# Thalidomide use in the management of oromucosal disease: A 10-year review of safety and efficacy in 12 patients

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**Objective.** Thalidomide is an effective systemic agent in the management of ulcerative oromucosal conditions. However, its clinical use is limited because of its known adverse effect profile, including teratogenicity, peripheral neuropathy, and thromboembolic risk. The aim of this study was to review the efficacy and safety of thalidomide over a 10-year period in an Oral Medicine specialty clinic.

**Study Design.** Clinical records of the Oral Medicine Department at the Royal National ENT and Eastman Dental Hospitals (London, UK) were retrospectively reviewed for patients prescribed thalidomide between 2009 and 2019 for the management of oromucosal ulceration. Twelve eligible patients were identified. Data on patient response to treatment and major/minor adverse events were obtained from their clinical and electrophysiologic records.

**Results.** A complete remission rate was noted in 50% (6 of 12) patients treated for recurrent aphthous stomatitis, HIV-related ulceration and oral Crohn disease. A thalidomide-induced neuropathy rate of 41.7% (5 of 12) was detected by electrophysiology testing, however clinical symptoms of neuropathy were only described by 3 subjects. No other major adverse effects were reported.

**Conclusions.** Thalidomide demonstrates a good efficacy-to-safety ratio in the management of oromucosal ulceration over a prolonged treatment period. Interval electrophysiologic testing is essential to monitor for thalidomide-induced neuropathy. In this cohort, neuropathy does not appear to be a dose-dependent outcome. (Oral Surg Oral Med Oral Pathol Oral Radiol 2020;130:398–401)

Thalidomide has been shown to be an effective systemic agent in the management of refractory oral ulceration. The role of thalidomide in HIV-related aphthae is well established,[1-3] with growing evidence regarding its efficacy in the management of recurrent aphthous stomatitis, as well as ulceration secondary to a number of mucocutaneous conditions, such as erosive lichen planus, Behcet disease, and erythema multiforme.[4-7]

The exact mechanism of thalidomide remains unknown; however, its anti-inflammatory action is believed to derive from modulation of the inflammatory cascade and from interaction with various cytokines, including tumor necrosis factor-$\alpha$, interleukin-6, and interleukin-10.[8]

Despite its efficacy, thalidomide is associated with a number of adverse effects, including peripheral neuropathy, thromboembolic disease, and embryofetal toxicity.[9] Strict regulation on distribution, in addition to patient education and pregnancy prevention programs, such as System for Thalidomide Education and Prescribing Safety (STEPS; Celgene Corporation, Warren, NJ), minimize the risk of teratogenicity and fetal exposure with modern prescribing.[10]

Neurotoxicity is considered the main factor limiting the clinical use of thalidomide currently because it induces bilateral, sensory, axonal paraesthesia in up to 70% of cases.[11] There is lack of consensus with regard to the dose–response relationship and the impact of cumulative thalidomide dose on the risk of clinical peripheral neuropathy.[12-14]

A recently published randomized control trial investigated the safety and efficacy of short-duration thalidomide therapy in reducing the interval of recurrent aphthous ulceration.[15] The present study aimed to support these findings by providing insight into outcomes associated with longer-term thalidomide therapy.

We aimed to retrospectively review thalidomide prescription and patient outcomes in a tertiary outpatient oral medicine department over a 10-year period.

## Statement of Clinical Relevance

Although thalidomide shows good efficacy, its use is limited because of the severity of potential adverse effects and the challenges in prescribing it. This article aims to highlight the efficacy-to-safety ratio of this medication.

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## MATERIALS AND METHODS

### Study population

Clinical records from the outpatient Oral Medicine Department at the Royal National ENT and Eastman Dental Hospitals (London, UK) were retrospectively reviewed to identify patients prescribed thalidomide between the years 2009 and 2019. The retrospective nature of this study precluded the use of a control group. Any patients prescribed thalidomide during this period for an ulcerative oromucosal condition were included. Patients with pre-existing peripheral neuropathy and those prescribed thalidomide in other units were excluded.

### Data collection

The following variables were recorded for each patient: demographic characteristics (age, sex); indication for therapy; previous pharmacotherapy; duration of thalidomide treatment; cumulative dose; and side-effect profile.

