CASE SERIES

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

Giovanna Malara¹, Chiara Verduci², Maria Altomonte³, Maria Cuzzola⁴, Caterina Trifirò¹, Cristina Politi⁵, Giovanni Tripepi⁵

¹Dermatology Unit, Grande Ospedale Metropolitano “Bianchi-Melacrino-Morelli” of Reggio Calabria, Italy; ²Pharmacology Department, Magna Graecia University, Catanzaro, Italy; ³Pharmacy Unit, Grande Ospedale Metropolitano “Bianchi-Melacrino-Morelli” of Reggio Calabria, Italy; ⁴Microbiology & Virology Unit, Grande Ospedale Metropolitano “Bianchi-Melacrino-Morelli” of Reggio Calabria, Italy; ⁵CNR-IFC, Section of Clinical Epidemiology and Biostatistics, of Reggio Calabria, Italy

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

Malara G, Verduci C, Altomonte M, Cuzzola M, Trifirò C, Politi C, Tripepi G. Thalidomide and discoid lupus erythematosus: case series and review of literature. Drugs Context. 2022;11:2021-9-8. https://doi.org/10.7573/dic.2021-9-8

Introduction

Following the chance discovery of the potent anti-inflammatory properties attributed to thalidomide in the treatment of patients with erythema nodosum leprosum, 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. Nowadays, thalidomide is used to treat or prevent certain skin conditions related to Hansen’s disease by reducing swelling and redness. Thalidomide is likewise used to treat multiple myeloma and reduces the formation of blood vessels that feed solid tumors. In patients with prostate cancer treated with thalidomide, a reduced expression of both MMP2 and MMP9 was observed. 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. Furthermore, in addition to having a potential anti-angiogenic role in the treatment of some solid tumours, thalidomide is also able to suppress activation of the latent HIV virus. 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. For example, it has been successfully used in Behçet disease, discoid lupus erythematosus (DLE), actinic prurigo and prurigo skin sarcoidosis. Randomized studies have shown its efficacy in foot-and-mouth disease, uremic pruritus, severe HIV-associated oropharyngeal ulcers
and Kaposi sarcoma.\textsuperscript{15} Dermatological side effects include exfoliative and erythrodermic reactions,\textsuperscript{16} erythema polymorph (which is also a therapeutic option), allergic vasculitis, purpura thrombocytopenia, toxic epidermal necrolysis\textsuperscript{17} and psoriasis exacerbation.\textsuperscript{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.\textsuperscript{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,\textsuperscript{20} the half-life in humans is about 10 hours and the clearance of the body is effectuated in approximately 10 L/hour.\textsuperscript{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.\textsuperscript{22} The major route of elimination is still undetermined, and it is metabolized mostly by non-enzymatic hydrolytic cleavage.\textsuperscript{23} Because thalidomide is not primarily metabolized by the cytochrome P450 enzyme system, it is unlikely to interact with drugs metabolized by this enzyme.\textsuperscript{24} Therefore, the interaction of the thalidomide with drugs metabolized by the cytochrome P450 enzyme system can be excluded.\textsuperscript{25} Mechanistic studies of the drug are further complicated by the rapid formation of a vast number of hydrolysis products and metabolites.\textsuperscript{26} Despite the large number of metabolites,\textsuperscript{27} our current knowledge of the mechanism of action of the drug is limited to studies based on the parent compound.\textsuperscript{28}

### Mechanism of action

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

The effects of thalidomide are exerted by the reduction of circulating CD4\textsuperscript{+} T cells and by the stimulation of the CD8\textsuperscript{+} T cells, natural killer (NK) cells and T helper 2 (T\textsubscript{H}2) cells.\textsuperscript{35} Thalidomide also acts on the proliferation of stimulated T cells and leukocyte chemotaxis\textsuperscript{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.\textsuperscript{37} In particular, thalidomide inhibits the production of TNFa, IL-5, IL-6, IL-8 and IL-12\textsuperscript{38} and increases that of IL-2,\textsuperscript{39} IL-10 and INF\textsubscript{Y}.\textsuperscript{40} Moreover, thalidomide acts as an inhibitor on two mediators of angiogenesis, the vascular endothelial growth factor (VEGF) and fibroblast growth factor 2 (FGF2).\textsuperscript{41} Evidence based on treatment opinion reported that thalidomide plays a role in connective tissue diseases and vasculitis.\textsuperscript{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,\textsuperscript{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\textsuperscript{+} T lymphocytes and thus the CD4 to CD8 ratio.\textsuperscript{44} It promotes an increase in the number of NK cells and T\textsubscript{H}2 lymphocytes compared to T\textsubscript{H}1 lymphocytes.\textsuperscript{45} In addition, thalidomide inhibits the proliferation of activated T lymphocytes and leukocyte chemotaxis and is responsible for modifications in the expression of integrins and CD44 and intercellular cell adhesion molecule 1 (ICAM1).\textsuperscript{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\textsuperscript{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.\textsuperscript{48} It also increases the response of T lymphocytes, resulting in increased production of IL-2, IL-10 and INF\textsubscript{Y}.\textsuperscript{49} Finally, thalidomide inhibits VEGF-mediated angiogenesis and FGF2.\textsuperscript{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 erythematous-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 erythematous 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 poly podium 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 Sjögren 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.

