Efficacy of Oral Antiviral Prophylaxis in Preventing Ocular Herpes Simplex Virus Recurrences in Patients With and Without Self-Reported Atopy

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PURPOSE: To compare the efficacy of oral antiviral prophylactic treatment for herpes simplex virus (HSV) recurrences in patients with and without self-reported atopy.

DESIGN: Retrospective cohort comparative study.

METHODS: SETTING: Cornea Service, Wills Eye Hospital. STUDY POPULATION: Patients who presented with previously diagnosed ocular HSV between March 2003 and March 2004. From 244 patients invited, 54 patients (58 eyes) were included. One hundred and ninety patients were excluded according to exclusion criteria: no active episode during follow-up, immunosuppression, less than one year of follow-up, or previous history of penetrating keratoplasty. The Questionnaire regarding history of atopic disease, considers: presence of allergic rhinitis, asthma or atopic dermatitis, and chart review of ocular history. MAIN OUTCOME MEASURES: Incidence of all types of HSV recurrences with and without antiviral prophylaxis within each group and between groups. HSV episodes were classified into infectious, inflammatory, and mixed for analysis.

RESULTS: Atopic/nonatopic (P value): mean follow-up without prophylaxis 8.1 (± 8.2)/7.3 years (± 8.6) (P = .71); mean follow-up with prophylaxis 2.9 (± 2.3)/2.6 years (± 2.2) (P = .51); the effect of prophylaxis significantly reduced the all recurrences in both groups except in the inflammatory recurrences in the atopic group and in the mixed recurrences in both groups. Prophylaxis decreased infectious episodes by 44% in nonatopic and 76% in atopics and decreased inflammatory manifestations by 69% in the nonatopic group and 8% in the atopic group.

CONCLUSION: Antiviral prophylaxis for HSV recurrences was more effective in reducing infections in atopics and less effective in reducing inflammatory episodes in atopics versus nonatopics. (Am J Ophthalmol 2006;142:563–567. © 2006 by Elsevier Inc. All rights reserved.)

Herpes Simplex Virus (HSV) is a leading cause of corneal opacification and infection-related visual loss. Approximately half a million people in the United States have experienced ocular HSV disease, and there are approximately 50,000 new and recurrent cases each year.1 The recurrences may lead to permanent structural damage to the cornea and uvea with scarring and loss of vision.2 4 The recurrence rate of ocular HSV has been estimated to be as high as 20% by two years, 40% by five years, and 67% by seven years.5

Acyclovir (ACV) is an acyclic purine nucleoside analog that binds to viral DNA polymerase resulting in incomplete DNA chains thus preventing replication of the virus.1 6 Newer drugs, for example, valacyclovir, a prodrug for acyclovir, and famciclovir, a prodrug of penciclovir, have the advantage of more convenient dosing schedule but they have the same mechanism of action as ACV and the disadvantage of higher cost. There are still no known agents to eliminate latent HSV from the nervous system; however, ACV has been extensively used to reduce severity and number of HSV recurrences in humans. The Herpetic Eye Disease Study (HEDS) demonstrated that the use of prophylactic treatment with oral acyclovir decreases by

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45% the rate of ocular HSV recurrences during a one-year period.\textsuperscript{7,8}

Over the past few years however, ACV-resistant HSV strains have been isolated from ocular sites in patients with impaired cellular immunity including patients with atopic disease.\textsuperscript{9–12} Atopy is associated with ocular, respiratory, and dermatologic manifestations of human hypersensitivity type I diseases, which include asthma, allergic rhinitis (hay fever), and atopic dermatitis (eczema).\textsuperscript{13} Atopy is also associated with impaired cell-mediated immunity. Yao and associates have demonstrated that cellular immune depression present in atopic patients may induce ACV-resistant HSV infection in the cornea.\textsuperscript{9} The purpose of this study is to compare the efficacy of oral prophylactic ACV treatment for HSV recurrences in patients with and without self-reported atopy.

