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CASE SERIES

Thalidomide and discoid lupus erythematosus: case series and review of literature

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Abstract

Background: The anti-inflammatory drug, thalidomide, is often administered off-label especially in dermatology patients with diseases refractory to different medications. The drug's mechanism of action is not well understood but clinical evidence suggests an immunomodulatory function. Although this drug is a useful tool for several dermatoses, there are associations between its use and neurotoxic and teratogenic side effects. Consequently, it is reserved only for severe and refractory cases.

Methods: Herein, we present a review about thalidomide focusing on its application in dermatology, particularly on discoid lupus erythematosus (DLE) treatment. We analyzed four cases of people who had a regression of DLE with a dosage of 50 mg thalidomide. Patients were followed to determine the conditions treated with thalidomide, dosage, efficacy, duration of treatment, side effects, adverse events and follow-up. A low dose of 50 mg/day induced a notable and rapid improvement within 1–2 months of treatment and no side effects have been reported so far.

Results: We report four cases of DLE treated previously with the most common immunomodulatory agents with no results and finally successfully treated with thalidomide. In all four patients, despite a low dose of 50 mg/day, a notable and rapid improvement was obtained within a few months of treatment with no side effects.

Conclusions: Notwithstanding the small cohort size, our experience confirms the efficacy of thalidomide for the treatment of DLE.

Keywords: cutaneous lupus erythematosus, discoid lupus erythematosus, thalidomide.

Citation

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Introduction

Following the chance discovery of the potent anti-inflammatory properties attributed to thalidomide in the treatment of patients with erythema nodosum leprosum,[1] thalidomide was approved by the US FDA and marketed for the treatment of this disease in 1954. The latest findings on the mechanisms of thalidomide use and possible therapeutic applications were subsequently reviewed, as can be seen from the most recent literature.[2] Nowadays, thalidomide is used to treat or prevent certain skin conditions related to Hansen's disease by reducing swelling and redness.[3] Thalidomide is likewise used to treat multiple myeloma and reduces the formation of blood vessels that feed solid tumors.[4] In patients with prostate cancer treated with thalidomide, a reduced expression of both MMP2 and MMP9 was observed.[5] In line with this finding, a clinical trial observed the decreased expression of MMP2 and MMP9 in the bone marrow cells of responder patients affected by myelodysplastic syndrome. Consequently, the pathway involved in the regulation of MMP levels seems to be implicated in the efficacy of thalidomide in the treatment of cancer.[6] Furthermore, in addition to having a potential anti-angiogenic role in the treatment of some solid tumours,[7] thalidomide is also able to suppress activation of the latent HIV virus.[8] Although the use of thalidomide entails the risk of teratogenicity and neurotoxicity, it has been useful in many serious and disabling dermatological conditions in which other treatments have failed.[9] For example, it has been successfully used in Behçet disease,[10] discoid lupus erythematosus (DLE),[11] actinic prurigo[12] and prurigo skin sarcoidosis.[13] Randomized studies have shown its efficacy in foot-and-mouth disease, uremic pruritus, severe HIV-associated[14] oropharyngeal ulcers

and Kaposi sarcoma.[15] Dermatological side effects include exfoliative and erythrodermic reactions,[16] erythema polymorph (which is also a therapeutic option), allergic vasculitis, purpura thrombocytopenia, toxic epidermal necrolysis[17] and psoriasis exacerbation.[18]

Metabolism

Thalidomide is an alpha-*N*-phtalimidoglutaride, which is a synthetic derivative of glutamic acid, whose structure has four amino acids. The drug is orally administered because of its insoluble structure not being adapted to parenteral preparation.[19] Regarding the pharmacokinetics of the thalidomide, absorption is slow after oral administration and reaches peak levels in the blood in an interval of 2–6 hours. This process can be delayed by 2 hours if administered in combination with a high-fat meal,[20] the half-life in humans is about 10 hours and the clearance of the body is effectuated in approximately 10 L/hour.[21] Thalidomide, due to its biochemical characteristic, can easily spread in body fluids and tissues and surpass the placental barrier due to being lipid soluble; however, higher concentrations of the drug are found in the skin and kidneys.[22] The major route of elimination is still undetermined, and it is metabolized mostly by non-enzymatic hydrolytic cleavage.[23] Because thalidomide is not primarily metabolized by the cytochrome P450 enzyme system, it is unlikely to interact with drugs metabolized by this enzyme.[24] Therefore, the interaction of the thalidomide with drugs metabolized by the cytochrome P450 enzyme system can be excluded.[25] Mechanistic studies of the drug are further complicated by the rapid formation of a vast number of hydrolysis products and metabolites.[26] Despite the large number of metabolites,[27] our current knowledge of the mechanism of action of the drug is limited to studies based on the parent compound.[28]

