Efficacy of Thalidomide in Discoid Lupus Erythematosus: Insights into the Molecular Mechanisms

Sandra Domingo^a Cristina Solé^a Teresa Moliné^b Berta Ferrer^b
Josep Ordi-Ros^c Josefina Cortés-Hernández^a

^aRheumatology Research Group, Lupus Unit, Vall d'Hebron University Hospital, Vall d'Hebron Research Institute (VHIR), Barcelona, Spain; ^bDepartment of Pathology, Vall d'Hebron University Hospital, Barcelona, Spain; ^cDepartment of Internal Medicine, Vall d'Hebron University Hospital, Vall d'Hebron Research Institute (VHIR), Barcelona, Spain

Keywords

Discoid lupus erythematosus · Systemic lupus erythematosus · Thalidomide · Refractory cutaneous lupus erythematosus · First-line treatment · Mechanism of action

Abstract

Background: Thalidomide has been used successfully in a variety of chronic refractory inflammatory dermatological conditions with underlying autoimmune or infectious pathogenesis. It was first used for refractory discoid lupus erythematosus (DLE) in 1983 and has steadily grown since then.

Method: In this review, we describe the therapeutic benefits of thalidomide for DLE treatment and its biological properties. We explain how new discoveries in DLE pathogenesis are relevant to understand thalidomide's mechanism of action and the need to find an alternative safe drug with similar therapeutic effects. **Summary:** Thalidomide's efficacy in DLE patients is significant, with 80–90% reaching clinical remission according to different studies. However, thalidomide's use is still limited by serious adverse effects such as teratogenicity, neurotoxicity, and thrombosis. In addition, there is a frequent rate of relapse and many patients require a long-term low dose of thalidomide as maintenance. The achievement of clinical response within weeks is key to avoid irre-

versible DLE fibrotic sequelae, making it critical to introduce thalidomide earlier in the DLE treatment algorithm. Recently, microarray and miRNA screenings demonstrated a significant CD4⁺ T enrichment and T-helper 1 response predominance with a dysregulation of regulatory T cell (Treg) expression in DLE lesions that induced high levels of proinflammatory, chemotaxis, and apoptotic proteins that induce the chronic inflammation response. Thalidomide's anti-inflammatory, antiangiogenic, and T-cell co-stimulatory effects may be beneficial for DLE since it promotes cytokine inhibition, inhibits macrophage activation, regulates Treg responses, inhibits angiogenesis, modulates T cells, and promotes NK cell-mediated cytotoxicity. © 2020 S. Karger AG, Basel

Introduction

Thalidomide is a derivative of glutamic acid, an oral non-barbituric drug, with sedative and antiemetic activity, introduced in the 1950s as a sedative for its rapid action and apparent safety [1]. However, teratogenicity of the drug was quickly described, estimating that 5,000–6,000 children suffered phocomelia secondary to its use during pregnancy, usually accompanied by other malfor-

mations. It was not until Sheskin [2] that beneficial effects on erythema nodosum leprosum were reported. Since then, there have been progressively more studies demonstrating the immunomodulatory and anti-inflammatory effect of thalidomide and its possible application in immune-mediated inflammatory diseases [3] and skin disorders such as chronic refractory purigo nodularis, erythema multiforme, Behçet's syndrome, and cutaneous lupus erythematosus (CLE) [4].

CLE is an autoimmune skin disease which includes a broad range of dermatologic manifestations. It may be associated with systemic lupus erythematosus (SLE). It is important to note that the skin is the second most frequent organ affected in SLE and that around 75% of SLE patients present skin manifestations at some point during the course of the systemic disease [5]. CLE is classified into several subtypes according to histological and clinical features. Of the different clinical subtypes, discoid lupus erythematosus (DLE) is one of the most prevalent and refractory form. DLE lesions tend to appear in sun-exposed skin, may be localized or generalized, and have a chronic relapsing-remitting course over time, having an important aesthetic and psychological impact and hence an impaired quality of life.

First-line therapies for DLE include antimalarial agents and/or topical steroids, together with sun protection. Although most patients respond to this regimen, approximately 30–40% of cases will be refractory [6]. For this significant minority, there is no consensus algorithm, and a trial and error approach using multiple systemic agents has shown a variable response. Thus, there is a need for new treatments.

