STUDY

A Randomized, Double-blind, Placebo-Controlled Trial of Pentoxifylline for the Treatment of Recurrent Aphthous Stomatitis

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Objective: To evaluate pentoxifylline for the treatment of recurrent aphthous stomatitis.

Design: A 60-day, randomized, double-blind, placebo-controlled trial with a 60-day no treatment follow-up.

Setting: An oral medicine specialist referral center in Manchester.

Participants: Forty-nine volunteers who passed the initial assessment for recurrent aphthous stomatitis entered a pretrial phase in which their eligibility for the trial phase of the study was assessed. Sixteen subjects were deemed ineligible, and 7 failed to attend or withdrew. The remaining 26 subjects were randomized to placebo or treatment. Six subjects withdrew because of adverse effects, and 1 was unavailable for follow-up.

Intervention: Pentoxifylline (also called oxpentifyline), 400 mg 3 times daily, or matching placebo.

Main Outcome Measure: A reduction in the median pain score, ulcer size, number of ulcers, or total number of ulcer episodes.

Results: Patients taking pentoxifylline had less pain and reported smaller and fewer ulcers compared with baseline. Patients taking placebo reported no improvement in these variables. Patients taking pentoxifylline also reported more ulcer-free days than those taking placebo. However, the differences were small and, with the exception of median ulcer size ($P = .05$), did not reach statistical significance. Adverse effects were common with pentoxifylline, but not significantly different from those experienced by patients taking placebo.

Conclusions: Although pentoxifylline may have some benefit in the treatment of recurrent aphthous stomatitis, the benefit is limited. It may have a role in the treatment of patients unresponsive to other treatments, but cannot yet be recommended as a first-line treatment.

Trial Registration: clinicaltrials.gov Identifier: NCT00315679

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RECURRENT APHTHOUS STOMATITIS (RAS) is a common oral condition, affecting around 20% of the population. The etiopathogenesis of RAS is unknown. Clinically, it is characterized by the development of recurrent episodes of oral ulceration in an otherwise healthy individual. Three different clinical forms are recognized:

- Minor RAS
- Major RAS
- Herpetiform RAS

Minor RAS, major RAS, and herpetiform, with minor RAS accounting for more than 80% of patients with RAS. The ulcers of minor RAS are usually less than 5 mm in diameter and occur mainly on the labial and buccal mucosa, the borders of the tongue, and the floor of the mouth. Several ulcers may be present simultaneously, and healing without scarring occurs spontaneously within 7 to 14 days. Episodes of ulceration are usually followed by an ulcer-free period lasting a few days to several weeks before the next episode occurs.

Treatment for RAS is usually palliative, because there is no known cure. Many different therapies have been tried for RAS, including topical and systemic corticosteroids, colchicine, thalidomide, and dapsone. In each case, the effectiveness is variable, the treatment is long term, and the potential adverse effects and complications are a major restricting factor in their use, particularly for systemic preparations.

Thalidomide is one of the few drugs that has been effective in the management of RAS, and it is believed to work through its ability to inhibit tumor necrosis factor α (TNF-α) production and neutrophil...
function. However, it has several serious adverse effects, including a well-documented teratogenic potential and irreversible polyneuropathy. Colchicine has also been effective in some patients and is thought to work through its inhibitory effect on neutrophil function, chemotaxis, and adhesion molecule expression. Unfortunately, only a proportion of patients benefit from it, and its use is complicated by potentially serious adverse effects, including gastrointestinal upset, renal and hepatic damage, male infertility, and blood dyscrasias.

Pentoxifylline (also called oxpentifylline) is a drug used in the treatment of peripheral vascular disease, and it has a good safety record even in long-term use. Like thalidomide, it inhibits TNF-α production, and like colchicine, it inhibits neutrophil function and chemotaxis, without the well-known adverse effects of these drugs. Theoretically, therefore, it is a good candidate for the treatment of RAS.