All patients underwent sensory nerve action potential (SNAP) conduction studies before initiation of therapy. Repeat neurophysiologic studies were undertaken on a 6-monthly basis throughout treatment. A greater than 50% reduction in sural SNAP amplitude was selected as the criterion for defining peripheral neuropathy, which has been reported in a number of studies to be closely related to clinical sensory changes.[14,16,17]

Complete remission (CR) rates were calculated on the basis of the definition of CR as complete clearing of aphthae within a 1-month period of treatment onset and maintained during the second month of therapy.[18]

### Statistical analysis

The Mann-Whitney U test was applied to the nonparametric data collected on the duration of thalidomide therapy and cumulative dose to statistically compare cases of peripheral neuropathy vs asymptomatic patients in this cohort.

Spearman's rank correlation coefficient was calculated to analyze the dose−response relationship between cumulative thalidomide dose and percentage reduction in SNAP amplitude.

## RESULTS

### Patient cohort

A total of 16 patients were treated with thalidomide in the Oral Medicine Department at the Royal National ENT and Eastman Dental Hospitals (London, UK) between 2009 and 2019. Four patients were excluded from the study because of missing records (n = 1), thalidomide initiation by another Oral Medicine Department (n = 2), and pre-existing neuropathy (n = 1). The remaining 12 patients included 7 males and 5 females, 4 of whom were of child-bearing age at the time of treatment initiation. Mean age at treatment onset was 42 years (range 15−61 years). Nine patients were treated for recurrent aphthous stomatitis; 2 for HIV-related oral ulceration; and 1 for the oral manifestation of Crohn disease. Two patients reported extraoral ulceration. Patients received thalidomide for a mean period of 37 months (range 1−79 months), with doses ranging from 50 mg every 3 days to 100 mg once daily. The mean cumulative dose for this cohort was 20.8 g (range 1.1−60.2 g).

### Treatment before thalidomide

Topical corticosteroid preparations were received by all patients as an ineffective first-line treatment. Ten patients were then prescribed an alternative systemic therapy—prednisolone (n = 8); azathioprine (n = 7); colchicine (n = 7); pentoxifylline (n = 2); and dapsone (n = 1)—before initiation of thalidomide therapy. The mean number of systemic medications trialed before thalidomide initiation was 2.3 (range 0−6). Two patients, both with HIV-related oral ulceration, were prescribed thalidomide as the first-line systemic medication after unsuccessful topical treatment.

### Response to thalidomide

A CR rate of 50% (6 of 12) was seen in this cohort. The mean time to complete remission was 3.3 weeks, and all patients who achieved CR received a dose of 50 mg once daily. An additional 3 patients achieved remission at 6 to 8 weeks. Three patients continued to experience ongoing oral ulceration, although all reported a subjective improvement in terms of frequency, severity, and duration of ongoing ulcerative episodes. No objective outcome measures were available to quantify these findings.

### Major adverse effects

A thalidomide-induced neuropathy rate of 41.7% (5 of 12) was seen in this cohort (Table I). Symptoms were

**Table I.** Patient demographic characteristics and oromucosal conditions in patients with or without thalidomide-induced neuropathy

| *Parameter* | *Patients with clinical thalidomide-induced neuropathy (n = 5)* | *Patients without clinical thalidomide-induced neuropathy (n = 7)* |
|---|---|---|
| **Sex (n)** | | |
| Male | 2 | 5 |
| Female | 3 | 2 |
| **Diagnosis (n)** | | |
| Recurrent aphthous stomatitis | 3 | 6 |
| HIV-related oral ulceration | 1 | 1 |
| Orofacial granulomatosis | 1 | 0 |

**Table II.** Mann-Whitney U test comparing cumulative thalidomide dose and duration of therapy between patients who developed peripheral neuropathy and asymptomatic cases*

| Parameter | Patients who developed peripheral neuropathy | Patients without peripheral neuropathy | P value |
|---|---|---|---|
| Duration of thalidomide treatment (months) median [Q1;Q3; range] | 38 [34.5;52.5; 33−60] | 24 [10; 72; 1−79] | .254 |
| Cumulative thalidomide dose (milligrams) median [Q1;Q3; range] | 15.5 [7.75;29.8; 7.2−38.3] | 15.7 [9.3; 43.9; 1.1−60.2] | .748 |

*Significance level $P = .05$.

