

Acyclovir and trifluorothymidine in herpetic keratitis: a multicentre trial

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SUMMARY A randomised double blind study was performed on 59 patients with dendritic herpetic keratitis treated with 3% acyclovir or 2% trifluorothymidine ointment. Both drugs were highly effective and gave 87% (ACV) and 82% (TFT) success rates. Punctate keratopathy occurred in 70% of the patients, but serious side effects were not observed.

Since the introduction of idoxuridine (IDU) as an antiviral drug for the treatment of herpetic keratitis more potent drugs have become available. Arabinoside adenine and trifluorothymidine (TFT) are both effective and relatively nontoxic alternatives widely used in the management of herpetic disease.¹ Acyclovir (ACV) (9-(2-hydroxyethoxymethyl) guanine)² and (E)-5(2-bromovinyl)-2' deoxyuridine,³ recently developed antiviral compounds with potent inhibitory activity against herpes simplex DNA polymerase, do not inhibit normal human cell DNA polymerase.

For a comparative study we selected 2 of the antiviral drugs which we considered to be the most potent—acyclovir and trifluorothymidine.^{4,5}

Material and methods

Fifty-nine patients with dendritic keratitis were studied. Patients with stromal keratitis and patients treated by antiviral agents and/or corticosteroids prior to referral were excluded. In a randomised double-blind study we used 3% acyclovir and 2% trifluorothymidine ointment, both specially prepared for this trial and packed in identical tubes obtained through the kind co-operation of Wellcome Laboratories (England) and Dr Gerhard Mann, Hamburg (FRG), respectively. The ointment was prescribed 5 times daily. Cycloplegics were given for intraocular irritation.

After healing was complete the treatment was continued for 7 days. It was discontinued if after 7 days no therapeutic effect was observed or if after 14 days the keratitis had not healed completely.

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The keratitis was considered to be cured when the lesion no longer stained with fluorescein 10–20%. Slit-lamp examination was performed in the out-patient department, usually every day so as to assess the exact day of healing. At all examinations colour slides were made of the cornea at 2× linear magnification without staining and after 10–20% fluorescein staining with a blue filter in front of the electronic flash. The findings were recorded on a proforma specially designed for this study. The results of a preliminary study have been published elsewhere⁶; this paper deals with the final results in 59 patients with herpetic dendritic keratitis.

Results

Thirty-one patients were treated with ACV and 28 with TFT. The groups were well matched in terms of sex and age, and there was no significant difference between them (Table 1). Most of the patients in both

Table 1 Distribution according to sex and age of acyclovir and trifluorothymidine treated patients

	ACV	TFT	
Number of patients entered	31	28	
Sex:			
male	22	12	No significant difference $\chi^2=3.21$ $p=>0.05$
female	9	16	
Age:			
younger than 50 years	16	12	No significant difference
50 years and older	15	17	

Table 2 Duration of symptoms at presentation

	ACV	TFT
Up to 7 days	26	24
8-14 days	3	4
15-21 days	2	0

Table 3 Duration of treatment in days

	ACV	TFT
Average	6.3	7.1
Standard deviation	2.4	4.0
Total duration of treatment	15.1	15.8

groups had had their eye complaints for less than 7 days (Table 2).

The results are summarised in Fig. 1, which shows that in 27 out of 31 ACV-treated patients and 23 out of 28 TFT-treated patients the keratitis had healed after 2 weeks of treatment. The average duration required for healing of the keratitis was 6.3 days in the ACV series and 7.0 days in the TFT series (Table 3). The difference was not statistically significant. Nor was there any statistical correlation between the duration of the complaints before treatment and the healing time after antiviral treatment was started.

