ORIGINAL ARTICLE

Treatment of idiopathic prurigo nodularis in Taiwanese patients with low-dose thalidomide

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ABSTRACT

Prurigo nodularis is an intensely pruritic dermatosis characterized by lichenified and excoriated papules and nodules. The course of prurigo nodularis is often chronic, and some patients respond very poorly to the standard therapeutic modalities. Because the pathogenesis of this disease remains obscure, the treatment of prurigo nodularis can be disappointing and frustrating for both the patients and physicians. Thalidomide, a tumor necrosis factor-alpha antagonist, has been suggested as an alternative treatment option for recalcitrant prurigo nodularis. In the past, the regimen for treatment of prurigo nodularis often required thalidomide at 200 mg/day. We recruited patients with intractable prurigo nodularis and treated them with low-dose thalidomide. Six patients with idiopathic prurigo nodularis were successfully treated with low-dose thalidomide (50–100 mg/day) without clinical development of peripheral neuropathy. In summary, our preliminary results suggest that low-dose thalidomide may be a safe and effective treatment option for patients with recalcitrant idiopathic prurigo nodularis.

Key words: low-dose thalidomide, prurigo nodularis, Taiwanese.

INTRODUCTION

Hardaway first described a pruritic skin disease characterized by multiple skin tumors in 1880.1 The condition was later named by Hyde as prurigo nodularis (PN).2 PN is characterized by intensely pruritic, lichenified or excoriated papules and nodules. The lesions are usually grouped and numerous, often found over the extensor surfaces of the extremities. There is a tendency for symmetrical distribution, and no part of body is exempt from development of PN.3 This disease most often begins during middle age, has a long duration and more commonly affects women than men.4 PN is assumed to be a cutaneous response to repeated physical manipulation, such as scratching and rubbing, following pruritus of various etiologies. Although PN has been associated with various systemic conditions, including atopic dermatitis, diabetes mellitus and chronic renal failure, the exact cause of PN remains obscure. As the pathogenesis of PN is unclear, the treatment of PN is often disappointing and frustrating for both the patients and the physicians.

In 1973, Sheskin reported successful treatment of PN with thalidomide.5 Thalidomide inhibits polymorphonuclear leukocyte chemotaxis6 and selectively inhibits tumor necrosis factor-alpha (TNF-α) production by enhancing degradation of TNF-α mRNA.7,8 There have been reports indicating that thalidomide at 200 mg daily induced improvement on pruritus and flattening of lesions in PN patients with no serious adverse events.9,10

In this study, we documented the clinical responses of PN to low-dose thalidomide in six Taiwanese
patients and propose that low-dose thalidomide should be considered for patients with recalcitrant PN.

MATERIALS AND METHODS

Subjects
Patients with biopsy-proven PN, refractory to standard treatment, were recruited for thalidomide treatment. The standard therapeutic regimen included combination therapy with oral antihistamines, potent topical corticosteroids and ultraviolet light therapy for a duration of at least 3 months. The associated risks of thalidomide were thoroughly related to the prospective patients. Before thalidomide treatment, informed consent was obtained. Because the clinical experiences of using thalidomide for treating PN in Taiwanese patient were limited, we imposed a strict exclusion criterion on our patient selection. Women of reproductive potential were excluded from our study. Other exclusion criteria included the presence of active systemic diseases with the exception of hypertension. Thalidomide was given starting at 100 mg per day. The treatment protocol was then tailored according to the clinical response. No topical medication was given but use of non-medicated emollient was allowed. During the follow-up visits, the clinician was vigilant about the presence of adverse effects, paying particular attention to possible neuropathy. For clinical evaluation, the overall condition of PN was scored during regular outpatient visits, using the following 6-point scale: (0) no lesions; (1+) incomplete flatness evident; (2+) still some nodules remaining; (3+) marked nodularity but no excoriations; (4+) extensive number and nodularity with excoriations; and (–) worse with new lesion occurrence.

