Risk factors for herpes simplex virus epithelial keratitis recurring during treatment of stromal keratitis or iridocyclitis

K R Wilhelmus, C R Dawson, B A Barron, P Bacchetti, L Gee, D B Jones, H E Kaufman, J Sugar, R A Hyndiuk, P R Laibson, R D Stulting, P A Asbell, for the Herpetic Eye Disease Study Group*

Abstract

***Aims*—Possible risk factors were evaluated for herpes simplex virus (HSV) epithelial keratitis in patients with stromal keratouveitis.**

***Methods*—The study population included 260 patients who had active stromal keratitis and/or iridocyclitis without epithelial disease and who were enrolled in one of three clinical trials of the Herpetic Eye Disease Study. Study treatment involved a 10 week course of topical placebo, topical prednisolone phosphate, or topical prednisolone phosphate with oral acyclovir. All groups received topical trifluridine four times daily for 3 weeks then twice daily for another 7 weeks. Patients were examined for HSV epithelial keratitis for 16 weeks.**

***Results*—Dendritic or geographic epithelial keratitis occurred in 12 (4.6%) study patients. Adverse effects attributable to trifluridine prophylaxis were acute allergic blepharoconjunctivitis in 10 (3.8%) study patients and corneal epithelial erosions in 11 (4.2%) study patients. No significant difference in the occurrence of HSV epithelial keratitis was found among the study treatment groups: one (2.0%) of 49 topical placebo treated patients, nine (6.5%) of 138 patients treated with topical corticosteroids without acyclovir, and two (2.7%) of 73 patients treated with topical corticosteroids and oral acyclovir. Univariate exponential models suggested that patients with a history of previous HSV epithelial keratitis and non-white patients were more likely to develop HSV epithelial keratitis during treatment of stromal keratouveitis.**

***Conclusion*—Individuals with prior HSV epithelial keratitis and certain ethnic groups may have a higher rate of recurrent epithelial keratitis during the acute treatment of HSV stromal keratouveitis.**

(*Br J Ophthalmol* 1996;80:969–972)

*For the list of participants see appendix.

Correspondence to: Chandler R Dawson, MD, Francis I Proctor Foundation, University of California San Francisco, San Francisco, CA 94143-1412, USA.

Accepted for publication 23 August 1996

The development of a topical ophthalmic antiviral agent was a historic advance in the therapy of herpes simplex virus (HSV) eye disease.[1] Placebo controlled clinical trials demonstrated that a topical antiviral agent significantly reduced the rate of occurrence of HSV epithelial keratitis during corticosteroid treatment of HSV stromal keratitis.[2,3] Combined antiviral and corticosteroid agents became a widespread therapeutic option for controlling anterior segment inflammation caused by HSV.

The Herpetic Eye Disease Study evaluated the efficacy of topical corticosteroids and oral acyclovir in the acute treatment of HSV stromal keratitis and/or iridocyclitis.[4-6] A fixed schedule of topical trifluridine was given to all patients. This report is an ancillary, observational study that provides more information about the occurrence of HSV epithelial keratitis during study treatment.

Patients and methods

Study patients had non-necrotising or necrotising stromal keratitis and/or iridocyclitis attributable to HSV on the basis of clinical findings. Patients were eligible if they had active stromal keratitis or iridocyclitis without active epithelial keratitis, an epithelial defect, or any history of allergy or adverse reaction to trifluridine. The study design was approved by the institutional review board at each participating centre and informed consent was obtained before study enrolment.

Patients were enrolled into one of three parallel clinical trials. One trial compared topical placebo with a tapering dosage of topical corticosteroids in patients with stromal keratitis[4]; another compared oral placebo with oral acyclovir in patients with stromal keratitis using topical corticosteroids[5]; and a third compared oral placebo with oral acyclovir in patients with iridocyclitis.[6] The topical study regimen began with prednisolone phosphate 1% or placebo used eight times daily for 1 week and was subsequently changed to six times daily for 1 week, four times daily for 1 week, twice daily for 1 week, then once daily for the fifth week. At the sixth week, prednisolone phosphate 0.125% or placebo was used four times daily for 1 week, then twice daily for the next week, then once daily for the final 3 weeks. Patients randomised to oral acyclovir received two 200 mg capsules five times daily for 10 weeks. While using study medications, patients were treated with trifluridine 1% solution one drop four times daily for the first 3 weeks then one drop twice daily for the remaining 7 weeks of study therapy. Compliance with trifluridine was assessed at each visit by weighing eyedropper bottles, and the rate of compliance was determined by comparison with the expected weight reduction.