In 1995, a Spanish group reported a 50% cure rate and 27% marked improvement in the pattern of RAS in an open-label uncontrolled study of 22 patients with RAS treated with 400 mg of pentoxifylline 3 times daily for 6 months. This was an extension of a small open-label study of 6 patients treated with 400 mg of pentoxifylline 2 to 3 times daily by the same group in 1993, in which treatment suppressed the ulcers in 5 patients. In 1995, a study by Wahba-Yahav, of 6 patients treated with 400 mg of pentoxifylline 3 times daily for 3 months, reported complete or almost complete resolution of ulceration in all 6 patients. Three of these patients were followed up for 9 months, 14 months, and 2 years. The patient followed up for 9 months had no recurrences, and the other 2 had only 1 mild recurrence each. This generated some interest because the author claimed that, unlike other existing treatments for RAS, pentoxifylline could induce long-term remission. A further trial of 24 patients with RAS treated for 1 month with 400 mg 3 times daily was reported in 1999. This study reported great improvement in 14 (58%) of the patients, slight improvement in 1 (4%), and no change in 8 (33%); 1 patient (4%) got worse with treatment (percentages do not total 100 because of rounding). However, recurrence of RAS was noted in all patients after cessation of treatment. Other studies have also reported improvement in RAS in human immunodeficiency virus–positive patients and in patients with Behcet disease. Unfortunately, all of the reported studies have been open-label studies without a placebo control and, to our knowledge, no double-blind placebo-controlled study has been reported for the use of pentoxifylline in the treatment of RAS.

The aim of this study was, therefore, to determine the safety and efficacy of pentoxifylline in the treatment of patients with RAS in a randomized, double-blind, parallel-arm, placebo-controlled, clinical trial.

### METHODS

#### STUDY POPULATION

Participants were recruited using posters placed in the offices or surgical areas of general medical and general dental practitioners in the greater Manchester area. People responded to the posters by telephone and were screened for suitability using a standardized telephone questionnaire. Screening eligibility criteria included the following: (1) more than 2 ulcers per month for longer than 6 months, (2) no current treatment for ulceration or a willingness to stop the current treatment, (3) being aged 16 to 65 years, (4) not taking ketorolac, theophylline, or antihypertensive medications except diuretics (contraindicated in patients taking pentoxifylline), and (5) no systemic condition that would contraindicate the use of pentoxifylline (eg, pregnancy, hypotension, ischemic heart disease, acute myocardial infarction, cerebral or ocular hemorrhage, renal or hepatic failure, porphyria, or allergy to pentoxifylline).

#### TREATMENT PHASE OF THE STUDY

Participants who were still eligible were entered into the treatment phase of the study (days 61-120) and allocated a sequential trial number. The pharmacy at the Manchester Royal Infirmary randomized the dispensing of active drug or placebo.

### PRETRIAL PHASE OF THE STUDY

Participants who successfully completed the telephone screening were scheduled for an appointment (visit day 0) at the Oral Medicine Clinic, Turner Dental School, University Dental Hospital of Manchester. At this visit, the study was explained in more detail, and patients still interested in joining the study signed an informed consent form. The previously described exclusion criteria were rechecked, patients underwent an oral examination, and patients were asked questions regarding any family history of RAS. Participants were also taught how to complete a self-examination, and were given a standardized diary to be completed daily for the entire duration of the study. A blood sample was taken to help identify any underlying systemic conditions that could influence their oral ulceration. Their weight and blood pressure were also recorded. The following tests were performed on the blood sample: full blood cell count, serum ferritin level, vitamin B12 level, folic acid level, and a celiac screen (antigliadin, antiendomysial, and antitransglutaminase antibodies). A sample of plasma was also stored so that the pretreatment level of circulating IL-1β (interleukin 1β) and TNF-α could be measured. Participants then entered the pretrial phase of the study (days 1-60) and completed a daily ulcer diary. The purpose of the pretrial phase was 2-fold: (a) to confirm eligibility for the trial and (b) to collect baseline data on the pattern of ulceration that, for those subsequently entered into the trial (treatment phase of the study), could be compared with the pattern of ulceration while being treated with the active drug or placebo.

In the diary, patients were asked to record the presence of ulcers (yes or no) and associated level of pain daily (on a 10-point scale, where 0 indicates no pain and 10, the worst pain ever experienced with mouth ulcers). In addition, once during each episode of ulcers, on the day after the patient experienced the worst pain (ie, the first day during an episode of ulcers when the pain score recorded a decrease compared with the preceding day), the patient recorded the number of ulcers that were present and their average size. The size was assessed by comparing ulcer size to a chart showing 6 circles of increasing diameter between 1 and 10 mm and numbered 1 to 6, respectively.

