Thalidomide Treatment for Prurigo Nodularis in Human Immunodeficiency Virus–Infected Subjects

Efficacy and Risk of Neuropathy

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Objective: To evaluate safety and efficacy of thalidomide in the treatment of prurigo nodularis in a group of human immunodeficiency virus (HIV)–infected patients whose condition was recalcitrant to standard treatment.

Design: Prospective study.

Setting: Outpatient dermatology and neurology clinic, both referral settings.

Patients: Eight HIV-infected patients with refractory prurigo nodularis; a total of 10 met inclusion criteria, but 2 could not be followed up.

Interventions: Treatment with thalidomide, 100 mg/d. Subjects were randomized after 1 month to receive 100 or 200 mg/d. If side effects were noted, the drug was reduced to a tolerable dose or discontinued. Subjects were monitored at baseline and monthly for degree of pruritus and total area of body involvement of prurigo nodularis. Sequential neurologic assessments were performed.

Main Outcome Measures: Efficacy and toxic effects.

Results: The dosage of thalidomide ranged from 33 to 200 mg/d. Eight subjects had a greater than 50% response in reduction of itch over 3.4 months (average). Seven subjects had a greater than 50% reduction of skin involvement over 5 months (average). Three subjects developed thalidomide peripheral neuropathy (TPN). There was no correlation between duration of treatment, daily or cumulative dose, and TPN. A change in the Neuropathy Impairment Score of 10 points was a good marker of TPN, as was a greater than 50% decrease in the sural sensory nerve action potential amplitude.

Conclusions: Thalidomide reduced the signs and symptoms of prurigo nodularis in HIV-infected subjects. One third of subjects developed TPN, underscoring the importance of careful neurologic assessment.

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PRURIGO NODULARIS (PN) IS A chronic dermatosis of unknown etiology characterized by discrete, intensely pruritic, symmetric, papulonodular lesions primarily on the extensor surfaces of the extremities.1,2 It may occur in human immunodeficiency virus (HIV) disease.3-5 The standard treatment of PN includes antihistamines, ultraviolet light, and topical and systemic corticosteroids.6-9 The treatment of PN in the context of HIV infection is particularly challenging given the recalcitrant nature of the skin disease and possible risk of immunosuppressive therapy in these subjects.

Thalidomide has been used to treat refractory PN in non–HIV-infected subjects and 2 HIV-infected subjects.3,4 In HIV-infected subjects, thalidomide has been used to treat cachexia10,11 and oral aphtous ulcers.12 Thalidomide is associated with teratogenicity (phocomelia),13-15 peripheral neuropathy,16-20 and drug reactions.21-23 Because drug reactions and peripheral neuropathies are prevalent in HIV-infected subjects24 and because peripheral neuropathies have been reported in up to 70% of immunocompetent patients with PN,25-27 this study is particularly relevant in examining the efficacy and safety of thalidomide in a group of HIV-infected individuals with PN.

METHODS

From August 1, 1995, to September 30, 1997, 15 HIV-infected subjects with biopsy-proved PN, refractory to standard treatment, were screened for the study. The standard therapies included combination therapy with oral antihistamines, potent topical corticosteroids, and ultraviolet light therapy for a duration of at least 3 months. This study was approved by the University of California, San Francisco, Committee for Human Research.
The use of thalidomide (Andrusis Pharmaceuticals Corp, Beltsville, Md) was approved through the Food and Drug Administration investigation for new drug classification. Informed consent was obtained. Women of reproductive potential were included in this study if they agreed to use 2 forms of birth control and undergo baseline and monthly serum pregnancy testing. Exclusion criteria included ongoing treatment with prednisone or chemotherapeutic agents. Subjects were excluded from receiving thalidomide on the basis of results of their neurologic examination if they had a preexisting polyneuropathy that was greater than grade 1 (mild) according to the AIDS Clinical Trials Group (ACTG) protocol 251.20 Grade 1 neuropathy was defined as preserved ability to walk on the toes and heels, decreased or absent ankle reflexes, and/or mild impairment of sensation in the toes.

The baseline dermatologic evaluation included a rating of the total body area of PN involvement according to the modified neuropathy target symptom questionnaire (NIS).20 This scale measures total body area involvement of erythema, excoriations, nodularity, and pigment changes. Subjects were given a questionnaire evaluating their level of pruritus based on a visual analog 10-point scale. Complete blood cell count, liver function tests, CD4 count, and serum pregnancy tests when applicable were obtained at baseline and monthly thereafter. Baseline weights and photographs were taken.

