CONCISE COMMUNICATION

Thalidomide in Low Intermittent Doses Does Not Prevent Recurrence of Human Immunodeficiency Virus–Associated Aphthous Ulcers

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A multicenter, double-blind, randomized, placebo-controlled study was conducted to determine the safety and efficacy of thalidomide in reduced, intermittent doses for preventing recurrences of oral and esophageal aphthous ulcers in patients with human immunodeficiency virus (HIV) infection. Forty-nine HIV-infected patients whose ulcers previously had healed as a result of thalidomide therapy were randomly assigned to receive either 100 mg of oral thalidomide or placebo 3 times per week for 6 months. Ulcers recurred in 14 (61%) of 23 thalidomide-randomized patients, compared with 11 (42%) of 26 placebo-randomized patients, with no significant difference in the median time to recurrence of ulcers (P = .221). There were no changes in plasma levels of HIV RNA, tumor necrosis factor (TNF)-α, and soluble TNF receptor II at the time of ulcer recurrence. Adverse events among patients treated with thalidomide included neutropenia (5 patients), rash (5 patients), and peripheral sensory neuropathy (3 patients). Thalidomide in lower intermittent doses is ineffective at preventing recurrence of aphthous ulcers in HIV-infected persons.

Persistent aphthous ulceration of the mouth, oropharynx, and esophagus is a complication of advanced human immunodeficiency virus (HIV) infection [1]. Frequently, it is accompanied by severe pain and impaired ability to eat. The etiology is presumed to be immunologic. We previously reported the results of National Institute of Allergy and Infectious Diseases (NIAID) AIDS Clinical Trials Group (ACTG) protocol 251, which demonstrated that thalidomide was effective in the acute treatment of these ulcers [2, 3]. The maintenance phase of this protocol was designed to determine the recurrence rate of ulcers after complete healing was achieved with thalidomide therapy and whether thalidomide was effective for prevention of these recurrences. In the doses used for acute therapy (200 mg/day), a 4-week course of thalidomide could not be tolerated by about half the patients. Anticipating this, thalidomide was studied in lower intermittent doses (100 mg 3 times/week) in the maintenance-phase study.

Methods

Study population. Patients were enrolled in the maintenance-phase study of ACTG 251 if they had complete healing of oral and/or esophageal aphthous ulcers at the end of acute-phase treatment with thalidomide as part of ACTG 251. The entry criteria and study design of the acute-phase study of ACTG 251 were reported elsewhere [2, 3].

Patients were recruited at 11 sites in the United States. Strict precautions were taken to prevent and detect pregnancy in women of childbearing potential [2, 3].

Treatment regimens. Patients were randomly assigned (double-blind) to receive either thalidomide or placebo (100 mg 3 times/week for 6 months). Ulcers recurred in 14 (61%) of 23 thalidomide-randomized patients, compared with 11 (42%) of 26 placebo-randomized patients, with no significant difference in the median time to recurrence of ulcers (P = .221). There were no changes in plasma levels of HIV RNA, tumor necrosis factor (TNF)-α, and soluble TNF receptor II at the time of ulcer recurrence. Adverse events among patients treated with thalidomide included neutropenia (5 patients), rash (5 patients), and peripheral sensory neuropathy (3 patients). Thalidomide in lower intermittent doses is ineffective at preventing recurrence of aphthous ulcers in HIV-infected persons.
Figure 1. Estimated distribution of time to recurrence of aphthous ulcers, by treatment group

Criteria for recurrence. Recurrence was defined as the occurrence of either an oral or esophageal aphthous ulcer. Culture was done to exclude herpes simplex virus, and biopsy was done to exclude herpes simplex virus, cytomegalovirus, and other causes of ulceration.

Evaluation of patients and follow-up. Patients were seen every 4 weeks for 24 weeks. Subjects were told to see their physician if an aphthous ulcer recurred between scheduled visits so that the recurrence could be documented by either oral examination or endoscopy. Clinical evaluations included observation for potential toxicities. On the visit documenting ulcer recurrence, measurements of plasma levels of tumor necrosis factor (TNF)-α, soluble TNF receptor II (TNFR-II), and HIV RNA were made.

