Thalidomide: dermatological indications, mechanisms of action and side-effects

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Summary

Thalidomide was first introduced in the 1950s as a sedative but was quickly removed from the market after it was linked to cases of severe birth defects. However, it has since made a remarkable comeback for the U.S. Food and Drug Administration-approved use in the treatment of erythema nodosum leprosum. Further, it has shown its effectiveness in unresponsive dermatological conditions such as actinic prurigo, adult Langerhans cell histiocytosis, aphthous stomatitis, Behçet’s syndrome, graft-versus-host disease, cutaneous sarcoidosis, erythema multiforme, Jessner–Kanof lymphocytic infiltration of the skin, Kaposi sarcoma, lichen planus, lupus erythematosus, melanoma, prurigo nodularis, pyoderma gangrenosum and uraemic pruritus. This article reviews the history, pharmacology, mechanism of action, clinical uses and adverse effects of thalidomide.

Thalidomide was first synthesized in West Germany in 1954 and was introduced to the German market as Contergan in 1956 as an over-the-counter medication.1 Two years later it was marketed to other industrialized nations. In the U.K. it was known as Distaval. It was thought to be one of the safest sedatives ever produced as it was effective in small doses, was not addictive, and did not have acute side-effects such as motor impairment.2,3 Accidental overdosing or deliberate suicide attempts at doses as high as 14 g did not result in adverse effects. Its use started to become widespread in the home and hospital, and it became popular among pregnant women to reduce morning sickness.2

However, by 1960 it became clear that long-term thalidomide use was associated with polyneuritis.4 Further, rare congenital abnormalities such as phocomelia (Fig. 1) [courtesy of the Thalidomide Victims Association of Canada (TVAC): http://www.thalidomide.ca/en/index.html] began to appear in infants born to women who used thalidomide during pregnancy. In mid-1961, thalidomide was withdrawn from the world market due to the increasing numbers of infants born with deformities. It was estimated to have caused more than 12 000 congenital birth defects, mostly in West Germany, and to have incurred more than $27 million in legal expenses.5

In 1965, it was given to patients with leprosy in Israel for use as a sedative to relieve ‘lepra suffering’.6 Researchers noticed an unexpected clinical improvement in the signs and symptoms of erythema nodosum leprosum (ENL). After multiple reports from other countries confirmed the results, thalidomide emerged as an effective treatment for ENL. In Europe, thalidomide has not been approved by any health authority, but it has received orphan drug status. Pharmion, the pharmaceutical company producing thalidomide in Europe, filed for a Marketing Authorization Application (MAA) for multiple myeloma and ENL to the European Agency for the Evaluation of Medicinal Products. However, in May 2004 it withdrew the MAA for ENL to focus on the multiple myeloma indication. In 1998, thalidomide was approved by the U.S. Food and Drug Administration (FDA) for ENL and is classified as an orphan drug.7 The orphan drug status has led to its use in many currently unapproved dermatological conditions that are refractory to other medications.
In preparing this manuscript, the following literature searches were performed over the course of July 2002 to September 2004. Using the National Library of Medicine website at http://www.pubmed.org, the word combinations of ‘thalidomide and dermatology’, ‘thalidomide and cutaneous’ and ‘thalidomide and skin’ generated 20, 125 and 294 separate entries, respectively. Each of these articles was examined to determine relevance and suitability. Finally, to ensure that all relevant articles had been cited, the word ‘thalidomide’ was used to generate over 3700 entries, and all articles published after 1990 (appropriately 2000 articles) were briefly scanned. This comprehensive article reviews the pharmacology, adverse effects and use of thalidomide in multiple dermatological conditions.

**Mechanism of action**

It appears that thalidomide may have several modes of action through its sedative, immunomodulatory and other properties (Table 1).

**Therapeutic use**

Although thalidomide is FDA-approved only for ENL, many dermatological conditions appear to be treated effectively with thalidomide (Table 2). In most of these situations, patients received thalidomide only after conventional treatment failed. The following diseases have been grouped into very effective, moderately effective, possibly effective and contraindicated when treated with thalidomide.

**Very effective**

**Erythema nodosum leprosum**

ENL is a lepra reaction that occurs in lepromatous patients on multiple drugs or from interferon (IFN)-γ intradermal injections. It usually presents within the first year of multidrug therapy with both cutaneous and visceral manifestations. Skin reactions are erythematous nodules (Figs 2 and 3) associated with arthralgia, fever, iritis, malaise and neuritis. Visceral manifestations can include hepatosplenomegaly, nephritis, orchitis and pleuritis.

ENL is the only approved indication for thalidomide. The first case report of six patients with ENL treated successfully with thalidomide 300 mg daily led to further clinical trials. In a crossover study, 44 patients received thalidomide for active lepromatous leprosy and chronic ENL. Based on prevention of new ENL lesions and a temperature of less than 37.6 °C, 68% of patients treated with thalidomide responded to therapy, whereas none of the patients treated with placebo responded.

A double-blind trial of thalidomide vs. acetylsalicylic acid was conducted by the World Health Organization. After the first course of treatment until the end of the 9-month study, 48% of patients in the thalidomide group did not have any infectious reactions compared with 21% of patients in the acetylsalicylic acid group. Within 48 h of treatment, 75% of patients in the thalidomide group were afebrile compared with 36% of patients in the acetylsalicylic acid group. Thalidomide caused regression of skin lesions twice as often as did acetylsalicylic acid.

Sheskin reviewed 4522 patients treated with thalidomide for ENL, and found that 4479 (99%) improved while only 43 (1%) had no change or worsened. The best initial dose seemed to be 400 mg daily, with a maintenance dose of 50–100 mg daily. The duration of therapy ranged from sporadic use to continuous use for greater than 6 years. As in the clinical studies, most skin lesions regressed after 24–48 h of therapy, and other signs and symptoms such as arthralgia, emesis, headache, myalgia, hepatosplenomegaly and orchitis resolved quickly as well. Laboratory findings such as white blood cell count and erythrocyte sedimentation rate decreased. Patients with ENL also had rapid improvement in their various neurological conditions, and neuropathy was found not to be a common side-effect.

Although thalidomide is considered first-line for ENL, no trials have compared it with corticosteroids or clofazimine. It has been noted that ENL is not a serious disease and that thalidomide should not be used because of its well-documented risks, but most would agree that thalidomide greatly lessens the morbidity of ENL.