RESULTS

Six patients with idiopathic PN were included in our clinical study. The detailed background information of the patients is shown in Table 1. The first patient was a 76-year-old woman with no systemic disease except hypertension. She had visited our outpatient department for more than 3 years with no obvious improvement in her condition. Thalidomide was given at 100 mg/day for 10 days. Due to excessive drowsiness, the dosage of thalidomide was decreased to 50 mg/day. The patient reported reduction in pruritus 6 weeks after thalidomide regimen. Twelve weeks after initiation of thalidomide, the patient showed dramatic improvement in pruritus and skin lesions (Fig. 1). As the clinical condition ameliorated, the dose of thalidomide was tapered to 25 mg/day. No evidence of peripheral neuropathy was observed 15 months after the initiation of therapy. Currently, the patient is free of recurrence 20 months after cessation of thalidomide. The second patient was a 48-year-old man. He had no remarkable medical history except for being a hepatitis B carrier. He had visited our department for more than 2 years without obvious improvement in his condition. One particularly disturbing aspect of his condition was that besides intractable pruritus, the distribution of his lesions was generalized, with prominent facial involvement. The patient received thalidomide at 100 mg/day for 5 weeks. The dosage of medication was tapered to 50 mg/day due to clinical response and sedative effect associated with thalidomide. At 6 weeks after initiation of treatment, the condition of this patient showed remarkable improvement (Fig. 2). No evidence of neuropathy was observed 4 months after initiation of therapy. The patient is currently in remission 18 months after cessation of thalidomide therapy. The third patient was a 40-year-old man with recalcitrant PN for approximately 2 years. He had no remarkable medical history. The excessive pruritus and extensive excoriated nodular lesions over his hands had prevented this patient from...
from enjoying regular social activities. The patient received thalidomide 100 mg/day for 6 weeks and experienced much improvement in pruritus and excoriation of skin lesions (Fig. 3). Thalidomide was tapered to 50 mg/day 2 weeks later due to improvement in clinical condition. No evidence of neuropathy was noted 5 months after beginning of therapy. Subsequently, the patient was lost during follow up.

The fourth patient was an 86-year-old man with extensive, generalized PN for more than 9 years. He had an atopic constitution and had had several bouts of severe atopic dermatitis in his younger years. The patient was otherwise healthy with no remarkable medical history. He had received various treatment modalities and visited numerous dermatologists for his condition but the PN lesions persisted. Thalidomide was given at 100 mg/day for more than 9 years. He had an atopic constitution and had had several bouts of severe atopic dermatitis in his younger years. The patient was otherwise healthy with no remarkable medical history. He had received various treatment modalities and visited numerous dermatologists for his condition but the PN lesions persisted. Thalidomide was given at 100 mg/day for 10 weeks. Marked improvement was noted with reduction in pruritus and flattening of lesions. However, this man developed generalized erythema with bilateral lower leg edema 10 weeks into thalidomide regimen. No underlying cause except for thalidomide was found to be associated with the newly developed condition. Thalidomide was reduced to 50 mg/day. Three weeks later, the erythema and leg edema resolved without further intervention, and 1 week later, the patient stopped medication altogether. At present, the patient is off thalidomide for 3 months with no signs of relapse. The fifth patient was a 53-year-old woman with generalized PN for approximately 6 years. The patient had a history of atopic dermatitis with intermittent flares. Her intractable PN developed after the menopausal period. The patient had no other remarkable medical history. Thalidomide was given at 100 mg/day. Three weeks after medication, the patient reported improvement in pruritus, and excoriation of the skin lesions were markedly reduced. After 7 weeks of thalidomide at 100 mg/day, the patient stopped further medication due to resolution of clinical condition. However, the patient returned to our clinic 8 weeks after cessation of thalidomide due to recurrence of PN. Thalidomide 100 mg/day was given. Six weeks after second course of treatment, the patient again experienced disease remission. No evidence of neuropathy was observed throughout the course of treatment. Currently, the patient has experienced no recurrence for 4 months after stopping thalidomide therapy. The sixth patient was a 55-year-old man with progressive PN for 4 months. He had no other remarkable medical conditions. Despite conventional

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**Figure 2.** (a) A 48-year-old man with generalized intractable PN. Involvement of face was particularly disturbing for this patient. (b) Reduced pruritus and flattening of skin lesions were noted 6 weeks after thalidomide regimen (100 mg/day for 5 weeks; followed by 50 mg/day for 1 week).