| 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 |

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. Approximately 80% of all patients with LE present cutaneous features that are usually divided in specific and non-specific types. The former can be further classified into acute cutaneous LE, subacute cutaneous LE, chronic cutaneous LE (CCLE) and bullous LE. The different categories of CCLE differ for clinical as well as prognosis aspects. Amongst CCLE there are additional subtypes; DLE is the most common subtype of cutaneous lesions in CCLE and can be either localized or generalized. The plaques covered with a thin scaly tissue, such as the hair follicle, are called discoid lesions. 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. 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. The treatment of CLE is based on lifestyle measures, control of inflammation, organ damage, and the prevention and relief of symptoms. 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. 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).

Although several therapeutic agents are approved for systemic LE, 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
controlled trials. Several medications can be prescribed after the failure of topical therapies and antimalarial therapy in CLE, including dapsone, retinoids, systemics, corticosteroids, methotrexate, azathioprine, cyclophosphamide, mycophenolate mofetil and cyclophosphamide. They are prescribed as monotherapy in combination with antimalarial therapy or with other drugs. Further, they are not only used for the treatment of present lesions in CLE patients but also to prevent progression to systemic disease. In particular, antimalarials are associated with a higher rate of remission, fewer flares and relapses, also reducing organ damage during the disease. 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 cyclophosphamide and azathioprine in patients with CLE without systemic involvement. Nevertheless, current insights into the management of DLE suggest the use of thalidomide in severe refractory cases. In a high number of DLE cases, successful therapy with thalidomide is achieved, characterized by the immunomodulatory and anti-inflammatory activities discussed above.

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. A prospective study, that involved 60 patients with refractory CLE reported a 98% clinical response rate to 100 mg of thalidomide daily treatment. However, the rate of relapse after stopping the drug was approximately 70%. This high relapse was confirmed in a recent meta-analysis 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.

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%. 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. 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. 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. The recommended thalidomide dosage has decreased over time, with initial studies administering doses of up to 400 mg/day followed by studies that reported the same efficacy with reduced doses of 100 mg/day. 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. Despite our small sample size, our experience reinforces the efficacy of thalidomide as shown in several previously discussed studies.
References

1. Tseng S, Pak G, Washenik K, Pomeranz MK, Shupack JL. Rediscovering thalidomide: a review of its mechanism of action, side effects, and potential uses. *J Am Acad Dermatol.* 1996;35(6):969–979. https://doi.org/10.1016/s0190-9622(96)90122-x

2. Nasca MR, Micali G, Cheigh NH, West LE, West DP. Dermatologic and nondermatologic uses of thalidomide. *Ann Pharmacother.* 2003;37(9):1307–1320. https://doi.org/10.1345/aph.19255

3. Stirling DI. Thalidomide and its impact in dermatology. *Semin Cutan Med Surg.* 1998;17(4):231–242. https://doi.org/10.1016/s1085-5629(98)80019-9

4. Grabstald H, Golbery R. Clinical experiences with thalidomide in patients with cancer. *Clin Pharmacol Ther.* 1965;40:298–302. https://doi.org/10.1002/cpt196563298

5. Bowen DT. Treatment strategies and issues in low/intermediate-1-risk myelodysplastic syndrome (MDS) patients. *Semin Oncol.* 2005;32(4 Suppl. 5):S16–S23. https://doi.org/10.1053/j.seminoncol.2005.06.017