Aphthous stomatitis

The first report of thalidomide for recurrent aphthous stomatitis was in 1979. Six patients had scrotal and mouth ulcers and were treated with thalidomide 100 mg daily. The lesions were painless after 2–3 days and completely resolved after 7–10 days. Multiple small clinical studies (Table 3) and case reports have reported similar results. Thalidomide is also beneficial for human immunodeficiency virus (HIV)-associated aphthous ulcers (Table 3). However, it appears that thalidomide in lower intermittent doses is not effective for preventing recurrence of aphthous ulcers in patients with HIV. As aphthous ulcers often heal on their own, thalidomide should be reserved for only the most severe or recalcitrant cases of orogenital ulceration.

Behçet’s syndrome

After reports of the efficacy of thalidomide in treating aphthous ulcers, thalidomide was used for the first time in Behçet’s syndrome in an open trial of 22 patients. Thalidomide was given at 400 mg daily for the first 5 days, followed by 200 mg daily for the next 15–60 days. Oral and genital lesions healed very rapidly, with milder and shorter recurrences. However, there was no effect on ocular lesions or arthritis. These results were similar to that of another open trial. Other trials showed similar efficacy (Table 4). A pilot study was conducted from 1993 to 1996 to determine the dosage of thalidomide leading to the best efficacy/toxicity ratio, and it was concluded that an initial dose of 50 mg daily is efficacious and that 50 mg every 2 or 3 days is efficacious to maintain remission in more than 60% of patients.

Thalidomide may work in Behçet’s syndrome by reducing the production of hydroxyl and superoxide radicals that cause tissue damage at sites of inflammation. The pathogenesis of Behçet’s syndrome is associated with an increase in chemotactic activity of neutrophils, neutrophil migration, and circulating immune complex-mediated vascular damage. Although thalidomide decreases chemotaxis of neutrophils and cell-mediated immunity, no change in these factors was found when patients with Behçet’s syndrome were successfully treated with thalidomide. As the lesions of Behçet’s syndrome tend to resolve on their own, thalidomide should be used only in severe or unresponsive cases.

Lupus erythematosus

In 1977, thalidomide was first used successfully for discoid lupus erythematosus in 20 patients. Several studies have...
shown strong efficacy (Table 5). The response rates are lower than the published literature might suggest, as most of these trials consisted of patients who were refractory to other conventional therapies. Not only is it effective, thalidomide administration also allowed a reduction in prednisone and azathioprine. In our own clinical experience, thalidomide is very effective for systemic lupus erythematosus (Figs 4 and 5), discoid lupus erythematosus, subacute cutaneous lupus erythematosus and tumid lupus erythematosus. However, it seems that the skin manifestations recur within days to 1 week after stopping the medicine.

The mechanism of thalidomide in lupus erythematosus is not known. It may stabilize lysosomal membranes, inhibit hydroxyl and superoxide free radical production by neutrophils, inhibit the synthesis of IgM and its subsequent deposition on the basement membrane, or suppress neutrophil chemotaxis and macrophage phagocytosis. One study found that thalidomide 100 mg daily for 4 weeks inhibited acute ultraviolet (UV) B erythema at 24 h after exposure, with the equivalent of a sun protection factor of 1–56 to > 4–0, which may explain the therapeutic effects of thalidomide in photosensitive disorders.

**Prurigo nodularis**

In 1965, Sheskin was also the first to treat prurigo nodularis with thalidomide. Twelve patients had a decrease in pruritus after 2–3 weeks of treatment and had a disappearance of lesions after several months. After receiving thalidomide 100–300 mg daily, four patients had a response after 1 month and resolution within 4–6 months. Two to 3 years later, two patients were still in remission.

Twenty-two patients with prurigo nodularis were treated with thalidomide 50–300 mg daily for an average of 12 months (range 2 weeks–5 years). Twenty patients had an immediate relief from pruritus and a significant decrease in size and number of skin lesions after 1–2 months. However, the therapy had to be discontinued in 13 patients (59%) due to side-effects, of which neuropathy occurred in five patients.

In an uncontrolled, prospective case series, 10 HIV-positive patients with prurigo nodularis were treated with thalidomide. Two of the patients were lost to follow-up, but the...
remaining eight all had a greater than 50% decrease of itch over a mean of 3–4 months. Seven patients had a greater than 50% decrease of skin involvement over a mean of 5 months. However, three patients developed thalidomide-induced peripheral neuropathy.

Phototherapy also has efficacy in prurigo nodularis, and a prospective open trial sought to determine if both thalidomide and phototherapy could effectively treat the disease. Thalidomide administration was followed by narrowband UVB (TL-01) irradiation until complete or almost complete remission of the disease occurred. A high rate of response was achieved after an average of 12 weeks of thalidomide therapy and 32 UVB courses.

In patients with prurigo nodularis treated with thalidomide, 70% of patients have been reported to have peripheral neuropathy. In our clinical experience, thalidomide works very well in prurigo nodularis in terms of alleviating the pruritus. Neupathy has not been a major problem in our experience in treating these patients.

Several theories have been proposed about the mechanism of thalidomide in prurigo nodularis. Thalidomide may have a local effect on proliferated neural tissue in prurigo nodularis. A central effect of thalidomide may be the secondary peripheral neuropathy (to lose the sensation to scratch) and the sedation. The sedative properties of thalidomide may disrupt the itch–scratch cycle, but this seems unlikely as other sedatives do not control pruritus well. With treatment, zinc and iron content in the lesions of prurigo nodularis decreased towards the normal range.

**Moderately effective**

**Actinic prurigo**

The first study of thalidomide in treating actinic prurigo was in the early 1970s. Thirty-four patients were given thalidomide 300 mg daily tapered to maintenance doses of 15 mg daily. All but two patients showed clinical improvement within an average of 50 days. However, upon discontinuing treatment, the condition recurred. Another study of 51 patients with actinic prurigo reported similar results. An additional 14 patients were treated with thalidomide 50–200 mg daily, with 11 showing prolonged improvement within 1–3 weeks. Eight of these patients required a maintenance dose of 50–100 mg weekly, while the other three patients did not need to continue treatment.

One group of investigators performed immunohistochemical studies on biopsy specimens from 20 Mexican patients with actinic prurigo. It was found that keratinocytes contained high amounts of tumour necrosis factor (TNF-α) and calprotectin. They believed that in these genetically predisposed patients, UV radiation may trigger excessive TNF-α production by keratinocytes, which could be prevented by treatment with the TNF-α antagonist thalidomide. Another study demonstrated that complete resolution of actinic prurigo cheilitis was more frequently seen with the combination of topical steroids, thalidomide and sun-protection measures (42.2%) than with topical steroids and sun-protection measures (16.3%).