Mechanism of action

Thalidomide is an immunomodulatory, anti-inflammatory[29] and anti-angiogenic drug.[30] Anti-angiogenesis[31] and immune modulation[32] can be attributed to its anti-tumour activity[33] because these two effects can be related to the effects of thalidomide on cytokine secretion.[34]

The effects of thalidomide are exerted by the reduction of circulating $CD4^+$ T cells and by the stimulation of the $CD8^+$ T cells, natural killer (NK) cells and T helper 2 (T_H2) cells.[35] Thalidomide also acts on the proliferation of stimulated T cells and leukocyte chemotaxis[36] modifying the quantity of integrin receptors and of other receptors of the leukocytic surface. Furthermore, it acts by down-modulating the cell-adhesion molecules involved in leukocyte migration.[37] In particular, thalidomide inhibits the production of TNFα, IL-5, IL-6, IL-8 and IL-12[38] and increases that of IL-2,[39] IL-10 and INFγ.[40] Moreover, thalidomide acts as an inhibitor on two mediators of angiogenesis, the vascular endothelial growth factor (VEGF) and fibroblast growth factor 2 (FGF2).[41] Evidence based on treatment opinion reported that thalidomide plays a role in connective tissue diseases and vasculitis.[42] The drug seems to be beneficial in the treatment of cutaneous and mucocutaneous disorders in patients affected by systemic lupus erythematosus and Behçet disease, respectively,[43] with an independent dose-drug response. However, given the known side effects related to thalidomide, it should be restricted to selected patients. The mechanism of action of thalidomide, being complex, is not yet fully understood. Thalidomide is able to reduce the circulating proportion of $CD4^+$ T lymphocytes and thus the CD4 to CD8 ratio.[44] It promotes an increase in the number of NK cells and T_H2 lymphocytes compared to T_H1 lymphocytes.[45] In addition, thalidomide inhibits the proliferation of activated T lymphocytes and leucocyte chemotaxis and is responsible for modifications in the expression of integrins and CD44 and intercellular cell adhesion molecule 1 (ICAM1).[46] This synthetic derivative of glutamic acid can also block the cell cycle in G1 in tumour cells for the induction of p21 and apoptosis. Many studies show that it inhibits the production of tumour necrosis factor (TNF) through increased degradation of the m-RNA[47] of TNF and binding of α-glycoprotein acid. Thalidomide also blocks the activity of transcription factor NF-κB, thereby also inhibiting the production of IL-5, IL-6, IL-8 and IL-12.[48] It also increases the response of T lymphocytes, resulting in increased production of IL-2, IL-10 and INFγ.[49] Finally, thalidomide inhibits VEGF-mediated angiogenesis and FGF2.[50]

Case presentations

Ethics statement

The study received approval from the local ethical committee, and informed consent was obtained from each participant.

Case 1

A 45-year-old man, smoker, with a diagnosis of DLE, came to our hospital because of the presence of painful and disfiguring scars on his skin (Figure 1).

The disease started in 2003 after a stressful situation. The patient underwent a skin biopsy, which led to a diagnosis of dermatomyositis, treated first with hydroxychloroquine (200 mg twice a day), interrupted for irritability and then with chloroquine for several years with no significant improvements.

In 2010, a new histological examination revealed a diagnosis of DLE; thus, he was started on hydroxychloroquine and topic corticosteroids (clobetasol propionate) for a few months then on azathioprine (100 mg/day), with poor results. At the time of our observation, in February 2018, the physical examination

Figure 1. A 45-year-old man, with a diagnosis of DLE, with the presence of painful and disfiguring scars on his skin.