6. Invernizzi R, Travaglino E, De Amici M, et al. Thalidomide treatment reduces apoptosis levels in bone marrow cells from patients with myelodysplastic syndromes. *Leuk Res.* 2005;29(6):641–647. https://doi.org/10.1016/j.leukres.2004.11.008

7. Fife K, Howard MR, Gracie F, Phillips RH, Bower M. Activity of thalidomide in AIDS-related Kaposi’s sarcoma and correlation with HHV8 titre. *Int J STD AIDS.* 1998;9(12):751–755. https://doi.org/10.1258/0956462981921512

8. Reyes-Terán G, Sierra-Madero JG, Martínez del Cerro V, et al. Effects of thalidomide on HIV-associated wasting syndrome: a randomized, double-blind, placebo-controlled clinical trial. *AIDS.* 1996;10(13):1501–1507. https://doi.org/10.1097/00002030-199611000-00007

9. Efstratiou E, Troncoso P, Wen S, et al. Initial modulation of the tumor microenvironment accounts for thalidomide activity in prostate cancer. *Clin Cancer Res.* 2007;13(4):1224–1231. https://doi.org/10.1158/1078-0432.CCR-06-1938

10. Brik R, Shamali H, Bergman R. Successful thalidomide treatment of severe infantile Behçet disease. *Pediatr Dermatol.* 2001;18(2):143–145. https://doi.org/10.1046/j.1525-1470.2001.018002143.x

11. Sato EI, Assis LS, Lourenzi VP, Andrade LE. Long-term thalidomide use in refractory cutaneous lesions of systemic lupus erythematosus. *Rev Assoc Med Bras.* 1998;44(4):289–293. https://doi.org/10.1590/s0104-42301998000400007

12. Wu JJ, Huang DB, Pang KR, Hsu S, Tying SK. Thalidomide: dermatological indications, mechanisms of action and side-effects. *Br J Dermatol.* 2005;153(2):254–273. https://doi.org/10.1111/j.1365-2133.2005.06747.x

13. Wines NY, Cooper AJ, Wines MP. Thalidomide in dermatology. *Australas J Dermatol.* 2002;43(4):229–240. https://doi.org/10.1111/j.1440-0960.2002.00608.x

14. Little RF, Wyvill KM, Pluda JM, et al. Activity of thalidomide in AIDS-related Kaposi’s sarcoma. *J Clin Oncol.* 2000;18(13):2593–2602. https://doi.org/10.1200/JCO.2000.18.13.2593

15. Hall VC, El-Azhary RA, Bouwhuis S, Rajkumar SV. Dermatologic side effects of thalidomide in patients with multiple myeloma. *J Am Acad Dermatol.* 2003;48(4):548–552. https://doi.org/10.1067/mjd.2003.87

16. Duong DJ, Spigel GT, Moxley RT III, Gaspari AA. American experience with low-dose thalidomide therapy for severe cutaneous lupus erythematosus. *Arch Dermatol.* 1999;135(9):1079–1087. https://doi.org/10.1001/archderm.135.9.1079

17. Brik R, Shamali H, Bergman R. Successful thalidomide treatment of severe infantile Behçet disease. *Pediatr Dermatol.* 2001;18(2):143–145. https://doi.org/10.1046/j.1525-1470.2001.018002143.x

18. Tseng S, Pak G, Washenik K, Pomeranz MK, Shupack JL. Rediscovering thalidomide: a review of its mechanism of action, side effects, and potential uses. *J Am Acad Dermatol.* 1996;35(6):969–979. https://doi.org/10.1016/s0190-9622(96)90122-x

19. Teo SK, Sabourin PJ, O’Brien K, Kook KA, Thomas SD. Metabolism of thalidomide in human microsomes, cloned human cytochrome P-450 isozymes, and Hansen’s disease patients. *J Biochem Mol Toxicol.* 2000;14(3):140–147. https://doi.org/10.1002/(SICI)1099-0461(2000)14:3-140:AID-JBT3.3.CO;2-P