**Adult Langerhans cell histiocytosis (histiocytosis X)**

The first successful treatment of Langerhans cell histiocytosis with thalidomide was documented in 1987. Another patient with cutaneous histiocytosis treated with thalidomide 300 mg daily had complete remission after 1 month and no recurrence after cessation of therapy. Eight other patients with adult Langerhans cell histiocytosis remitted after 1–3 months of therapy, but they had frequent relapses after cessation of therapy. There was little or no effect on the visceral features of the condition. Histopathological examination after treatment in one patient showed no histiocytic infiltrate, implying an effect on the proliferative Langerhans cell population. A patient with both cutaneous Langerhans cell granulomatosis and systemic lupus erythematosus was first successfully treated with the purine analogue, 2-chlorodeoxyadenosine (cladribine), and then with thalidomide. One patient did not respond to 100 mg daily, which led to neuropathy.

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**Fig 3.** A patient with erythema nodosum leprosum, with violaceous plaques and nodules on the legs.
<table>
<thead>
<tr>
<th>Publication</th>
<th>No. of patients</th>
<th>Description of study</th>
<th>Clinical response</th>
<th>Other comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torras et al.128</td>
<td>9</td>
<td>100 mg daily for 10 days for aphthous stomatitis</td>
<td>Healed ulcers, reduced pain, and lengthened intervals between relapses in 8 of 9 patients</td>
<td>Although remission was maintained during therapy, most relapsed within 1 month of treatment cessation.130</td>
</tr>
<tr>
<td>Jenkins et al.129</td>
<td>15</td>
<td>400 mg daily for 5 days and then 200 mg daily for 28 days for aphthous stomatitis</td>
<td>Within 5–21 days, 14 patients had total healing, and 1 had major improvement</td>
<td>Patients with relapses were successfully treated with 100 mg daily for 12 days</td>
</tr>
<tr>
<td>Grinspan131</td>
<td>40</td>
<td>If severe aphthous stomatitis, 300 mg daily for 7–30 days was given, and if less severe, 100 mg daily</td>
<td>Regardless of treatment group, 75% of patients responded well</td>
<td>Patients treated with thalidomide also had fewer ulcers and less impairment</td>
</tr>
<tr>
<td>Ranselaar et al.132</td>
<td>67</td>
<td>A large randomized, double-blind, placebo-controlled, crossover for aphthous stomatitis: 100 mg daily or placebo for 2 months each and then switched treatment without a washout period</td>
<td>In the group treated with thalidomide, 48% had a complete remission compared with only 9% in the group treated with placebo</td>
<td></td>
</tr>
<tr>
<td>Revuz et al.133</td>
<td>73</td>
<td>A randomized, placebo-controlled, crossover trial for aphthous stomatitis: thalidomide 100 mg daily vs. placebo each for 2 months</td>
<td>In the group treated with thalidomide, 32 of 73 patients (44%) had a complete remission compared with only 6 (8%) in the group treated with placebo</td>
<td>Thalidomide-induced remission lasted an average of 20 days before recurrence</td>
</tr>
<tr>
<td>Paterson et al.134</td>
<td>20 HIV- positive patients</td>
<td>A retrospective review from 1989 to 1993 for aphthous ulceration of the oropharynx, oesophagus and rectum, 200 mg daily for 2 weeks</td>
<td>14 patients had complete healing and 6 had clinical improvement</td>
<td>There was no change in CD4+ cell counts during or after treatment</td>
</tr>
<tr>
<td>Weidle135</td>
<td>14 HIV- positive men</td>
<td>7-day course of thalidomide 300 or 600 mg daily was compared with placebo</td>
<td>Three-quarters of the thalidomide group responded to therapy vs. none of the placebo group</td>
<td></td>
</tr>
<tr>
<td>Jacobson et al.136</td>
<td>57 HIV- positive patients</td>
<td>A double-blind, randomized, placebo-controlled study for oral aphthous ulcers, 4-week course of either thalidomide 200 mg daily or placebo</td>
<td>In the thalidomide group, 16 of 29 patients (55%) had complete healing of the ulcers after 4 weeks compared with only 2 of 28 patients in the placebo group (7%) (P &lt; 0.001)</td>
<td>Thalidomide also improved the ability to eat and decreased pain. 7 patients complained of both somnolence and rash each, and 6 of the 29 patients ceased treatment because of toxicity</td>
</tr>
</tbody>
</table>
Cutaneous sarcoidosis

The first case report of cutaneous sarcoidosis in four patients treated successfully with thalidomide was in 1983. 47 Ten patients with chronic cutaneous sarcoidosis resistant to conventional therapy were treated with thalidomide.48 With a daily dose of $1.84 \, \text{mg} \, \text{kg}^{-1}$ for 2.8 months there was a complete response in three patients and a partial response in four patients. Thalidomide was gradually reduced in five of seven patients who had clinical improvement. Three of these five patients relapsed and thalidomide was again given, which reduced or resolved the symptoms.

In another open study, eight patients with chronic skin sarcoidosis were treated with thalidomide for 16 weeks. 49 All skin biopsies showed reductions in granuloma size and in epidermal thickness after treatment. In another open-label study, 15 patients with cutaneous sarcoidosis were treated with thalidomide.50 Of the 14 patients who completed 4 months of therapy, all showed partial improvement, and 10 of 12 showed improvement based on photography. In a retrospective study of 12 patients with chronic sarcoidosis, four patients achieved complete response and six had partial response.

Table 3 (Continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of HIV-positive patients</th>
<th>Study Design</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramirez-Amador et al.137</td>
<td>16</td>
<td>A double-blind, randomized, placebo-controlled clinical trial</td>
<td>where 10 participants were given thalidomide and 6 were given placebo. After 8 weeks, 9 patients (90%) in the thalidomide group had complete healing of their oral ulcers, compared with 2 of 6 patients (33%) in the placebo group ($P = 0.03$)</td>
</tr>
<tr>
<td>Jacobson et al.138</td>
<td>49</td>
<td>A multicentre, double-blind, randomized, placebo-controlled study for oral and esophageal aphthous ulcers, 100 mg or placebo 3 times per week for 6 months</td>
<td>There was no difference in plasma levels of HIV RNA, TNF-$\alpha$, and soluble TNF receptor II at the time of ulcer recurrence</td>
</tr>
</tbody>
</table>

HIV, human immunodeficiency virus; TNF, tumour necrosis factor.

