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Treatment of amoeboid herpetic ulcers with adenine arabinoside or trifluorothymidine

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SUMMARY In previous studies adenine arabinoside and trifluorothymidine were found to be equally effective treatments for dendritic ulcers of the cornea, but a trend emerged which suggested that in amoeboid ulcers trifluorothymidine was more effective. The collection of additional cases confirms the superiority of trifluorothymidine in such cases.

Despite extensive research 5-iodo-2′-deoxyuridine (IDU) has remained until recently the only antiviral agent generally available to clinicians for treating ulcerative herpetic keratitis.

Adenine arabinoside (Ara-A) and trifluorothymidine (F_3T) (Wellings *et al.*, 1972; Pavan-Langston, 1975; Coster *et al.*, 1976) are both highly effective in treating herpetic corneal ulceration. In a large series of herpetic ulcers treated with one or other of these agents no difference could be found in the dendritic ulcer group (Fig. 1), but a trend emerged which suggested that F_3T had some advantage over Ara-A in treating the less common but more severe amoeboid ulcers (Coster *et al.*, 1976).

Not only are amoeboid ulcers less common than dendritic ulcers, they have often been treated with steroids before referral to an ophthalmologist, and many have associated stromal disease and uveitis. They constitute the most difficult therapeutic challenge for antiviral drugs used for ulcerative epithelial herpetic keratitis. Cases of this type are therefore more likely to show a difference in effectiveness between 2 highly active antiviral compounds than the less challenging cases of dendritic ulcer.

In the initial trial 102 patients were treated—87 with dendritic ulcers, 15 with amoeboid ulcers (Coster *et al.*, 1976). A further 15 amoeboid ulcers were treated under the same protocol in an effort to clarify the trend which seemed to be emerging in the initial study. This paper reports the results.

Patients and methods

Thirty unselected patients with typical amoeboid ulcers who consented to enter the study were included. All completed the course of treatment; 17 were treated with Ara-A and 13 with F_3T.

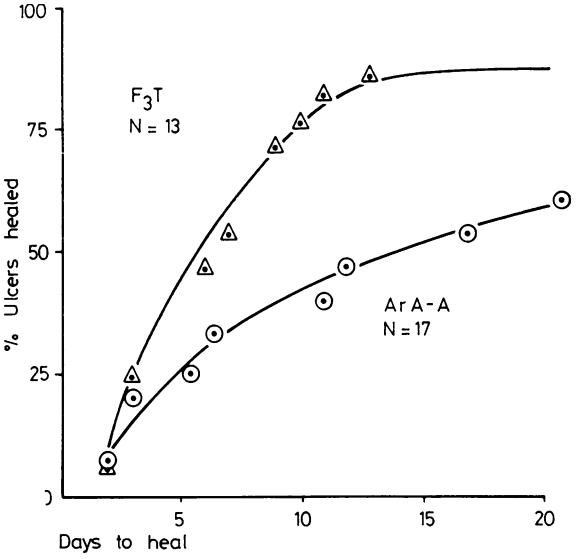

Fig. 1 *Cumulative frequency graph of times for healing of dendritic ulcers under treatment with 3% adenine arabinoside ointment or 1% trifluorothymidine eye drops 5 times daily*

The coded treatments were randomly allocated by the pharmacist within closely matched strata. The stratification was based on the features considered to be related to poor prognosis. These were: the size of the epithelial defect, whether the patient had been treated with steroids before coming to hospital. and whether or not the patient was atopic.

All patients were treated on an outpatient basis. The coded preparations consisted of either 3·3% Ara-A ointment or 1% F_3T drops, which were

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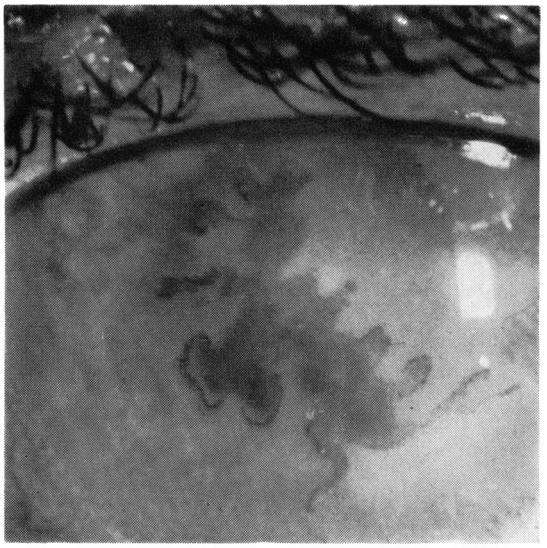
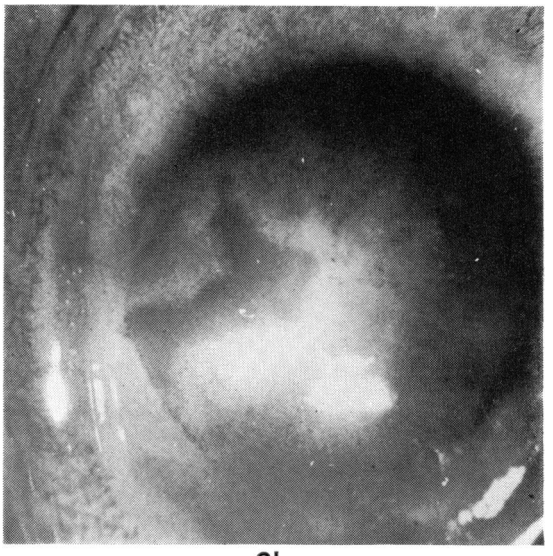