reported in 3 of these patients. Two remained asymptomatic despite 57% and 67% reductions from baseline sural SNAP. No statistically significant difference was shown between cumulative thalidomide dose or treatment duration between patients who developed peripheral neuropathy and those with no neurophysiologic evidence of peripheral neuropathy (Table II). In terms of correlation between thalidomide dose and percentage reduction in SNAP amplitude, a Spearman's Rank correlation coefficient of 0.045 was calculated ($P > .05$), showing no statistically significant association. All patients with thalidomide-induced neuropathies continued therapy with regular electrophysiologic monitoring. In 1 case, SNAP amplitudes progressively worsened, and despite no subjective change to the existing neuropathy symptoms, thalidomide therapy was stopped. The remaining 4 patients' SNAP amplitudes remained stable on maintenance therapy, and no subjective worsening of symptoms or new-onset neuropathy symptoms was reported by this group.

Of the remaining 7 patients without clinical thalidomide-induced neuropathy, all reported mild transient, self-limiting paraesthesia. One patient elected to stop thalidomide therapy after 1 month because of subjective neuropathy despite no reduction in the baseline sural SNAP. No other major adverse effects of thalidomide therapy, including teratogenicity, were reported by the patient cohort.

### Minor adverse effects

Minor adverse effects were reported in 4 patients: somnolence (n = 2), dizziness (n = 2), and constipation (n = 1).

## DISCUSSION

The complete remission rate of 50% reported in this cohort is lower than published findings from the literature review. Hello et al.[12] reported an 85% CR rate in 92 patients treated for severe recurrent aphthous stomatitis. A similar remission rate was shown by Gardner-Medwin et al.[14] with 81.3% of a total cohort of 59 patients who were ulcer free at 1 month. Of note, a lower remission rate was evident in patients with ulceration secondary to a mucocutaneous condition or with a systemic cause of ulceration, rather than idiopathic recurrent aphthous stomatitis. This, coupled with the smaller cohort size, may account for this discrepancy in the reported CR rate. Indeed, in a cohort of 17 patients, de Wazières et al.[19] reported only a 32% remission rate in patients with orogenital ulceration.

Current findings, however, support the consensus that induction of remission is independent of the initial thalidomide dose,[14,19,20] with all the patients in this study achieving remission with a dosage of 50 mg once daily.

We are aware of a recently published randomized control trial by Zeng et al.,[15] which found thalidomide to be superior to alternative systemic medications in reducing the recurrence interval of recurrent aphthous ulceration. Patients in this randomized controlled trial received a reducing dose of thalidomide for 30 days. No record of electrophysiologic monitoring was included in this trial, and indeed, no observations of thalidomide-induced neuropathy were made. The 10-year time frame of the present study allowed us to investigate the prevalence of adverse effects associated with long-term thalidomide therapy, with objective measurement of thalidomide-induced neuropathy, and provided insight into longer-term outcomes for thalidomide therapy in patients with recurrent aphthous ulceration and other oromucosal ulcerative conditions.

In the present study, clinical peripheral neuropathy was detected in 41.7% of cases. The prevalence of thalidomide-induced neuropathy varies widely and has been reported to be as high as 70%.[21] This variation has been attributed to heterogeneity in study design, including defined electrophysiologic criterion, in addition to a proposed "disease-related susceptibility," given the number of dermatologic and hematologic conditions treated with thalidomide.[13] When the focus is oromucosal disease, neuropathy is reported in the region of 13.5% to 17%.[12,14]

Although the relationship between cumulative thalidomide dose and onset of neuropathy remains equivocal, the present study's findings support the body of evidence[12,13,14] for induced neuropathy being independent of dose, suggesting an idiosyncratic process, rather than a dose-dependent relationship.

Although the present study allowed long-term review of the safety and efficacy of thalidomide in a group of 12 patients, its retrospective nature precluded the use of a control group and, thus, the measurement of any variables.

## CONCLUSIONS

This study demonstrates the efficacy-to-safety ratio of thalidomide therapy in the management of oral ulceration over a prolonged treatment period. Thalidomide demonstrates good efficacy in the management of recalcitrant ulceration that proves refractory to a number of alternative systemic treatments. Peripheral neuropathy remains the main adverse side effect of significance with modern prescribing; therefore, neurophysiologic studies are of utmost importance throughout treatment.

## PRESENTATION

An abstract of this manuscript was accepted for oral presentation at the American Academy of Oral Medicine (AAOM) 2020 Annual Conference at Orlando, FL, USA.

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