Erythema multiforme

The first case report of recurrent erythema multiforme treated with thalidomide was in 1982. 55 After receiving thalidomide 200 mg daily for a few days, the lesions on the hands, feet, lips and glans penis had healed. The patient did not have any relapses while on 100 mg daily for 6 months. After thalidomide administration, two patients with recurrent erythema multiforme had fewer and milder episodes. 56 A 23-year-old woman with disseminated skin erythema multiforme eruptions that had started at menarche and spread during two pregnancies responded well to thalidomide treatment.57 Two other patients responded, but eventually discontinued therapy due to neuropathy. A 73-year-old woman with recurrent erythema multiforme was treated successfully with thalidomide, but later relapsed after tapering the drug and eventually discontinuing therapy. 58
### Table 4: Clinical trials of thalidomide for Behçet’s syndrome

<table>
<thead>
<tr>
<th>Publication</th>
<th>No. of patients</th>
<th>Description of study</th>
<th>Clinical response</th>
<th>Other comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamza¹⁸</td>
<td>30 men</td>
<td>Open study, 100–300 mg daily for 1–2 months</td>
<td>20 had a complete response, and 6 had a partial response</td>
<td>However, withdrawing thalidomide caused recurrence in 12 of 13 patients, which was controlled in all 12 after restarting thalidomide</td>
</tr>
<tr>
<td>Gardner-Medwin et al.¹³⁹</td>
<td>59 patients with severe oral or genital ulcerations (23 of whom had Behçet’s syndrome)</td>
<td>Retrospective study</td>
<td>There was complete resolution in 81% of patients within 1 month of thalidomide therapy at doses of 200 mg daily. No further thalidomide was required by 20% of patients responding, and in the remaining 80%, improvement was maintained with smaller doses of 7–200 mg daily.</td>
<td>The incidence of symptomatic neuropathy secondary to thalidomide use was determined to be 13.5%</td>
</tr>
<tr>
<td>Hamuryudan et al.¹⁴⁰</td>
<td>96</td>
<td>In a randomized, double-blind, placebo-controlled trial, thalidomide 100 or 300 mg or placebo was given daily for 24 weeks</td>
<td>In the thalidomide 100 mg daily group, 2 of 32 patients (6%) had a complete response. In the thalidomide 300 mg daily group, 5 of 31 patients (16%) had a complete response. In the placebo group, none had a response (P = 0.031)</td>
<td>Within 4 weeks after therapy ended, most patients had a recurrence</td>
</tr>
<tr>
<td>de Wazieres et al.¹⁷</td>
<td>17 patients with oral and genital ulcers, 4 of whom had Behçet’s syndrome</td>
<td>A pilot study was conducted from 1993 to 1996 to determine the dosage leading to the best efficacy/toxicity ratio, 50 mg daily for 1 month. If the patient improved, the dosage was reduced to 50 mg every other day for 1 month and 50 mg every 3 days thereafter</td>
<td>10 patients underwent remission within the first month, and 7 other patients improved. 6 patients had a complete remission after 2 months of treatment, and 1 patient after 4 months. A dosage of 200 mg over 8 days induced prolonged remission in 12 patients. A dosage of 100 mg over 8 days induced prolonged remission in 5 of 6 patients</td>
<td>Nerve conduction studies showed a decrease in sensory nerve action potentials in 6 patients after 8.5 months</td>
</tr>
<tr>
<td>Kari et al.¹⁴¹</td>
<td>10 children</td>
<td>Retrospective study, 1mg kg⁻¹ weekly to 1 mg kg⁻¹ daily</td>
<td>3 children had complete remission, and 2 had less frequent and milder oral ulcers</td>
<td>However, neuropathy developed in 2 children and was irreversible in one of them</td>
</tr>
</tbody>
</table>
Table 5 Clinical trials of thalidomide for lupus erythematosus (LE)

<table>
<thead>
<tr>
<th>Publication</th>
<th>No. of patients</th>
<th>Description of study</th>
<th>Clinical response</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Housman et al.</td>
<td>23 patients</td>
<td>Retrospective review, 100 mg daily</td>
<td>74% demonstrated complete resolution of the cutaneous manifestations of LE, 13% demonstrated 75% or greater improvement, and 13% had less than 75% improvement</td>
<td>Of the patients experiencing a complete or partial response, 91% saw improvement within 8 weeks of thalidomide treatment initiation</td>
</tr>
<tr>
<td>Kyriakis et al.</td>
<td>22 patients</td>
<td>An open uncontrolled trial, 50–200 mg daily</td>
<td>There was a 55% complete response rate, 23% partial response rate, and 14% were withdrawn from the trial due to drug intolerance</td>
<td>Relapses, which were mild, occurred within 39.4 ± 21.4 days after drug discontinuation</td>
</tr>
<tr>
<td>Knop et al.</td>
<td>60 patients</td>
<td>200 mg twice daily, tapered to 50–100 mg daily after a clinical response</td>
<td>54 patients (90%) had at least a partial response, and 39 patients (65%) had complete regression of lesions</td>
<td>Of the patients treated for more than 3 months, 11 of 41 patients remained asymptomatic for 2–8 months after therapy. After cessation of therapy, 30 patients relapsed but responded to restarting thalidomide</td>
</tr>
<tr>
<td>Atra and Sato</td>
<td>23 patients</td>
<td>300 mg daily or 4 mg kg⁻¹ daily in children</td>
<td>18 of 20 patients (90%) had a complete response, and 2 had a partial response</td>
<td>7 of 20 relapsed on withdrawal of therapy</td>
</tr>
<tr>
<td>Sato et al.</td>
<td>18 patients</td>
<td>Maintained at low dose (25–100 mg daily) for a minimum of 6 months</td>
<td>72% complete response rate and 28% partial response rate</td>
<td></td>
</tr>
<tr>
<td>Ordí-Ros et al.</td>
<td>22 patients</td>
<td>A prospective study, 100 mg daily</td>
<td>Complete remission occurred in 12 of 16 patients (75%), partial response was achieved in 4 of 16 patients (25%), and no response occurred in 3 of 19 patients (16%)</td>
<td></td>
</tr>
<tr>
<td>Hasper</td>
<td>11 patients</td>
<td>100–300 mg daily</td>
<td>7 patients had a complete remission, 2 improved significantly, and 1 had no response after 3 months of treatment</td>
<td>Of the responding patients, 6 relapsed after discontinuing therapy, and responded to a maintenance dose of 12.5–50 mg daily</td>
</tr>
<tr>
<td>Stevens et al.</td>
<td>11 patients</td>
<td>50–100 mg daily</td>
<td>7 of 16 patients (44%) had a complete response, 6 of 16 (37%) had a partial response, and 3 did not respond</td>
<td>11 patients were maintained on 25–50 mg daily. All relapses after withdrawal of thalidomide improved with restarting the drug</td>
</tr>
</tbody>
</table>
In a retrospective study, 26 patients with chronic erythema multiforme unresponsive to conventional therapies were treated with thalidomide 100 mg daily. On average, the duration of each episode was reduced by 11 days. Six of the patients had subacute erythema multiforme, and lesions resolved within 5–8 days. A maintenance dose kept the patients in remission.

