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.

Arch Dermatol. 2004;140:845-849

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 aphthous ulcers.12 Thalidomide is associated with teratogenicity (phocomelia),13-15 peripheral neuropathy,16-20 and drug reactions.10,21-23 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

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The use of thalidomide (Andrus 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 251.28 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 psoriasis area and severity index.29 This scale measures total body area involvement of PN according to the modified PSII. The total body area of PN involvement was determined by a dermatologist, and the severity of PN involvement was graded from 1 (mild) to 4 (severe). The modified PSII was used to evaluate the extent of PN involvement in this study.

RESULTS

All 10 subjects had had PN recalcitrant to standard therapy for at least 1 year. Subjects were treated from 1 to 23 months (average, 8 months). Cumulative doses of thalidomide ranged from 3 to 41.75 g (average, 21.7 g). Daily dosages of thalidomide ranged from 33 to 200 mg/d.

Of the 8 subjects who took thalidomide for longer than 1 month, all had at least 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/
mm³ 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 with a maximum duration of treatment of 17 months. The NIS and sural SNAP did not change in subjects who did not develop TPN. Results of upper-extremity sensory and peroneal motor nerve conduction studies did not change significantly with the development of TPN.

In the 3 subjects who developed TPN, thalidomide was discontinued. One subject's condition continued to worsen slightly during the next month. Two of the subjects were taking antiretroviral treatment (1 with lamivudine and 1 with stavudine) when they developed neuropathy. All of the subjects improved symptomatically and by NIS within 2 to 8 months after cessation of the thalidomide treatment and without modification of their 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.

**COMMENT**

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/mm³, 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 dysesthasias 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-
increased 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 month from their study. Two of our patients with TPN developed symptoms at less than 4 weeks. Increased age is suggested as a predisposing factor but was not observed in our study or the study by Bastuji-Garin et al. Incomplete improvement of the neuropathy with termination of thalidomide treatment supports the view that TPN is a neuronopathy.

As in previous reports, the sural SNAP amplitude was the most sensitive neurophysiologic marker of TPN in our study. When the sural response was absent at baseline, we relied on symptoms and the NIS.

The incidence of TPN in published reports is extremely variable, from less than 1% in subjects with erythema nodosum leprosum, cutaneous lupus erythematosus, and Behcet disease to greater than 70% in non-HIV-infected patients with PN. Thalidomide use in subjects with AIDS who have aphthous ulcers and wasting syndrome has not been reported to result in TPN.

In contrast, Wulff et al suggested that with long-term treatment (1-6 years) in PN, all subjects develop signs of neuropathy. The relatively high incidence of TPN in our subjects may reflect an increased risk in PN rather than HIV infection. The presence of AIDS neuropathy did not clearly increase the risk of TPN in our cohort.

Thalidomide’s mechanism of action and increased neurotoxicity in PN could be related to an abnormal interaction between the peripheral nervous and immune systems. Nerves containing substance P can stimulate histamine release from mast cells. Skin biopsy specimens of PN show an increased number of mast cells in the dermis and epidermis. The mast cells lie close to or in contact with nerve fibers in the dermis. This close anatomic relationship is not seen in controls.

A change in the NIS of 10 points was a good marker of TPN. Neither the Neuropathy Targeted Symptom Questionnaire, which is a subjective scale, nor the ACTG grading scale, which is not specific for neuropathy, correlated completely with the presence of neuropathy. A combination of symptoms, careful neurologic examination, and nerve conduction studies was helpful to accurately monitor for TPN in this subject population.

An important limitation of the study is that it was an uncontrolled case series. Prurigo nodularis in HIV infection is uncommon and, in this patient population, is refractory to all other treatments, making it difficult to enroll patients to receive placebo. While we were able to randomize for dose of thalidomide, blinding for placebo is difficult because of the sedating effect of the drug. Another limitation is that the grading of pruritus is subjective and scales have not been validated in large studies. Lesion characteristics of PN allow us to develop an objective rating scale. An additional limitation was that protease inhibitors were just being introduced at the time of this study. While we could not find a consistent pattern of improvement or worsening of skin findings with the protease inhibitors, it is not clear what the contribution would have been if these patients had been followed up for a long period during treatment with the protease inhibitors alone or in combination with thalidomide.

This study has helped us to develop guidelines pertinent to thalidomide use in this special patient population. With careful monitoring of the noted side effects, thalidomide shows promise as an effective medication in HIV-infected patients with PN.

Accepted for publication November 20, 2003.

Thalidomide for this study was provided by Andrus Pharmaceuticals Corp.

We acknowledge Joanna Badger, MD, and Karen Legarre, MD, who were participating investigators; and Kate Shaw, MD, Catherine Hoffman, MD, Ziqiang Wong, MD, Judith Han, MD, and Ursula Dorsch, MD, who assisted in data analysis. We thank Michael Aminoff, MD, for his careful review of the manuscript.

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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), 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 1 mo 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 (>50% subjective change in pruritus and >50% objective change in excoriations, erythema, size of nodules, and pigment), consider drug holiday and monitor monthly for recurrence of disease. |