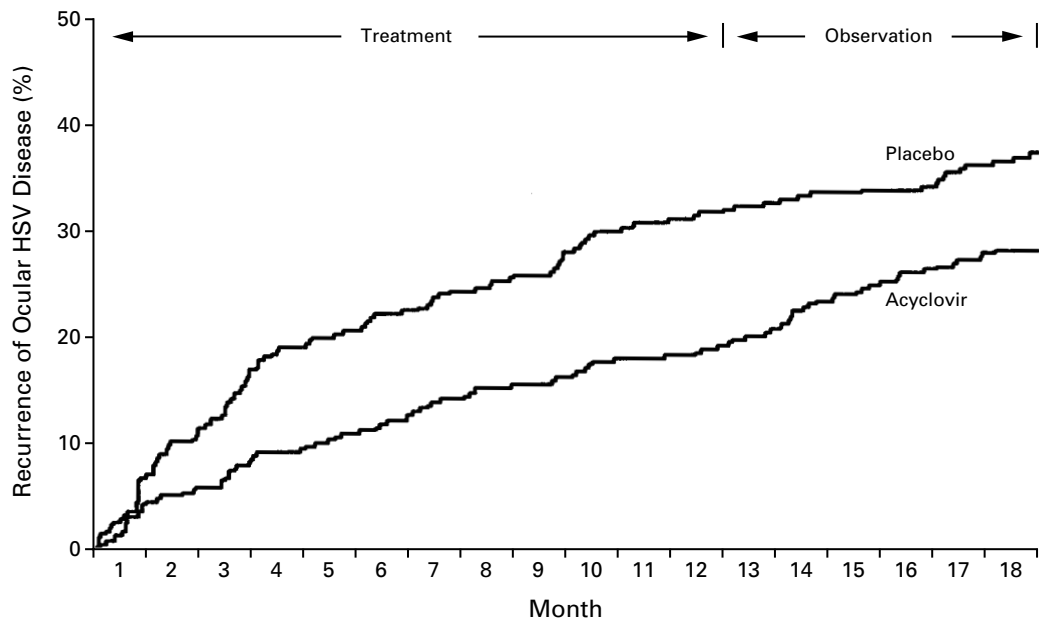
TABLE 2. REASONS FOR EARLY DISCONTINUATION OF TREATMENT.*

REASON FOR EARLY DISCONTINUATION	ACYCLOVIR GROUP (N=357)	PLACEBO GROUP (N=346)
	no. (%)	
Patient's decision, unrelated to side effect	34 (10)	17 (5)
Open-label oral acyclovir started	3 (1)	3 (1)
Side effects of medication	15 (4)	17 (5)
Gastrointestinal effect	7	9
Rash	1	2
Other†	7	6
Incomplete follow-up‡	18 (5)	21 (6)
Total	70 (20)	58 (17)

*Patients were not withdrawn from the trial if they discontinued the study medication or began to receive open-label acyclovir.

†Other side effects included dizziness, weight gain, headache, fatigue, sexual dysfunction, memory loss, anxiety, tinnitus, and hair loss.

‡This category includes patients who did not complete the 12-month treatment period and who were taking study medication at the time of their last study visit: 14 patients who voluntarily withdrew (9 in the acyclovir group and 5 in the placebo group), 15 who were lost to follow-up (6 in the acyclovir group and 9 in the placebo group), 3 who died (1 in the acyclovir group and 2 in the placebo group), and 7 who were withdrawn from the trial (2 in the acyclovir group and 5 in the placebo group).



ACYCLOVIR GROUP																	Total		
No. at risk	357	336	326	316	309	303	295	290	285	281	273	272	269	262	253	248	242	234	
Ocular HSV recurrence	15	6	8	4	5	6	5	5	2	6	1	3	5	9	5	5	5	1	96
Withdrawal or death	6	3	1	1	1	2				1						1	2		18
Loss to follow-up		1	1	2					2	1			2				1		10
PLACEBO GROUP																	Total		
No. at risk	346	309	293	269	261	256	250	243	239	230	224	220	216	212	208	203	198	192	121
Ocular HSV recurrence	23	13	20	7	5	6	6	4	8	6	4	2	3	3	1	1	6	3	19
Withdrawal or death	10	2	2	1			1		1						2				17
Loss to follow-up	4	1	2									2	1	1	2	4			

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 died; 11 and 8 patients, respectively, withdrew from the study; 3 and 8 patients, respectively, were withdrawn by their physicians; and 2 patients in the acyclovir 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.

the 12-month treatment period in 27 patients in the acyclovir group (8 percent) and in 46 patients in the placebo group (13 percent), whereas epithelial keratitis was the initial recurrence in 31 patients in the acyclovir group (9 percent) and 39 patients in the placebo group (11 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

TABLE 3. RECURRENCES OF OCULAR HSV DISEASE DURING THE 12-MONTH TREATMENT PERIOD.