After the initial pretrial period (days 1-60), participants were asked to return to the clinic for a second visit (visit day 60). At that time, participants were reexamined and reassessed for final eligibility for the trial. Individuals who were not able to complete the baseline diary satisfactorily, whose pattern of ulceration did not meet the eligibility criteria, whose blood test results fell outside the normal range, or whose blood pressure was 100/60 or below at the first or second visit were excluded from the trial.
to participants using a computer-generated random number. The active drug and placebo control were formulated as identical oblong pink tablets (provided by Hoechst Marion Roussel, Uxbridge, England), containing FD&C Red No. 3, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol, povidone, talc, and titanium dioxide as excipients, in a controlled-release formulation. They were dispensed as a complete course in identical brown plastic medicine bottles labeled with the trial details and trial number, but no means of distinguishing if the contents were active drug or placebo. Participants were instructed to take 1 tablet of the placebo, or 400 mg of pentoxifylline, 3 times daily with food for the duration of the treatment phase of the study (60 days). The computer-generated key identifying what had been dispensed to each patient (identified by trial number) was not released by the pharmacy until after the study had been completed. Thus, the study was double-blind.

Participants continued to record information in the diary throughout the treatment phase of the study. Participants returned to the clinic at day 90 (mid-treatment visit) and day 120 (posttreatment visit). At these times, participants were asked to answer questions regarding compliance, adverse effects, and perceived efficacy of the treatment. Blood pressure measurements were taken at each visit, and the number of remaining tablets was counted to verify compliance. At the mid-treatment visit, a blood sample was also taken to measure the plasma level of circulating IL-1β and TNF-α for comparison with the pretreatment level.

Patients who completed the treatment phase of the study were then asked to complete their daily ulcer diary for a further 60 days for the posttreatment “follow-up” phase of the study. They were seen in the clinic once more on completion of the follow-up diary (day 180).

Investigators, staff, and participants were blinded as to the type of treatment that each patient had received and received no financial compensation for their involvement. The study was approved by the Central Research Ethics Committee of the Manchester Healthcare Trust. In addition, the statistical analysis of the data was approved by the institutional review board of The University of Texas Health Science Center at San Antonio, where the analysis was performed.

CYTOKINE MEASUREMENTS

Plasma separated from blood samples taken from participants at day 0, prior to the treatment phase of the study, and at the mid-treatment visit (day 90) were frozen at −70°C and stored until after the study was complete. The levels of IL-1β and TNF-α in the samples were then quantified using a commercial sandwich enzyme-linked immunosorbent assay (Quantikine high sensitivity human IL-1β and TNF-α assays; R&D Systems, Abingdon, England). Serial dilutions of recombinant human IL-1β and TNF-α were used as positive controls.

STATISTICAL ANALYSES

All data management and analyses were conducted by a statistician (L.B.) blinded as to the type of treatment each patient had received. All data from the patients’ daily diaries and research charts were entered by a single investigator (L.B.) in a database (Excel) and then imported into SAS statistical software (SAS Institute Inc, Cary, NC) for data management. Data entry checks were performed to correct any errors.

The null hypothesis was that patients taking the active treatment would see a significant improvement in the pattern of their ulceration and associated pain over baseline compared with patients taking the placebo.

An intent-to-treat analysis was performed. Univariate analyses were initially conducted to identify any outliers, impossible values, or implausible values, and to report summary measures (mean, median, and percentage) for the demographic distribution of study participants and other outcomes. Frequencies and percentages were reported for categorical data. For continuous variables with nonnormal distributions, the median values of repeated measures were calculated for each patient, and then averaged across all patients.

Bivariate and multivariate analyses were then performed to assess response to treatment. The Fisher exact test and the Wilcoxon–Mann-Whitney 2-sample test (comparing ranks of differences in treatment phase vs baseline values for the 2 arms) were used for these analyses.

The significance level was set at \( P = .05 \). No adjustment was made for multiple comparisons. All data management and analyses were conducted using SAS statistical software, version 8.2.

As well as studying individual variables, we also analyzed a global index of ulcer severity. The global ulcer severity score was calculated from the patients’ ulcer diaries. For each study phase, we added the change from baseline in (1) median ulcer size (measured in millimeters), (2) median ulcer number, and (3) median pain score. From that sum, we subtracted the change in the proportion of the 90 days of the study phase that were ulcer free (expressed as a decimal fraction) to determine a global ulcer severity score. Based on this score, a value of 0 would indicate no overall change in the outcome measures compared with baseline values, a negative value would indicate an improvement, and a positive value would suggest a worsening of the condition.