**METHODS**

**THE PROTOCOL, THE QUESTIONNAIRE, AND INFORMED consent forms were approved by the Wills Eye Hospital Institutional Review Board; all study patients provided written informed consent. The study was performed in accordance with Health Insurance Portability and Accountability Act regulations (HIPAA).

The patients were enrolled between March 2003 and March 2004 when they came for ophthalmic examination on the Cornea Service, Wills Eye Hospital, Thomas Jefferson University. All patients had been previously or were just diagnosed at the same institution as having ocular HSV. The diagnosis of every HSV episode was made by an experienced cornea specialist (E.J.C., C.J.R., P.R.L., or K.H.) who prescribed prophylactic antiviral medications when indicated.

All eligible patients were invited to participate in the study and, after informed consent was obtained, they filled out a questionnaire regarding their personal and familial history of atopic disease. The questionnaire was developed in consultation with a dermatologist (G.W.), and was based on the European Community Respiratory Health Survey\textsuperscript{14} and the International Study of Asthma and Allergies in Childhood.\textsuperscript{15}

In April 2004, the completed questionnaires were reviewed by G.W., who was blinded to the patient's ocular history with regards to ocular HSV severity. He classified the patients as atopic based on the presence of at least one of the following disorders: allergic rhinitis or “hay fever”; asthma; or atopic dermatitis or “eczema.” A history of atopic conjunctivitis was not considered a criterion for atopy; however, the presence of allergic conjunctivitis was recorded after review of the medical records.

The diagnosis of ocular HSV was clinical, and the classification was based on the one proposed by Holland and Schwartz.\textsuperscript{2} The classic HSV episodes were further grouped into three categories based on the pathogenesis of each event: “infectious” episodes were related to active viral replication (blepharo-conjunctivitis and classic HSV epithelial keratitis); “inflammatory” episodes related to immune reaction to the virus (immune stromal keratitis and endotheliitis); and “mixed” episodes related to both active viral replication and to immune reaction to the virus (necrotizing stromal keratitis, HSV iritis, and the combined presentation of an infectious along with an inflammatory episode). Neurotrophic ulceration was not considered an active HSV episode.

In March 2005, the medical records were retrospectively reviewed without the knowledge of the atopic status of each patient. The effect of prophylactic ACV therapy in the reduction of HSV recurrences was retrospectively reviewed in patients with and without self-reported atopy.

We included patients who had at least one classic HSV episode based on the Holland classification during follow-up on the Cornea Service. In addition, to be included, each patient needed at least six months follow-up both with and without oral antiviral prophylaxis, totaling a minimum one-year follow-up. Exclusion criteria were immunosuppression (primary immune deficiency disorders, AIDS, high doses of immunosuppressive medications, malignancies, and chemotherapy) and previous history of penetrating keratoplasty (PK) before the first visit.

We considered antiviral prophylaxis (AVP) as the use of acyclovir (400 mg twice daily) or valacyclovir (500 mg every day) or famciclovir (250 mg twice daily) for more than 30 consecutive days. The periods of 30 days of prophylaxis did not have to be consecutive, but had to add up to at least six months. The indication for AVP on the Cornea Service was based on a history of stromal keratitis or uveitis, frequent recurrences, and patient’s decision. Total follow-up was computed from the first visit to the last visit or, in the case of a patient who underwent a PK, the last visit before the PK.