**Graft-versus-host disease**

The first use of thalidomide in humans for graft-versus-host disease (GVHD) was in 1988 when a patient with acute cutaneous GVHD unresponsive to corticosteroids after allogeneic bone marrow transplant improved within 3 days of starting thalidomide. Several trials have shown moderate efficacy (Table 6) in patients refractory to other therapies. The response rates are lower than the published literature might imply as most of these studies consisted of patients who were refractory to other conventional therapies. Similar to lupus patients, patients with GVHD may be able to decrease or cease other immunosuppressive drugs.

One prospective randomized trial showed that thalidomide may not offer any clinical benefit when incorporated as an initial therapy for chronic GVHD. Patients were randomized to receive either ciclosporin and alternate-day prednisone (n = 27) or ciclosporin, prednisone and thalidomide (200–800 mg daily; n = 27). In the thalidomide group and no-thalidomide group, response rates were 83% vs. 89% at 2 months (P = 0.7), 88% vs. 84% at 6 months (P > 0.8) and 85% vs. 73% at 1 year (P = 0.5). In the thalidomide group and no-thalidomide group, survival rates were 66% vs. 74% at 1 year, and 66% vs. 54% at 2 years (P = 0.85). The authors concluded that despite a high response rate and survival rate, thalidomide offers no clinical benefit as initial therapy for chronic GVHD. Thalidomide is not useful as prophylaxis of chronic GVHD; it is associated with a higher rate of GVHD and higher mortality rate.

It is believed that the metabolites of thalidomide act at an early stage in the antigen recognition-activation pathway of graft T lymphocytes, which downregulates normal lymphocyte function. This may be achieved by allowing the development of antigen-specific suppressor cells and inhibiting the development of cytotoxic cells.
Table 6  Clinical trials of thalidomide for graft-versus-host disease (GVHD)

<table>
<thead>
<tr>
<th>Publication</th>
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<td>Vogelsang et al.\textsuperscript{148}</td>
<td>44 patients refractory with or high-risk chronic GVHD</td>
<td>800 mg daily was given for 3–6 months</td>
<td>14 patients had a complete response, 12 had a partial response (defined as improvement in more than 50% but less than 100% of all affected organ systems), and 18 had no response</td>
<td>In the refractory GVHD group survival was 76%, and in the high-risk GVHD group survival was 48%</td>
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<tr>
<td>Parker et al.\textsuperscript{149}</td>
<td>80 patients with chronic GVHD unresponsive to prednisone with or without ciclosporin</td>
<td>100 mg four times daily, which was increased to 200–400 mg four times daily depending on the response</td>
<td>16 patients (20%) had a response, with 56% experiencing a complete response and 44% a partial response</td>
<td>Of those with the standard-risk chronic GVHD, 24% responded, compared with 16% of the high-risk chronic GVHD group</td>
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<tr>
<td>Rovelli et al.\textsuperscript{150}</td>
<td>14 children with refractory or high-risk chronic GVHD</td>
<td>3–9.5 mg kg\textsuperscript{-1} daily given twice or four times daily</td>
<td>After 2 months of treatment, 6 patients had a complete response, 4 patients had a partial response, and 4 did not respond</td>
<td>3 with a complete response and 1 with a partial response were able to stop thalidomide without any relapses</td>
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<tr>
<td>Browne et al.\textsuperscript{151}</td>
<td>37 allogeneic bone marrow transplantation patients with chronic GVHD refractory to standard immunosuppressive therapy</td>
<td>Single-institution study</td>
<td>14 of 37 patients (38%) had a response after thalidomide was started (1 complete, 13 partial). 4 of 16 adults (25%) and 10 of 21 children (46%) responded</td>
<td>Overall, the 2-year Kaplan–Meier survival was 41% (95% confidence interval 24–59%) after thalidomide was started</td>
</tr>
<tr>
<td>van de Poel et al.\textsuperscript{152}</td>
<td>12 patients with GVHD refractory to chronic prednisone and ciclosporin</td>
<td>Clinic patients between 1991 and 2001</td>
<td>4 patients had a complete response, and 5 showed a partial response</td>
<td>However, of these 5 patients, 3 died eventually of ongoing GVHD, pneumonia and recurrent leukaemia</td>
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<tr>
<td>Arora et al.\textsuperscript{62}</td>
<td>54 patients with chronic GVHD</td>
<td>A prospective randomized trial, randomized to receive either ciclosporin or alternate-day prednisone (n = 27) or ciclosporin, prednisone and thalidomide (200–800 mg daily; n = 27)</td>
<td>In the thalidomide group and no-thalidomide group, response rates were 83% vs. 89% at 2 months (P = 0.7), 88% vs. 84% at 6 months (P &gt; 0.8) and 85% vs. 73% at 1 year (P = 0.5)</td>
<td>In the thalidomide group and no-thalidomide group, survival rates were 66% vs. 74% at 1 year, and 66% vs. 54% at 2 years (P = 0.85)</td>
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</table>
Jessner–Kanof lymphocytic infiltration of the skin

The first clinical trial of thalidomide for Jessner–Kanof lymphocytic infiltration of the skin was in 1983.66 Three of the five patients had a prior inconsistent or negative response to chloroquine. All five cases had an excellent response with thalidomide 100 mg daily. However, skin lesions in four patients reappeared when treatment was stopped. With a maintenance dose of 25–50 mg daily for more than 2 years, three of five patients had normal skin.

In a randomized controlled trial, 28 patients were randomly assigned to receive thalidomide 100 mg daily or placebo over a period of 2 months and were then switched to the other treatment.67 After the first period, 11 of 13 patients treated with thalidomide were in complete remission, and the other two patients did not respond. For those who received placebo, there was no complete remission in the patients (P < 0.0001). After the switch, nine of 14 patients who had received thalidomide in the second period were in complete remission, and 10 of the 13 patients who had received thalidomide during the first period were in complete remission. Complete remission occurred in 19 (76%) after thalidomide therapy and in four (16%) after placebo (P < 0.001). Of the 27 patients who received thalidomide, 16 (59%) were in complete remission after 1 month and 20 (74%) were in complete remission after 2 months.