Patients were evaluated weekly for 10 weeks then every other week for an additional 6

Table 1 Occurrence of herpes simplex virus (HSV) epithelial keratitis during treatment of HSV stromal keratitis or iritis, compared by HEDS diagnosis and treatment group

	Study treatment					
Study group	*Topical*	*Oral*	*Topical antiviral*	*No*	*No developing HSV epithelial keratitis (frequency)*	*Day of occurrence*
Stromal keratitis, not recently using corticosteroid	Placebo	—	Trifluridine	49	1 (2.0%)	55
Stromal keratitis, not recently using corticosteroid	Prednisolone	—	Trifluridine	57	4 (7.0%)	24, 26, 36, 63
Stromal keratitis, recently using corticosteroid	Prednisolone	Placebo	Trifluridine	53	3 (5.7%)	4, 35, 51
Stromal keratitis, recently using corticosteroid	Prednisolone	Acyclovir	Trifluridine	51	1 (2.0%)	64
Iritis, with or without stromal keratitis	Prednisolone	Placebo	Trifluridine	28	2 (7.1%)	10, 39
Iritis, with or without stromal keratitis	Prednisolone	Acyclovir	Trifluridine	22	1* (4.5%)	8
Total or average (SD)				260	12 (4.6%)	35 (21)

* Geographic epithelial keratitis. All others were dendritic epithelial keratitis.

weeks. Patients withdrawn from the study because of epithelial keratitis, progressive or persistent stromal keratitis or uveitis, drug related adverse reaction, or other reason were re-evaluated at the 16 week visit, at which time any interim events were recorded. The time to development of HSV epithelial keratitis was defined as the number of days between randomisation and the first recognition of epithelial keratitis. HSV epithelial keratitis was defined as a characteristic linear or branching lesion or a geographic ulceration that had elevated, granular epithelium at the edges.

Statistical analysis was performed with SAS software (Cary, NC, USA) that used an exponential model to evaluate the rate of occurrence of epithelial keratitis per person week for categorical groups. Variables included in univariate exponential models were demographic characteristics (age, sex, and ethnicity), clinical history of HSV disease occurring within the previous 2 years (prior HSV epithelial keratitis, prior HSV stromal keratitis, and prior non-ocular HSV disease), treatment group, and status at the time of development of epithelial keratitis (trifluridine frequency, corticosteroid concentration, and activity of stromal disease).

Results

Twelve (4.6%) of 260 patients developed HSV epithelial keratitis while using study medications. No case of epithelial keratitis occurred during the 6 weeks after stopping study medications. Eleven patients, all with stromal keratitis, developed dendritic epithelial keratitis; the dendritic lesions were located over the areas of prior stromal keratitis in eight patients and at the margin in three others. One patient treated for iritis without stromal keratitis developed geographic epithelial keratitis.

The median compliance rate for patients not developing epithelial keratitis was 97% (25th and 75th quartiles of 50% and 139%) and for patients developing epithelial keratitis was 136% (25th and 75th quartiles of 114% and 150%). Adverse effects attributed to trifluridine solution were acute blepharitis (one patient), acute conjunctivitis (nine patients), and corneal epithelial erosions (11 patients).

No statistically significant differences in the occurrence of HSV epithelial keratitis were found when comparing the study treatment groups (Table 1). There was no significant difference in the rate of epithelial keratitis in the topical placebo group compared with the topical steroid without acyclovir group (p=0.56), the topical placebo group compared with the topical steroid with acyclovir group (p=0.81), the topical steroid without acyclovir group compared with the topical steroid with acyclovir group (p=0.24), or the combined topical placebo and oral acyclovir groups compared with the topical steroid without acyclovir group (p=0.21). Of the variables tested in the univariate exponential models, only a prior history of symptomatic HSV epithelial keratitis and a non-white ethnicity were significantly correlated with a higher rate of HSV epithelial keratitis during the 16 weeks after beginning treatment for stromal keratitis or iridocyclitis (Table 2).