20. Czejka MJ, Koch HP. Determination of thalidomide and its major metabolites by high-performance liquid chromatography. *J Chromatogr.* 1987;413:181–187. https://doi.org/10.1016/0021-9673(87)80225-6
21. Chen TL, Vogelsang GB, Petty BG, et al. Plasma pharmacokinetics and urinary excretion of thalidomide after oral dosing in healthy male volunteers. Drug Metab Dispos. 1989;17(4):402–405.
22. Tseng S, Pak G, Washenik K, Pomeranz MK, Shupack JL. Rediscovering thalidomide: a review of its mechanism of action, side effects, and potential uses. J Am Acad Dermatol. 1996;35(6):969–979. https://doi.org/10.1016/s0190-9622(96)90122-x
23. Calabrese L, Fleischer AB. Thalidomide: current and potential clinical applications. Am J Med. 2000;108(6):487–495. https://doi.org/10.1016/s0002-9343(99)00408-8
24. Czejka MJ, Koch HP. Determination of thalidomide and its major metabolites by high-performance liquid chromatography. J Chromatogr. 1987;413:181–187. https://doi.org/10.1016/0021-9673(87)80225-6
25. Ando Y, Fuse E, Figg WD. Thalidomide metabolism by the CYP2C subfamily. Clin Cancer Res. 2002;8(6):1964–1973.
26. Marriott JB, Muller G, Dalgleish AG. Thalidomide as an emerging immunotheatrical agent. Immunol Today. 1999;20(12):538–540. https://doi.org/10.1016/s0167-5699(99)01531-5
27. McCarty MF. Thalidomide may impede cell migration in primates by down-regulating integrin beta-chains: potential therapeutic utility in solid malignancies, proliferative retinopathy, inflammatory disorders, neointimal hyperplasia, and osteoporosis. Med Hypotheses. 1997;49(2):123–131. https://doi.org/10.1016/s0306-9877(97)90217-6
28. Sampaio EP, Kaplan G, Miranda A, et al. The influence of thalidomide on the clinical and immunologic manifestation of erythema nodosum leprosum. J Infect Dis. 1993;168(2):408–414. https://doi.org/10.1093/infdis/168.2.408
29. Rowland TL, McHugh SM, Deighton J, et al. Differential regulation by thalidomide and dexamethasone of cytokine expression in human peripheral blood mononuclear cells. Immunopharmacology. 1998;40(1):11–20. https://doi.org/10.1016/s0162-3109(98)00010-1
30. D'Amato RJ, Loughnan MS, Flynn E, Folkman J. Thalidomide is an inhibitor of angiogenesis. Proc Natl Acad Sci USA. 1994;91(9):4082–4085. https://doi.org/10.1073/pnas.91.9.4082
31. Quilitz R. Thalidomide in oncology: the peril and the promise. Clin Exp Dermatol. 2000;25(5):370–378. https://doi.org/10.1111/j.1365-2230.2000.tb03254.x
32. Moreira AL, Friedlander DR, Shif B, Kaplan G, Zagzag D. Thalidomide and a thalidomide analogue inhibit endothelial cell proliferation in vitro. J Neurooncol. 1999;43(2):109–114. https://doi.org/10.1023/a:10066202700039
33. Haslett PA, Corral LG, Albert M, Kaplan G. Thalidomide costimulates primary human T lymphocytes, preferentially inducing proliferation, cytokine production, and cytotoxic responses in the CD8+ subset. J Exp Med. 1998;187(11):1885–1892. https://doi.org/10.1084/jem.187.11.1885
34. Tavares JL, Wangoo A, Dilworth P, Marshall B, Kotecha S, Shaw RJ. Thalidomide reduces tumour necrosis factor-alpha production by human alveolar macrophages. Respir Med. 1997;91(1):31–39. https://doi.org/10.1054/resp.1997.0554
35. Gad SM, Shannon EJ, Krotoski WA, Hastings RC. Thalidomide induces imbalances in T-lymphocyte sub-populations in the circulating blood of healthy males. Lepr Rev. 1985;56(1):35–39. https://doi.org/10.5935/0305-7518.19850006
36. Thomas DA, Kantarjian HM. Current role of thalidomide in cancer treatment. Curr Opin Oncol. 2000;12(6):564–573. https://doi.org/10.1097/0001622-200011000-00009
37. Haslett PA, Corral LG, Albert M, Kaplan G. Thalidomide costimulates primary human T lymphocytes, preferentially inducing proliferation, cytokine production, and cytotoxic responses in the CD8+ subset. J Exp Med. 1998;187(11):1885–1892. https://doi.org/10.1084/jem.187.11.1885
38. Moller DR, Wysocka M, Greenlee BM, et al. Inhibition of IL-12 production by thalidomide. J Immunol. 1997;159:5157–5161.
39. Shannon EJ, Sandoval F. Thalidomide increases the synthesis of IL-2 in cultures of human mononuclear cells stimulated with Concanavalin-A, Staphylococcal enterotoxin A, and purified protein derivative. Immunopharmacology. 1995;31(1):109–116. https://doi.org/10.1016/s0167-5699(95)00039-7
40. Von Moos R, Stolz R, Cerny T, Gillessen S. Thalidomide: from tragedy to promise. Swiss Med Wkly. 2003;133:77–87.
41. Turk BE, Jiang H, Liu JO. Binding of thalidomide to alpha1-acid glycoprotein may be involved in its inhibition of tumor necrosis factor alpha production. Proc Natl Acad Sci USA. 1996;93(15):7552–7556. https://doi.org/10.1073/pnas.93.15.7552
42. Mujagic H, Chabner BA, Mujagic Z. Mechanisms of action and potential therapeutic uses of thalidomide. Croat Med J. 2002;43(3):274–285.
43. Calderon P, Anziliotti M, Phelps R. Thalidomide in dermatology. New indications for an old drug. Int J Dermatol. 1997;36(12):881–887. https://doi.org/10.1111/j.1365-4362.1997.00298.x
44. Ribatti D, Vacca A. Therapeutic renaissance of thalidomide in the treatment of haematological malignancies. Leukemia. 2005;19(9):1525–1531. https://doi.org/10.1038/sj.leu.2403852
45. Hideshima T, Chauhan D, Shima Y, et al. Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy. Blood. 2000;96:2943–2950.
46. Thomas DA, Kantarjian HM. Current role of thalidomide in cancer treatment. Curr Opin Oncol. 2000;12(6):564–573. https://doi.org/10.1097/00001622-200011000-00009
47. Moreira AL, Sampaio EP, Zmuizdinas A, et al. Thalidomide exerts its inhibitory action on tumor necrosis factor alpha by enhancing mRNA degradation. *J Exp Med*. 1993;177(6):1675–1680. https://doi.org/10.1084/jem.177.6.1675