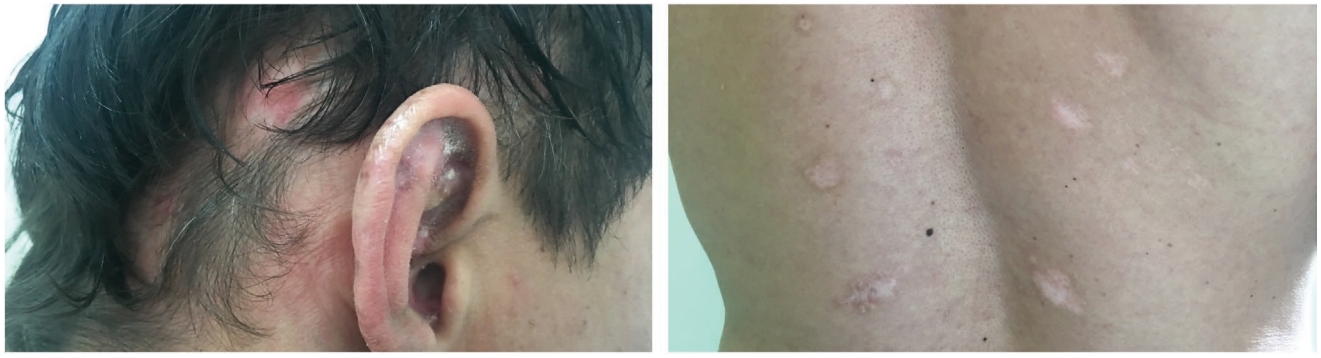
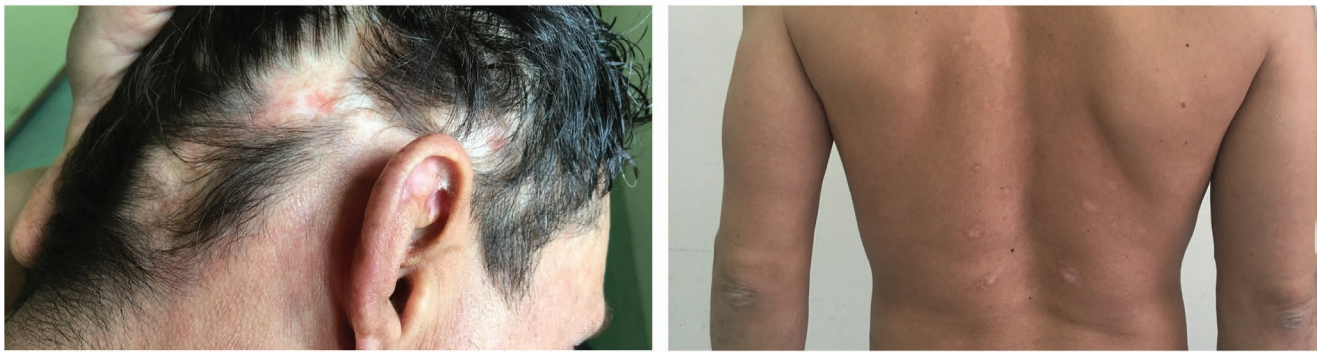


Figure 2. The patient was put on thalidomide 50 mg daily and within 1 month he showed remarkable improvements.



showed erythematosus-violaceous skin lesions on the retro-auricular area, on the scalp, face, upper and lower limbs, no signs of systemic involvement, and with normal blood tests. In February 2018, because of the persistence of the previously mentioned lesions, the man was put on thalidomide 50 mg daily at bed time; within 1 month, he showed remarkable improvements (Figure 2).

Case 2

A 55-year-old woman, who had never been a smoker, complained of painful erythematosus lesions, which started in 2009, initially on her back, and was treated with systemic corticosteroids (Figure 3).

After the relapse and appearance of new lesions on her face and neckline, biopsy and histological examination led to a diagnosis of DLE.

The patient first started dapsone 50 mg/day for 3 months with no results and then hydroxychloroquine (200 mg/day), withdrawn after 2 months owing to severe itching. Afterward, she was retreated with systemic corticosteroids with poor benefit. Her family history revealed cerebral vasculopathy, rheumatic and allergic disease, and hypertension. Her physical examination revealed glaucoma and fibromyalgia. Laboratory tests, including complete blood picture, urine, C-reactive protein (CRP) test, and autoimmune profile and cardiological examination/ECG, were within normal limits. Chest X-ray revealed pulmonary emphysema.

In September 2018, thalidomide 50 mg daily was started along with polypodium leucotomos tablets and topic sunscreen with remarkable clinical results (Figure 4).