Discussion

Kaufman *et al* [1] first suggested that an antiviral agent be used in combination with a topical corticosteroid for treating HSV stromal keratitis. Placebo controlled clinical trials subsequently confirmed that a topical antiviral agent reduced the risk of recurrent epithelial keratitis during corticosteroid treatment.[2 3]

PROPHYLACTIC ANTIVIRAL SELECTION

Patterson and Jones[2] reported that, of patients with herpes simplex stromal keratitis who were treated with a topical corticosteroid for up to 4 months, 42% in a placebo group developed dendritic epithelial keratitis compared with 15% among those using idoxuridine ointment five times daily. Sundmacher[3] further showed that trifluridine solution five times daily reduced the occurrence of HSV epithelial keratitis from 21% in a placebo group to none in a trifluridine group during 4 months of treatment with topical dexamethasone. Vidarabine and acyclovir ointments are also effective in preventing HSV epithelial keratitis during corticosteroid therapy.[7 8] The Herpetic Eye Disease Study (HEDS) designated trifluridine prophylaxis for all study patients with stromal keratitis or iridocyclitis and found that HSV epithelial keratitis recurred in 4.6% during 16 weeks of treatment and follow up.

Oral acyclovir is as effective as a topical antiviral in preventing recurrent epithelial disease during corticosteroid therapy of HSV stromal keratitis.[8] Two HEDS trials evaluated the role of oral acyclovir in treating HSV stromal keratitis or iridocyclitis at a dosage providing therapeutic levels in the tear film[9] and aqueous humour.[10] In evaluating the effect of oral

Table 2 Rate of herpes simplex virus (HSV) epithelial keratitis occurring during treatment of HSV stromal keratouveitis using univariate exponential models for selected demographic and clinical factors

Variable	*Epithelial keratitis*	*Person weeks*	*Epithelial keratitis per 10 person weeks*	*p Value*
Demographic characteristics:				
Age (continuous)	12	1849	0.065	0.23
Sex				
Male	6	932	0.064	0.98
Female	6	917	0.065	
Ethnicity				
Non-white	6	441	0.136	0.044
White	6	1408	0.043	
Clinical history in previous 2 years:				
History of HSV epithelial keratitis				
Prior episode	12	1484	0.081	0.022
No prior episode	0	364	0	
History of HSV stromal keratitis				
Prior episode	1	588	0.017	0.12
No prior episode	11	1261	0.087	
History of non-ocular HSV disease				
Prior episode	8	771	0.104	0.093
No prior episode	4	1078	0.037	
Treatment and disease status at onset of HSV epithelial keratitis:				
Oral acyclovir use				
Acyclovir	2	583	0.034	0.28
Placebo or none	10	1265	0.079	
Topical antiviral frequency*				
Trifluridine 4 times/day	3	702	0.043	0.36
Trifluridine 2 times/day	9	1147	0.078	
Topical corticosteroid use				
Prednisolone phosphate	11	1632	0.067	0.72
Placebo	1	217	0.046	
Topical corticosteroid concentration*				
Prednisolone phosphate 1%	7	937	0.075	0.68
Prednisolone phosphate 0.125%	4	695	0.058	
Status of stromal disease at onset of epithelial keratitis				
Inflamed	6	897	0.067	0.92
Resolved	6	952	0.063	

* Time dependent since dosage reduction occurred during therapy. Corticosteroid concentration category does not include the placebo patients.

acyclovir on recurrent epithelial keratitis, our analysis was limited by the small study population and the use of topical trifluridine by all enrolled patients. While the differences were not statistically significant there is a suggestion that oral acyclovir as used in the HEDS treatment trials may have had an additive suppressive effect in patients using topical corticosteroids. We did note, however, that HSV epithelial keratitis occasionally recurred despite combined treatment with oral and topical antiviral agents. Whether antiviral resistance plays a role in cases that recur during antiviral prophylaxis has not been determined.