Two major analyses were performed: the effect of antiviral prophylaxis in reducing all types of HSV recurrences within each group (each patient was his or her own control) and between atopic and nonatopic groups. The variables used to evaluate the effect of ACV were: incidence (episodes/year of follow-up) of all types of HSV recurrences with and without ACV in both groups (atopic and nonatopic). Secondary outcome measures were: bilaterality of HSV ocular disease; loss of vision, need for PK (based on decreased visual acuity and patient’s wish to improve vision), and presence of allergic conjunctivitis (atopic, vernal or hayfever conjunctivitis). Visual acuity evaluation included the initial best spectacle corrected visual acuity considered as the best corrected visual acuity on the first visit without an active HSV episode. It was compared with the final best corrected visual acuity, considered the best corrected visual acuity at last visit of follow-up. All visual acuities were converted from Snellen chart visual acuity to logMAR for analysis. Other variables
TABLE 1. Demographic Characteristics of the Sample, Presence of Allergic Conjunctivitis, Orofacial Herpes Simplex Virus, and Bilaterality of Herpetic Disease

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Nonatopic (n = 23 Patients)</th>
<th>Atopic (n = 31 Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>11/12</td>
<td>11/15</td>
</tr>
<tr>
<td>Age (SD)*</td>
<td>53.5 (± 16.7)</td>
<td>47.6 (± 17.4)</td>
</tr>
<tr>
<td>Caucasian/non-Caucasian</td>
<td>22/1</td>
<td>28/3</td>
</tr>
<tr>
<td>Orofacial HSV</td>
<td>13</td>
<td>23</td>
</tr>
<tr>
<td>Bilateral HSV</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

SD = standard deviation; HSV = herpes simplex virus.
*Mean age at presentation in years.

TABLE 2. Types of Atopy Presenting in the Atopic Group With Herpes Simplex Keratitis

<table>
<thead>
<tr>
<th>Type of Atopy</th>
<th>Number of Patients (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic rhinitis</td>
<td>16</td>
</tr>
<tr>
<td>Asthma</td>
<td>1</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>2</td>
</tr>
<tr>
<td>Allergic rhinitis + asthma</td>
<td>3</td>
</tr>
<tr>
<td>Allergic rhinitis + atopic dermatitis</td>
<td>4</td>
</tr>
<tr>
<td>Atopic dermatitis + asthma</td>
<td>1</td>
</tr>
<tr>
<td>Allergic rhinitis + asthma + atopic dermatitis</td>
<td>4</td>
</tr>
</tbody>
</table>

evaluated were ethnicity, age at first visit, gender, and history of oral facial herpes simplex infection.

An active episode on first presentation was used for diagnostic purposes but was not computed in the incidence calculation due to the absence of previous follow-up. The incidence of the episodes was calculated on an eye/year of follow-up basis. Statistical analysis was done using SPSS/PC 10.1 software (Windows, SPSS Inc, Prentice Hall, Upper Saddle River, New Jersey, USA). Comparisons within groups and between groups using Student t test for paired samples, and Student t test for independent samples were made using the Student t test for independent samples and χ² test. Levels of statistical significance were set at P < .05, using a two-tailed test.

RESULTS

BETWEEN MARCH 2003 AND MARCH 2004, 244 PATIENTS were invited to fill out the questionnaires; a response rate of 91.4% (223 patients) was obtained. Our final study population was 54 patients, 58 eyes. One hundred and sixty-nine patients were excluded after the retrospective review of their medical records for the following reasons: 56.2% (95/169) had fewer than six months’ follow-up with or without antiviral prophylaxis, 13% (22/169) patients had no classic active episode of HSV during their follow-up; 13% (22/169) underwent a PK before one year of follow-up on the service, 7.1% (12/169) underwent PK before their first visit to the service; 4% (7/169) immuno-suppressed (four on chemotherapy for breast or lung cancer treatment, two lymphoma, one multiple sclerosis); 3.5% (6/169) had a doubtful diagnosis of HSV; and 2.9% (5/169) did not mail back the questionnaire, despite reminder letters.

