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Role of Prophylactic Oral Acyclovir in Recurrent Herpes Simplex Eye Disease

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Abstract
Purpose*: To study the role of long-term treatment with oral acyclovir to prevent recurrences of ocular HSV disease.*
Material & methods: *A retrospective study was carried out in the Department of Ophthalmology at Government Medical College, Patiala, Punjab, India. A total of 50 immunocompetent patients who had had ocular HSV disease within the preceding year in the age group 25 to 45 years were selected to receive 400 mg of acyclovir orally twice daily over a period of 12 months. The history of each patient was taken including a record of age, sex, place of residence, change of place of residence, age at onset of the disease, best-corrected visual acuity was assessed and each patient was thoroughly examined with a slit lamp. Follow-up was done at 1, 3, 9 and 12 months during the treatment period and 6 weekly in the post-treatment observation period. The study outcomes were the rates of development of ocular HSV disease during a 12-month treatment period and a 6-month observation period.*
Results: *The recurrence during the treatment period was 11 cases, (22 %) and the observation period was 8 cases (16 %). During 12 month treatment period, 1 case (2%) had blepharitis or conjunctivitis, 5 cases (10 %) had epithelial keratitis, 4 cases (8 %) had stromal keratitis and 1 case (2%) had iritis. During 6 month observation period, 2 cases (4%) had blepharitis or conjunctivitis, 3 cases (6 %) had epithelial keratitis, 2 cases (4 %) had stromal keratitis and 1 case (2%) had iritis.*
Conclusion: *After the resolution of ocular HSV disease, 12 months of treatment with acyclovir reduces the rate of recurrent ocular HSV disease. Long-term oral acyclovir prophylaxis is most important for patients with a history of HSV stromal keratitis as it can prevent additional episodes and potential loss of vision.*
Keywords: *Infectious epithelial keratitis ,acyclovir, dendritic ulcer, blepharitis*

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I. Introduction

Herpes simplex virus type 1 (HSV-1) is a human alpha-herpesvirus that is endemic worldwide. The virus is typically acquired during early childhood via the orofacial route, leading to the establishment of a life-long latent infection of neurons located within the trigeminal ganglia. Intermittent reactivations lead to virus shedding and occasionally to recurrent disease [1] . Corneal HSV-1 infections, referred to as herpetic keratitis (HK), are a common infectious cause of visual impairment mainly due to their recurrent nature ,[2, 3] can lead to disease of one or both eyes.HK manifests as infectious epithelial keratitis (IEK), which is characterized by superficial viral replication, or it can infect the underlying corneal stroma and cause herpetic stromal keratitis (HSK) [2] . 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. The drug of choice to treat HSV-1 infections is acyclovir . Acyclovir is a potent and specific antiviral agent that is effective in the treatment of and prophylaxis against HSV infection. Controlled trials have established that oral acyclovir significantly reduces the rate of recurrent genital [5,6] and orofacial[7,8]HSV infections in otherwise healthy persons.We conducted a randomized 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 .

II. Material & Methods

This is a retrospective study conducted in a tertiary care hospital in Patiala, Punjab. It was conducted with data collected from a total of 50 immunocompetent patients who had had ocular HSV disease (i.e., blepharitis, conjunctivitis, epithelial keratitis, stromal keratitis, or iritis) in one or both eyes within the preceding year but their disease had been inactive and untreated during the 30 days before the study began ,in age group 25 to 45 years were selected to receive 400 mg of acyclovir orally twice daily over a period of 12 months . 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 of reproductive age agreed to use contraception during the one year treatment period and for three months thereafter. The history of each patient was taken including a record of age, sex, place of residence, change of place of residence, age at onset of the disease, best-corrected visual acuity was assessed and each patient was thoroughly examined with a slit lamp. Follow-up was done at 1 , 3, 9 and 12 months during treatment period and 6 weekly in post treatment observation period. The study outcomes were the rates of development of ocular HSV disease during a 12-month treatment period and a 6-month observation period. 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, every 6 weekly 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. The primary outcome was the recurrence of any type of ocular HSV disease during the 12-month treatment period.

Table 1 displays the age and sex distribution at the onset of herpetic eye disease; the highest incidence of VKC occurred in the age group of 35–45 years. Table 2 describes the distribution of past episodes of ocular HSV disease. Table 3 shows the type of prior ocular HSV involvement. Table 4 depicts types of ocular involvement in initial recurrences of HSV disease.

III. Results

Of 50 patients, 32 (64%) were male and 18 (36%) were female. Table 1 displays the age and sex distribution at the onset of ocular HSV; the highest incidence occurred in the age group 35–45 years that is 35 cases (70 %).

Table 1: Age & Sex distribution at time of presentation

	Number of Cases (%)
Age group(years)	
25-35	15 (30%)
35-45	35 (70%)
Gender	
Male	32 (64%)
Female	18 (36%)

As shown in Table 2, past episodes of ocular HSV disease, 11 (22%) cases had history of one episode of HSV infection, while 23(46%) had 2-3 episodes and 16 cases had history of more than 4 episodes.

