A RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, CONTROLLED DOSE COMPARISON OF THALIDOMIDE FOR TREATMENT OF ERYTHEMA NODOSUM LEPROSUM

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Abstract. In a randomized, double-blind, double-dummy controlled study, 22 men with erythema nodosum leprosum (ENL) received six capsules containing either 100 mg (group A, n = 12) or 300 mg (group B, n = 10) of thalidomide daily for one week. A six-week, four capsules per day taper followed, in which group A received 50 mg/day of thalidomide in weeks 2 and 3, then dummy capsules in weeks 4 through 7, while group B had gradual decrements every two weeks. Both regimens caused comparable improvement in 19 patients at day 7 (group A [12 of 12] versus group B [7 of 10]; P = 0.08), but slower tapering in group B showed less re-emergence of ENL through week 7 (P = 0.02, versus group A). Most patients developed new lesions soon after stopping treatment. Slower tapering from a higher initial thalidomide dose may improve clinical ENL responses, but high recurrence rates after discontinuation indicates further assessment is needed to identify better tapering regimens.

INTRODUCTION

Erythema nodosum leprosum (ENL) is a serious inflammatory reaction that occurs in up to 50% of patients with lepromatous patients and 25% with borderline lepromatous leprosy, most commonly late in treatment or after completion of treatment. ENL typically presents as a debilitating febrile illness with few to hundreds of tender, inflamed cutaneous papules or nodules, along with inflammation of the nerves, eyes, and testes. Conventional therapies include anti-inflammatory compounds such as oral corticosteroids, aspirin, and non-steroidal anti-inflammatory drugs (NSAIDs), but each is associated with side effects and limited efficacy.

Thalidomide, first introduced in 1957 in West Germany, was used as a sedative until reports of teratogenicity caused its withdrawal from the market in the early 1960s. Thalidomide administered as a sedative to leprosy patients with ENL in the mid 1960s led to dramatic improvement, typically within 24–48 hours. Between 1965 and 1971, six controlled studies (five placebo-controlled) with 201 enrollees showed that thalidomide doses of 300–400 mg/day were safe and highly effective for treatment of acute ENL. However, some studies included concurrent administration of oral corticosteroids or anti-leprosy medication, which complicated interpretation. Relapse on discontinuation of thalidomide was common, especially if tapered too fast, prompting recommendations for tapering by 50–100 mg every two weeks as tolerated. Numerous open label trials with thousands of patients generally support the findings of the controlled studies. The effectiveness of thalidomide in ENL may be due to inhibition of the production of tumor necrosis factor-α (TNF-α) and urine neopterin levels, and in vitro lymphocyte proliferation assays.

METHODS

Study design. The study was conducted between July 1996 and August 1998 at the Leonard Wood Memorial (LWM) Center for Leprosy Research (Cebu City, The Philippines). The design was a double-blind, double-dummy, randomized comparison of two fixed doses of thalidomide for one week, followed by a six-week taper for the acute treatment of moderate ENL. Twenty to 30 patients were to be enrolled over a two-year period. This sample size was not large enough to provide adequate power to compare the efficacy of the two regimens. The protocol, which was reviewed and approved by the LWM Institutional Review Board, was part of an investigational new drug application filed with the U.S. Food and Drug Administration (FDA) and was conducted according to the guidelines of Good Clinical Practices. The U.S. FDA and Celgene Corporation (Warren, NJ) monitored the study.

Patients and test articles. Patients 18 years old with lepromatous leprosy (multi-bacillary) who signed an informed consent form were eligible for enrollment if they had an acute, histologically confirmed episode of ENL consisting of 10 inflamed skin nodules, with or without systemic symptoms that included fever, neuritis, arthralgias, or orchitis. Any woman considered for enrollment was required to provide evidence of non-childbearing potential that included fever, neuritis, arthralgias, or orchitis. Any woman considered for enrollment was required to provide evidence of non-childbearing potential that included menstruation within at least 24 months of amenorrhea or surgical sterilization. Exclusion criteria included incapacitating ENL or corticosteroid ingestion within 2 weeks of enrollment. During the study, anti-leprosy therapy was continued, but ingestion of corticosteroids, aspirin, or NSAIDs was prohibited.