PROPHYLACTIC ANTIVIRAL DOSAGE AND SIDE EFFECTS

The dosage of prophylactic antiviral medications has evolved empirically. Options for the frequency of topical administration include the recommended therapeutic dose, a fixed lesser dose, or a variable schedule corresponding to concomitant corticosteroid instillation (for example, 'drop-for-drop'). The HEDS treatment protocols specified topical trifluridine four times daily for 3 weeks and twice daily thereafter. During the period of trifluridine administration four times per day, there was a slightly (but not statistically significantly) lower rate of HSV epithelial keratitis compared with the later period of twice daily use. More patients are needed to determine the optimal dosing frequency of prophylactic trifluridine during corticosteroid treatment. Although not evaluated in this study, the occurrence of active HSV infection during antiviral prophylaxis suggests inadequate dosing or possible resistance and may indicate the need for alternate dosage or drug selection.

Previous experience with trifluridine used for various periods of time showed that 4% of treated patients experienced local hypersensitivity and 3% developed punctate corneal epitheliopathy.[11] The frequency of adverse reactions in the HEDS trials was similar: during 10 weeks of trifluridine use 4% of patients developed allergic blepharoconjunctivitis, and 4% developed toxic corneal epitheliopathy. Periodic follow up of patients using an antiviral agent is justified to detect side effects to the drug or its preservative.

RISK FACTORS FOR RECURRENT EPITHELIAL KERATITIS

It remains unclear why HSV epithelial keratitis recurs in some patients despite trifluridine prophylaxis during the treatment of HSV stromal keratitis or iritis. Because of the small number of episodes of epithelial recurrences observed in this study, the scope for statistical analysis of risk factors is limited. Furthermore, a bias towards underrecognition of epithelial keratitis could have occurred because patients with persistent or progressive stromal keratouveitis were not periodically evaluated for recurrent dendrites after they failed study medications. We therefore performed only univariate analyses, used survival analytic methods that included the exact time to onset of all recurrences, assumed the simplest possible

parametric model for survival times, and provided sufficient information for future meta-analysis should additional data become available.

Despite potential limitations, our analysis suggests that patients with previous HSV epithelial keratitis have a higher rate of HSV epithelial keratitis during treatment of stromal keratitis or iritis and thus supports previous observations that patients with multiple past episodes of HSV keratitis tend to have future recurrences.[12] We also noted that the dendrite often occurred at or near the location of recent stromal inflammation, an observation that could be due to shedding from the same corneal nerves, by increased susceptibility of damaged epithelium, or by reactivation of latent corneal virus. Our additional finding that non-white patients were more liable to develop an epithelial recurrence is difficult to explain. Whether certain people are more susceptible to recurrent ocular HSV infection needs to be further assessed.

Viral and host factors may play roles in recurrent episodes of HSV keratitis. Some patients may be predisposed to recurrent epithelial keratitis despite antiviral prophylaxis and may need to be followed more closely during treatment of HSV stromal keratouveitis.

This study was supported by the National Eye Institute, National Institutes of Health, USA. IOLAB Corp and Glaxo Wellcome Co supplied the study medications.