2a



2b

2c

Fig. 2 (a) *At presentation, a large amoeboid ulcer with underlying stromal infiltrate and oedema;* (b) *5 days after beginning treatment with adenine arabinoside ointment 3% the epithelial defect is smaller, but the stromal involvement appears more marked;* (c) *after 12 days of treatment the epithelial healing is very slow and there has been a further deterioration in the state of the underlying stroma*

applied topically 5 times a day. In addition to the coded antiviral substance the patients received atropine drops 1% once daily. If they were already receiving topical steroids, these were gradually reduced over the first 3 days of the treatment programme and then stopped. The coded antiviral substance was given 5 times a day until the epithelial defect had healed, as indicated by the absence of staining with fluorescein. The frequency of administration was then reduced to 3 times a day for an additional 3 days.

Patients were reviewed on alternate days, and at each attendance a comprehensive examination of the external eye was performed. The ulcer was drawn and measured with an attachment to the Haag-Streit 900 slit lamp, the extent of the stromal disease was assessed and recorded, and attention was paid to structures likely to show signs of antiviral toxicity—the cornea, conjunctiva, and lacrimal puncta.

Treatment was considered to have failed when the epithelial defect had not healed after 21 days, had failed to decrease in size, or had enlarged over 3 successive visits.

Fig. 3 *Slit-lamp photograph of the cornea stained with 1% Bengal rose after 20 days' treatment with trifluorothymidine. The ulcer has failed to heal and there is widespread superficial punctate keratopathy indicative of antiviral toxicity. The ulcer healed rapidly after the antiviral was withdrawn*

Results

In 6 patients the ulcers failed to heal. Four were treated with Ara-A and 2 with F_3T. The pattern of failure was different in the 2 treatment groups. The failures on Ara-A treatment showed epithelial healing initially, but the stromal disease progressed with failure of the epithelium to continue healing (Figs. 2*a*, 2*b*, and 2*c*).

One patient treated with F_3T showed good healing initially, developed punctate epithelial staining with Bengal rose after 10 days, and despite the absence of stromal disease failed to heal until the antiviral treatment was withdrawn (Fig. 3). The other failure on F_3T had severe stromal disease when entered into the trial. This gradually improved, and the epithelium healed on the twenty-fourth day, 3 days after the arbitrary 'closing date' beyond which treatment was considered to have failed.

Standard actuarial survival curves, or cumulative distribution curves, provide the most accurate and easily assimilated statement of the time taken to heal by ulcers in each group. The logrank test is the most appropriate for assessing differences between groups as displayed on the survival curves. The test is the most powerful available, being effective when dealing with quite small samples (Peto and Peto, 1972). In addition it can be used to assess differences between groups of patients when the groups are defined not only by treatment schedule but by any factor thought to influence prognosis such as size of ulcer and extent of stromal disease (Mantell and Haenszell, 1959). An additional advantage is that it is not a parametric test and does not assume that the healing times follow a normal distribution. The distribution of healing times is set out in Fig. 4, and clearly does not follow such a distribution.

A logrank analysis was performed on the data set out above. It indicates that the difference between the 2 treatment groups is likely to be significant ($P=0{\cdot}05$). The results are displayed in Fig. 5.

COMPLICATIONS AND DRUG REACTIONS

Apart from failure to heal, complications were few. The only recurrence in the immediate post-treatment

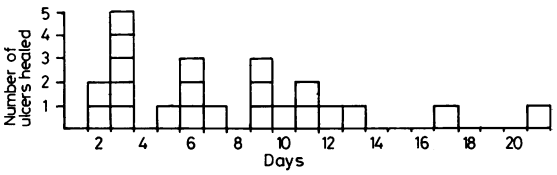


Fig. 4 *Distribution of times of healing of amoeboid ulcers treated with either adenine arabinoside or trifluorothymidine*