From the 54 patients included, 50% (27/54) were female, 92.6% (50/54) were Caucasian, and 57.4% (31/54) were atopic (Table 1). The most common type of atopy was allergic rhinitis present in 87.1% (27/31) of the atopic patients (Table 2). Most of the atopic patients, 64.5% (20/31), had used oral antihistamines alone or in combination with other medications, only 16.1% (5/31) of the patients had used oral corticosteroids in low dosage (less than 20 mg/day), 6.4% (2/31) patients had used nasal corticosteroids, and only one patient had used topical corticosteroids to treat eczema. None of the patients included in the study had used oral corticosteroids in high dosage (higher than 1 mg/kg/day), and therefore none of the atopic patients was excluded because of high doses of immunosuppressive medications.

Fifty-one of the fifty-four patients were on oral acyclovir (400 mg twice daily) and only three patients were on other antiviral medications (two patients on valacyclovir 500 mg every day and one on famciclovir 250 mg twice daily).

The final follow-up computed for all the analyses ranged from one to 38.4 years. The mean follow-up was 9.9 years (SD ± 9.1, median of 5.9 years) in the nonatopic group compared with a mean follow-up of 11.1 year (SD ± 8.1, median of 9.0 years) in the atopic group (P = .59). The nonatopic group had a mean follow-up without antiviral prophylaxis of 7.3 years (SD ± 8.6, median of 3.2 years) and a mean follow-up with antiviral prophylaxis of 2.6 years (SD ± 2.2, median of 1.9 years). The atopic group had a mean follow-up without antiviral prophylaxis of 8.1 years (SD ± 8.2, median of 5.3 years) and a mean follow-up with antiviral prophylaxis of 2.9 years (SD ± 2.3, median of 2.4 years). The analysis of the incidence of the HSV episodes considered the follow-up period of each
eye, resulting in a total of 237 eyes/year of follow-up in the nonatopic group and of 378 eyes/year of follow-up in the atopic group.

The most common types of HSV recurrences observed were dendritic keratitis, followed by immune stromal keratitis, uveitis, blepharoconjunctivitis, endotheliitis, geographic ulcer and necrotizing keratitis. All episodes observed during the follow-up were grouped into categories and are listed in Table 3. Infectious episodes were more common in the atotics.

The Figure shows a reduction of the mean incidence of all types of recurrences with the use of antiviral prophylaxis. There was a reduction in the incidence of all types of HSV from 0.46 to 0.24 episodes/year in the nonatopic group (48% reduction, \( P < .01 \)) and from 0.64 to 0.34 in the atopic group (47% reduction, \( P < .01 \))/year was observed. The rate of infectious episodes decreased from 0.16 to 0.09 in the nonatopic (44% reduction, \( P < .01 \)) and from 0.33 to 0.08 in the atopic (76% reduction, \( P < .01 \)); in inflammatory episodes, the reduction was from 0.16 to 0.05 in nonatopic (69% reduction, \( P < .01 \)) and from 0.13 to 0.12 in the atopic (8% reduction, \( P = .62 \)); and in mixed episodes from 0.14 to 0.10 in nonatopic (29% reduction, \( P = .08 \)) and from 0.18 to 0.15 in the atopic group (17% reduction, \( P = .14 \)).

When both groups were compared we found no statistically significant difference in reduction of incidence of all episodes with ACV prophylaxis (48% in the nonatopic and 47% in the atopic, \( P > .05 \)) and in the reduction of mixed episodes (29% in nonatopic and 17% in the atopic, \( P > .05 \)). A statistically significant difference was found in the reduction of infectious episodes with ACV between groups (44% in nonatopic and 76% reduction in atopic, \( P < .01 \)) and in the reduction of inflammatory episodes (69% in the nonatopic group and 8% in the atopic group, \( P < .01 \)).

There was no significant difference between atopic and nonatopic groups regarding the bilaterality of HSV ocular disease (Table 1). Nor was there a significant difference in the mean visual loss in logMAR (0.59, SD ± 0.70 in the nonatopic and 0.42, SD ± 0.70 in the atopic group, \( P = .39 \)). There was a trend for significance when we compared the need for PK (six eyes in the nonatopic and two eyes in the atopic group, \( P = .05 \)).