Celgene Corporation provided the test articles, which were composed of identically appearing capsules containing 50 mg of thalidomide or inert material (dummy) in coded blister packs, in sufficient quantity for seven weeks of treatment. All medication was kept in a locked cabinet at room temperature.
Eligible patients were randomized to receive thalidomide 100 mg/day (group A) or 300 mg/day (group B) for seven days under direct observation, which was designated acute treatment (Table 1). All patients received six capsules per day and were asked to fast for one hour before and two hours after dosing. Acetaminophen was offered to patients for fever (temperature ≥ 38.6°C) during the first 72 hours of the study.

At daily clinic visits during week 1, one investigator (LGV) recorded the number of inflamed skin lesions, a physician’s global assessment for non-cutaneous signs and symptoms, and thalidomide-related adverse events. The global assessment was a semi-quantitative assessment measuring anorexia, arthralgias, chills, malaise, neuritis, and orchitis on a 0–3-point scale for none, mild, moderate, or severe, respectively, relative to the investigator’s experience in managing ENL. Fever scores were 0 (< 37.6°C), 1 (37.6–38.6°C), 2 (38.7–39.4°C), and 3 (> 39.4°C). For neurologic assessments, patients were asked about paresthesias and relevant nerves were examined for sensation, tenderness, and enlargement. Any patient with a marked increase in ENL lesions or an unimproved or worsening global assessment score could be classified a failure and treated conventionally with oral corticosteroids or NSAIDs.

On day 7, treatment responses based on inflamed lesion counts were classified as complete (no lesions), partial (lesion counts reduced 50–99% from enrollment) or failure (lesion counts reduced < 50% from enrollment). Treatment failures were withdrawn, treated with oral steroids and NSAIDs, and automatically designated a failure for the taper.

Patients with complete or partial responses at week 1 were tapered from thalidomide during weeks 2 through 7, as shown in Table 1. To maintain the blind, all patients received four capsules per day. Clinical evaluations were conducted daily by one investigator (LG) and reported at weeks 3, 5, and 7. During tapering, any patient with a marked increase in ENL lesions or a global assessment score could be classified a failure and treated conventionally with oral corticosteroids or NSAIDs, and automatically designated a failure for the taper.

Patients who were complete responders at week 1 (no acutely inflamed lesions) and had no new lesions during the taper were monitored for recurrence for up to two months after study completion. A successful taper was defined as a complete response at day 7, with no new acutely inflamed lesions during the taper and for two months after study completion.

**Safety and tolerability.** At enrollment and at week 7, patients provided a medical history and underwent a physical examination, including routine hematologic and biochemical studies, and thyroid function tests including thyrotropin-stimulating hormone, total T₄, and T₃ uptake. Vital signs, including supine and upright blood pressures, were assessed before and at four hours after dosing. Adverse events, defined as any unfavorable sign or symptom temporally associated with the administration of thalidomide, were categorized according to the preferred terms of the International Committee on Harmonization and the U.S. FDA Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) system. Adverse events were graded as mild (hardly noticeable), moderate (altering daily activity), or severe (bed rest). Responses were recorded categorically as present or absent. Examinations were conducted through week 7, regardless of treatment response.

**Plasma levels of TNF-α and interleukin-6 (IL-6), lymphocyte proliferation assays (LPAs), and urine levels of neopterin.** Peripheral blood samples were collected from patients willing to undergo additional blood sampling immediately before thalidomide administration and at study weeks 3 and 7 for measurement of plasma levels of TNF-α (Biosite enzyme-linked immunosorbent assay [ELISA]; T Cell Sciences, Boston, MA) (lower limit of detection = 10 pg/mL) and serum levels of IL-6 (Interst-6 ELISA; Genzyme, Boston, MA) (lower limit of detection = 0.313 ng/mL) and selected in vitro cell-mediated immunology assessments. Blood for measurement of plasma TNF-α levels was collected in heparinized tubes containing 10 U/mL of the protease inhibitor aprotinin (Sigma, St. Louis, MO). For LPAs, paired samples, consisting of whole blood and peripheral blood mononuclear cells (PBMC) isolated by density-centrifugation, were assessed for mitogen responsiveness using two concentrations of phytohemagglutinin (PHA; 5 and 10 μg/mL) and one concentration of concanavalin A (Con A; 5 μg/mL). Results were expressed as a stimulation index. Urine samples were collected on a similar schedule for determination of levels of neopterin and creatinine by a high-performance liquid chromatography method as described previously. Neopterin was assessed by its native fluorescence (353 nm excitation and 438 nm emission) and creatinine by ultraviolet light absorbance at 235 nm. Results were expressed as μmol of neopterin/mol of creatinine by a method integrating renal function into neopterin concentration. Neopterin and LPA values were compared by the Mann-Whitney U test, with P ≤ 0.05 considered significant.