Uraemic pruritus

One patient with severe pruritus of unknown cause did not improve with thalidomide.56 In a randomized, double-blind, crossover trial, 29 patients with refractory uraemic pruritus were treated with thalidomide 100 mg daily or placebo daily for 1 week.68 Two-thirds of patients had an 80% reduction in pruritus (P < 0.05). Those with less severe symptoms seemed more likely to respond. The mechanism is not known, but it may be related to interference of inflammatory mediators.

Possibly effective

Kaposi sarcoma

A 14-year-old girl with HIV and Kaposi sarcoma was treated with thalidomide for oral ulcers.69 There was a reduction in the size of existing Kaposi sarcoma lesions, and no new lesions appeared. Further, there was a decrease in the human herpesvirus type 8 DNA level in the peripheral blood. However, it was also argued that the response was due to the withdrawal of corticosteroids rather than treatment with thalidomide.70 A 46-year-old woman with chronic myelogenous leukaemia who had received an allogeneic haematopoietic stem cell transplantation presented with human herpesvirus 8-associated Kaposi sarcoma involving her left leg.71 Since her transplant, she had been on continuous immunosuppressive therapy because of chronic GVHD. Irradiation was administered to debulk disease on her legs. Thalidomide was started with altretinoin 0.1% gel applied twice daily to the nonirradiated lesions. Over 7 months, there was a partial response in both irradiated and nonirradiated lesions.

A phase II study of thalidomide was performed to evaluate its efficacy and toxicity for cutaneous AIDS-related Kaposi sarcoma and to determine if the clinical response correlated with a decrease in titre of human herpesvirus 8 DNA in peripheral blood.72 Seventeen men with AIDS-related Kaposi sarcoma were given thalidomide 100 mg daily for 8 weeks. Six of 17 patients (35%) had a partial response, and eight patients withdrew (six due to toxicity, one to noncompliance, and one to early progression of disease). Human herpesvirus 8 DNA load decreased to undetectable levels in three of the five partial responders.

In a phase II dose-escalation study, 20 patients with AIDS-related Kaposi sarcoma were treated with an initial dose of thalidomide 200 mg daily, which was increased to a maximum of 1 g daily for up to 1 year.73 The overall response rate was 40%. The median duration of drug treatment was 6.3 months; the median time to progression was 7.3 months. The median thalidomide dose at the time of response was 500 mg daily (range 400–1000). The antiangiogenic properties of thalidomide may have possible clinical efficacy in a malignancy very dependent on angiogenesis such as Kaposi sarcoma.

Lichen planus/lichen planopilaris

A patient with generalized lichen planus refractory to multiple drugs was given thalidomide 300 mg daily for 2 weeks and then 200 mg daily for another 10 weeks, which resulted in resolution of all his lesions.74 Four patients with refractory oral lichen planus were successfully treated with thalidomide 25–150 mg daily for 15–36 months without recurrence or adverse effects.56,75,76 A patient with erosive flexural lichen planus was successfully treated with a combination of thalidomide and tacrolimus 0.1% ointment.77

In a retrospective study of six patients with severe erosive lichen planus treated with thalidomide, four patients had complete healing for 4 months, one had partial healing, and one had no change in the disease. In the five patients with a clinical improvement, oral erosions rapidly relapsed after thalidomide therapy ended.78

A 53-year-old woman with recalcitrant lichen planopilaris was successfully treated with thalidomide 50 mg twice daily for 6 months.79 We reported a woman with lichen planopilaris who was started on 150 mg daily for 1 month, which resulted in regrowth of hair.80 One month later, the thalidomide was tapered to 50 mg daily, which prevented a recurrence of hair loss. Despite the positive results in our case report, the use of thalidomide has not consistently yielded good results in other patients.81 Since the publication of our case report, we have treated several more patients with lichen planopilaris with positive results in terms of decreasing any associated erythema.
Melanoma

Solid tumours must develop their own blood supply by neoangiogenesis to grow and metastasize. As thalidomide inhibits the processing of mRNA encoding peptide molecules for the angiogenic substance, vascular endothelial growth factor, there has been recent research studying its efficacy for tumours such as melanoma. Thalidomide and pentoxyfylline potentiate each other’s antiangiogenic effect, as demonstrated in human malignant melanoma cells in the cornea of Macaques. A phase I/II study of thalidomide and temozolomide for metastatic melanoma was completed recently. Preliminary results have shown significant antitumour activity, even in brain metastases.

The complete results of the above preliminary study showed that thalidomide and temozolomide were well tolerated and had significant antitumour activity in patients with advanced melanoma. Twelve patients with inoperable stage III or IV melanoma without brain metastases were entered into four treatment cohorts: level 1, temozolomide 50 mg m\(^{-2}\) daily for 6 weeks followed by a 4-week break; and levels 2, 3 and 4, temozolomide 75 mg m\(^{-2}\) daily for 6 weeks followed by breaks of 4, 3 and 2 weeks, respectively. Thalidomide was started at 200 mg daily and increased to a maximum of 400 mg daily. There were one complete response and four partial responses all at dose levels 2–4, and three of these patients were over 70 years of age. The median duration of response was 6 months (range 4–17+), and the median overall survival was 12.3 months (range 4–19+). All regimens were well tolerated.

One study used low-dose thalidomide for several advanced malignant diseases including melanoma and breast, ovarian and renal cell cancer. Sixty-six patients with advanced measurable cancer (17 melanoma, 12 breast, 19 ovarian, 18 renal cell cancer) received thalidomide 100 mg daily until disease progression or unacceptable toxicity was encountered. Although three of 18 patients with renal cell cancer showed partial responses, no objective responses were seen in the other tumour types. However, there were significant improvements in appetite ($P < 0.05$) and sleeping ($P < 0.05$).

In another study, 20 patients with metastatic melanoma without symptomatic brain metastases were administered thalidomide 200 mg daily, with increments of 100 mg every 7 days to a maximum dose of 800 mg daily. Although none of the patients had an objective response, seven patients (35%) experienced stable disease for 12–32 weeks (median 16). The authors believed that the antiangiogenic property of thalidomide is the basis of cytostatic activity in patients with metastatic melanoma. Considering that metastatic melanoma has very few therapeutic options, thalidomide seems to be a promising avenue for further research.