Rapid improvement of subacute lesions of 2 CLE patients was first observed using thalidomide as treatment in 1983 [7]. Since then, further studies in CLE have shown its efficacy [8–22]. Currently, it is used in severe CLE, especially in profundus and discoid lupus. However, despite its efficacy, its use is limited because large-scale clinical trials have not been conducted and due to the serious adverse events that include teratogenicity, peripheral neuropathy, and thrombotic events. Patients need baseline nerve conduction studies given the high risk of polyneuropathy (20–30%), which may be irreversible [23].

Thalidomide's Efficacy for DLE Treatment

The effectiveness of thalidomide has been reported by several cohort studies of more than 60 patients; however, despite its proven clinical efficacy, it is still considered

second-line therapy. Our experience confirms that thalidomide is effective for the treatment of refractory DLE [14]. We reported 60 patients with refractory CLE of whom 25 were diagnosed with refractory DLE. Most patients (98%) improved following therapy and 85% achieved complete remission over a period of 8 years of follow-up. Clinical improvement was observed within the first 2 weeks of treatment, although a complete response usually occurred between weeks 4 and 8. Although no studies have established an induction and maintenance dosage for the control of skin lesions, the different studies have used between 100 and 400 mg/day. Our experience has been with an initial dose of 100 mg/day to better withstand the drowsiness that can occur, and subsequently, the dose was raised according to clinical response, not exceeding 400 mg/day [21].

Since 1983, several series of patients with different CLE subtypes have been published with good results (Table 1). The majority of the included patients were those with DLE, to a lesser extent with subacute cutaneous lupus (SCLE), and much less frequently acute lupus, profundus lupus, lupus tumidus, or non-specific lesions such as pyoderma gangrenous [21]. The response rates were significantly higher in DLE and SCLE (98%), whereas in the other CLE subtypes the response rates only reached 50%. Among patients with DLE, the generalized subtype tended to recur more than the localized one (92 vs. 73%, $p = 0.013$).

Relapse was frequent after thalidomide's withdrawal and most common in DLE. Kyriakis et al. [24] were the first to highlight the best and sustained response of patients with SCLE vs. DLE. In our series, recurrence reached 70% of all cases (35 of 50) [21], occurring mainly when decreasing or interrupting treatment [24]. Relapse occurred between 4 and 8 weeks after the interruption of thalidomide, but all cases responded to the drug reintroduction. In some cases of DLE, low-dose maintenance, 50 mg/day or even every other day, was sufficient to maintain the remission of the cutaneous disease to avoid future scars and side effects. In our studies, up to 16% of patients with DLE required long-term treatment but at lower doses.

One of the limitations of the retrospective studies has been the lack of use of validated scales to assess clinical response, such as the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) that allows us to assess the extent, activity, and sequelae of skin lesions objectively during treatment [25]. This is key to evaluate the effectiveness of new drugs in future clinical trials in CLE.

Table 1. Clinical studies of thalidomide and analogue lenalidomide for refractory cutaneous lupus erythematosus

Reference	Drug	Condition	N	Efficacy, <i>n</i> (%)		Relapse after thalidomide withdrawal, <i>n</i> (%)
				complete response	partial response	
Knop et al. [8], 1983	Thalidomide	60 DLE	60	54/60 (90, complete/partial response)		30/41 (71)
Hasper [9], 1983	Thalidomide	7 DLE 4 SCLE	11	7/11 (64)	2/11 (18)	6/11 (54)
Naafs and Faber [10], 1985	Thalidomide	5 DLE 4 SCLE 3 disseminated CLE 1 lupus profundus 5 SLE 1 MCTD	19	17/19 (89, complete/partial response)		1/17 (6)
Atra and Sato [11], 1993	Thalidomide	20 refractory CLE	20	18/20 (90)	2/20 (10)	N.D.
Stevens et al. [12], 1997	Thalidomide	11 DLE 3 SCLE 1 SCLE/malar rash 1 chronic erythema	16	7/16 (44)	6/16 (37)	6/8 (75)
Sato et al. [13], 1998	Thalidomide	2 DLE 3 SCLE 13 rash and/or vasculitis	18	13/18 (73)	5/18 (28)	18/18 (100)
Ordi-Ros et al. [14], 2000	Thalidomide	9 DLE 7 SCLE 4 lupus profundus 2 rash	22	12/16 (75)	4/16 (25)	9/16 (65)
Thomson et al. [15], 2001	Thalidomide	20 DLE 2 SCLE 5 SLE	27	7/27 (26)	11/27 (41)	4/11 (36)
Housman et al. [16], 2003	Thalidomide	8 CCLE 1 CCLE/lupus profundus 3 SCLE 4 lupus profundus 13 SLE	29	17/23 (74)	3/23 (13)	N.D.
Briani et al. [17], 2005	Thalidomide	5 CCLE 1 CCLE/vasculitis 4 SCLE 2 SCLE/vasculitis 1 ACLE/SCLE 1 vasculitis	14	14/14 (100, complete/partial response)		N.D.
Coelho et al. [18], 2005	Thalidomide	19 DLE 15 DLE/SLE 15 SCLE 12 SCLE/SLE 3 lupus profundus 1 bullous lupus	65	63/65 (97, complete/partial response)		23/27 (85)
Cuadrado et al. [19], 2005	Thalidomide	18 DLE 6 SCLE 24 SLE	48	29/48 (60)	10/48 (21)	26/39 (67)
Lyakhovisky et al. [20], 2006	Thalidomide	10 DLE	10	9/10 (90)	1/10 (19)	5/10 (50)