**DISCUSSION**

OCULAR HSV IS CONSIDERED THE MOST COMMON CAUSE of corneal opacification in developed countries. The recurrent nature of the HSV infection is the main cause of ocular morbidity.2 After a person is infected with HSV, the virus remains in a latent state within the nervous tissue indefinitely.16 The pathogenesis of HSV keratitis involves not only reactivation and centrifugal migration of latent trigeminal ganglion virus but also, potentially, replication of latent virus in the cornea itself.17–19 Although there are no medications to eliminate latent HSV from the nervous system, prophylactic antiviral therapy has been shown to decrease ocular HSV recurrences.7,8

Atopic patients may have unusually severe keratitis and poor therapeutic response to topical antivirals.20 Some authors have isolated ACV-resistant HSV strains from ocular sites in patients with impaired cellular immunity.9–12 It is known that atopy is associated with a number of functional abnormalities of the immune system, including T-cell number, imbalance of T-cell subpopulations, poor response to certain T-cell mitogens, cutaneous anergy, and decreased susceptibility to contact sensitization.21 The precise way in which immune processes operate to protect the host against HSV infections is not yet clear.

This study showed that antiviral prophylaxis considerably reduced the recurrences in both atopic and nonatopic groups in every type of ocular HSV, except in the inflammatory recurrences in the atopic group and in the mixed recurrences in both groups (Figure). As we had demonstrated in a previous study,22 infectious HSV episodes seem to be more common in atotics. It is noteworthy that AVP was more effective in decreasing this category of HSV episodes (infectious) in atopic than in nonatopic patients (44% in nonatopic and 76% reduction in atopic, \( P < .01 \)). AVP was less effective in decreasing inflammatory manifestations in atopic than nonatopic patients (69% in the nonatopic group and 8% in the atopic group, \( P < .01 \)), but atopic patients are less prone to them than nonatotics.

The finding of this study that patients with atopic disease have fewer inflammatory HSV recurrences is consistent with our previous finding22 and with Schmid and Rouse’s report20 that stromal keratitis appears to result from the induction of an excessive T-cell response to HSV. Therefore, atopic patients’ impaired T-cell immunity seems to make them make them less susceptible to inflammatory
recurrences. This is also supported by this study's finding of slightly less loss of vision in the atopic group. With larger numbers, it is possible that we could have demonstrated that atopics are less likely to need penetrating keratoplasty than nonatopics due to fewer inflammatory episodes.

The HEDS demonstrated that oral ACV 400 mg twice a day used for one year decreased the rate of recurrence by 45%.7,8 We found a similar effect of 48% reduction in nonatopics and 47% in atopics when we looked at all episodes together during a longer follow-up period. The HEDS study found the acyclovir prophylaxis was most beneficial in patients with a history of stromal keratitis because they are likely to have recurrences. Our results suggest that antiviral prophylaxis is especially beneficial in preventing recurrent infections in atopics who are especially prone to them. Our findings support their use in atopics who have frequent HSV infections.

Considering that there is no available treatment that eradicates HSV infection, major efforts are still concentrated on moderating and preventing viral reactivations. The current study demonstrates that antiviral prophylaxis for HSV recurrences in patients with atopic disease seems to be as effective as in patients without atopic disease.

REFERENCES

Renata A. Rezende, MD, graduated from medical school in 1998 and did three years of ophthalmology residency in Rio de Janeiro, Brazil, and completed a one year cornea research fellowship at Wills Eye Hospital. Dr Rezende is preparing her PhD thesis on “Herpes simplex keratitis and atopic disease” for the Federal University of Sao Paulo by the end of 2006. Currently, she is an Assistant Professor of Ophthalmology of Catholic University of Rio de Janeiro (PUC-RJ) and a Cornea Specialist at Hospital Sao Vicente de Paulo.