Case 3

A 55-year-old woman who was diagnosed with DLE, complained of a skin condition which started in 2011 when she was first treated with systemic corticosteroid and then, in 2012, owing to a further spread of cutaneous disease, with hydroxychloroquine (200 mg/day), which was withdrawn after

Figure 3. **A 55-year-old woman, complained of painful erythematous lesions, initially on her back.**

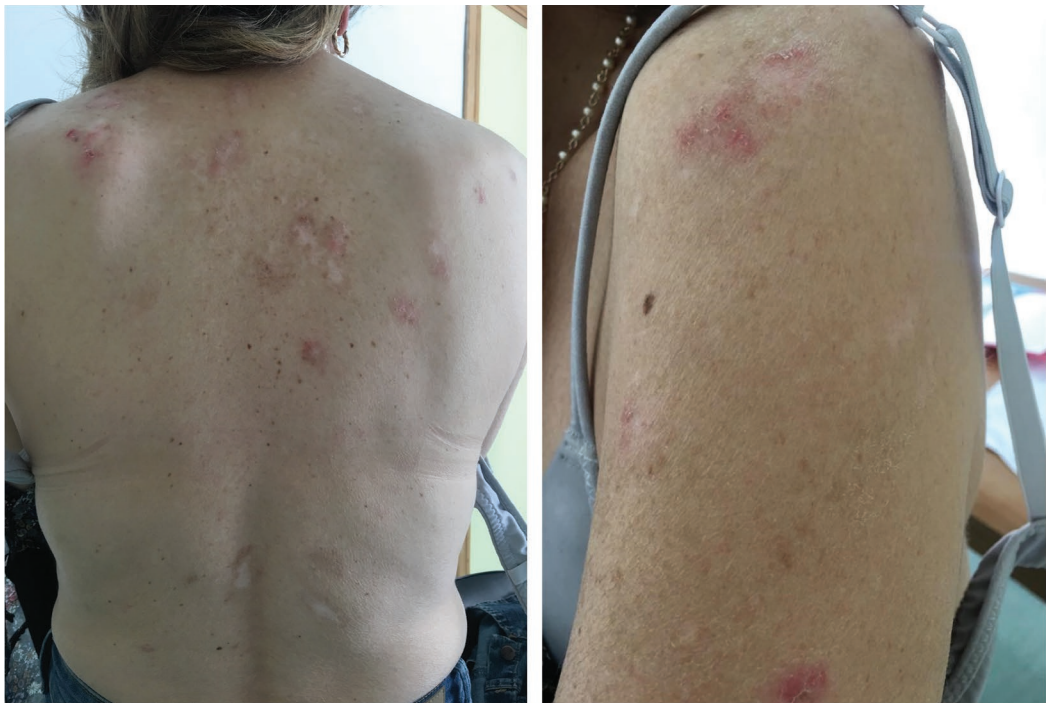
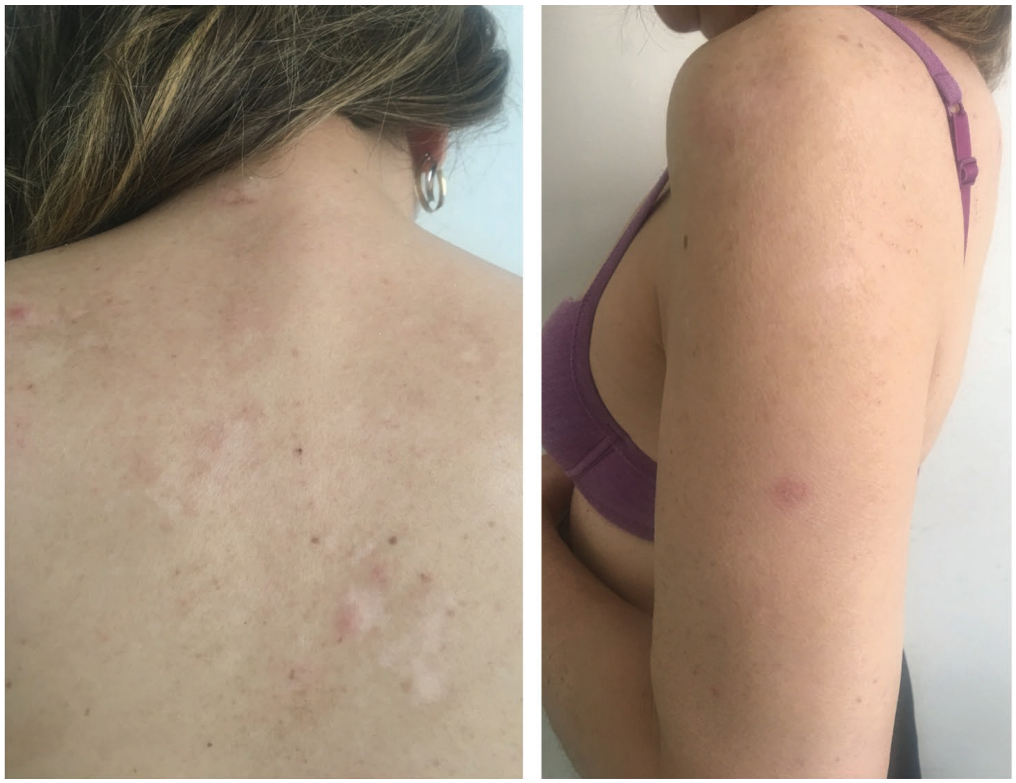