Table 1 (continued)

Reference	Drug	Condition	N	Efficacy, n (%)		Relapse after thalidomide withdrawal, n (%)
				complete response	partial response	
Cortés-Hernández et al. [21], 2012	Thalidomide	25 DLE 18 SCLE 6 ACLE 5 lupus profundus 3 chilblain LE 2 lupus tumidus 1 pyoderma gangrenosum	60	50/59 (85)	8/59 (14)	35/50 (70)
Wang et al. [22], 2016	Thalidomide	9 DLE 12 vasculitis 48 facial rash	69	49/69 (71)	20/69 (29)	N.D.
Shah et al. [67], 2009	Lenalidomide	2 DLE	2	0/2 (0)	1/2 (50)	N.D.
Cortés-Hernández et al. [68], 2012	Lenalidomide	9 DLE 2 SCLE 1 ACLE 2 lupus profundus 1 lupus tumidus	15	12/14 (86)	2/14 (14)	9/12 (75)
Braunstein et al. [69], 2012	Lenalidomide	3 DLE 1 SCLE/lupus tumidus 1 DLE/SCLE	5	0/5 (0)	4/5 (80)	N.D.
Kindle et al. [70], 2016	Lenalidomide	6 DLE 1 SCLE 2 profundus lupus	9	5/9 (56)	2/9 (22)	N.D.
Fennira et al. [71], 2016	Lenalidomide	14 DLE 2 SCLE	16	2/14 (14)	12/14 (86)	0/13 (0)
Wu et al. [72], 2017	Lenalidomide	10 recalcitrant CLE/SLE	10	10/10 (100 complete/partial response)		N.D.

CLE, cutaneous lupus erythematosus; DLE, discoid lupus erythematosus; SCLE, subacute cutaneous lupus erythematosus; ACLE, acute cutaneous lupus erythematosus; SLE, systemic lupus erythematosus; N.D., Not detailed.

Described Biological Properties of Thalidomide

Thalidomide is known for its anti-inflammatory, anti-angiogenic, and immunomodulatory properties.

Anti-inflammatory. In 1991, it was discovered that thalidomide inhibited the synthesis of tumour necrosis factor- α (TNF- α) [26]. Both soluble and membrane-bound TNF bind to 2 transmembrane receptor molecules: TNFR1 and TNFR2, which are present in almost all cells, giving the cytokine a broad function according to the tissue and/or organ where it acts. TNF- α induces an increased vascular permeability leading to a greater recruitment of inflammatory cells, immunoglobulins, and complement, as well as causing activation of T and B lymphocytes. Thalidomide's effect on TNF- α release plays an important role in its ability to modulate the immune system [27]. Activated macrophages are the main producers

of TNF- α and also highly reactive to it, although it can be produced by many other cell types. It has been demonstrated that thalidomide inhibits the alternative activation of macrophages accompanied by a reduction of TNF- α , interleukin (IL)-4, IL-5, IL-13, and IL-17 [28]. It can also modulate other inflammatory cytokines such as IL-1, IL-2, IL-6, IL-8, IL-10, IL-12, and interferon- γ (IFN- γ) [29].

Antiangiogenic. It was in 1994 when the antiangiogenic effect of thalidomide was discovered [30]. Angiogenesis occurs physiologically in wound healing, bringing oxygen, nutrients, and cytokines involved in tissue repair. Using a rabbit model, it was demonstrated that thalidomide could inhibit fibroblast growth factor and vascular endothelial growth factor (VEGF) induced in angiogenesis. Due to its antiangiogenic effects, thalidomide is able to alter foetal development in pregnant women, which

leads to foetal deformity. However, at the same time this effect is one of the mechanisms for its antitumour activity [31]. In vitro and in vivo studies suggest that immunomodulatory drugs (IMiDs) may inhibit angiogenesis by antimigratory rather than antiproliferative mechanisms due to inhibiting the secretion of VEGF [32]. Thalidomide reduces metastasis by reducing the expression of proangiogenic cytokines such as VEGF that decreases both capillary density and the number of adhesion cells.