48. Singhal S, Mehta J, Desikan R, et al. Antitumor activity of thalidomide in refractory multiple myeloma. *N Engl J Med*. 1999;341(11):1565–1571. https://doi.org/10.1056/NEJM19991118341102

49. Partida-Sanchez S, Favila-Castillo L, Pedraza-Sanchez S, et al. IgG antibody subclasses, tumor necrosis factor and IFN-gamma levels in patients with type II lepra reaction on thalidomide treatment. *Int Arch Allergy Immunol*. 1998;116(1):60–66. https://doi.org/10.1159/000023926

50. D’Amato RJ, Loughnan MS, Flynn E, Folkman J. Thalidomide is an inhibitor of angiogenesis. *Proc Natl Acad Sci USA*. 1994;91(9):4082–4085. https://doi.org/10.1073/pnas.91.9.4082

51. Blake SC, Daniel BS. Cutaneous lupus erythematosus: a review of the literature. *Int J Womens Dermatol*. 2019;5(5):320–329. https://doi.org/10.1016/j.iwd.2019.07.004

52. Vera-Recabarren M, Garcia-Carrasco G, Ramos-Casals M, Herrero C. Comparative analysis of subacute cutaneous lupus erythematosus and chronic cutaneous lupus erythematosus: clinical and immunological study of 270 patients. *Br J Dermatol*. 2010;162(1):91–101. https://doi.org/10.1111/j.1365-2133.2009.09472.x

53. Filho JPM, Peixoto RL, Gomes Martins L, et al. Lupus erythematosus: considerations about clinical, cutaneous and therapeutic aspects. *An Bras Dermatol*. 2014;89(1):118–125. https://doi.org/10.1590/abd1806-4841.20142146

54. Walling HW, Sontheimer RD. Cutaneous lupus erythematosus: issues in diagnosis and treatment. *Am J Clin Dermatol*. 2009;10(6):365–381. https://doi.org/10.2165/11310780-000000000-00000

55. Böckle BC, Sepp NT. Smoking is highly associated with discoid lupus erythematosus and lupus erythematosus tumidus: analysis of 405 patients. *Lupus*. 2015;24(7):669–674. https://doi.org/10.1177/0961234314559630

56. Kiriakidou M, Ching CL. Systemic lupus erythematosus. *J Am Acad Dermatol*. 2010;62(1):91–101. https://doi.org/10.1016/j.jaad.2010.06.017