For the cytokine data, a paired \( t \) test was used to compare the pretreatment with midtreatment values within each arm of the study, while a 2-sample \( t \) test was used to compare values between the 2 treatment arms.

RESULTS

STUDY POPULATION

The study protocol and the number of participants at each stage are outlined in the Figure. Ninety-three people responded to the posters and called the telephone assessment line. Seventy of these people successfully completed telephone screening and were offered an initial appointment (day 0). Of these 70 people, 14 failed to attend the appointment and 7 declined to take part in the study. The remaining 49 people were entered into the pretrial phase of the study. At the second visit (day 60), 7 people failed to attend and were unavailable for follow-up; a further 16 individuals were deemed ineligible for the study and were excluded. The reasons for exclusion were as follows: inability to attend all the appointments needed to complete the study (n = 1), unable to successfully complete the diary (n = 1), low vitamin B12 level (n = 2), low ferritin level (n = 2), low folic acid level (n = 2), positive celiac screen result (n = 1), low blood pressure (n = 1), or fewer than 2 ulcers per month recorded in the diary (n = 2). In addition, 1 patient had an excessively elevated blood pressure (230/140) at the second visit. In the patient’s best interests, the decision was made not to enter the patient into the study even though the patient did not fulfill the exclusion criteria. A further patient was excluded because of the inability to swallow the tablets, and 2 female patients were excluded at the second visit because they had decided they wanted to try to have a
baby. Therefore, 26 patients were entered into the treatment phase of the study.

Demographic data on the 26 patients entering the treatment phase of the study are shown in Table 1. Most patients entering the treatment phase were female, their mean age was 33 years, and 62% reported having at least 1 other family member with a history of aphthous ulcers.

**CLINICAL DATA**

The 26 treatment phase participants were randomized to the active drug (n = 14) or placebo (n = 12). Of these individuals, 7 (4 taking placebo and 3 taking the active drug) discontinued treatment before the end of the treatment phase of the study. Despite discontinuing treatment, 4 (3 taking placebo and 1 taking the active drug) continued to record information in their diaries for the entire treatment phase of the study, whereas 3 only partially completed their diaries. The reasons for discontinuing treatment were adverse effects (4 individuals taking placebo and 2 taking the active drug) and unavailable for follow-up (1 taking the active drug).

All available data from the 26 participants were analyzed based on the original randomization (intention-to-treat analysis). The results are shown in Table 2. More participants taking the active drug reported adverse effects compared with those taking placebo. The most common adverse effects were dizziness (4 taking the active drug and 3 taking placebo), headaches (4 taking the active drug and 3 taking placebo), stomach upset (4 taking the active drug and 3 taking placebo), increased heart rate (2 taking the active drug and 2 taking placebo), and nausea (3 taking the active drug and 3 taking placebo). In addition, patients taking the active drug reported feeling tired and experiencing conjunctivitis, motion sickness, brief flushing of the face, nearly fainting, frequent dreams/hallucinations, and depression/increased appetite (1 patient each). Patients taking placebo reported increased eczema, dry mouth and bloating, and a genital ulcer (1 patient each).

More participants taking the active drug vs placebo stated that if the drug was shown to be effective they would not want to use it. Patients in both treatment arms stated that the reason for not wanting to use the drug in the future was the presence of adverse effects. Twenty-two patients reported no difficulty taking the tablets, but 4 found them difficult to swallow.

More participants taking the active drug believed their RAS was better during the trial phase compared with those taking placebo (Table 2). On average, participants taking the active drug had a greater increase in the proportion of ulcer-free days while receiving treatment compared with those taking placebo. For half of the participants taking the active drug, the increase was deemed substantial (>15% difference in the proportion of ulcer-free days during the trial compared with baseline values).
Participants taking the active drug experienced a reduction in the median pain score during the 60-day treatment phase, whereas those taking placebo reported a higher pain level compared with baseline values. A similar trend was observed when pain level was measured only during those days that patients had active ulcers.

The median ulcer size and number recorded at the peak of each ulcer episode decreased in the active treatment group, whereas in the placebo group, worsening or no improvement in these outcome measures was noted (Table 2). No differences between the 2 treatment arms were noted in the number of episodes.