Immunomodulatory. The process of co-stimulation of lymphocytic T-cell populations is important for the activation of the immune system and the generation of antibodies against relevant antigens. In particular, to avoid immunological tolerance or anergy, activation of T cells by antigen-presenting cells (APCs) requires the interaction of the major histocompatibility complex with cellular T receptors, and other secondary molecules such as B7 (in APCs) with CD28 (in T cells). To date, immunomodulatory effect of thalidomide is poorly understood. In 1998, it was discovered that thalidomide could co-stimulate T cells independently of the secondary interaction between B7 and CD28 molecules [33]. It has been shown that thalidomide has a major effect on the immune response in T-helper 1 (Th1) diseases by shifting Th1 to a Th2 response. A potential denominator to explain thalidomide's effect in the modulation of graft vs. host, erythema nodosum leprosum, and auto-immune disorders would be the activation of T lymphocytes leading to the synthesis of IL-2, the expression of high-affinity IL-2 receptors, and the induction of lymphocyte proliferation [34]. However, Fernandez et al. [35] could not demonstrate a modulatory effect on the immune response in human leukemia cell line Jurkat cells via IL-2 production. In addition, drugs derived from thalidomide, IMiDs such as lenalidomide and pomalidomide, have been shown to have a clear co-stimulatory effect in both CD4⁺ and in CD8⁺ T cells [36]. IMiDs exert their effects by activating protein kinase C delta (PKC- θ) and acting on AP-1 DNA-binding activity in T cells, resulting in augmented IL-2 synthesis and activation of IL-2-dependent downstream effectors, such as natural killer cells (NK) [37]. The increment of IL-2 production by these drugs has been confirmed by several studies [38]. Moreover, in 2010, cereblon (CRBN) was discovered as the main protein target of thalidomide. CRBN forms an E3 ubiquitin ligase complex with damaged DNA binding protein 1 (DDB1) and Cul4A that is important for limb outgrowth. When thalidomide binds to CRBN, the associated ubiquitin ligase activity of CRBN is inhibited, producing teratogenic effects [39]. Subsequently, it was demonstrated that CRBN was also required for the anti-

myeloma activity of thalidomide, and downstream targets of CRBN were investigated in order to understand the reason [40]. Two critical CRBN-mediated downregulation genes have been identified: transcription factor Ikaros (IKZF1) and Aiolos (IKZF3) [41]. Ikaros family genes regulate immune cell development [42] and the pathological dysregulation of c-Myc and IRF4 [43].

Plausible Biologic Mechanism in DLE

Potential Biologic Thalidomide Mechanism of Action in DLE

The pathogenesis of DLE is currently not completely understood and likely to be multifactorial, involving genetics, epigenetics, and environmental factors. The findings indicate that there is an initial trigger in order to develop the disease. UVB light is a known CLE trigger, which causes apoptosis of keratinocytes and inflammation in CLE skin. The apoptotic keratinocytes release autoantigens which are recognized by APCs, and there is an activation of autoreactive B and T cells. This promotes an immune cell recruitment and production of cytokines, chemokines, and autoantibodies [44]. Deposition of IgGs and C3 is frequently detected in DLE-affected skin. As a result, the skin is damaged and inflamed leading to the DLE lesions. Other potential DLE-described triggers are viral infections, drugs, chemicals, and smoking habits. However, further studies are required in order to obtain clear evidence concerning their role in DLE [45].

Gene expression microarray analysis of DLE have shown an increase in the IFN signalling pathway genes as well as a significant CD4⁺ T enrichment with a Th1 response predominance [46]. In addition, an increase of the apoptotic signalling molecules CD95, TRAIL-R1, and caspase-8 has been identified by tissue microarray analysis [47]. Microarray analysis comparing lesional and non-lesional DLE areas showed an upregulation in lesioned sites of IFN, apoptosis makers, NK, dendritic cell, chemotaxis genes, and leucocyte activation [48]. DLE peripheral blood gene expression has also been studied, revealing that IFN, immune response, and stress pathways are significantly increased in comparison with healthy individuals [49]. Another study in which an miRNA screening profile was conducted in DLE showed that an overexpression of miR-31 in DLE lesional skin induced an increased production of IL-8 and IL-12 in keratinocytes, suggesting that these cytokines play a key role in the inflammatory environment of DLE lesions [50].

