

Randomised double-blind trial of acyclovir (Zovirax) and adenine arabinoside in herpes simplex amoeboid corneal ulceration

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SUMMARY Fifty-one patients were treated in a dual-centre, double-blind comparison of acyclovir and adenine arabinoside in herpetic amoeboid (geographic) corneal ulceration. Twenty-four of the 25 patients receiving acyclovir healed in a mean time of 12.2 days, while 24 of the 26 patients treated with adenine arabinoside healed in a mean time of 11.0 days. There was no statistically significant difference between the two groups in terms of healing. A second analysis, excluding any patients who had received antiviral treatment immediately prior to entry into the study, showed that 18 of the 19 who received acyclovir healed in an average of 11.7 days and 18 of the 19 recipients of adenine arabinoside healed in a mean time of 11.2 days. Again the difference was not statistically significant.

Acyclovir (Zovirax) is a highly selective and relatively non-toxic antiherpes agent.^{1,2} It has become a standard treatment for dendritic corneal ulceration over the past few years and is at least as effective as^{3,5} or superior to⁶⁻¹⁰ idoxuridine (IDU) and adenine arabinoside (Ara-A) and broadly similar to trifluorothymidine (TFT)¹¹. Acyclovir also has a role in the management of stromal herpetic keratitis.¹²

Geographic (amoeboid) corneal ulceration is a much more difficult problem than dendritic ulceration. It is frequently associated with the previous use of corticosteroids and is often complicated by deep keratitis and anterior uveitis. Topical administration of acyclovir ophthalmic ointment has been shown to produce potentially therapeutic levels of the drug in the aqueous humour,¹³ which may be of benefit in the treatment of geographic ulceration. In this paper the role of acyclovir in the management of herpetic geographic corneal ulceration is examined and its efficacy is compared with that of Ara-A.

Materials and methods

Two centres were involved in this study. Patients presenting with geographic ulcers and who gave their

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informed consent were included. Each patient was randomly allocated to receive either 3% acyclovir, or 3% Ara-A in ointment form, together with cycloplegics and eye padding as appropriate. The ointments were applied five times daily until the healing of the lesions and then for a further three days. Both drugs were identically packaged and coded. Patients were seen as frequently as necessary but at least twice weekly. At each visit a full ocular examination was carried out. The ulcer was stained and its size measured, the extent and severity of any stromal reaction and uveitis were recorded, and symptoms were scored on a points basis (0-3). Healing was reached when there was no further staining of the ulcer area. Patients were withdrawn from the study if the ulcer worsened over three days or remained static for more than 10 days. Patients were to be withdrawn if any toxic signs or symptoms appeared.

The treatment groups were compared on entry for distribution of sex, ulcer size, occurrence of previous attacks, and previous therapy by χ^2 tests. Age and symptom duration, and severity of symptoms, stromal infiltration, and uveitis were compared by Mann-Whitney tests. A number of patients had received antiviral treatment before entry into the study, and, as it was felt that this might prejudice the results, a separate analysis was performed by the same methods but with the exclusion of these patients.

Table 1 Characteristics of patients at presentation

| | | All patients | | Patients with no previous antiviral therapy for this attack | |
|------------------------------|----------------|---------------------|-----------|---|-----------|
| | | Adenine arabinoside | Acyclovir | Adenine arabinoside | Acyclovir |
| Sex | Male | 13 | 16 | 7 | 11 |
| | Female | 13 | 9 | 12 | 8 |
| Ulcer size | Small | 18 | 7 | 14 | 5 |
| | Large | 8 | 18 | 5 | 14 |
| Previous attack | Percent | 52 | 40 | 42 | 42 |
| Age (years) | Median | 57 | 54 | 61 | 45 |
| Duration of symptoms (days) | Median | 14 | 10 | 11 | 7 |
| Severity of symptoms (score) | Mean | 2.0 | 2.0 | 2.0 | 1.9 |
| Stromal infiltration (score) | Mean | 1.2 | 1.1 | 1.3 | 1.0 |
| Uveitis (score) | Mean | 0.5 | 0.8 | 0.7 | 0.9 |
| Previous therapy this attack | Corticosteroid | 6 | 3 | 6 | 3 |
| | Antiviral | 7 | 6 | 0 | 0 |
| | Antibiotic | 4 | 8 | 3 | 8 |

Results

Fifty-four patients entered the study. Three patients randomly allocated to acyclovir treatment failed to return after their initial assessment and were excluded from the analysis. Of the 51 remaining patients 26 received Ara-A and 25 acyclovir. Characteristics of the patients at entry are summarised in Table 1. Statistical analyses showed no significant differences between the two groups at entry, except that the acyclovir group had a significantly higher proportion of patients with large ulcers than the Ara-A group ($p < 0.05$). A number of patients were receiving corticosteroids or antibiotics on entering the study.