Using the global ulcer severity score, patients taking pentoxifylline reported a slight overall improvement (a negative change in score), whereas the score worsened for patients taking placebo (a positive change in score).

When asked to compare the treatment they had received during the trial with other treatments that they had previously used, in most cases, patients believed that the current treatment was more acceptable than previous treatments. However, there was no difference in response between the active drug and placebo groups (Table 3).

All 19 patients who completed their trial phase diaries also completed a 60-day posttreatment follow-up diary. All 19 patients recorded further episodes of oral ulceration during the follow-up period, and there was no significant change in the pattern of ulceration between the follow-up period and either the pretreatment baseline or treatment (trial) phases of the study.

IMMUNOLOGICAL DATA

For the 19 patients who completed the trial phase of the study, a comparison was made between the circulating plasma level of IL-1β and TNF-α at day 0 (pretreatment) and day 90 (midtreatment). The results are shown in Table 4. There was no significant change in the plasma concentration of IL-1β or TNF-α between the pretreatment and midtreatment phases of the study for patients allocated to either pentoxifylline or placebo. There was also no significant difference in the pretreatment cytokine levels between the placebo or pentoxifylline arm of the study ($P = .51$ for IL-1β and $P = .49$ for TNF-α) or the

| Table 1. Characteristics of the 26 Participants Enrolled Into the Treatment Phase of the Study* |
|----------------------------------|-----------------|-----------------|------------------|
| **Characteristic**              | **Pentoxifylline** | **Placebo**     | **Overall**      |
| **Age, y**                       | (n = 14)         | (n = 12)        | (N = 26)         |
| Mean (SD)                        | 34.0 (8.1)       | 33.0 (12.6)     | 33.0 (10.2)      |
| Range                            | 21-55            | 18-53           | 18-55            |
| **Sex**                          |                  |                 |                  |
| Female                           | 9 (64)           | 8 (67)          | 17 (65)          |
| Male                             | 5 (36)           | 4 (33)          | 9 (35)           |
| **Family history**               |                  |                 |                  |
| Yes                              | 10 (71)          | 6 (50)          | 16 (62)          |
| No                               | 4 (29)           | 6 (50)          | 10 (38)          |

*Data are given as number (percentage) of each group unless otherwise indicated.

| Table 2. Response of the 26 Participants to Treatment* |
|----------------------------------|-----------------|-----------------|------------------|
| **Variable**                     | **Pentoxifylline** | **Placebo**     | **P**            |
|                                  | (n = 14)         | (n = 12)        | Value            |
| Treatment compliant†             | Yes             | 11 (79)         | 8 (67)           | .67†               |
|                                  | No              | 3 (21)          | 4 (33)           |                   |
| Adverse effects†                 | Yes             | 9 (69)          | 6 (50)           | .43†               |
|                                  | No              | 4 (31)          | 6 (50)           |                   |
| If the drug is shown to be effective, would you be happy to take it in the future?† | Yes | 7 (64) | 10 (83) | .37† |
|                                  | No              | 4 (36)          | 2 (17)           |                   |
| Subjective changes at day 120 (ie, how do you think your ulcers have been while taking the medication vs 2 mo before)?† | A lot worse | 0 | 0 | .45† |
|                                  | A little worse  | 0               | 1 (8)            |                   |
|                                  | No different    | 6 (46)          | 5 (42)           |                   |
|                                  | A little better | 2 (15)          | 4 (33)           |                   |
|                                  | A lot better    | 5 (38)          | 2 (17)           |                   |
| % of Ulcer-free days§            | Baseline        | 34              | 31               | .43               |
|                                  | Trial           | 46              | 38               |                   |
|                                  | Difference (trial vs baseline) | 12 | 7 |                   |
| Difference in proportion of ulcer-free days (trial vs baseline)† | Worse than baseline (<0%) | 3 (21) | 3 (25) | .17† |
|                                  | Little to no improvement | 4 (29) | 7 (58) |                   |
|                                  | (0%-15%)        | Substantial improvement (>15%) | 7 (50) | 2 (17) |                   |
| Pain score§                      | All days        | Baseline        | 1.43             | 1.79              | .24               |
|                                  | Trial           | 1.21            | 2.17             |                   |
|                                  | Difference      | −0.21           | 0.38             |                   |
| Only days with ulcers            | Baseline        | 2.50            | 3.04             | .62               |
|                                  | Trial           | 2.43            | 3.17             |                   |
|                                  | Difference      | −0.07           | 0.13             |                   |
| Ulcer size (1 record per episode)§ | Baseline        | 2.79            | 2.50             | .05               |
|                                  | Trial           | 2.39            | 2.73             |                   |
|                                  | Difference      | −0.39           | 0.27             |                   |
| Ulcer number (1 record per episode)§ | Baseline        | 2.46            | 2.21             | .30               |
|                                  | Trial           | 2.14            | 2.18             |                   |
|                                  | Difference      | −0.32           | −0.05            |                   |
| Total No. of episodes§           | Baseline        | 4.86            | 4.36             | >.99              |
|                                  | Trial           | 4.00            | 3.82             |                   |
|                                  | Difference      | −0.86           | −1.08            |                   |
| Change in global ulcer severity scores§ | −1.05 | 0.84 | .10 |                   |