Pyoderma gangrenosum

A 3-year-old girl with pyoderma gangrenosum refractory to corticosteroids and clofazimine was given thalidomide 100 mg daily, leading to complete resolution. Another patient was successfully treated with thalidomide 100 mg daily, resulting in complete remission for 2 years, but cessation of therapy secondary to neuropathy led to immediate relapse. After 6 months of therapy, one patient had healing with scarring and no new lesions. One case of pyoderma gangrenosum involving the penis refractory to high doses of prednisolone improved within 5 days of thalidomide 100 mg daily. A 47-year-old man with pyoderma gangrenosum unresponsive to methylprednisolone had complete healing after 10 weeks of thalidomide. Two patients with pyoderma gangrenosum in association with Behçet’s syndrome were given thalidomide 400 mg daily, later tapered to 50–100 mg daily, which resulted in immediate, complete healing of skin lesions and prevented the development of new mucocutaneous lesions. Despite these case reports, thalidomide has not been effective in our clinical experience. Most of our patients have discontinued the medication after 3–4 months due to lack of efficacy.

Contraindicated use

Toxic epidermal necrolysis

The pathogenesis of toxic epidermal necrolysis was believed to be related to an increased level of TNF-α. Thalidomide was used in a randomized, double-blind, placebo-controlled trial as thalidomide is known as an inhibitor of TNF-α. Ten of 12 patients who received thalidomide 400 mg daily for 5 days died, compared with only three of 10 who received placebo (relative risk 2.78, $P = 0.03$). The study was stopped prematurely because of excess mortality in the thalidomide group. It was found that there was a paradoxical enhancement of TNF-α after therapy with thalidomide. In diseases such as toxic epidermal necrolysis in which T-cell activation is involved in the pathogenesis, the use of thalidomide, which may stimulate T cells in vivo, may further worsen the condition. Toxic epidermal necrolysis was later found not to be related to TNF-α but to the system of Fas receptors on keratinocytes. However, regardless of the mechanism, thalidomide should not be used to treat toxic epidermal necrolysis.

Adverse effects

Thalidomide is well-known for its side-effects of teratogenicity and peripheral neuropathy, but it also has endocrine effects and other more benign adverse effects (Table 7).

Teratogenicity

Birth defects are the most devastating adverse effect of thalidomide, which is classified as pregnancy category X. A single dose of 100 mg within the first 35–50 days of pregnancy can result in deformities. It is not known whether it has an effect on spermatogenesis. Of 380 children born to thalidomide victims, 11 had congenital limb defects. This occurrence...
was five times higher than in the general population. Further, an Australia study by William McBride (who was the first to report the association between thalidomide and phocomelia in 1961 in The Lancet) claimed that thalidomide altered DNA in the sperm and egg cells of rats. In an open letter dated 30 August 1997 by Randy Warren, Chief Executive Officer, and Giselle Cole, President, of TVAC, which can be found at http://www.thalidomide.c./en/information/open_letter_2nd_generation.html, it was stressed that these disabled children of thalidomide victims were born as a result of some other unrelated genetic birth disorder. They mentioned that the media falsely reported, for the sake of sensationalism, that thalidomide disabilities could be passed to their children or grandchildren. They also highlighted that William McBride was discredited in 1982 for falsifying the results of his experiments regarding the antinausea drug Debendox and was taken off the Australian Medical Register in 1993. The TVAC has been in communication with the British Thalidomide Society, the FDA, and Celgene Corporation, and the TVAC is confident that thalidomide has not doomed future generations.

The classification of the teratogenic effects are deformities of the upper and lower extremities such as amelia; absence of bones, phocomelia; abnormalities of the external ear such as anotia and micro pina; abnormalities of the eye such as anophthalmos, with or without association with facial palsy; and defects of the internal organs. 99 At or shortly after birth, the mortality rate is 40%.

The exact mechanism of action is still not known. It has been proposed that the categories of thalidomide-induced teratogenicity be divided into those affecting angiogenesis, cell injury or death, chondrogenesis, DNA synthesis or gene transcription, growth factors, or integrins. 100 It has been theorized that thalidomide blocks a mesonephric signal that is essential for normal limb growth. 101 Elimination of the mesonephros resulted in limb reduction defects similar to those induced by thalidomide, and upper extremities were more likely to have defects compared with lower extremities, just as observed in thalidomide-induced teratogenicity. The mesonephros also produces insulin-like growth factor, which is important in normal limb initiation and development. 102 Thalidomide-induced teratogenicity may be related to the antiangiogenic properties of thalidomide. 103

### Peripheral neuropathy

Peripheral neuropathy is the other well-known side-effect of thalidomide. The neuropathy has no relation to the total cumulative dose, 13 and it can be slow to resolve or may be irreversible. 29 A 2-year prospective study monitoring 135 patients treated with thalidomide for different dermatological diseases showed that the incidence rate of peripheral neuropathy was greatest in the initial year of treatment (20%). The risk was related to the daily dose regardless of duration of therapy, with no neuropathy detected in those patients receiving 25 mg or less per day. 104 In one study of patients with neuropathy secondary to thalidomide for 4–6 years after ending therapy, 25% had a full recovery, 25% had some improvement, and 50% had no change. 105 The incidence has been reported to be from 0–5% to over 70%, with the elderly and women being at a higher risk. 106

Neuropathy usually first presents as symmetrical painful paraesthesias of the hands and feet with sensory loss in the lower extremities. Muscle weakness or cramps may or may not be present, and pyramidal tract signs and carpal tunnel syndrome may occur. 107 A high incidence of ‘tightness around the feet’ has been reported. 108 After discontinuing thalidomide, muscle weakness improves rapidly, but sensory deficits may improve slowly, worsen, or stay the same. 109

Biopsy findings show loss of large-diameter fibres without segmental demyelination and increased numbers of small fibres from regeneration. 110 Electrophysiological studies show axonal neuropathy with reduced sensory nerve action potential amplitude and increased latency in somatosensory-evoked potentials. 111

### Miscellaneous side-effects

The most common side-effect is sedation, which diminishes over time. Other common side-effects are rash, constipation and dizziness. Uncommon side-effects include headache, hypotension, oedema, neutropenia, increased appetite, mood changes, nausea, pruritus and weight gain.