TYPE OF OUTCOME AND PATIENT GROUP	ACYCLOVIR GROUP		PLACEBO GROUP		RATE RATIO (95% CI)†
	NO. OF PATIENTS	CUMULATIVE PROBABILITY OF RECURRENCE*	NO. OF PATIENTS	CUMULATIVE PROBABILITY OF RECURRENCE*	
		%		%	
Any type of ocular HSV disease					
No. of prior episodes of any type of ocular HSV disease‡					
1	101	13	101	22	0.56 (0.28–1.15)
2–3	115	18	115	29	0.55 (0.32–0.96)
≥4	141	25	130	42	0.53 (0.34–0.82)
Total	357	19	346	32	0.55 (0.41–0.75)
Stromal keratitis§					
No. of prior episodes of stromal keratitis					
0	192	4	174	3	1.76 (0.53–5.83)
1	60	4	69	13	0.25 (0.05–1.15)
2–3	47	13	60	33	0.34 (0.14–0.86)
≥4	58	27	43	44	0.56 (0.28–1.12)
Total	357	9	346	15	0.57 (0.36–0.89)

*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.

period, as compared with 43 of the 315 placebo-treated patients (14 percent, $P=1.0$).

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 a history of orofacial HSV infection, the cumulative probability of an orofacial recurrence during the 12-month treatment period was 29 percent among 170 patients in the acyclovir group and 50 percent among 177 patients in the placebo group (rate ratio, 0.52; 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, 0.27 to 0.84; $P=0.01$). Sixteen patients in the acyclovir group (4 percent) and 49 patients in the placebo group (14 percent) had both ocular and nonocular infections (although not necessarily simultaneously) ($P<0.001$).

During the observation period, nonocular HSV infections occurred in 87 of the 335 patients still in follow-up in the acyclovir group (26 percent) and in 80 of the 315 patients in the placebo group (25 percent) ($P=0.93$).

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

TABLE 4. TYPES OF OCULAR INVOLVEMENT IN INITIAL RECURRENCES OF HSV DISEASE.*

TYPE OF OCULAR HSV DISEASE	ACYCLOVIR GROUP (N=357)	PLACEBO GROUP (N=346)
	no. (%)	
Recurrence during the 12-mo treatment period	66 (18)	104 (30)
Blepharitis or conjunctivitis	6 (2)	16 (5)
Epithelial keratitis†	31 (9)	39 (11)
Stromal keratitis‡	27 (8)	46 (13)
Iritis	2 (1)	3 (1)
	ACYCLOVIR GROUP (N=269)§	PLACEBO GROUP (N=216)§
	no. (%)	
Recurrence during the 6-mo observation period	30 (11)	17 (8)
Blepharitis or conjunctivitis	8 (3)	2 (1)
Epithelial keratitis¶	10 (4)	9 (4)
Stromal keratitis	10 (4)	5 (2)
Iritis	2 (1)	1 (0.5)

*Each patient with a recurrence is counted in only one category.

†This category includes two patients who also had iritis as part of the same episode (one in each group) and four who also had blepharitis or conjunctivitis (two in each group).

‡This category includes 14 patients who also had iritis as part of the same episode (3 in the acyclovir group and 11 in the placebo group).

§This group includes patients with at least 12 months of follow-up who did not have a recurrence in the first 12 months.

¶This category includes two patients who also had iritis as part of the same episode (one in each group).

||This category includes one patient in the acyclovir group who also had epithelial keratitis and iritis as part of the same episode.

was also found; the rate of genital HSV infections was too low for us to assess whether treatment was beneficial. Acyclovir treatment was generally well tolerated, with no serious adverse effects. The benefit was not sustained after treatment was stopped, but there was also no acute rebound effect.

The two treatment groups were similar, and there was no evidence of confounding in the analyses. Masking was well maintained, and the placebo capsules included a lactose filler that served to mimic the gastrointestinal side effects of the acyclovir formulation used in the study. The percentage of patients with incomplete follow-up was similar in the two groups. Most patients (82 percent) received the full 12 months of treatment and their rates of compliance were satisfactory. The characteristics of our patients appear similar to the reported profile of people with ocular HSV disease.^{1,15} The generalizability of our results is enhanced by the participation

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 recurrences⁴ and of 80 percent in the rate of genital recurrences¹⁶ with acyclovir prophylaxis. At the time the trial was initiated, acyclovir was the only commercially available oral antiherpetic 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.¹⁷ 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

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