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Thalidomide and Its Dermatologic Uses

Kapila Paghdal, Robert Schwartz

Department of Dermatology, New Jersey Medical School, Newark, New Jersey, USA

Corresponding author:
Kapila V. Paghdal, PharmD
Department of Dermatology
New Jersey Medical School
185 South Orange Avenue
Newark, New Jersey 07103
USA
roschwar@cal.berkeley.edu

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SUMMARY Thalidomide is a beneficial agent for treating a variety of refractory dermatologic disorders including erythema nodosom leprosum, lupus erythematosus, prurigo nodularis, actinic prurigo, pyoderma gangrenosum and aphthous stomatitis. Two thalidomide analogues, lenalidomide and CC-4047, are considerably more potent with decreased side effects when compared to thalidomide. They are currently undergoing trials and show promise, as they have increased immunomodulatory and anti-angiogenic activity. This category of medication and its use will be reviewed.

KEY WORDS: thalidomide, erythema nodosom leprosum, teratogenicity, immunomodulation

BACKGROUND

Thalidomide, first introduced as a sedative but quickly withdrawn from the market as a cause of severe birth defects, is making a comeback (1). It now has U.S. Food and Drug Administration (FDA) approved use in the treatment of erythema nodosum leprosum. It may be useful in unresponsive dermatologic conditions including 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, prurigo nodularis, pyoderma gangrenosum and uremic pruritus (1). This article reviews the history, pharmacology, mechanism of action, clinical uses and adverse effects of thalidomide.

Thalidomide was first synthesized in Germany in 1954 as α-N-phthalimidoglutarimide (1,2) (Fig. 1). In 1957, it was first approved in Germany as a sedative and hynoptic under the trade name Contergan®. Other countries including the United Kingdom, Canada and Australia marketed this drug under various trade names. Additional uses at that time was for the treatment of irritability, stage fright, depression and hypothyroidism (3). Subsequently, thalidomide was used as an antiemetic because of its efficacy in treating morning sickness in pregnant women (4). In spite of its clinical efficacy, it is the safety profile that is the most disturbing aspect of this drug.

In 1961, thalidomide was implicated in causing a severe fetal defect known as phocomelia. The neonates had congenital foreshortening of the limbs that was usually bilateral and non-symmetric. Approximately 6,000-10,000 live births were affected by this drug; this incurred medico-legal costs totaling more that 27 million dollars (2,5). Due to the concerns about the side effects, the approval of thalidomide was delayed by the U.S. FDA (3). However, its uses continued to be explored on an experimental basis (2).

Then in 1965, thalidomide was used as a sedative to relieve the suffering of leprosy patients. In

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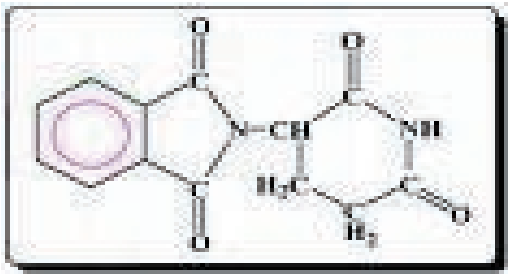

Figure 1. The structure of thalidomide.

addition to its sedative effect, there were marked clinical improvement in the signs and symptoms of erythema nodosum leprosum (ENL). These results were duplicated in other countries and eventually in 1998, thalidomide was granted an "orphan drug" status in the treatment of ENL by the U.S. FDA. However, the dispensing of thalidomide is highly restricted through the System for Thalidomide Education and Prescribing Safety (STEPS) program, implemented to reduce the potential for fetal toxicity (4).

Thalidomide has also shown potential in the treatment of multiple myeloma, myelodysplasia, leukemia, mantle cell lymphoma, glioblastoma multiforme, metastatic melanoma, pancreatic cancer, prostatic cancer, colorectal cancer, renal cell carcinoma, cancer cachexia, HIV or tuberculosis associated wasting, neuropathic pain and intractable insomnia (4,5). This review will focus on the off-label uses of thalidomide in the treatment of refractory dermatologic diseases (Table 1). The dosage for dermatologic conditions ranges from 100 to 400 mg/day orally while other conditions, mainly oncologic, may require higher doses at 200-800 mg/day (4).