Three patients were withdrawn from the study owing to failure of treatment, two in the Ara-A group

and one in the acyclovir group. The lesions in all the remaining patients healed. Log rank analysis of the two treatment groups showed no significant difference in healing times. The mean healing time for the Ara-A group was 11.0 days, and for the acyclovir group, 12.2 days ($p = 0.62$; Fig. 1). Owing to the imbalance in ulcer size between the two groups at entry, an analysis with treatment and ulcer size as factors was carried out. This showed no effect of ulcer size on healing time. Previous steroid therapy for the current attack did not appear to influence healing times. The only adverse reaction noted was superficial punctate epitheliopathy in two patients receiving acyclovir and five patients receiving Ara-A.

Seven patients treated with Ara-A and six on acyclovir had received antiviral treatment immediately prior to entry into the study. It was possible that

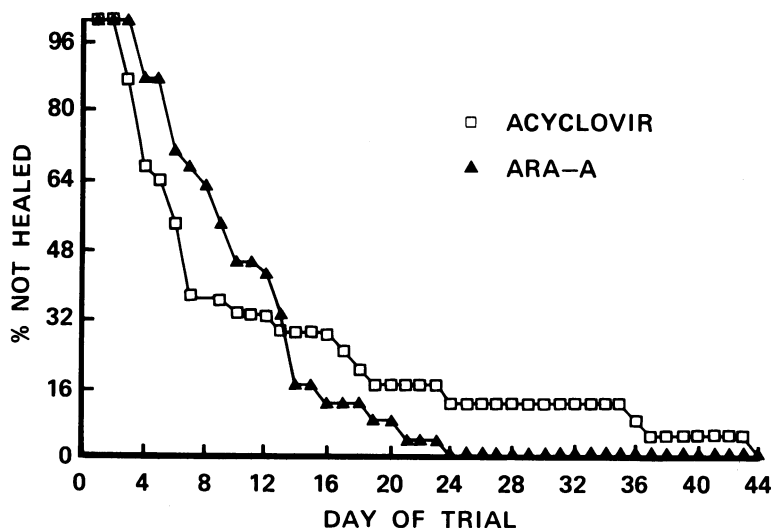


Fig. 1 Cumulative frequency distribution of time taken to heal.

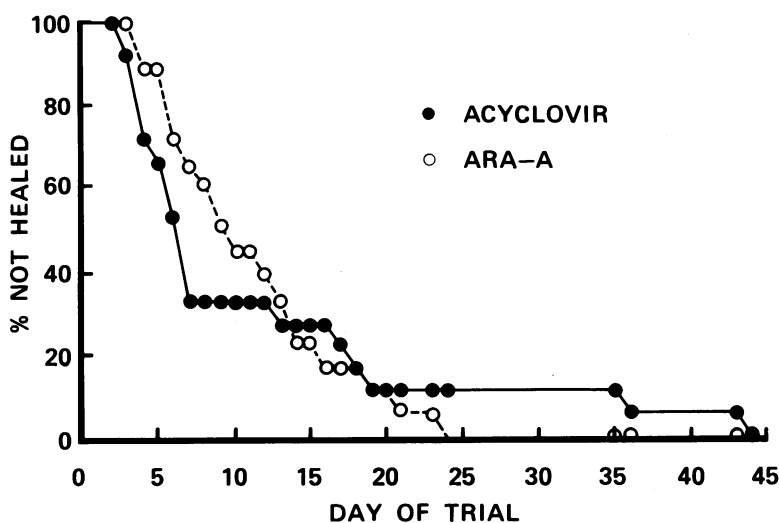


Fig. 2 Cumulative frequency distribution of time taken to heal (apart from patients with previous antiviral therapy for the current attack).

this might prejudice the results, so a separate analysis was performed with these patients excluded. The characteristics of the remaining patients are summarised in Table 1. The acyclovir group again had a significantly higher proportion of large ulcers than the Ara-A group ($p < 0.01$), but there were no other significant differences between the two groups at entry. The mean healing time in the Ara-A group was 11.2 days as compared with 11.7 days in the acyclovir group ($p = 0.39$; Fig. 2).

Discussion

Geographical corneal ulcers are difficult to treat and are associated with many complications. They frequently require more prolonged therapy than simple dendritic ulcers. Many are associated with previous corticosteroid therapy, which complicates their management. It is important therefore that these lesions are managed with an agent which can be used for as long as necessary and with no toxic effects. It is clear that prolonged treatment with IDU is associated with significant toxicity. Acyclovir should be a suitable agent because of its solubility and low incidence of toxicity.

This study has shown that acyclovir and Ara-A are effective and of equal potency in the management of geographical herpetic corneal ulceration. Healing rates were not affected by either ulcer size or the previous use of antiviral agents. The previous use of corticosteroids did not appear to influence the healing times. No significant toxic effects were recorded in either group.

Previous experience with acyclovir has not been associated with any significant side effects even when

given for up to 61 days.¹⁴ Acyclovir therefore is particularly suitable for the treatment of amoeboid corneal ulceration, which frequently requires more prolonged treatment than simple dendritic ulceration.

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