Fig. 1. Plausible thalidomide mechanism of action in discoid lupus erythematosus (DLE). 1. Anti-inflammatory: thalidomide may act as an anti-inflammatory agent by inhibiting TNF- α production that is essential for macrophage, T- and B-cell activation. It could also reduce cytokines present in DLE lesions, IL-8, and IL-12, and as a result, there may be less immune cell recruitment in the lesion site. 2. Immunomodulatory effects: thalidomide induces ubiquitination of IKZF1/3 by targeting CRBN complex resulting in their proteasomal degradation. Consequently, IRF4 transcription de-

creases and it could cause T-cell immunomodulatory effects and dendritic cell dysfunction. IL-10 and TGF- β in DLE are induced by regulatory T cells (Tregs) and initiate fibrosis. Thalidomide may decrease IL-10 and TGF- β Treg production. 3. Antiangiogenesis: thalidomide could improve DLE lesions, reducing erythema and telangiectasia and decreasing blood vessel formation by decreasing vascular endothelial growth (VEGF). 4. Photoprotection: thalidomide photoprotective properties could contribute to its therapeutic effects in UVB-exposed skin.

Given thalidomide's efficacy in the treatment of DLE, the inhibition of IL-8 and IL-12 might be one of the possible anti-inflammatory mechanisms of action of this drug (Fig. 1). However, no studies have assessed the effect on these cytokines in patients with DLE. Regarding TNF- α , it is unclear if thalidomide acts by inhibiting its production, since studies show contradictory results [51, 52]. In addition, anti-TNF- α drugs seem to induce cutaneous lupus lesions [53].

Thalidomide angiogenic properties may play a role in its ability to treat DLE lesions as DLE patients present high levels of VEGF in serum, and several chronic inflammatory skin diseases such as atopic dermatitis and psoriasis are characterized by altered angiogenesis and overexpression of VEGF. Moreover, one of the beneficial effects of chloroquine treatment in DLE may be due to its antiangiogenic properties reducing erythema, lowering photosensitivity and decreasing blood vessel formation and telangiectasia

[54]. However, it is important to note that lesions of SCLÉ have been reported as a response to bevacizumab, a recombinant humanized antibody against VEGF [55], therefore it is not totally clear if the antiangiogenic properties of thalidomide could be beneficial for DLE treatment (Fig. 1).

DLE skin lesions display a significant CD4⁺ T-cell enrichment with a high level of production of IL-2 and a relative increase of Treg response [46]. IL-2 is a relevant cytokine and induces an expansion of Tregs. Some studies show that IMiDs have an inhibitory effect on Tregs [56], and thalidomide regulates Treg activity [57]. So, a reduction or regulation of Treg response in DLE lesions may decrease IL-10 and TGF- β production and slow down the TGF- β -dependent mechanism of fibrosis, reducing scarring (Fig. 1). But restoration of abnormal immune function should be addressed more carefully in cutaneous and non-cutaneous lupus patients considering the complexity of disease pathogenesis.

Fig. 2. Novel safety thalidomide derivate for refractory DLE treatment. Early resolution of inflammation in DLE is very relevant to avoid irreversible sequelae. In many cases, current treatments are not powerful enough to prevent scarring in refractory DLE patients. An alternative could be a thalidomide derivate with a better safety profile, avoiding serious adverse effects, such as teratogenicity, peripheral neuropathy, drowsiness, amenorrhea, and thrombotic events, but preserving anti-inflammatory and immunomodulatory thalidomide properties.

Polymorphisms in the IKZF1 and IKZF3 loci are associated with an increased risk of SLE, but their roles are still being studied [58]. On the other hand, IRF4 plays a fundamental role in dendritic cell differentiation, and it has been suggested that an IRF4-dependent pathway contributes to their dysfunction in lupus [59]. Consequently, thalidomide's T-cell modulatory properties in DLE patients could also be related to the initial binding to CRBN that induces proteasomal degradation of IKZF1/3 and inhibition of IRF4 transcription (Fig. 1). Further specific study of CRBN downstream signalling in skin biopsies will help to delineate the underlying mechanisms for thalidomide's efficacy in DLE treatment.