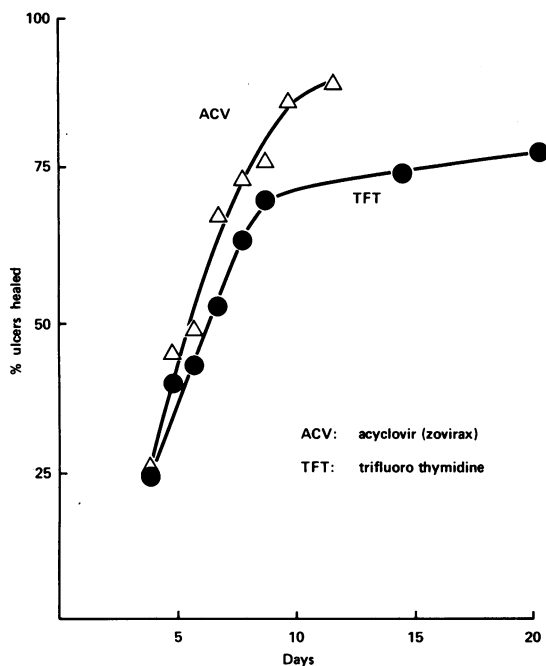


Fig. 1 Cumulative frequency distribution of time taken to heal dendritic keratitis in 27 acyclovir and 23 trifluorothymidine treated patients.

The most frequently observed side effect was superficial punctate keratopathy, showing fluorescein staining outside the area of the herpetic lesions. This occurred in about 70% of patients in both groups, with an average duration of slightly more than one week. In both groups a few patients complained of a stinging sensation after application of the ointment, but extensive conjunctival hyperaemia was seen in only 3 patients receiving TFT, and it disappeared a few days after discontinuation of the treatment. In neither groups were there short-term recurrences of herpetic keratitis.

Discussion

There is ample evidence that TFT is an effective antiviral agent, with up to 95% healing of dendritic herpetic keratitis.^{4,5} This induced us to test the more recently developed ACV in a double-blind study with TFT. The results showed that both compounds are highly effective, and there was no statistical difference between them. Our results of ACV treatment in patients agree with the favourable results of experiments in rabbits.¹⁷⁻¹¹ Other results of clinical trials with 3% ACV ointment in dendritic or geographic herpetic keratitis are also favourable and agree with our results.¹²⁻¹⁵ The average healing time in our series of ACV-treated patients was 6.3 days, which is longer than the 4.4 days in the series of Collum *et al.*¹³

In our preliminary study 20 ACV-treated patients had healed within 10 days,⁶ but in the present series 4 out of the 31 eyes failed to heal. In previous studies, totalling 84 ACV-treated eyes, the keratitis in all eyes responded well to the treatment and healed.¹³⁻¹⁵ The lack of efficacy which we observed may have been caused by resistance against herpes virus strains comparable to that of strains refractory to TFT. But this cannot be proved because inadequate treatment could be the explanation in patients treated on an outpatients basis.

As this was a multicentre study, special care was taken to make a strict protocol and a proforma for each patient. Moreover, regular, often daily, photographic recording was performed after 20% fluorescein staining. Joint sessions for evaluation helped us to detect even the slightest epithelial lesions. This accounts for the high percentage of punctate keratopathy (about 70%) observed in both ACV and TFT treated patients, as the slightest of punctate lesions outside the dendritic area were included. Other workers have described a much lower rate of punctate keratopathy in patients on ACV treatment, namely, 14%¹⁵ or none in 30 patients.¹³ After discontinuation of the treatment the punctate keratopathy disappeared in an average of

8.5 days in the ACV series and 7.6 days in the TFT series. Surprisingly, the ACV-treated group had the same frequency of punctate keratopathy as the TFT-treated group. If this effect is caused by a metabolic disturbance of the corneal epithelium due to DNA inhibition, we should expect less keratopathy in the ACV group, as ACV is known not to inhibit cell DNA polymerase. Moreover, Lass *et al.*¹⁶ found that ACV had no detrimental effect on regeneration of corneal epithelium. However, we do not know to what extent the keratopathy may be related to the ointment base used.

Our results indicate that both ACV and TFT are safe, have a high therapeutic efficacy against dendritic herpetic keratitis, and are of low toxicity.

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