**Table 1**  
Double-blind, double-dummy acute and tapering medication administration

<table>
<thead>
<tr>
<th>Initial thalidomide dose</th>
<th>Acute dosing</th>
<th>Tapering period (weeks 2–7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 1</td>
<td>Weeks 2–3</td>
</tr>
<tr>
<td>Group A: 100 mg/day</td>
<td>100 mg/day (2 × 50 mg capsules, 4 × dummy capsules)</td>
<td>50 mg/day (1 × 50 mg capsule, 3 × dummy capsules)</td>
</tr>
<tr>
<td>Group B: 300 mg/day</td>
<td>300 mg/day (6 × 50 mg capsules, 0 × dummy capsules)</td>
<td>200 mg/day (4 × 50 mg capsules)</td>
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</table>
Data management and statistical analysis. Data were entered into a SAS database (version 6.12; SAS Institute Inc., Cary, NC) reviewed against source documents, and locked. StatXact version 6 (Cytel Software Corporation, Cambridge, MA) and S-PLUS 4.5 (Insightful Corporation, Seattle, WA) were used for analyses.

The primary outcome for efficacy was the resolution of inflamed ENL nodules during the initial seven-day treatment compared between the two treatment groups. The primary analysis was complete response; secondary analyses were complete or partial responses, and time to complete or partial remission. Secondary outcomes included global assessment, re-emergence of skin lesions during taper, week 7 lesion counts, recurrence of lesions after the taper, safety, and tolerability.

For efficacy, dose group comparisons were assessed by twosided statistical tests at the 5% significance level. Data conventions for skin lesion counts included the reported and estimated numbers. The reported number of lesions was the value recorded. Most values were integers but some values were estimates (e.g., ≤10 or ≥50). The estimated number of lesions was adjusted to an integer, where “< x” was x ÷ 2, “≥ x” was 2x, and x – y was (x + y) ÷ 2. In general, the reported number described complete responses and the estimated number described partial responses and failures.

The Mann-Whitney U test was used for all statistical tests of continuous variables and Fisher’s exact test was used to compare dichotomous variables.

RESULTS

Patients. Twenty-two men, ranging in age from 18 to 46 years old, met enrollment criteria and were randomized to receive either 100 mg/day (n = 12, group A) or 300 mg/day (n = 10, group B) of thalidomide in the acute dose period. Enrollment characteristics of the treatment groups were similar (Table 2). All had completed leprosy therapy, consisting of either World Health Organization multi-drug therapy (n = 7) or monthly rifampin, ofloxacin, and minocycline (n = 15).16,17 Nineteen patients had documented episodes of ENL before enrollment, but none had previously received thalidomide. At enrollment, all patients had anorexia, arthralgias, chills, fever, or neuritis, and one patient had mild orchitis. One patient (P14) randomized to group B had no inflamed lesions on the first dosing day, received no medication, and was omitted from efficacy and safety analyses.

Efficacy. Treatment responses at one week (primary endpoint). Figure 1 shows the percent change in the number of inflamed ENL lesions compared with pre-treatment during week 1 for groups A (100 mg/day, taper) and B (300 mg/day, taper), respectively. Group A had eight complete and four partial responders and Group B had five complete and two partial responders, and three failures. The failures included two patients withdrawn on days 6 and 7 with increased ENL lesions (P01 and P05, respectively), and one patient (P20) who had a complete response for lesions but a poor global assessment score.

Among the 22 total patients, 19 (86%) were complete or partial responders. The proportion of complete (group A [8 of 12] versus group B [5 of 10]; P = 0.67) or complete plus partial responders (group A [12 of 12] versus group B [7 of 10]; P = 0.08) between groups A and B at day 7 was comparable. Kaplan-Meier plot analyses showed similar times to complete or partial remission in the two groups (log rank, \( P = 0.86 \)). All complete and partial responders during acute therapy entered the tapering phase.