Figure 4. **The patient was started along thalidomide 50 mg daily with remarkable clinical results after 3–4 weeks.**



12 months for inefficacy. She then underwent a short cycle of azathioprine (100 mg/day) which was also ineffective.

At the time of our observations, the patient displayed diffuse erythematosus-to-violaceous, scaly plaques with prominent follicular plugging resulting in scarring and atrophy on the trunk and on the upper and lower limbs. On examination, the woman suffered from Sjogren syndrome, thyroiditis, asthma, chronic bronchitis and hiatal hernia. The lab tests, including complete blood picture, renal and liver functions as well as autoimmune profile, were within normal limits. Skin biopsy confirmed the diagnosis of DLE. Owing to the ineffectiveness of both systemic steroids and hydroxychloroquine, we decided to administer thalidomide treatment at 50 mg/day with evident clinical improvements from the first follow-up.

Case 4

A 59-year-old man with a long history of DLE (started 12 years prior) presented to our outpatient clinic after being treated for many years with several immunosuppressant agents (systemic corticosteroids, azathioprine, cyclosporine and cyclophosphamide) with modest results. Complete laboratory and instrumental tests were performed, and no abnormalities were documented. Although the patient was under multiple drugs, including rivaroxaban and carvedilol to prevent blood clots and the increase of blood pressure, respectively, as he previously suffered from heart attack, pulmonary embolism and deep vein thrombosis, we decide to administer thalidomide treatment at the dosage of 50 mg/day together with polypodium leucotomos tablets and sunscreen cream. He did not report either any drug–drug interactions or any of the well-known thalidomide adverse effects. The patient was treated for 6 months with the initial clearing of skin lesions.

Table 1 outlines the clinical response to thalidomide observed in the cases examined.

Discussion

Lupus erythematosus (LE) is a common autoimmune disease with a multifactorial nature dependent on interactions of genetic, environmental, hormonal and ethnic factors and characterized by systemic and cutaneous manifestations.[51] Approximately 80% of all patients with LE present cutaneous features that are usually divided in specific and non-specific[52] types. The former can be further classified into acute cutaneous LE,[53] subacute cutaneous LE,[54] chronic cutaneous LE (CCLE) and bullous LE.[55] The different categories of CCLE differ for clinical as well as prognosis aspects.[56] Amongst CCLE there are additional subtypes; DLE is the most common subtype of cutaneous lesions in CCLE and can be either localized or generalized.[57] The plaques covered with a thin scaly tissue, such as the hair follicle, are called discoid lesions.[58] The phenotype of these lesions is dynamic with an initial hyperpigmented aspect that may lead to depigmentation and progress to painful, deeper cicatricial lesions, most often permanent.[59] Although the discoid form is usually limited exclusively to the cutaneous region, in approximately 10% of cases it may progress to the systemic form, especially when lesions are disseminated.[60] The treatment of CLE is based on lifestyle measures, control of inflammation, organ damage, and the prevention and relief of symptoms.[61] Patients with CLE should take preventive measures, including protection from UV-B and UV-A radiation, by applying broad-spectrum sunscreens or wearing wide-brimmed hats and tightly woven clothes.[62] Additionally, doctors should encourage the patients to stop smoking because of a reduction in the efficacy of antimalarial therapy and increases in disease activity associated with CLE and systemic lupus erythematosus (SLE).[63]

Although several therapeutic agents are approved for systemic LE,[64] including the newer monoclonal antibody belimumab, no drugs have been licensed for the treatment of CLE thus far. Consequently, topical and systemic agents in CLE are mostly administered 'off-label' without specific randomized

Table 1. Clinical response to thalidomide therapy.