Subjects received thalidomide, 100 mg/d for 1 month, and then were randomized to receive 100 or 200 mg/d. They were seen by a dermatologist (T.B. or T.M.) every month for evaluation (psoriasis area and severity index and visual analog score). Thalidomide toxicity, including drug reaction, sedation, constipation, weight gain, mood change, and neuropathy symptoms, was monitored. If side effects were noted, the drug was reduced to a tolerable dose or discontinued.

The neurologic assessment was performed by a neurologist (A.P.) at baseline and every 3 months or earlier if neuropathy symptoms developed. The neurologic assessment included the Neuropathy Targeted Symptom Questionnaire, a complete neurologic examination, and nerve conduction studies. The Neuropathy Targeted Symptom Questionnaire is a 10-point symptom scale for pain, paresthesia, numbness, and weakness in the arms and legs. The neurologic examination was quantified by means of the ACTG 231 neurologic grading scale and a modified version of the Neuropathy Impairment Score (NIS).20 The former grades sensory, motor, neuropsychiatric, and cerebellar signs from 1 (mild) to 4 (severe). The modified NIS is a 132-point scale based on peripheral sensory, motor, and reflex changes in the distal upper and lower extremities. The nerve conduction studies of the sural, superficial peroneal, median, and ulnar sensory nerves and peroneal motor nerves were performed on the same side at each visit, with the use of standard techniques. Limb temperature was maintained above 31°C in the lower extremity and 32°C in the upper extremity. The baseline nerve conduction study values were compared with normal age-controlled values for our laboratory in determining the presence of an underlying neuropathy. A significant change in serial studies was considered to be a greater than 50% decrease in response amplitude compared with baseline.21 Thalidomide neuropathy was determined by the development of acute symptoms and changes on clinical examination and nerve conduction studies that could not be accounted for by other factors, including medications, progression of AIDS neuropathy, and nutritional factors.

Fifteen subjects were examined for participation in the study. Five subjects were excluded: 1 had a peripheral neuropathy greater than grade 1, 1 refused birth control, 1 died of urosepsis before the neurologic assessment, and 2 subjects refused neurologic assessment. In addition, 2 subjects had baseline dermatologic and neurologic assessments but dropped out of the study after 1 month of study drug treatment. One subject had a 1-month dermatologic assessment but discontinued the drug because of flulike symptoms. He had no neurologic follow-up but did not have symptoms of neuropathy. The second subject who dropped out was admitted to the hospital for severe constipation, and thalidomide was discontinued. This patient died within 3 weeks of probable Mycobacterium avium complex infection, without a follow-up dermatologic or neurologic assessment, and was therefore excluded from the follow-up analysis.

Among the 10 included subjects, 8 were African American or Native American. One patient was white and one was Asian. Two of the subjects were female. The age range was 37 to 65 years. The mode of transmission for HIV was intravenous drug use for 5 of the 10 subjects. The remaining 5 subjects were homosexual. In 8 subjects, the diagnosis of AIDS was based on a history of opportunistic infection or a CD4 count less than 200/mm³ at the time of recruitment to the study. The average CD4 count was 53/mm³ (range, 0-374/mm³).

Subjects received thalidomide, 100 mg/d for 1 month, and then were randomized to receive 100 or 200 mg/d. They were seen by a dermatologist (T.B. or T.M.) every month for evaluation (psoriasis area and severity index and visual analog score). Thalidomide toxicity, including drug reaction, sedation, constipation, weight gain, mood change, and neuropathy symptoms, was monitored. If side effects were noted, the drug was reduced to a tolerable dose or discontinued.