Another adverse event in patients treated with thalidomide is thromboembolic complications, such as deep vein thrombosis and pulmonary embolism. 112 A review of data from MedWatch, the FDA’s spontaneous reporting programme, and

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### Table 7 Side-effects

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<tr>
<th>Serious Teratogenicity</th>
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<td>Sedation</td>
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<td>Constipation</td>
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<td>Rash</td>
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<td>Peripheral neuropathy</td>
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<td>Thromboembolism</td>
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<td>Dizziness</td>
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<td>Uncommon</td>
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<td>Amenorrhoea</td>
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<td>Oedema</td>
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<td>Neutropenia</td>
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<td>Bradycardia</td>
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<td>Dry mouth and skin</td>
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<td>Pruritus</td>
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<td>Headache</td>
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<td>Hypotension</td>
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<td>Increased appetite</td>
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<td>Mood changes</td>
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<td>Male sexual dysfunction</td>
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<td>Tachycardia</td>
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<td>Weight gain</td>
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phase II and III clinical trials involving patients with multiple myeloma, renal cell cancer, melanoma and other cancers, revealed that events occurred after a mean of 2 months of thalidomide therapy, at a reported rate of 0–43% of treated patients, with a marked incidence when chemotherapy was given with thalidomide. In a group of 521 patients who received thalidomide and chemotherapy without venous thrombosis prophylaxis, 16% developed thrombotic events; of 60 patients who received thalidomide with dexamethasone, 15% developed thrombotic events; and among 326 patients who received thalidomide monotherapy, 5% developed thrombotic events. It has been suggested that there is a high rate of thromboembolic events in cancer patients treated with thalidomide because thalidomide may alter tumour cell interactions with coagulation factors; generate procoagulant factors; activate platelets or vascular endothelium; increase thrombogenicity of endothelial cells through increased secretion of IFN by T-helper 1 cells; and induce increases in integrin levels which, combined with chemotherapy-induced endothelial damage, might lead to tumour cell adhesions and platelet clumps that can be thrombogenic. Thrombotic events have also been reported in lupus patients who had antiphospholipid antibodies. Some clinicians recommend a coagulation assessment of patients before starting thalidomide, and limited evidence suggests that with the addition of warfarin prophylaxis, patients may be safely continued on thalidomide after having thalidomide-associated thrombotic events.

Rarely, thalidomide depresses thyroid function, stimulates adrenocorticotropic hormone and prolactin production, and causes hypoglycaemia. Thalidomide has also been reported to cause amenorrhoea and male sexual dysfunction. Thalidomide may also cause dermatological side-effects. Cases of exfoliative and erythrodermic reactions, allergic vasculitis and thrombocytopenic purpura, toxic epidermal necrolysis and psoriasis exacerbation have been reported. Patients with HIV receiving thalidomide may be more likely to experience hypersensitivity reactions.

Monitoring guidelines

Thalidomide should be carefully selected for appropriate patients, and for those who are of childbearing age both counselling and contraceptives should be offered. British guidelines for the use of thalidomide include informed consent being obtained in every case and routine dispensing of information leaflets. Women of childbearing potential should have a negative pregnancy test 2 weeks prior to starting treatment, along with appropriate contraceptive advice. Baseline nerve conduction studies (NCS) are recommended to monitor for the subclinical development of peripheral neuropathy. Sensory nerve action potential amplitudes should be measured in at least three peripheral nerves, usually the median, radial and sural nerves. Falls of 30–40% should lead to a review of thalidomide use, and a fall from baseline values of > 40% on repeat testing should lead to discontinuation of the therapy. After every 10 g cumulative dose or every 6 months, follow-up testing is recommended. However, NCS every 6 months are not practical in the U.K. If any symptoms develop between tests, patients should stop thalidomide immediately and seek medical advice.

To prevent teratogenic exposure, the manufacturer of thalidomide has created a comprehensive programme to control prescribing, dispensing and use of the drug, known as the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.™), which is now running in the U.K. Its main goal is to prevent fetal exposure to thalidomide.

The three-step approach is to: control access to the drug; educate and register prescribers, pharmacists and patients; and monitor compliance. Prescribers are sent information about
the S.T.E.P.S.™ programme, devised by Celgene Corporation, the manufacturer of thalidomide. If they are interested in participating, they must agree to: (i) give comprehensive patient counselling on the risks and benefits of thalidomide; (ii) give appropriate contraception counselling and pregnancy testing; (iii) have patients complete informed consent forms and submit them to the Slone Epidemiologic Unit; (iv) complete and submit the prescriber section of the patient-monitoring survey; (v) prescribe no greater than 28 days of therapy without refill; and (vi) tell patients to return unused thalidomide to the pharmacy.126 Pharmacies must also register in the S.T.E.P.S.™ programme to dispense thalidomide.

To receive the medicine, women of childbearing potential must agree to use two forms of reliable contraception.126 Only women who are postmenopausal, who have undergone a hysterectomy, or who have not had menses for at least 24 consecutive months are considered sterile. Women must use contraception for 4 weeks before the start of therapy and for 4 weeks after ending therapy. Those who wish to be abstinent must remain so during this same period.

Women must also agree to undergo pregnancy testing before and during treatment.126 This is required every week for the first month and monthly afterwards in women with regular menstrual cycles and every 2 weeks in those whose cycles are irregular. Pregnancy testing must also be done if a patient misses her cycle or there is any abnormality in menstrual bleeding. To encourage compliance with the pregnancy-testing requirement, women should receive no more than a 1-week supply for each of the first 4 weeks. If pregnancy does occur during therapy, thalidomide must be stopped immediately, and the prescriber and patient must meet to discuss the implications.126 Celgene Corporation must be informed immediately. The patient must be referred to a board-certified obstetrician/gynaecologist who has training in reproductive toxicity.

Male patients must receive oral and written warnings of the risk of possible contraception failure and the need to use condoms. All patients must agree not to donate blood or share thalidomide with others.

Patients and prescribers must both sign a four-copy informed consent form. They must also complete frequent follow-up questionnaires (every month for women and every 3 months for men). The surveys have questions about demographics, knowledge of the teratogenic risks of thalidomide, sexual activity, use of contraception, and not sharing thalidomide. The surveys have questions about demographics, knowledge of the teratogenic risks of thalidomide, sexual activity, user of contraception, and not sharing thalidomide.

Drug interactions
Thalidomide enhances the activity of alcohol, barbiturates, chlorpromazine and reserpine.106 It raises serum levels of acetaminophen and increases its toxicity.19 It antagonizes acetylcholine, histamine, prostaglandins and serotonin in vitro. Other drugs that cause sedation, neuropathy, or decrease the efficacy of oral contraceptives should be used carefully if thalidomide is added to the patient’s regimen.

Conclusions
Thalidomide is an effective medication for ENL as well as several other dermatological diseases refractory to conventional therapies. However, the adverse effects of teratogenicity and peripheral neuropathy have to be considered before starting thalidomide. In appropriately selected patients, thalidomide can be an extremely efficacious medication.

References
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101 Smith DM, Torres RD, Stephens TD. Mesonephros has a role in limb development and is related to thalidomide embryopathy. Teratology 1996; 54:126–34.


Thalidomide in dermatology, J. Wu et al.