Table 2: Past episodes of ocular HSV disease

Past episodes of ocular HSV disease	Number of Cases (%)
1	11 (22%)
2-3	23 (46%)
>4	16 (32%)

Table 3 depicts type of prior ocular HSV involvement, 5 cases (10%) had blepharitis or conjunctivitis , 19 cases (38%) had only Epithelial keratitis and no stromal keratitis ,13 cases (26%) had stromal and epithelial keratitis , 10 cases (20%) had stromal keratitis and no epithelial keratitis and 3 cases (6%) had iritis .

Table 3: Types of prior ocular HSV involvement

Types of prior ocular HSV involvement	Number of Cases (%)
Blepharitis or conjunctivitis	5 (10%)
Only Epithelial keratitis and no stromal keratitis	19 (38%)
Stromal and epithelial keratitis	13 (26%)
Stromal keratitis and no epithelial keratitis	10 (20 %)
Iritis alone	3 (6%)

Table 4 depicts the recurrence during treatment (11 cases, 22 %) and observation period(8 cases, 16 %). During 12 month treatment period , 1 case (2%) had blepharitis or conjunctivitis, 5 cases (10 %) had epithelial keratitis , 4 cases (8 %) had stromal keratitis and 1 case (2%) had iritis. During 6 month observation period , 2 cases (4%) had blepharitis or conjunctivitis, 3 cases (6 %) had epithelial keratitis , 2 cases (4 %) had stromal keratitis and 1 case (2%) had iritis.

Table 4: Types Of Ocular Involvement In Initial Recurrences Of HSV Disease

Type of ocular HSV disease		Number of Cases (%)
1.	**Recurrence during the 12-month treatment period**	11 (22%)
	a. Blepharitis or conjunctivitis	1 (2%)
	b. Epithelial keratitis	5 (10%)
	c. Stromal keratitis	4 (8%)
	d. Iritis	1 (2%)
2.	**Recurrence during the 6-month observation period**	8 (16%)
	a. Blepharitis or conjunctivitis	2 (4%)
	b. Epithelial keratitis	3 (6%)
	c. Stromal keratitis	2 (4%)
	d. Iritis	1 (2%)

IV. Discussion

This study of 50 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 . The Herpetic Eye Disease Study (HEDS), performed in the USA, was a multi-armed set of five randomized, placebo-controlled trials designed to determine best treatments and prophylaxis for HSV keratitis and one epidemiologic study that investigated risk factors. Herpes simplex virus epithelial keratitis accounted for 47% of ocular HSV cases in the HEDS trial, compared to 66.1% of ocular HSV cases in the French study. [9, 10] Similarly, HSV stromal keratitis accounted for 16% of ocular HSV cases in the HEDS trial compared to 29.5% in the French study.The Herpetic Eye Disease Study focused in part on the use of oral acyclovir to prevent HSV epithelial and stromal keratitis and provides valuable epidemiologic data, particularly with regard to recurrence rates. [10, 11] A HEDS multi-center randomized trial enrolled 703 patients with at least one episode of ocular HSV in the previous 12 months and no disease activity within the previous 30 days. Patients received either 400 mg of acyclovir twice daily or placebo. Regardless of symptoms, ocular exams were performed at 1, 3, 6, 9, and 12 months after the start of treatment. [10] The placebo arm of the HEDS trial yields a cumulative probability of an ocular HSV recurrence of 32% during the 12-month period. [10, 11]Starting with a cohort of patients with a history of some form of ocular HSV, there are differences in "same type" recurrences between HSV stromal keratitis and epithelial keratitis. For example, the rates of HSV epithelial keratitis in patients with a history of ocular HSV other than epithelial keratitis, compared to those with a history of HSV epithelial keratitis, were essentially equal, 12% and 15% respectively. However, the recurrence rates for HSV stromal keratitis were strikingly different; only 3% of patients with a history of ocular HSV, but not stromal keratitis, developed HSV stromal keratitis compared to the 28% of patients with a positive history of HSV stromal keratitis. In addition, the number of recurrences (all types) was strongly associated with the number of past episodes (all types). Thus, a history of HSV stromal keratitis and a high number of previous episodes (any type) increase the risk of future recurrence. Evidence also exists to suggest that short intervals between attacks tend to be associated with short intervals between future attacks. [12, 13] In our study the recurrence during treatment period was 11 cases, (22 %) and observation period was 8 cases (16 %). During 12 month treatment period , 1 case (2%) had blepharitis or conjunctivitis, 5 cases (10 %) had epithelial keratitis , 4 cases (8 %) had stromal keratitis and 1 case (2%) had iritis. During 6 month observation period , 2 cases (4%) had blepharitis or conjunctivitis, 3 cases (6 %) had epithelial keratitis , 2 cases (4 %) had stromal keratitis and 1 case (2%) had iritis.

V. Conclusion

Our results show that long-term treatment with acyclovir helps prevent recurrences of ocular HSV disease in patients with a history of ocular HSV disease.

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Conflicts of interest

There are no conflicts of interest.

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