REVIEW

Thalidomide for the treatment of chronic refractory pruritus

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Pruritus is a common and often times difficult to treat symptom in many dermatologic and systemic diseases. For pruritus with an inflammatory or autoimmune origin, therapies such as topical corticosteroids and antihistamines are often initiated. However, in the case that these and additional systemic therapies are ineffective, thalidomide, an immunomodulator and neuromodulator, may be a useful alternative treatment. Considerable relief of chronic pruritus has been demonstrated with thalidomide in case reports, case series, and controlled trials. Double-blind controlled studies demonstrated thalidomide's efficacy as an antipruritic agent in patients with uremic pruritus, primary biliary cirrhosis, and prurigo nodularis. In case reports, case series, and open-label trials, thalidomide significantly reduced pruritus associated with conditions such as actinic prurigo and paraneoplastic pruritus. Because of variations in study design and evaluation of antipruritic effect, it is difficult to fully understand thalidomide's role based on the evidence described to date in the medical literature. In this review, we provide an overview of the reported findings and evaluate thalidomide's utility in managing refractory pruritus in the context of its adverse risk profile. We propose that thalidomide can be an alternative or combination antipruritic treatment for patients who do not obtain enough relief from conservative therapy. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2015.09.039.)

Key words: actinic prurigo; itch; prurigo nodularis; pruritus; thalidomide.

Thalidomide was first synthesized and introduced in the 1950s as an over-the-counter medication.[1,2] It was used as a sedative agent; touted for its rapid action, effectiveness in small doses, low addictive potential, and lack of adverse effects such as respiratory depression or motor compromise in the case of overdose.[3-5] Because of its anxiolytic, mild hypnotic, antiemetic, and adjuvant analgesic properties, its use became common among pregnant women to alleviate morning sickness. By 1960, long-term thalidomide use was found to be associated with polyneuritis and its use in pregnancy was linked with phocomelia, a congenital anomaly.[6] Thalidomide was withdrawn from the world market in 1961. In 1965, it was reported that when patients with leprosy were given thalidomide as a sedative to reduce suffering, they concomitantly experienced improvement in signs and symptoms of erythema nodosum leprosum.[7] Since then, thalidomide has been used for many refractory dermatologic conditions, most of which have an autoimmune or inflammatory origin.[5,8] Its use is limited because of the side effects of teratogenesis and peripheral neuropathy; however, it may be indicated for the treatment of chronic or refractory pruritus, a symptom associated with many systemic and dermatologic diseases. Thalidomide's efficacy as an antipruritic agent, mechanisms of action, and adverse effects are reviewed herein.

Abbreviations used:

FDA:	Food and Drug Administration
NCS:	nerve conduction studies
REMS:	Risk Evaluation and Mitigation Strategy

METHODS

Over the course of April to July 2015, we conducted a literature search on the National

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Library of Medicine, Ovid MEDLINE, and OLDMEDLINE databases for word combinations of "thalidomide" coupled with "pruritus," "itch," "antipruritic," and "urticaria." All of the results were recursively checked for relevance and suitability. No manufacturers or authors mentioned in these reports were contacted.

RESULTS

Our search yielded a total of 208 reports (with redundancy) from 1965 to 2014 containing the aforementioned key words. Ultimately, 33 clinical articles were included as they focused on chronic refractory pruritus. Case reports and studies concerning thalidomide analogs were excluded. In these studies, the pharmacology of thalidomide, neuronal mechanism, and clinical antipruritic potency were often discussed.

CAPSULE SUMMARY

- Thalidomide has been used in the treatment of many refractory autoimmune and inflammatory dermatologic conditions.
- We reviewed the response to thalidomide in more than 280 patients with refractory pruritus, most often because of prurigo nodularis. Most experienced considerable relief.
- Peripheral neuropathy was the most common adverse event, but was frequently reversible.
- Thalidomide can be considered as an option for patients with treatment-resistant pruritus.

PHARMACOLOGY OF THALIDOMIDE: METABOLISM AND EXCRETION

Thalidomide was first synthesized in 1954 in West Germany and marketed in 1956. It has since been shown to have sedative, immunomodulatory, and antiangiogenic properties among others.[1] Thalidomide is composed of a left-sided phthalimide ring and a right-sided glutarimide ring.[9,10] Its function as a central depressant has been attributed to its glutarimide ring, which is a moiety common in several hypnosedative drugs and may be implicated in the activation of a sleep center within the forebrain. It has high oral bioavailability and requires 2.9 to 5.7 hours to reach maximum plasma concentration.[11] Thalidomide is metabolized through spontaneous, nonenzymatic hydrolysis in blood and tissue, and minimally by the hepatic cytochrome P450 system. Its half-life to elimination is 5.5 to 7.3 hours, and 92% is excreted in the urine, with less than 1% is in its original form. Thalidomide is distributed under a special program, the "Thalomid" Risk Evaluation and Mitigation Strategy (REMS), which requires prescribers, patients, and pharmacies to be certified with the program.

Thalidomide analogs, namely lenalidomide and pomalidomide, are more potent and have fewer side effects; however, they are associated with greater myelosuppression. They are known to be effective as anticancer agents and are also approved by the Food and Drug Administration (FDA) for controlled distribution.

SIDE EFFECTS

Thalidomide is not addictive and does not have acute adverse effects if doses as high as 14 g are ingested, except for teratogenicity in pregnant women.[1] Thalidomide is classified as pregnancy category X because its use in pregnancy is linked with deformities of the extremities, bones, external ear, eye, internal organs, and/or facial palsy.[12,13] A 100-mg dose within the first 35 to 50 days of pregnancy can cause abnormalities. Mortality at the time of delivery is 40%. Thalidomide's effect on spermatogenesis is unknown. However, it can be present in semen, thereby necessitating the use of male condoms and advising female partners to use additional birth control.[14] Thalidomide-induced teratogenicity may be a result of interference of a mesonephric signal necessary for limb growth or its antiangiogenic properties.[15,16]

Common side effects of thalidomide are reviewed in Table I and include sedation, constipation, rash, peripheral neuropathy, thromboembolism, and dizziness.[1] Uncommon side effects include amenorrhea, edema, neutropenia, bradycardia, dry mouth and skin, pruritus, headache, hypotension, increased appetite, mood changes, male sexual dysfunction, nausea, tachycardia, weight gain, and dermatologic changes.

Sedation is the most common side effect, and it decreases with continued use of thalidomide. Another common, but more serious adverse effect is peripheral neuropathy, which may occur with more than 1 month of thalidomide use at a dosage greater than 25 mg daily and increases in frequency with long-term use (>6 months of therapy).[19,20] Incidence rate of peripheral neuropathy is the greatest, approximately 20%, in the first year of treatment. Affected patients typically report bilateral distal limb paresthesias or dysesthesias and sensory loss. Afterward, they may experience muscle weakness, hypotonia, cramps, tendon reflex decline, or a combination of these. Early changes in nerve conduction