Tapering responses (weeks 2–7). Figure 1 shows the percent change in the number of inflamed ENL lesions at weeks 3, 5, and 7 for groups A (100 mg/day, taper) and B (300 mg/day, taper), respectively, and the seven-week response classifications. Among the 19 patients with complete or partial responses at week 1, 9 (75%) of 12 group A versus 1 (14%) of 7 group B patients showed an increase in skin lesion counts by week 7 (95% confidence interval [CI] of the difference between the percentages = 11–88%, \( P = 0.02 \)). For the subset of complete responders during acute treatment (n = 13), 6 (75%) of 8 group A versus 1 (20%) of 5 group B patients developed new lesions by week 7 (95% CI of the difference between percentages = –6 to 89%, \( P = 0.10 \)).

Post-study assessment. A successful taper, defined as a complete response at 1 week (eight in group A and five in group B) and lack of new acutely-inflamed lesions during the taper and for at least two months after stopping thalidomide, occurred in only one patient (Group B). Three group B patients had new lesions within two weeks of stopping thalidomide.

Global assessment. Cumulative and symptom-specific mean global assessment scores by treatment group are shown in Figure 2. Before treatment, all patients exhibited at least one specified symptom of ENL. The mean scores for arthralgias and neuritis were modestly higher (worse) in group B (P > 0.05).

At week 1, the group A and B cumulative mean scores decreased by 87% and 64%, respectively (\( P = 0.063 \)). Among patients who became asymptomatic, group A (10 of 12, 83%) had a higher proportion than group B (5 of 10, 50%; \( P = 0.17 \)). Among the eight group A or B patients who exhibited symptoms at the end of acute dosing, all but three (P01, P05, and P20, all in group B and designated treatment failures) showed a reduction in severity.

During the taper, the global assessment scores in group A were higher than in group B. Overall, 5 (63%) of 8 patients in group A versus 1 (14%) of 7 patients in group B experienced at least one ENL-related symptom. At week 7, cumulative and individual symptom scores were modestly better in Group B. Collectively, the maximum severity for each patient and the associated proportions of patients with any symptom in each dose group were similar between dose groups at each time point.

Safety and adverse events. Hematology and biochemistry clinical laboratory values are shown in Table 3. Mild anemia was observed in 10 patients at enrollment and in 7 patients at...
FIGURE 1. Percent change in erythema nodosum leprosum (EML)–inflamed skin lesion counts during acute (week 1) and tapered (weeks 2–7) dosing. Treatment responses at weeks 1 and 7 are listed above (↑), and denoted by rectangular boxes. P in the box on the right side denotes patient study number. A, Group A (100 mg/day, taper). B, Group B (300 mg/day, taper). *P20, on day 7, was a complete responder for lesions but was classified a failure due to a poor global assessment score. This figure appears in color at www.ajtmh.org.
week 7. Levels of white blood cells, primarily neutrophils, were elevated at enrollment and decreased with treatment. Levels of platelets were elevated in both groups at study entry and at week 7. Eosinophil counts increased slightly in four patients during dosing. Erythrocyte sedimentation rates were elevated at enrollment and at seven weeks in both treatment groups, regardless of treatment response. There were no other clinically important laboratory values.

All adverse events during acute dosing and tapering were graded as mild or moderate (Table 4). Somnolence, rash, and pruritus were most common, all modestly higher in group B. The proportion of patients with at least one adverse event was higher in group B (9 of 10) than in group A (5 of 12) \( (P = 0.03, \text{by Fisher's exact test}) \). There were no missed doses or discontinuation of treatment due to any adverse event.

**Plasma levels of TNF-α and IL-6, LPAs, and urine levels of neopterin.** All plasma TNF-α levels were below the ELISA detection limit. Serum concentrations of IL-6 in treatment-responsive group A and B patients at weeks 0 (pretreatment), 3, and 7 are shown in Figure 3. From week 0 to week 3, the patients showed either no change or reduced IL-6 values, and some were undetectable. For group A patients who were treatment responsive at week 7 (dummy capsules administered weeks 3 through 7), two of five had increased IL-6 levels in comparison with week 3. In both group B patients who were treatment responsive at week 7 (thalidomide administered through week 7), IL-6 was undetectable at weeks 3 and 7.