57. Kuhn A, Ochsendorf F, Bonsmann G. Treatment of cutaneous lupus erythematosus. *Ann Rheum Dis*. 2010;69(6):e195–213. https://doi.org/10.1136/annrheumdis-2011-200831

58. Okon LG, Werth VP. Cutaneous lupus erythematosus: diagnosis and treatment. *Best Pract Res Clin Rheumatol*. 2013;27(3):391–404. https://doi.org/10.1016/j.berh.2013.07.008

59. Cortes-Hernandez J, Torres-Salido M, Castro-Marrero J, et al. Thalidomide in the treatment of refractory cutaneous lupus erythematosus: prognostic factors of clinical outcome. *Br J Dermatol*. 2012;166(3):616–623. https://doi.org/10.1111/j.1365-2133.2011.10693.x
CASE SERIES – Thalidomide and discoid lupus erythematosus

71. Chasset F, Tounsi T, Cesbron E, Barbaud A, Frances C, Arnaud L. Efficacy and tolerance profile of thalidomide in cutaneous lupus erythematosus: a systematic review and meta-analysis. *J Am Acad Dermatol.* 2018;78(2):342–350.e4. https://doi.org/10.7573/dic.2021-9-8

72. Knop J, Bonsmann G, Happle R, et al. Thalidomide in the treatment of sixty cases of chronic discoid lupus erythematosus. *Br J Dermatol.* 1983;108(4):461–466. https://doi.org/10.1111/j.1365-2133.1983.tb04600.x

73. Company-Quiroga J, Alique-Garcia S, Romero-Maté A. Current insights into the management of discoid Lupus Erythematosus. *Clin Cosmet Investig Dermatol.* 2019;12:721–732. https://doi.org/10.2147/CCID.S184824

74. Duong DJ, Spigel GT, Moxley RT III, Gaspari AA. American experience with low-dose thalidomide therapy for severe cutaneous lupus erythematosus. *Arch Dermatol.* 1999;135(9):1079–1087. https://doi.org/10.1001/archderm.135.9.1079

75. Cuadrado MJ, Karim Y, Sanna G, et al. Thalidomide for the treatment of resistant cutaneous lupus: efficacy and safety of different therapeutic regimens. *Am J Med.* 2005;118(3):246–250. https://doi.org/10.1016/j.amjmed.2004.04.030

76. Wang D, Chen H, Wang S, et al. Thalidomide treatment in cutaneous lesions of systemic lupus erythematosus: a multicenter study in China. *Clin Rheumatol.* 2016;35(6):1521–1527. https://doi.org/10.1007/s10067-016-3256-3

77. Frankel HC, Sharon VR, Vleugels RA, et al. Lower-dose thalidomide therapy effectively treats cutaneous lupus erythematosus but is limited by neuropathic toxicity. *Int J Dermatol.* 2013;52(11):1407–1409. https://doi.org/10.1111/j.1365-4632.2011.05200.x

78. Moura Filho JP, Peixoto RL, Martins LG, et al. Lupus erythematosus: considerations about clinical, cutaneous and therapeutic aspects. *An Bras Dermatol.* 2014;89(1):118–125. https://doi.org/10.1590/abd1806-4841.20142146

79. Tseng S, Pak G, Washenik K, Pomeranz MK, Shupack JL. Rediscovering thalidomide: a review of its mechanism of action, side effects, and potential uses. *J Am Acad Dermatol.* 1996;35(6):969–979. https://doi.org/10.1016/s0190-9622(96)90122-x

80. Knop J, Bonsmann G, Ret H, et al. Thalidomide in the treatment of sixty cases of chronic discoid lupus erythematosus. *Br J Dermatol.* 1983;108(4):461–466. https://doi.org/10.1111/j.1365-2133.1983.tb04600.x

81. Frankel HC, Sharon VR, Vleugels RA, Merola JF, Qureshi AA. Lower-dose thalidomide therapy effectively treats cutaneous lupus erythematosus but is limited by neuropathic toxicity. *Int J Dermatol.* 2013;52(11):1407–1409. https://doi.org/10.1111/j.1365-4632.2011.05200.x

82. Cuadrado MJ, Karim Y, Sanna G, et al. Thalidomide for the treatment of resistant cutaneous lupus: efficacy and safety of different therapeutic regimens. *Am J Med.* 2005;118(3):246–250. https://doi.org/10.1016/j.amjmed.2004.04.030