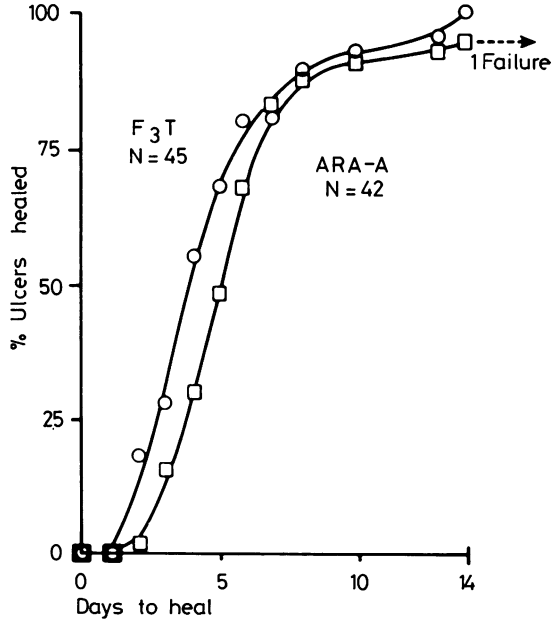


Fig. 5 *Cumulative frequency graph of times of healing of amoeboid ulcers treated with either 3% adenine arabinoside ointment or 1% trifluorothymidine eye drops 5 times daily*

phase occurred in a patient treated with Ara-A; a small epithelial defect developed 13 days after the initial ulcer had healed and 10 days after treatment had ceased.

Stromal disease progressed in 4 patients, all of whom had been treated with Ara-A: the epithelial defect failed to heal, and these cases were designated treatment failures.

The only manifestation of antiviral toxicity observed was punctate staining of the corneal epithelium with Bengal rose. This occurred in 3 patients treated with Ara-A and 4 treated with F_3T; in one of the latter the epithelial defect failed to heal until the F_3T was withdrawn (Fig. 3).

Discussion

These results indicate that F_3T is more effective than Ara-A in dealing with amoeboid ulcers. The superiority of F_3T over Ara-A in the treatment of amoeboid ulcers, when no difference could be found in the dendritic ulcer group, reflects important differences between these 2 conditions. We were able to compare the patterns of these conditions during a period in which patients with dendritic or amoeboid ulcers were admitted to a treatment trial under the same protocol (Coster *et al.*, 1976). In addition to the obvious difference in the size of the epithelial defect it was evident that, in comparison with dendritic ulcers, amoeboid ulcers occurred more often in patients who had been treated with topical steroids before coming to hospital and were more often complicated by stromal disease and uveitis. The duration of symptoms before coming to hospital was longer in the amoeboid group (Table 1). No difference was evident with regard to sex or age of patients.

The apparent superiority of F_3T over Ara-A in the treatment of such ulcers may be due to superior antiviral activity of F_3T in the corneal epithelium, or it may be related to a more pronounced effect of this compound against stromal virus. The compounds may differ in their transepithelial absorption into the corneal stroma, or alternatively the large epithelial defect of amoeboid ulcers may allow greater stromal uptake of the more-water-soluble F_3T than with the less-water-soluble Ara-A.

Table 1 *Differences in distribution of pretreatment with steroids, stromal disease, uveitis, and length of history before presentation at hospital between patients with dendritic and amoeboid ulcers*

	Dendritic ulcers (n = *87*)	*Amoeboid ulcers* (n = *30*)
Pretreated with steroids	19 (22%)	16 (53%)
Stromal disease at presentation	39 (45%)	27 (90%)
Uveitis at presentation	28 (32%)	19 (63%)
Symptoms for more than 2 weeks prior to presentation	14 (16%)	13 (43%)

The results of this trial have obvious implications for the clinician. They also indicate the need for stratifying, randomising, and ranking the nature of the epithelial defect and the extent of deep disease of the corneal stroma and uvea when planning clinical trials of antiherpetic agents.

Herpetic corneal ulceration has provided an important proving ground for antiviral compounds with clinical potential, the disease providing a wide range of therapeutic challenges. After debridement, ulcers, with their reduced viral load, provide the opportunity to demonstrate antiviral activity in low-potency agents (Jones *et al.*, 1976). Dendritic ulcers are appropriate for showing differences in more active compounds, and amoeboid ulcers provide the highest order of clinical challenge, capable of sorting out clinically important differences in activity between highly active compounds.

We thank our colleagues at Moorfields Eye Hospital, City Road, London, who referred the cases. Mr R. Watkins, Chief Pharmacist, supervised the allocation to treatment groups. The adenine arabinoside was supplied by the Parke Davis Company, Ann Arbor, Michigan, USA, and the trifluorothymidine by the Wellcome Foundation, Beckenham, Kent. The figures included were prepared by the Audio-Visual Department of the Institute of Ophthalmology, London, and Fig. 1 is reproduced by courtesy of the University of Chicago Press.

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