Of the 8 subjects who took thalidomide for longer than 1 month, all had a greater than 50% subjective response on the visual analog scale. Seven of the 8 had a greater than 50% objective response on the psoriasis area and severity index. The eighth subject had a 25% to 50% objective response. The time to a greater than 50% subjective response ranged between 1 and 9 months (average, 3.4 months; mode, 4 months), and the cumulative dose of thalidomide ranged from 3 to 18 g (average, 8.1 g). The 7 subjects who achieved a greater than 50% objective response were treated for 2 to 13 months (average, 5 months) with a cumulative dose of thalidomide of 3 to 15 g (average, 11.8 g). The onset of improvement was noted between 1 and 3 months, beginning with a decrease in the number of excoriations. Erythema and the size of prurigo nodules decreased significantly between 3 and 6 months of treatment. Pigment changes were the last to resolve, from 8 to 16 months of treatment. All subjects were able to discontinue their antihistamine and topical corticosteroids. Subjective changes preceded objective changes by 1 to 2 months. There was no correlation between thalidomide dose and responses. Four subjects were followed up for 1.5 to 9.5 months after the thalidomide treatment was discontinued. Three subjects maintained a greater than 50% objective response, whereas the fourth reverted to his original scores at entry to the study.

Protease inhibitors were started in 6 of the subjects, 4 to 6 months after enrollment. Only 1 subject entered the study while taking protease inhibitors. There was no consistent pattern of improvement or worsening of skin findings with the addition of protease inhibitors. Even when patients discontinued their thalidomide treatment and continued taking proteases, there was no consistent pattern of improvement or worsening of skin findings. Three subjects with CD4 counts less than 200/
mm$^3$ developed opportunistic infections while in the study. There was no correlation between thalidomide treatment and CD4 count. Seven of the 8 subjects gained an average of 7.7 kg during the study period. Other side effects in our subjects included constipation in 4, initial mild to moderate sedation in 5, and mild to moderate mood change in 3, which was not further classified. One subject who had a psychiatric history had an episode of acute psychosis requiring hospitalization. Her thalidomide treatment was discontinued at that time. This same patient also reported short-term memory loss for 3 months before the psychotic episode. She was examined 6 weeks after thalidomide was discontinued and no longer reported memory difficulties. She was not taking psychiatric medications at this time. All of our study subjects took thalidomide at bedtime, with minimal, transient daytime sedation. Complete blood cell counts and results of liver function tests were similar to baseline values. Drug reactions were not observed.

At baseline, 2 of 8 subjects had a mild generalized peripheral neuropathy and 2 had carpal tunnel syndrome. The duration of neurologic follow-up ranged from 1 month to 2 years. Three subjects developed thalidomide peripheral neuropathy (TPN), 1 of whom had a baseline neuropathy. Their ages were 41, 47, and 53 years. Two developed TPN within 1 month, the other at 7 months. There was no correlation between cumulative dose and development of TPN. Complaints of new numbness, tingling, or pain were always present with the development of TPN, as was an increase in the Neuropathy Targeted Symptom Questionnaire score and the ACTG grading scale. All subjects who developed TPN had an increase of at least 10 points on the NIS and a decrease of more than 50% in sural sensory nerve action potential (SNAP) amplitude, with the exception of 1 subject who had an absent sural response at baseline. The severity of the neuropathy ranged from an NIS of 14 or ACTG grading scale score of 2 (loss of sensation in the feet and hands) to an NIS of 24 or ACTG grading scale score of 3 (loss of sensation in the feet and hands and loss or reduction of deep-tendon reflexes). None of the subjects with thalidomide neuropathy had disabling pain, weakness, or significant loss of function due to their neuropathy.

One other subject developed possible TPN at 5 months, with an increase in NIS of 6 points (sensory only) without a significant decrease in sural SNAP. Thalidomide was discontinued at that time because of psychiatric difficulties. Three subjects remained neuropathy free after 1 year because of psychiatric difficulties. Three subjects had a psychiatric history and were taking antiretroviral therapy. The sural SNAP did not recover in any of these subjects. Thalidomide was restarted at a lower dose in 2 of these subjects without progression of the neuropathy.

Thalidomide for the treatment of refractory PN in HIV is well tolerated and effective. The effective dosage of thalidomide (average, 100 mg/d), the time to response (average, 5 months), and the period of remission after treatment (average, 5 months) are similar to findings in preliminary studies. There is no correlation between daily or cumulative doses of thalidomide and response. Even low-dose thalidomide is effective, a pattern that appears to be consistent in other dermatologic diseases.

The pathogenesis of PN, particularly in HIV, is unclear and thought to be multifactorial. In our HIV clinics in San Francisco, 18% of the patients are African American or Native American. Eighty percent of the study subjects were African American or Native American, which may support a mechanism of genetic susceptibility. Most of our subjects had CD4 counts less than 100/mm$^3$, which may suggest that dysregulation of T-cell subsets specific to HIV disease plays a role.