**Figure 3.** A 40-year-old man with recalcitrant PN. Excessive pruritus and excoriations over bilateral hands was interfering with this patient’s social activities. (b) Improvement in pruritus and excoriations were noted 6 weeks after thalidomide treatment (100 mg/day for 6 weeks).
therapy, the number and size of his skin lesions continue to increase. The pruritus was intractable. Four weeks after receiving thalidomide 100 mg/day, the patient reported prominent reduction in pruritus, and flattening of skin lesions were also observed. Two weeks later, the patient was satisfied with the treatment results and stopped the thalidomide regimen. Currently, the patient has remained in a disease-free condition for 6 weeks without medication. No evidence of neuropathy was observed.

The summary of the clinical response is presented in Table 1.

**DISCUSSION**

Thalidomide was first introduced in West Germany during the 1950s as a sedative with little side-effects. However, by 1960, it became clear that long-term thalidomide use was associated with polyneuritis and rare congenital abnormalities such as phocomelia. In mid-1961, thalidomide was withdrawn from the world market due to the increasing numbers of congenital deformities. In 1965, thalidomide was used as a sedative for treating “lepra suffering”. Subsequently, thalidomide has been considered as an effective treatment modality for erythema nodosum leprosum (ENL). In 1998, thalidomide was approved by the US Food and Drug Administration (FDA) for ENL and is classified as an orphan drug. The orphan drug status has led to its use in many currently unapproved dermatological conditions that are refractory to other medications. Among the conditions described above, discoid lupus erythematosus, PN, Behcet's disease, oral aphthosis, pyoderma gangrenosum, actinic prurigo, infiltration of Jessner–Kanof, sarcoidosis, and recurrent erythema multiforme have been reported to show favorable responses to thalidomide. Since the initial report

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age</th>
<th>Sex</th>
<th>IgE level (IU/mL)</th>
<th>Pre-treatment score/duration of prurigo nodularis</th>
<th>Post-treatment score/duration of treatment</th>
<th>Recurrence</th>
<th>Notable side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>76</td>
<td>Female</td>
<td>36.0</td>
<td>4+/−3 years</td>
<td>0/12 weeks</td>
<td>No recurrence 20 months after cessation of thalidomide</td>
<td>Sedation</td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>Male</td>
<td>92.8</td>
<td>4+/−3+/−2 years</td>
<td>1+/6 weeks</td>
<td>No recurrence 18 months after cessation of thalidomide</td>
<td>Sedation</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>Male</td>
<td>13.1</td>
<td>4+/2 years</td>
<td>2+/6 weeks</td>
<td>Lost during follow-up</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>86</td>
<td>Male</td>
<td>287.3</td>
<td>4+/−9 years</td>
<td>1+/10 weeks</td>
<td>No recurrence 3 months after cessation of thalidomide</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>53</td>
<td>Female</td>
<td>780.5</td>
<td>4+/6 years</td>
<td>1+/6 weeks</td>
<td>Recurrence 8 weeks after cessation of thalidomide</td>
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</tr>
<tr>
<td>6</td>
<td>55</td>
<td>Male</td>
<td>82.2</td>
<td>3+/4 months</td>
<td>0−1+/6 weeks</td>
<td>No recurrence weeks after cessation of thalidomide</td>
<td>None</td>
</tr>
</tbody>
</table>