It has been described that thalidomide has a photoprotective effect by inhibiting acute UVB erythema in non-lesional skin of DLE (Fig. 1). However, no differences were observed in the frequency of apoptotic keratinocytes in the UVB-exposed areas before and after thalidomide treatment [60]. The authors conclude that these photoprotective properties may partly contribute to the therapeutic effect of thalidomide in cutaneous UVB-related diseases. As UVB exposure is an initial CLE trigger, this needs to be investigated in order to get more insights into the mechanism of action of thalidomide in DLE and other cutaneous diseases.

Limited Clinical Use of Thalidomide in DLE: Need of Novel Safety Analogues

Around 25–30% of DLE thalidomide-treated patients can develop minor side effects that resolve after its withdrawal or dose adjustment. Drowsiness, dizziness, flatulence, constipation, and dry skin are frequent and dose dependent. However, side effects could be more serious,

such as an exfoliative dermatitis, toxic epidermolysis, and exacerbation of psoriasis, allergic vasculitis, or hereditary purpura caused by thrombocytopenia [61]. According to several studies, peripheral neuropathy incidence ranges from 20 to 30% for thalidomide-treated CLE patients [23]. Other side effects that deserve to be mentioned include ovarian toxicity and the risk of thrombotic events [62, 63]. Thalidomide could also induce a state of hypercoagulation [64], and this risk can increase significantly in the presence of concomitant oral contraceptive use and antiphospholipid antibodies [65, 66]. For this reason, thalidomide treatment is given only for refractory cases.

There is no clear definition of refractory cutaneous lupus, nor is there consensus about when thalidomide should be introduced. Thalidomide treatment always requires an accurate analysis of each case, and it is important to have its toxicity in mind. For this reason, analogues of thalidomide have been developed in order to avoid the undesired side effects. Of these, lenalidomide displayed similar efficacy and relapse rates as thalidomide [67–72], and iberdomide (CC-220) improved significantly moderate-to-severe lupus skin manifestations [73]. Lenalidomide has greater immunomodulatory properties than thalidomide, being more potent in the stimulation of T-cell proliferation and IFN- γ /IL-1 production [74]. CC-220 binds cereblon with a higher affinity than previous IMiDs, and degradation of Ikaros and Aiolos is more potent [75]. In addition, thalidomide analogues seem to be safer with less risk of developing side effects such as has been observed with lenalidomide-treated patients who seem to present a decreased risk of peripheral neuropathy [68, 76]. Regarding CC-220, frequency of side effects and its efficacy is still under investigation. IMiDs are an expensive therapeutic option compared to thalidomide. There is a need to develop novel thalidomide analogues

with a better safety profile that could be introduced at early stages in the management of DLE after failure of conventional standard therapy to avoid irreversible sequelae (Fig. 2).

Conclusion

Thalidomide is a notable drug to be used in human immune complex diseases for its potential biological effect. Its therapeutic efficacy has been described as anti-inflammatory, antiangiogenic, and T-cell co-stimulatory. In recent years, data suggest that it is a successful treatment for DLE. Its mechanism in DLE patients may be due to cytokine inhibition, inhibition of macrophage activation, Treg response regulation, inhibition of angiogenesis, T-cell modulation, and promotion of NK cell-mediated cytotoxicity. Nevertheless, serious side effects of thalidomide limited its use for refractory cases only. In DLE, where early resolution of inflammation is so important to avoid irreversible scarring and sequelae, it will be critical to introduce a safe derivative of thalidomide earlier. Further study with molecular biology techniques is required in order to get more insights into the biological mechanism of thalidomide in DLE and, therefore, be able to discover and develop novel thalidomide analogues effective for DLE, safer and without side effects.