*Data are given as median value unless otherwise indicated.
†Data are given as number (percentage) of each group unless otherwise indicated.
‡Results obtained using the Fisher exact test. If not specified, the Wilcoxon-Mann-Whitney 2-sample test was used.
§Estimates are averaged across patients.
¶Score = [(difference in median ulcer size) − (difference in median ulcer number) + (difference in median pain score)] − (difference in the proportion of ulcer-free days), where 0 indicates no change; a positive score, worsening; and a negative score, improvement.
midtreatment cytokine levels between the 2 arms (P = .23 for IL-1β and P = .16 for TNF-α).

Current therapies for RAS are unsatisfactory. Systemic immunomodulatory drugs, such as corticosteroids and thalidomide, have been most effective at suppressing disease activity, presumably by modifying the underlying disease process. However, most such drugs are associated with serious long-term adverse effects that limit their use.

Pentoxifylline is a nonselective phosphodiesterase inhibitor with hemorheological properties that is commonly used for managing symptomatic vascular insufficiency problems, such as intermittent claudication. However, it has many other potential uses. It has been shown to inhibit irritant and contact hypersensitivity,30,31 and has been used in the treatment of rheumatoid arthritis, multiple sclerosis, and other immune-mediated conditions. Although its mode of action in these conditions is incompletely understood, it seems to possess important immunomodulatory properties. In particular, like thalidomide, it inhibits TNF-α production32-34 and possibly the production of some other T helper cell 1 and proinflammatory cytokines, such as IL-1β,35,36 that are thought to be important in the RAS disease process. In addition, like colchicine, it inhibits neutrophil function, chemotaxis, and adhesion molecule expression,37,38 leading to reduced neutrophil, and T lymphocyte, recruitment into sites of inflammation.

Theoretically, then, pentoxifylline is a good candidate for treating RAS, and initial findings from small open-label studies have been encouraging. However, it has not previously been subject to a randomized, placebo-controlled, clinical trial. This is important because previous studies have shown a significant placebo effect in the treatment of RAS.

This study identified several improvements in the pattern of ulceration in patients taking pentoxifylline compared with those taking placebo. Compared with baseline values, patients taking pentoxifylline had more ulcer-free days, lower median pain scores, and a reduction in their median ulcer size, median ulcer number, and the global ulcer severity index, whereas there was no improvement in these variables for patients taking placebo. However, these differences were small and, with the exception of ulcer size, did not reach statistical significance.

All previous studies have shown a substantial improvement in RAS during treatment with pentoxifylline using a similar dosage regimen to that used in this study, and the study claimed long-term resolution of lesions even after treatment had been discontinued. Our own study, although showing some benefit with pentoxifylline, did not demonstrate a similar level of benefit, and we found no evidence of long-term cure. However, all the previous studies were open-label studies with no placebo control and, with the exception of the study by Chandrasekhar et al, little information was given on the criteria used for patient selection. Indeed, in 1 case, it is clear that 5 of the 22 patients in the study had associated systemic diseases, including rheumatoid arthritis, lupus erythematosus, ulcer-
ative colitis, anorexia nervosa, and Parkinson disease, and some were taking systemic drugs, including corticosteroids and mesalazine. Furthermore, although patients were used as their own control, some studies provided little or no baseline data on the pattern of ulceration to which the treatment phase was being compared. A further difficulty with most of the earlier studies is the crude or ill-defined nature of the measures being used to assess any change in the pattern of ulceration. We attempted to address some of these issues in the design of this study.