Figure 4 shows LPA stimulation index values in whole blood and PBMCs incubated with 5 μg/mL of PHA. In comparison with normal control median values, pre-thalidomide treatment (week 0) medians in both treatment groups, including PBMCs and whole blood samples, were low. Group A showed a general trend towards normalized responsiveness at weeks 3 and 7. In group B, medians at week 7 were notably higher than in group A, and for PBMCs, higher than normal control values. The group B week 7 PBMC median was also higher than the week 0 or 3 medians, and the week 7 whole blood median was higher than the week 0 median. Similar trends were observed when cells were incubated with a higher concentration of PHA (10 μg/mL) and Con A (10 μg/mL).

Figure 5 shows both treatment groups with higher median neopterin values than normal controls at weeks 0, 3, and 7. Median neopterin values in group B patients were higher than in group A patients at all three time points \( (P < 0.05, \text{by Mann-Whitney U test}) \). The two patients with the highest pre-treatment neopterin levels in group B (P01 and P04) had lesion counts near the group median. Patient P01 was withdrawn on day 6 for because of increased lesion counts and patient P04 was a complete responder at weeks 1 and 7. An unscheduled neopterin assay on patient P01 one day after withdrawal from the study showed that levels had increased from a pre-treatment value of 559 to 630.

**DISCUSSION**

Daily doses of 100 or 300 mg of thalidomide were comparable in eliminating or significantly reducing inflamed skin lesions and constitutional symptoms of moderate ENL during a seven-day acute therapy period. Moreover, the time to reach complete or partial response in the two dose groups was similar, suggesting that 100 mg/day may be a sufficient starting dose in some patients. However, the slower reduction in the 300 mg dose group over a six-week period, resulting in seven weeks of treatment with thalidomide, had significantly better ENL lesion responses, consistent with observations that better responses occur with higher initial doses and slow tapering. Even so, nearly all (12 of 13) patients who were lesion-free on day 7, including those in the higher dose group B, developed new lesions during the taper or soon after thalidomide was discontinued. This suggests that thalidomide should be administered for longer than six weeks, and perhaps with an even slower taper than in group B. Despite modestly higher side effect rates, better long-term responsiveness may justify higher starting doses and slower tapers of thalidomide in treatment of ENL.

Thalidomide is estimated to be effective in up to 99% of ENL patients, typically causing notable improvement within days. However, concurrent administration of anti-inflammatory medication in earlier studies may have improved treatment response rates. Here, only 86% of the patients had complete or partial responses at day 7, with three patients who were treatment failures. This was especially surprising because all three received the higher 300 mg doses.
Notably, two patients initially showed > 50% improvement in lesion counts, but then showed dramatic increases in lesion numbers that triggered withdrawal from the study. The third patient had complete resolution of skin lesions, but was withdrawn because of a poor global assessment score. Thalidomide failures in ENL have been attributed to incorrect diagnosis or poor compliance. However, this is unlikely here because of histologic confirmation and monitored therapy. All three patients had pre-treatment lesion counts near group median values and, on study withdrawal, responded well to oral corticosteroids. ENL can become chronic and treatment-resistant in some patients, but the factors associated with thalidomide failure here remained unclear.

Formally assessing ENL treatment response is challenging, and study design clearly affects interpretation. Hastings and others used rigorous lesion response and fever criteria and reported that only 68% of ENL patients given 400 mg/day of thalidomide for four days qualified as treatment successes, underscoring the importance of the definition of success. In some controlled studies, ENL response to thalidomide was graded on a numerical severity scale, a method that introduces uncertainty. Some of our patients received anti-pyretic acetaminophen for fever, but unlike several other controlled studies, did not receive potent anti-inflammatory medications such as oral corticosteroids concurrently with thalidomide. Moreover, all patients had completed leprosy treatment, eliminating any anti-inflammatory influence of medications such as clofazimine or minocycline. Our study had an objective primary outcome, a global response score for non-cutaneous signs and symptoms, and a double-blind, double-dummy design to minimize bias. Nonetheless, two patients with complete or partial lesion responses (one at day 7 and one at week 7, respectively) were classified as treatment failures because of worsening global assessment scores, underscoring the difficulty in objectifying ENL treatment responses on the basis of lesion responses alone.