References

- 1 Mellin GW, Katzenstein M. The saga of thalidomide. Neuropathy to embryopathy, with case reports of congenital anomalies. *N Engl J Med*. 1962 Dec;267:1184–92.
- 2 Sheskin J. Thalidomide in the treatment of lepra reactions. *Clin Pharmacol Ther*. 1965 May-Jun;6(3):303–6.
- 3 Baker KF, Isaacs JD. Novel therapies for immune-mediated inflammatory diseases: what can we learn from their use in rheumatoid arthritis, spondyloarthritis, systemic lupus erythematosus, psoriasis, Crohn's disease and ulcerative colitis? *Ann Rheum Dis*. 2018 Feb;77(2):175–87.
- 4 Calderon P, Anzilotti M, Phelps R. Thalidomide in dermatology. New indications for an old drug. *Int J Dermatol*. 1997 Dec;36(12):881–7.
- 5 Obermoser G, Sontheimer RD, Zelger B. Overview of common, rare and atypical manifestations of cutaneous lupus erythematosus and histopathological correlates. *Lupus*. 2010 Aug;19(9):1050–70.
- 6 Chang AY, Piette EW, Foering KP, Tenhave TR, Okawa J, Werth VP. Response to antimalarial agents in cutaneous lupus erythematosus: a prospective analysis. *Arch Dermatol*. 2011 Nov;147(11):1261–7.
- 7 Volc-Platzer B, Wolff K. [Treatment of subacute cutaneous lupus erythematosus with thalidomide]. *Hautarzt*. 1983 Apr;34(4):175–8.
- 8 Knop J, Bonsmann G, Happle R, Ludolph A, Matz DR, Mifsud EJ, et al. Thalidomide in the treatment of sixty cases of chronic discoid lupus erythematosus. *Br J Dermatol*. 1983 Apr;108(4):461–6.
- 9 Hasper MF. Chronic cutaneous lupus erythematosus. Thalidomide treatment of 11 patients. *Arch Dermatol*. 1983 Oct;119(10):812–5.
- 10 Naafs B, Faber WR. Thalidomide therapy. An open trial. *Int J Dermatol*. 1985 Mar;24(2):131–4.
- 11 Atra E, Sato EI. Treatment of the cutaneous lesions of systemic lupus erythematosus with thalidomide. *Clin Exp Rheumatol*. 1993 Sep-Oct;11(5):487–93.
- 12 Stevens RJ, Andujar C, Edwards CJ, Ames PR, Barwick AR, Khamashta MA, et al. Thalidomide in the treatment of the cutaneous manifestations of lupus erythematosus: experience in sixteen consecutive patients. *Br J Rheumatol*. 1997 Mar;36(3):353–9.
- 13 Sato EI, Assis LS, Lourenzi VP, Andrade LE. Long-term thalidomide use in refractory cutaneous lesions of systemic lupus erythematosus. *Rev Assoc Med Bras (1992)*. Oct-Dec 1998;44(4):289–93.
- 14 Ordi-Ros J, Cortés F, Cucurull E, Mauri M, Buján S, Vilardell M. Thalidomide in the treatment of cutaneous lupus refractory to conventional therapy. *J Rheumatol*. 2000 Jun;27(6):1429–33.
- 15 Thomson KF, Goodfield MJ. Low-dose thalidomide is an effective second-line treatment in cutaneous lupus erythematosus. *J Dermatolog Treat*. 2001 Sep;12(3):145–7.
- 16 Housman TS, Jorizzo JL, McCarty MA, Grummer SE, Fleischer AB Jr, Sutej PG. Low-dose thalidomide therapy for refractory cutaneous lesions of lupus erythematosus. *Arch Dermatol*. 2003 Jan;139(1):50–4.
- 17 Briani C, Zara G, Rondinone R, Iaccarino L, Ruggero S, Toffanin E, et al. Positive and negative effects of thalidomide on refractory cutaneous lupus erythematosus. *Autoimmunity*. 2005 Nov;38(7):549–55.

Key Message

The recent new insights into thalidomide's mechanism of action and discoid lupus erythematosus (DLE) pathogenesis could be used to design a novel treatment for refractory DLE.

Acknowledgements

We would like to acknowledge the Instituto de Salud Carlos III (Spain Government, PI15/02145), Catalan Lupus Foundation, and A. Bosch Foundation for their financial support.

Conflict of Interest Statement

The authors declare that they have no conflict of interest regarding the publication of this article.

Funding Sources

This work was funded by the Instituto de Salud Carlos III (Spanish Government, PI15/02145), Catalan Lupus Foundation, and A. Bosch Foundation.

Author Contributions

This paper was planned and written in collaboration with all the authors.