PHARMACOLOGY OF THALIDOMIDE

The exact mechanism of action of thalidomide is still unclear. However, thalidomide has been shown to have sedative, anti-inflammatory, immunomodulatory and anti-angiogenesis activity (Table 2). Thalidomide has also been found to inhibit tumor necrosis factor-α (TNF-α) synthesis, possibly by increasing the degradation of TNF-α mRNA (4). This cytokine, produced by various proinflammatory cells, has been implicated in various infections and autoimmune disorders such as ENL (4). Thalidomide is well absorbed orally reaching maximal plasma levels of 1-4 µg/mL within 2-4 hours. It has a half-life of 10 hours and a clearance of 10 L/h (3). Thalidomide is metabolized into inactive chemical metabolites via pH dependent spontaneous hydrolysis (5). The excretion route of thalidomide is still unclear; furthermore, enhanced effects of alcohol and barbiturates were demonstrated when taken concomitantly with thalidomide. Thalidomide also raises the levels of acetaminophen; it, however, was not shown to alter the pharmacokinetics of oral contraceptive pills (1,3).

ADVERSE EFFECTS

Thalidomide is teratogenic and therefore contraindicated for use in pregnant patients. It is designated as pregnancy category X. Peripheral neuropathy is also a side effect that greatly affects compliance. It has been found to occur with the greatest risk in the first year of treatment (1). Other common side effects include sedation, constipation, pruritus, weight gain and dizziness. It is important to note that dermatologic side effects can also occur, including but not limited to exfoliative

Table 1. Dermatologic uses of thalidomide (3,11)

Actinic prurigo	Kaposi sarcoma
Prurigo nodularis	Lupus erythematous profundus
Behçet disease	Chronic discoid lupus erythematosus
Polymorphous light eruption	Leishmaniasis cutanea recidivans
Pemphigoid disorders	Cold hemagglutinin disease
Plantar vasculitis	Jessner-Kanof disease
Immune complex vasculitis	Lichen planus
Histiocytosis	Erosive lichen planus
Langerhans cell histiocytosis	Porphyria cutanea tarda
Postherpetic neuralgia	Photodermatosis
Uremic pruritis	Rheumatoid arthritis
Pyoderma gangrenosum	Cutaneous sarcoidosis
Erythema multiforme	Cutaneous lymphoid hyperplasia
Esophageal ulceration in AIDS	Perineal ulceration in AIDS
Recurrent aphthous stomatitis	Laryngo-onychocutaneous syndrome (26)

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Table 2. Effects of thalidomide (1,5)

Sedative effects:
Activity at the sleep center in the forebrain
Immunomodulatory:
Inhibit tumor necrosis factor-α (TNF-α) synthesis
Inhibit interleukin (IL) 6, 8, 12 synthesis
Inhibit NF-κβ gene expression
Enhance interferon-γ (IFN-γ) synthesis
Enhance IL-2, 4, 5, 10
Inhibit phagocytosis by neutrophils
Inhibit chemotaxis of monocytes and leukocytes
Switch cytokine production from Th1 to Th2 lineage
Anti-angiogenesis:
Inhibit synthesis of vascular endothelial derived growth factor
Inhibit synthesis of basic fibroblast growth factor

dermatitis, toxic epidermal necrolysis (TEN), exacerbation of psoriasis, and allergic vasculitis (1).

Thalidomide showed an increased risk of venous thrombosis in patients that had thrombotic risk associated diseases including cancer and lupus with antiphospholipid antibody syndrome (6). Therefore, thalidomide should be used with caution in these individuals. In addition, thalidomide at one time was thought to be effective as a therapy for TEN; however, it is not recommended in the treatment of this condition because of the increased mortality that was demonstrated (1,7).

IMiD ANALOGUES

Lenalidomide (Revlimid®) and CC-4047 (Actimid®) are analogues of thalidomide that are 2,000 and 20,000 times more potent, respectively (4). These analogues, referred to as iMiDs, are currently undergoing trials for various indications including multiple myeloma, amyloidosis and prostate cancer (4,8). They show promise as they have increased immunomodulatory and anti-angiogenic activity and decreased side effects when compared to thalidomide (4). These analogues were found to costimulate T cells, possibly allowing these drugs to act as adjuvants to promote T cell responses for antitumor activity (8). In addition, lenalidomide was shown to be non-teratogenic in animal studies, which adds to its favorable side effect profile (4). However, the cutaneous side effects that did occur were similar to thalidomide (9).