The effectiveness of thalidomide for ENL is reported in at least 1,750 patients (6 controlled and 26 open label trials), prompting the World Health Organization to recommend thalidomide as a treatment of choice for ENL. However, daily dose recommendations ranging from 100 mg to 400 mg suggest dose regimens are empirical. Discontinuation of thalidomide, either abruptly or by taper, is frequently characterized by recurrence, typically within 1–2 weeks. In a Thai study with patient demographics similar to those in our study, up to 77% of those treated with thalidomide had ENL recurrence soon after medication discontinuation. Here, gradual tapering from the higher initial dose (group B) was infrequently associated with new ENL lesions during thalidomide dosing, but nearly all week 1 complete responders had new lesions within two months of discontinuation of treatment with thalidomide. Several group B patients recurred as quickly as two weeks after discontinuation of thalidomide, clearly indicating the need for a better tapering regimen, or even combining other anti-inflammatory drugs with thalidomide.

Global assessment scores for non-cutaneous ENL-related signs and symptoms at the end of acute treatment were modestly better in group A, reflecting three failures and a higher (worse) pre-treatment score in group B. However, during the taper, far more signs and symptoms occurred in group A. We
attribute this notable difference to rapid thalidomide tapering of group A over a two-week period. In contrast, group B thalidomide dosing was gradually tapered over a six-week period.

The most common non-reproductive adverse events associated with thalidomide are drowsiness, rash, peripheral neuropathy, constipation, lower extremity edema, and eosinophilia. Here, the most common adverse events were sedation, rash, and pruritus, and, as expected, all were more common in group B. As previously described in ENL, many patients had mild anemia, manifested primarily by low hemoglobin values, and a leukocytosis characterized by neutropenia. Eosinophilia during administration of thalidomide, which occurs in patients infected with human immunodeficiency virus and rarely in patients with ENL, often with an allergic-like dermatitis, was noted in up to four patients, but not necessarily with a rash. Thrombocytosis was present before and at week 7, a feature described previously with unclear etiology and little clinical importance. Alkaline phosphatase, which was slightly elevated before treatment in both treatment groups, improved by week 7. Thyroid functions, reported to be altered by thalidomide, were unaffected.

The effectiveness of thalidomide in the treatment of ENL is often attributed to anti-inflammatory properties, particularly by inhibiting the production of TNF-α, a monokine associated with ENL toxicity. However, similar to some studies, plasma TNF-α levels were undetectable, which prevented a correlation with disease severity or treatment response. However, for IL-6, a related cytokine released during stress or inflammation, reduced plasma concentrations between weeks 0 (pre-treatment) and 3 paralleled improving ENL in five of seven patients. Between weeks 3 and 7, however, two of five group A patients (four weeks after completion of treatment with thalidomide) had increased levels of IL-6. In contrast, both group B patients had undetectable levels of IL-6 at weeks 3 and 7, a finding that may have reflected the longer gradual thalidomide taper in group B.

For neopterin, a pteridine by-product released from IFN-γ-stimulated macrophages, values were persistently elevated in both treatment groups through week 7, regardless of clinical response. This finding supports the notion of the specificity of thalidomide, with little effect on the general inflammatory milieu. Elevated erythrocyte sedimentation rates at enrollment that persisted through week 7, regardless of treatment group or clinical response, also supported this contention and underscored the chronic inflammatory nature of ENL. Some LPA responses were notable, especially in group B, with pre-treatment hyporesponsiveness becoming normalized or hyper-responsive during therapy. Improved re-

**Figure 3.** Serum concentrations of interleukin-6 (IL-6) in group A and B patients. Connected symbol sets from left to right represent weeks 0 (pre-treatment), 3, and 7, respectively. All patients were complete (c) or partial (p) treatment responders at weeks 1 and 7.
sponsiveness may have reflected resolving ENL or the enhancement of T cell responsiveness by thalidomide.\textsuperscript{28,29}

In 2003, there were approximately 500,000 reported new leprosy diagnoses worldwide, many at risk for developing ENL.\textsuperscript{1,16} Despite the teratogenicity and other toxicities of thalidomide, the drug offers an effective treatment of this serious condition that merits further study to establish improved regimens, especially for tapering. Efforts to produce thalidomide analogs that maintain anti-inflammatory properties, but without drowsiness or teratogenic effects, are ongoing,\textsuperscript{30} and would be a welcome addition for management of ENL.

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