Statistical analysis. The primary analysis, whether there was a treatment difference in time to ulcer recurrence (censored at 6 months), was tested by use of an exact stratified permutation test based on a generalized Wilcoxon kernel U statistic for interval-censored data, by means of a 2-sided test, with a type I error of 5% [4]. Distributions of time to ulcer healing were estimated by use of the Turnbull curve for interval-censored data [5]. A secondary analysis was done censoring time to recurrence at the date of permanent discontinuation of study treatment. In cases of death, loss to follow-up, or other reasons for absence of 6-month follow-up data, censoring time points were determined by the most recent available documentation on ulcer status. All analyses were done on an intent-to-treat basis.

A 2-tailed nonparametric Wilcoxon rank sum test was used to test for differences in the data distributions of the treatment groups [6]. A Wilcoxon signed rank test was used to study within-treatment group changes from baseline [6]. Two-tailed exact tests were used to compare the frequency of adverse events in the treatment groups [7].

Results

Study population. Fifty-two patients were enrolled in the maintenance phase of ACTG 251 between April 1994 and December 1996. Three patients never received thalidomide treatment during the acute-phase study and were excluded from the maintenance-phase study analysis. Of the 49 patients included in the analysis, 26 were randomized to receive placebo and 23 to receive thalidomide. Acute-phase baseline characteristics and ulcer-healing responses were similar for the patients in the 2 maintenance-phase study groups (data not shown).

Clinical data. Of the 49 patients, ulcers recurred in 14 (61%) of 23 thalidomide-randomized patients, compared with 11 (42%) of 26 placebo recipients. The median time to ulcer recurrence was 80 days for the thalidomide group and 145 days for the placebo group (figure 1). The 25th percentile for time to ulcer recurrence was 22.5 days (95% confidence interval [CI], 12–68.5 days) for the thalidomide group and 37.5 days (95% CI, 20 to >175 days) for the placebo group. The time to recurrence of ulcers was not significantly different between treatment groups (P = .221; 99% CI, .213–.229). This study had 80% power to detect a hazard ratio of 3.1 between the placebo and thalidomide arms.

There was no evidence of treatment effect in the secondary analysis of ulcer recurrence that censored observation at the...
permanent discontinuation of study treatment instead of at 6 months after randomization (P = .579; 99% CI, .569–.589).

**Immunologic and virologic data.** Thirteen patients had repeated plasma HIV RNA measurements, and 5 patients had repeated plasma TNF-α and soluble TNFR-II measurements at the time of ulcer recurrence. There were no significant changes in median plasma HIV RNA, TNF-α, and soluble TNFR-II levels from the maintenance-phase baseline. In addition, there were no significant differences in changes in these measurements between the treatment groups (data not shown).

**Safety data.** One patient randomized to placebo discontinued the study medication because of development of peripheral sensory neuropathy. One thalidomide-randomized patient had the dosage of study medication reduced because of neutropenia, and 1 placebo-randomized patient had the dosage reduced because of somnolence.

Sixty-one percent of thalidomide-randomized patients versus 23% of placebo-randomized patients reported grade 3 or higher adverse events (P = .016). All adverse events are shown in table 1.

Thirteen patients died, 6 (2 thalidomide and 4 placebo) during the study and 7 (5 thalidomide and 2 placebo) in the 6-month follow-up period after having completed the study. The deaths were due to HIV disease progression and were not related to the study treatment. These deaths reflect the advanced state of HIV disease of the study population and the fact that the study was conducted before the availability of the newer potent antiretroviral regimens. Four AIDS-associated events occurred in each treatment group: Kaposi’s sarcoma (2 patients), cryptosporidiosis, cytomegalovirus retinitis, cytomegalovirus colitis, and Pneumocystis carinii pneumonia in the thalidomide group and P. carinii pneumonia, microsporidial infection, cryptococcosis, and Kaposi’s sarcoma in the placebo group. No pregnancies occurred.

**Discussion**

In this study, thalidomide in doses of 100 mg 3 times per week was not effective in preventing recurrences of oral and esophageal aphthous ulcers in patients with HIV infection. The ulcers in these patients had healed from previous treatment with thalidomide. No benefit of thalidomide was seen, as assessed by either the number of recurrences that occurred during the 6-month study treatment period or the time to recurrence of ulceration. In fact, there was a nonsignificant trend toward a higher risk of ulcer recurrence in the thalidomide-randomized group, compared with that in the placebo-randomized group.