A shortcoming of the present study was the few patients ultimately eligible for the treatment phase of the study. This was due, in large part, to the attrition of subjects because of the study design and the rigid application of inclusion/exclusion criteria. This is an inherent problem with double-blind placebo-controlled studies of conditions such as RAS, and has been an issue for other similar studies. Although only 26 patients were randomized to treatment, our sample size was larger than that in most of the previous open-label studies and our power calculations indicated that had pentoxifylline been as effective as suggested by earlier open-label studies, we would have seen a clear-cut and statistically significant improvement in the pattern of ulceration with the number of patients described herein.

Based on our results, pentoxifylline may have a role to play in the management of RAS, where other treatments have failed or as an adjunct to other treatments. However, our study does not provide sufficient evidence to recommend it as the first line of treatment for RAS. Pentoxifylline’s immunomodulatory properties have shown great promise in open-label studies for several other conditions. However, when it has been subjected to properly conducted placebo-controlled studies, it has not always performed as well as expected. Larger-scale, randomized, double-blind, placebo-controlled trials might help further elucidate the precise value of pentoxifylline in the management of RAS.

Any benefit from treatment with pentoxifylline also has to be balanced against its adverse effects. The open-label studies of pentoxifylline treatment of RAS reported few adverse effects. In the present study, however, 69% of patients taking pentoxifylline reported adverse effects. The most common were dizziness, headaches, stomach upset, increased heart rate, and nausea. However, 50% of patients taking placebo also reported adverse effects, and these included all of those previously listed. Indeed, there was no significant difference in the number of patients taking pentoxifylline or placebo who experienced adverse effects, and the number of patients who withdrew from the treatment phase of the study because of adverse effects was larger for those taking the placebo (n=4) than the active drug (n=2). Nevertheless, fewer patients taking the active drug (64%) instead of placebo (83%) would have been prepared to continue taking it to treat their RAS, even if it was shown to be effective. Despite this, most patients expressed a clear preference for pentoxifylline, or the placebo, over the previous topical treatments they had tried for their RAS. This suggests that patients preferred taking a tablet to treat their RAS to the more complex application of topical agents.

We measured the circulating plasma concentrations of IL-1β and TNF-α, before treatment and during the middle of the treatment phase of the study. The secretion of both these cytokines is thought to be inhibited by pentoxifylline, and both are thought to play a role in the pathogenesis of RAS. Nevertheless, we detected no significant difference in the circulating level of these cytokines between patients taking pentoxifylline and those taking placebo. Also, we could not detect a difference in the pretreatment and treatment phase levels of cytokines for either arm of the study. The circulating levels of TNF-α and IL-1β measured at all phases within this study were within normal limits. Other studies with pentoxifylline have shown a reduction in circulating levels of the cytokines only in conditions such as septic shock, for which the levels are markedly elevated. Furthermore, circulating levels of TNF-α and other cytokines may not accurately reflect local tissue changes that are potentially more important in the cause of aphthous ulcers. Drugs such as pentoxifylline could inhibit abnormal increases in cytokine production within the local tissues without appreciably altering circulating levels. A similar observation was made when the levels of circulating TNF-α were measured in human immunodeficiency virus–positive patients in whom aphthous ulcers were treated with thalidomide. Surprisingly, despite inhibiting the aphthous ulcers, the circulating levels of TNF-α were elevated during treatment with thalidomide.

In conclusion, participants taking pentoxifylline reported lower pain levels, a smaller ulcer size, and a reduced ulcer number during the treatment phase compared with baseline, whereas participants taking placebo did not show an improvement in these variables. Participants taking the active drug also tended to have more ulcer-free days compared with those taking placebo. However, the differences between the 2 groups were small and, with the exception of ulcer size, were not significantly different.

Pentoxifylline did not prevent the ulcer episodes from occurring or result in a long-term cure. Thus, given the potential for significant adverse effects and the small benefits of the drug demonstrated in this clinical trial, we cannot recommend pentoxifylline as the drug of first choice for treatment of RAS, although it may have a second-line role in the management of patients unresponsive to other treatments or as an adjunct to other treatments.

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REFERENCES

20. O'Delloncourt, Diw L, Corillet P. Gournounou M. Differential regulation of TNF[], IL-1, IL-6, IL-8, TNF[], and IL-10 by pentoxifylline. Int Immunopharmacol. 1996;18:739-748.
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REFERENCES