For clinical evaluation, the overall condition of prurigo nodularis was scored during regular outpatient visits, using the following 6-point scale: (0) no lesions; (1+) incomplete flatness evident; (2+) still some nodules remaining; (3+) marked nodularity but no excoriations; (4+) extensive number and nodularity with excoriations; and (−) worse with new lesion occurrence. IgE, immunoglobulin E.
by Sheskin in 1975,12 additional studies have reported cases supporting the effect of thalidomide on PN. There have been cases where oral thalidomide at 200 mg/day demonstrated improvement of pruritus and flattening of skin lesions with no serious side-effects.9,10 Another case series demonstrated that low-dose thalidomide (100–200 mg/day) improved but was not able to induce remission in PN patients.20 Contrary to the previous reports, our PN patients showed rapid and favorable responses to low-dose thalidomide treatment (50–100 mg/day). This phenomenon has important clinical implications. It is well-known that peripheral neuropathy is an important adverse-effect associated with thalidomide.21 It was reported that while thalidomide-associated neuropathy has no relation to the total cumulative dose of the drug,22 the risk of neuropathy was related to the daily dose regardless of duration of treatment.23 In fact, no neuropathy was detected in case series in which the patients received thalidomide 25 mg or less per day.23 We did not find neuropathy in our patients treated with thalidomide, even after taking the drug for more than 1 year. Therefore, low-dose thalidomide may be an effective and safe treatment option for patients with recalcitrant idiopathic PN. It should be pointed out here that although low-dose thalidomide may induce rapid and favorable clinical response, patients who withdraw from the medication abruptly may experience disease recurrence as seen in the fourth patient. Thalidomide given at the same dosage was able to control the disease flare in a reasonable amount of time for this patient, therefore the initial clinical response to low-dose thalidomide was confirmed.

Several hypotheses have been proposed as the mechanisms on how thalidomide imparts its therapeutic effects on PN. Thalidomide has been suggested to have a local effect on proliferating neural tissue in PN.10 The central effect of thalidomide may be the secondary peripheral neuropathy and sedation. The sedative effect of thalidomide is unlikely to play a major role in its therapeutic success as other sedatives do not control PN related pruritus well. Another possible mechanism involves regulation of TNF-α because thalidomide is a known TNF-α antagonist. TNF-α is an important inflammatory modulator and activator of nuclear factor kappa-B (NF-κB). Previous studies have shown that in psoriatic skin where the expression of TNF-α is prominent, hyperplasia of the epidermis is observed.24 In addition, topical application of NF-κB activator has been shown to induce epidermal thickening.25 Therefore, it is possible that the pathogenesis of PN involves dysregulation of NF-κB pathway, resulting in prominent epidermal hyperplasia. Moreover, because thalidomide is a suppressor for TNF-α, modulation of NF-κB cascade via inhibition of TNF-α by thalidomide may contribute to its therapeutic effect on PN. It should be pointed out that the reduction in pruritus seemed to occur prior to the flattening of skin lesions in our patients, as described in the result section. However, it is difficult to assess whether the flattening of skin lesions were induced exclusively by either reduced scratching behavior or immune modulatory action imposed by thalidomide. It is more likely that both mechanisms contribute to the improvement of skin lesions. Further investigations are warranted to elucidate the mechanisms involved in the flattening of PN induced by thalidomide.

In summary, we have shown that low-dose thalidomide may be an effective and safe therapeutic modality for treating idiopathic PN. In our patients, despite the relatively low dose given, excessive sedation was still the most commonly encountered side-effect but peripheral neuropathy was not observed. It should be noted that one of our patients developed transient generalized erythema and leg edema which resolved within 3 weeks without withdrawing from thalidomide completely. It remains to be determined whether different patient subgroups (i.e. with different underlying systemic diseases) respond differently to low-dose thalidomide treatment and whether thalidomide should be withdrawn completely once clinical response is obtained. Future studies comprising a larger patient group with more complex study protocols are warranted to address these important questions.

REFERENCES