Thalidomide-randomized patients experienced significantly more serious adverse events than did the placebo-randomized patients. Neutropenia and rash were the most frequent toxicities. In the acute-phase study, there was a hint of neutropenia as a potential toxicity of thalidomide therapy in this patient population. The longer-term treatment, albeit at lower intermittent doses, established this association more clearly. New or progressed peripheral sensory neuropathy occurred both in patients randomized to receive thalidomide and in those randomized to receive placebo in this maintenance-phase study. All patients had previously received thalidomide to heal their aphthous ulcers, which could have been a factor in the development of neuropathy in the placebo recipients. Alternatively, advanced HIV infection itself may have played a role.

Plasma levels of TNF-α and soluble TNFR-II did not change at the time of recurrence of ulcers in the 6 patients who had these measured. This further undermines the hypothesis that aphthous ulceration may be related to systemic overproduction of TNF-α [2]. Aphthous ulceration of the oral cavity and esophagus responds to treatment with immune modulators, such as thalidomide [2, 3] and prednisone [8]; therefore, it is likely that the cause of this form of ulceration is immunologic. However, the exact immunologic mechanism has yet to be discovered.

We previously reported the results of our double-blind, randomized, controlled studies of thalidomide for the treatment of acute oral and esophageal aphthous ulcers in HIV-infected persons [2, 3]. Thalidomide in doses of 200 mg per day for 4 weeks was shown to be effective in treating both forms of aphthous ulceration, with complete healing rates of 55% for oral ulcers and 73% for esophageal ulcers. Almost all patients who received thalidomide had at least partial healing.

Two controlled studies of thalidomide for recurrent aphthous stomatitis in non–HIV-infected persons have been done. In both studies, aphthae did not have to be present at the beginning of the study treatment period. Hence, these studies measured a mixture of treatment and prevention effects of thalidomide. In one placebo-controlled crossover trial with no washout period before crossover, 17 (45%) of 38 thalidomide-treated patients had complete healing of ulcers present and remained free of

### Table 1. Adverse events among human immunodeficiency virus–infected patients whose aphthous ulcers had healed previously when treated with thalidomide and who then were treated with thalidomide or placebo in a maintenance-phase study.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Thalidomide (n = 23)</th>
<th>Placebo (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 or higher</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated absolute neutrophil count</td>
<td>5 (22)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Weakness</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Elevated triglyceride level</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Ataxia</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Fever</td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Seizures</td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Total</td>
<td>12 (52)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Any grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>5 (22)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>3 (13)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Total</td>
<td>8 (35)</td>
<td>5 (19)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of patients with ≥1 episode of an adverse event during study treatment.
ulcers during the first 2-month treatment period [9]. This occurred in 1 (3%) of 35 who received placebo. In a double-blind, randomized, placebo-controlled study of recurrent oral ulceration in patients with Behçet’s syndrome, thalidomide in doses of 100 and 300 mg per day over a 6-month period was evaluated similarly for its combined treatment and prevention effects [10]. Only 2 (6%) of 32 patients who received thalidomide at 100 mg per day and 5 (16%) of 31 patients who received 300 mg per day remained free of ulcers over the 6-month study period, compared with 0 of the 32 patients in the placebo group. The differences between thalidomide and placebo treatment were statistically significant. However, the low rate of achieving a 6-month period free of ulcers demonstrates the limited effectiveness of thalidomide treatment over this length of time.

Results of uncontrolled studies have shown that topical, intralresional, and systemic corticosteroids heal aphthous ulceration in HIV-infected patients [8]. However, the relapse rate with this form of treatment is substantial as well.

Our results suggest that thalidomide should not be continued after healing of aphthous ulcers occurs with thalidomide treatment in HIV-infected patients, at least in the reduced, intermittent doses studied here. It is conceivable that higher daily doses of thalidomide, particularly the 100-mg dose given to patients with Behçet’s syndrome [10], could prove effective at preventing relapses. However, serious adverse events were frequent with the doses used in this study. Daily doses of >100 mg are unlikely to be tolerated by most patients for >1–2 months [2, 3]. A study evaluating this dosage is underway. Furthermore, the immune reconstitution that results from the newer potent antiretroviral therapies seems to have reduced the incidence of aphthae and is likely to reduce the recurrence rate of aphthous ulceration. In addition, in our previously reported studies, thalidomide was shown to elevate plasma HIV RNA levels moderately [2, 3].

Hence, it seems reasonable to conclude that thalidomide should be used only for the acute treatment of oral and esophageal aphthous ulcers in HIV-infected patients. Thalidomide in the doses studied here is not effective in preventing recurrences. Patients should begin a potent antiretroviral regimen as soon as possible, to improve immune function and counteract thalidomide’s enhancement of HIV replication.

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Protocol 251

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References