One study showed that at least one third of patients on lenalidomide therapy developed rashes (9). The prevalence of rashes in those taking lenalidomide was similar to those taking lenalidomide with systemic steroids. There appeared to be less dermatologic side effects in this study when compared to thalidomide studies. In addition, there was one patient with neutrophilic dermatosis attributed to treatment with lenalidomide (10).

THALIDOMIDE AND DERMATOLOGIC CONDITIONS

Erythema nodosum leprosum

Thalidomide has shown efficacy in the treatment of ENL; however, the mechanism by which it helps is unknown. There are increased levels of TNF-αand interferon-γ (INF-γ) in ENL; thalidomide has been shown to exert an immunomodulatory effect by decreasing these levels. Currently, thalidomide's only approved indication is in the treatment of ENL. Clinically, a decrease in skin lesions was observed in the first 2 days with complete remission within 2 weeks at response rates greater than 90% (1,11). In addition, headaches, myalgia, emesis and iritis resolved as well with this treatment. The optimal initial dose is 300-400 mg/day with maintenance doses of 50-100 mg/day. Fifty percent of the patients usually require treatment for at least 6 years (3).

Lupus erythematosus

Thalidomide was demonstrated to be effective in the treatment of cutaneous lupus erythematosus and discoid lupus erythematosus. Cutaneous lupus erythematosus (LE) patients refractory to other options showed marked clinical improvement with the use of low dose thalidomide (100 mg/day) (12). Of the 23 subjects in this study, 21 (91%) patients demonstrated a response in the first 8 weeks of treatment. However, it can recur soon after stopping the treatment, but was once again responsive when restarted on thalidomide (1).

Brocard *et al.* conducted a study in 18 patients who had chronic discoid LE. Fifteen patients showed complete or partial remission, two patients were stabilized, and one patient failed treatment. The mean initial dose ranged from 50 to 100 mg/day, followed by a maintenance dose of 50 mg/day (13). In another study of discoid LE patients on low dose thalidomide therapy, complete remission was observed in 54.5% of patients. The median remission rate was 1 month in 40% of patients (14).

Prurigo nodularis

Prurigo nodularis (PN) is an often troubling chronic disorder characterized by pruritic excori-

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ated nodules of 0.5-3 cm in diameter. The usual treatment with antihistamines and steroids, either topical or systemic, is often ineffective (15). Thalidomide has proven to be of value in the treatment of PN in several studies, possibly attributed to its effect on the proliferated neural tissue (1). In a study of 22 patients, thalidomide 50-300 mg daily was given to patients for an average of 1 year. Twenty patients had a significant decrease in pruritus, in addition to reporting a decrease in the size and number of skin lesions after 1-2 months. Seventy percent of patients on thalidomide treatment also had peripheral neuropathy as a side effect; some of these patients had to discontinue treatment (1).

Actinic prurigo

Actinic prurigo (AP) is a photodermatosis that is characterized by erythematous papules, crusts and lichenified plaques in association with chronic pruritus. This condition, prevalent in Latin America, usually develops on sun-exposed areas. Interestingly, cases that develop in the US, Canada and England have shown a pattern of exacerbation in the spring and summer, while Latin American cases generally are chronic with no remissions. This condition is treated with antibiotics, antihistamines, and oral or systemic corticosteroids (16).

Several studies show that thalidomide is effective in the treatment of this condition. Thirty-four patients were given 300 mg of thalidomide daily, which was tapered to 15 mg daily. Of these patients, only two patients did not show clinical improvement in 50 days (1). Another study consisted of a patient that was refractory to other standard treatments. He showed clinical improvement in 2 months at an initial dose of 100 mg daily, with a maintenance dose of 50 mg daily. It should be noted that the patient had multiple recurrences upon stopping the treatment and therefore had to continue the medication at 50 mg/day (17).