Case	Age	Sex	Improvement	Complete resolution	Follow-up
1 (Figure 1)	45	M	Decrease in erythema, size and thickness of lesion by 3–4 weeks	Complete resolution in size around 6–7 weeks (Figure 2)	For 36 weeks; no recurrence
2 (Figure 3)	55	F	Resolution by 3–4 weeks	By 6–7 weeks (Figure 4)	For 36 weeks; no recurrence
3	55	F	Decrease in erythema size by 2 weeks	Complete resolution by 3–4 weeks	For 36 weeks; no recurrence
4	59	M	Decrease in erythema, size and thickness of lesion by 9–10 weeks	By 12–13 weeks	For 36 weeks; no recurrence

controlled trials.[65] Several medications can be prescribed after the failure of topical therapies and antimalarial therapy in CLE, including dapsone, retinoids, systemics, corticosteroids, methotrexate, azathioprine, cyclosporine, mycophenolate mofetil and cyclophosphamide.[66] They are prescribed as monotherapy in combination with antimalarial therapy or with other drugs.[67] Further, they are not only used for the treatment of present lesions in CLE patients but also to prevent progression to systemic disease.[68] In particular, antimalarials are associated with a higher rate of remission, fewer flares and relapses, also reducing organ damage during the disease.[69] However, owing to the risk of adverse effects, the indication of the recent European guideline recommend methotrexate and mycophenolate mofetil for the treatment of CLE whilst discouraging the use of cyclosporine, cyclophosphamide and azathioprine in patients with CLE without systemic involvement.[70] Nevertheless, current insights into the management of DLE suggest the use of thalidomide in severe refractory cases.[71] In a high number of DLE cases, successful therapy with thalidomide is achieved, characterized by the immunomodulatory and anti-inflammatory activities discussed above.[72]

Already in 1983, 60 patients with DLE were treated with thalidomide initially at doses of 400 mg/day and a maintenance dose of 50–100 mg/day, 90% of whom obtained a complete or notable response, even though most patients relapsed after interrupting thalidomide treatment. Nevertheless, skin lesions were attenuated.[73] A prospective study, that involved 60 patients with refractory CLE reported a 98% clinical response rate to 100 mg of thalidomide daily treatment.[74] However, the rate of relapse after stopping the drug was approximately 70%. This high relapse was confirmed in a recent metanalysis of 21 studies that used thalidomide for the treatment of CLE, showing a pooled response rate of 90% but a high relapse rate of 71%. After cessation of treatment, 16% of patients manifested peripheral neuropathy but only 4% had persistent symptoms.[75]

The lowest effective dose of thalidomide is reported to be 50 mg daily. Wang et al., in a study of 69 patients with DLE at this dosage, showed an optimal level response rate of 71%.[76] The same dosage was administrated by Frankel et al. in 5 patients with refractory CLE, 4 (80%) of whom showed a partial or total response after 4–8 weeks of treatment.[77] The previous studies thus reported similar results to previous retrospective studies that used a classical dose of 100 mg/day albeit using half the daily dose. The beneficial effect of thalidomide is counterbalanced by its several side effects, which range from the less severe, such as constipation, drowsiness, rash, swelling and xerostomia, to the more severe such as peripheral polyneuropathy.[78] This adverse event may occur early during the first 4 weeks of treatment and is not always reversible. Thus, the use of thalidomide is limited because of its high relapse rate and well-known teratogenicity.

Conclusion

Thalidomide is recognized as a beneficial treatment for CLE, but the related neurotoxic and teratogenic side effects often limit its use to severe and refractory cases.[79] The recommended thalidomide dosage has decreased over time, with initial studies administering doses of up to 400 mg/day[80] followed by studies that reported the same efficacy with reduced doses of 100 mg/day.[81] Currently, successful treatment of CLE can be achieved using starting doses of 50 mg daily or every other day. In our four patients, we found that a low dose of 50 mg/day induced a notable and rapid improvement within 1–2 months of treatment and no side effects have been reported so far.[82] Despite our small sample size, our experience reinforces the efficacy of thalidomide as shown in several previously discussed studies.

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