The major adverse effect of thalidomide, other than neurotoxicity, is teratogenicity. The women in our study who were of reproductive potential were carefully monitored with regard to birth control. Weight gain and constipation are noted side effects but were generally well tolerated. There are reports of sedation and cognitive and mood changes in patients taking thalidomide. These side effects were noted in some of our patients. In addition, it is unclear what effect thalidomide might have on preexisting psychiatric conditions. Drug reactions, including toxic epidermal necrolysis, are reported with thalidomide but were not seen in this study. A recent review of thalidomide for the treatment of multiple myeloma cautions that thalidomide combined with dexamethasone or drugs known to cause toxic epidermal necrolysis can result in severe skin reactions. There is evidence of increased HIV replication in HIV-infected patients with aphthous ulcers who took thalidomide. CD4 counts did not change significantly while our subjects were taking thalidomide. Viral loads were not measured in our subjects because this was outside the standard of practice at the time of the study.

Thalidomide peripheral neuropathy developed in one third of our subjects, characterized by the acute onset of a distal, symmetric, axonal sensory neuropathy, with loss or reduction of lower-extremity reflexes and sparing of the hands, similar to TPN in non–HIV-infected subjects. Motor findings and painful dysesthesias are described with prolonged use, which were likely prevented in our cohort by careful monitoring and rapid adjustment of thalidomide dosing with the onset of TPN. The acute onset of symptoms and signs followed by stabilization or improvement of neuropathy with reduction in thalidomide dosage enabled distinction of TPN from AIDS neuropathy.

There was no association between duration of treatment, daily dosage, or cumulative dose and the development of neuropathy. Bastuji-Garin et al noted an in-

Guidelines for Thalidomide Therapy in Prurigo Nodularis

1. Document failure of conservative therapy with high-potency topical corticosteroids, intralesional corticosteroids, antihistamines, or UV light therapy.
2. Perform baseline neurologic examination to include complete neurologic history and physical examination (including evaluation of other risk factors for neuropathy), modified Neuropathy Impairment Score (NIS),23 and sural nerve conduction studies (NCS). If sural nerve response is absent, consider median and ulnar antidromic sensory NCS. Patients with a preexisting neuropathy should receive thalidomide only with careful neurologic monitoring every 3 mo or sooner if symptomatic.
3. Provide comprehensive counseling on risks and benefits of thalidomide therapy including discussion of contraceptive methods.
5. Follow pregnancy testing and contraceptive guidelines if applicable.
6. Monitor patient within 2 wk of starting thalidomide regarding drug reactions, sedation, constipation, and pregnancy testing (if applicable).
7. Monitor patient within 1 mo of starting thalidomide and every month thereafter for (a) pregnancy testing if applicable, (b) drug reactions, (c) subjective/objective changes of prurigo nodularis, adjusting dose of thalidomide according to side effects (sedation, weight changes, constipation, mood swings), and (d) subjective neurologic changes (if change noted, patient receives full neurologic examination).
8. Perform neurologic examination to include direct history, modified NIS, and sural NCS every 6 mo (or median and ulnar sensory NCS if baseline sural NCS absent) or with the development of any new neurologic symptoms.
9. If skin findings improve (Δ>50% subjective change in pruritus and Δ>50% objective change in excoriations, erythema, size of nodules, and pigment), consider drug holiday and monitor monthly for recurrence of disease.

creased incidence of neuropathy with dosages greater than 75 mg/d in a prospective study of 135 dermatologic patients treated with thalidomide. Our patients were randomized to receive 100 or 200 mg/d, so we were not able to assess the development of neuropathy with lower-dose thalidomide. Consistent with the series by Bastuji-Garin et al, we did not see an association with duration of treatment or cumulative dose. They excluded patients treated for less than 1 mo from their study. Two of our patients with TPN developed symptoms at less than 4 wk. Increased age is suggested as a predisposing factor42 but was not observed in our study or the study by Bastuji-Garin et al.42 Incomplete improvement of the neuropathy with termination of thalidomide treatment supports the view that TPN is a nonneuropathy.18,19,27,43 None of our subjects was disabled by residual neuropathy. Thalidomide can be successfully restarted or reduced with careful monitoring of the noted side effects, thalidomide shows promise as an effective medication in HIV-infected patients with PN.

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