Lichen planus

Oral lichen planus is an idiopathic condition that affects 1%-2% of the population and has a low remission rate of 5% (18). Lichen planus has been treated using a variety of medications. One patient with oral lichen planus refractory to the usual agents showed 75% improvement in symptoms after 4 months of treatment with 50-200 mg/day of thalidomide (18). In a retrospective study of six patients with erosive oral lichen planus, five patients showed a complete to partial response to thalidomide. These patients did, however, relapse once the drug therapy ended (1).

Melanoma

Thalidomide has anti-angiogenic properties that lend to its ability to be beneficial in selected patients with metastatic melanoma (1). A study including 20 patients presenting with malignant melanoma without symptomatic brain metastases showed stable disease in 7/20 patients (35%) for 12-32 weeks with thalidomide dosed at 200-800 mg/day (1). Alternatively, another study had 14 patients with metastatic malignant melanoma assessed for a response to thalidomide. In the light of unchanged serum levels of basic fibroblast growth factor (b-FGF) and vascular endothelial growth factor (VEGF), thalidomide was not recommended as a single agent in the treatment (19).

Melanoma is the third most common tumor to metastasize to the brain. In a phase II trial assessing the benefits of temozolomide and thalidomide, 15/26 patients completed at least one trial. Three patients had a complete or partial response and 7 had stable or minor responses (20). In a phase I study conducted by Bartlett *et al.*, lenalidomide was studied in patients with metastatic malignant melanoma and other advanced cancers. Their results demonstrated that lenalidomide was safe and tolerable in these cancers (8). In addition, although they were not testing efficacy, they have reported that their data suggest clinical activity in the treatment of these diseases (8). Further studies need to be conducted to assess the efficacy of the iMiD analogues in the treatment of these conditions.

Pyoderma gangrenosum

Pyoderma gangrenosum, a chronic painful ulcerative disorder, may benefit from thalidomide treatment (11). A patient with a 27-year history of pyoderma gangrenosum refractory to standard treatments showed improvement with a 6-month course of thalidomide. The lesions healed with scarring; no new ones appeared during this time (21). Another patient, refractory to methylprednisolone treatment, showed complete healing in 10 weeks with thalidomide therapy (1).

Aphthous stomatitis

Thalidomide was first reported to be beneficial in the treatment of recurrent aphthous stomatitis in 1979 (1). Six patients were treated with 100 mg/day of thalidomide with complete resolution in 7-10 days (1). In a multicenter, crossover, randomized

trial in patients with more that 6-month duration of severe aphthous stomatitis, thalidomide was compared to placebo. Complete remission was observed in 32 patients on thalidomide 100 mg/day compared to six patients in the placebo group (22). In 17 patients that were refractory to standard treatments for recurrent aphthous stomatitis, 59% achieved complete or partial response on doses of thalidomide ranging from 50 to 150 mg daily (23).

Other cutaneous disorders

Thalidomide may be useful for a wide variety of other disorders. It may improve the mucocutaneous findings and hypothalamic derangements of adult multisystem Langerhans cell histiocytosis. With 200 mg/day of thalidomide, one patient had a rapid response to treatment with a decrease in skin manifestations and diabetes insipidus (24). Severe cicatrical pemphigoid that is refractory to other standard treatments was also shown to benefit from thalidomide treatment (25). A patient demonstrated improved mucosal and cutaneous lesions after treatment with thalidomide for 26 months (25).

CONCLUSION

Thalidomide has been shown to be effective in the treatment of various refractory dermatologic conditions including erythema nodusom leprosum, lupus erythematosus, prurigo nodularis, actinic prurigo, lichen planus, pyoderma gangrenosum and aphthous stomatitis. The length of therapy and dosing, which ranges from 100-800 mg/day, depends on the condition. Many reports have shown that, upon stopping thalidomide therapy, recurrences of the condition can occur.

The side effect profile, i.e. teratogenicity and peripheral neuropathy, is an important factor to consider when recommending thalidomide as a treatment option. STEPS, a program created to restrict inappropriate thalidomide usage, has been implemented so that various patient factors are assessed prior to dispensing the prescription. Other iMiD analogues such as lenalidomide and CC-4047 show improved activity and side effect profiles compared to thalidomide. Further studies are necessary to prove the efficacy and safety of thalidomide and its analogues in the treatment of dermatologic conditions.

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