1 Kaufman HE, Martola E-L, Dohlman CH. Herpes simplex treatment with IDU and corticosteroid. *Arch Ophthalmol* 1963;**69**:468–72.
2 Patterson A, Jones BR. The management of ocular herpes. *Trans Ophthalmol Soc UK* 1967;**87**:59–84.
3 Sundmacher R. Trifluorothymidinprophylaxe bei der Steroidtherapie herpetischer Keratouveitiden. *Klin Monatsbl Augenheilkd* 1978;**173**:516–9.
4 Wilhelmus KR, Gee L, Hauck WW, Kurinij N, Dawson CR, Jones DB, *et al.* Herpetic Eye Disease Study. A controlled trial of topical corticosteroids for herpes simplex stromal keratitis. *Ophthalmology* 1994;**101**:1883–96.
5 Barron BA, Gee L, Hauck WW, Kurinij N, Dawson CR, Jones DB, *et al.* Herpetic Eye Disease Study. A controlled trial of oral acyclovir for herpes simplex stromal keratitis. *Ophthalmology* 1994;**101**:1871–82.
6 Herpetic Eye Disease Study Group. A controlled trial of oral acyclovir for iridocyclitis caused by herpes simplex virus. *Arch Ophthalmol* 1996;**114**:1065–72.
7 Collum LMT, Grant DM. A double-blind comparative trial of acyclovir and adenine arabinoside in combination with dilute betamethasone in the management of herpetic disciform keratitis. *Curr Eye Res* 1987;**6**:221–4.
8 Porter SM, Patterson A, Kho P. A comparison of local and systemic acyclovir in the management of herpetic disciform keratitis. *Br J Ophthalmol* 1990;**74**:283–5.
9 Collum LMT, McGettrick P, Akhtar J, Lavin J, Rees PJ. Oral acyclovir (Zovirax) in herpes simplex dendritic corneal ulceration. *Br J Ophthalmol* 1986;**70**:435–8.
10 Hung SO, Patterson A, Rees PJ. Pharmacokinetics of oral acyclovir (Zovirax) in the eye. *Br J Ophthalmol* 1984;**68**:192–5.
11 Falcon MG, Jones BR, Williams HP, Wilhelmus K, Coster DJ. Adverse reactions in the eye from topical therapy with idoxuridine, adenine arabinoside and trifluorothymidine. In: Sundmacher R, ed. *Herpetische Augenerkrankungen*. Munich: Bergmann, 1981:263–8.
12 Liesegang TJ. Epidemiology of ocular herpes simplex. Natural history in Rochester, Minn, 1950 through 1982. *Arch Ophthalmol* 1989;**107**:1160–5.

Appendix

PARTICIPANTS

Investigators

C R Dawson,[1] T P Margolis,[1] R A Nozik,[1] H B Ostler,[1] J P Dunn,[1] B A Barron,[2] M S Insler,[2] H E Kaufman,[2] D B Jones,[3] A Y Matoba,[3] K R Wilhelmus,[3] R D Stulting,[4] G O Waring III,[4] L A Wilson,[4] R A Hyndiuk,[5] S B Koenig,[5] B M Massaro,[5] P A Asbell,[6] A P Davis,[6] M J Newton,[6] J Sugar,[7] S Lam,[7] J B Robin,[7] H H Tessler,[7] P R Laibson,[8] E J Cohen,[8] K G Leavitt,[8] C J Rapuano,[8] A Sugar,[9] R F Meyer,[9] H K Soong.[9]

Clinic coordinators

S Banuvar,[1] D Williams,[2] L A Todaro,[3] D Coffman,[4] L Dubois,[4] J Sease,[4] K Edwards,[4] M A Fitzgerald,[5] L Talajkowsi,[5] Z Griswold,[5] J Scott,[5] N Justin,[6] K Rosheim,[7] M Lindeman,[7] R Rodiek,[7] C Montanez,[8] N Richman,[8] C Pope.[9]

Coordinating centre

W W Hauck,[1] L Gee,[1] J E Hidayat.[1]

Data and safety monitoring committee

S Bangdiwala,[10] W E Barlow,[11] J W Chandler,[7] L J Nelson,[12] A B Nesburn,[13] N Kurinij.[14]

Addresses

1 Francis I Proctor Foundation, University of California, San Francisco, CA, USA.
2 LSU Eye Center, Louisiana State University Medical Center, New Orleans, LA, USA.
3 Cullen Eye Institute, Baylor College of Medicine, Houston, TX, USA.
4 Emory Eye Center, Emory University, Atlanta, GA, USA.
5 Medical College of Wisconsin Eye Institute, Medical College of Wisconsin, Milwaukee, WI, USA.
6 The Mount Sinai Medical Center, New York, NY, USA.
7 University of Illinois at Chicago Eye Center, University of Illinois, Chicago, IL, USA.
8 Wills Eye Hospital, Philadelphia, PA, USA.
9 W K Kellogg Eye Institute, University of Michigan, Ann Arbor, MI, USA.
10 School of Public Health, University of North Carolina, Chapel Hill, NC, USA.
11 Center for Health Studies, Group Health Cooperative, Seattle, WA, USA.
12 Bioethics Consultation Group, Berkeley, CA, USA.
13 Cedars-Sinai Medical Center, Los Angeles, CA, USA.
14 National Eye Institute, Bethesda, MD, USA.