- 18 Coelho A, Souto MI, Cardoso CR, Salgado DR, Schmal TR, Waddington Cruz M, et al. Long-term thalidomide use in refractory cutaneous lesions of lupus erythematosus: a 65 series of Brazilian patients. *Lupus*. 2005;14(6): 434–9.
- 19 Cuadrado MJ, Karim Y, Sanna G, Smith E, Khamashta MA, Hughes GR. Thalidomide for the treatment of resistant cutaneous lupus: efficacy and safety of different therapeutic regimens. *Am J Med*. 2005 Mar;118(3):246–50.
- 20 Lyakhovitsky A, Baum S, Shpiro D, Salomon M, Trau H. [Thalidomide therapy for discoid lupus erythematosus]. *Harefuah*. 2006 Jul; 145(7):489–92.
- 21 Cortés-Hernández J, Torres-Salido M, Castro-Marrero J, Vilardell-Tarres M, Ordi-Ros J. Thalidomide in the treatment of refractory cutaneous lupus erythematosus: prognostic factors of clinical outcome. *Br J Dermatol*. 2012 Mar;166(3):616–23.
- 22 Wang D, Chen H, Wang S, Zou Y, Li J, Pan J, et al. Thalidomide treatment in cutaneous lesions of systemic lupus erythematosus: a multicenter study in China. *Clin Rheumatol*. 2016 Jun;35(6):1521–7.
- 23 Bastuji-Garin S, Ochonisky S, Bouche P, Gherardi RK, Duguet C, Djerradine Z, et al.; Thalidomide Neuropathy Study Group. Incidence and risk factors for thalidomide neuropathy: a prospective study of 135 dermatologic patients. *J Invest Dermatol*. 2002 Nov;119(5):1020–6.
- 24 Kyriakis KP, Kontochristopoulos GJ, Panteleos DN. Experience with low-dose thalidomide therapy in chronic discoid lupus erythematosus. *Int J Dermatol*. 2000 Mar;39(3):218–22.
- 25 Albrecht J, Taylor L, Berlin JA, Dulay S, Ang G, Fakharzadeh S, et al. The CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index): an outcome instrument for cutaneous lupus erythematosus. *J Invest Dermatol*. 2005 Nov;125(5):889–94.
- 26 Sampaio EP, Sarno EN, Galilly R, Cohn ZA, Kaplan G. Thalidomide selectively inhibits tumor necrosis factor alpha production by stimulated human monocytes. *J Exp Med*. 1991 Mar;173(3):699–703.
- 27 Moreira AL, Sampaio EP, Zmuidzinis A, Frindt P, Smith KA, Kaplan G. Thalidomide exerts its inhibitory action on tumor necrosis factor alpha by enhancing mRNA degradation. *J Exp Med*. 1993 Jun;177(6):1675–80.
- 28 Lee HS, Kwon HS, Park DE, Woo YD, Kim HY, Kim HR, et al. Thalidomide inhibits alternative activation of macrophages in vivo and in vitro: a potential mechanism of anti-asthmatic effect of thalidomide. *PLoS One*. 2015 Apr;10(4):e0123094.
- 29 Meierhofer C, Dunzendorfer S, Wiedermann CJ. Theoretical basis for the activity of thalidomide. *BioDrugs*. 2001;15(10):681–703.
- 30 D'Amato RJ, Loughnan MS, Flynn E, Folkman J. Thalidomide is an inhibitor of angiogenesis. *Proc Natl Acad Sci USA*. 1994 Apr; 91(9):4082–5.
- 31 Fanelli M, Sarmiento R, Gattuso D, Carillio G, Capaccetti B, Vacca A, et al. Thalidomide: a new anticancer drug? *Expert Opin Investig Drugs*. 2003 Jul;12(7):1211–25.
- 32 Dredge K, Marriott JB, Macdonald CD, Man HW, Chen R, Muller GW, et al. Novel thalidomide analogues display anti-angiogenic activity independently of immunomodulatory effects. *Br J Cancer*. 2002 Nov;87(10): 1166–72.
- 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 Jun;187(11):1885–92.
- 34 Hendler SS, McCarty MF. Thalidomide for autoimmune disease. *Med Hypotheses*. 1983 Apr;10(4):437–43.
- 35 Fernandez LP, Schlegel PG, Baker J, Chen Y, Chao NJ. Does thalidomide affect IL-2 response and production? *Exp Hematol*. 1995 Aug;23(9):978–85.
- 36 Marriott JB, Clarke IA, Dredge K, Muller G, Stirling D, Dalglish AG. Thalidomide and its analogues have distinct and opposing effects on TNF-alpha and TNFR2 during co-stimulation of both CD4(+) and CD8(+) T cells. *Clin Exp Immunol*. 2002 Oct;130(1):75–84.
- 37 Davies FE, Raje N, Hideshima T, Lentzsch S, Young G, Tai YT, et al. Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma. *Blood*. 2001 Jul;98(1):210–6.
- 38 Payvandi F, Wu L, Naziruddin SD, Haley M, Parton A, Schafer PH, et al. Immunomodulatory drugs (IMiDs) increase the production of IL-2 from stimulated T cells by increasing PKC-theta activation and enhancing the DNA-binding activity of AP-1 but not NF-kappaB, OCT-1, or NF-AT. *J Interferon Cytokine Res*. 2005 Oct;25(10):604–16.
- 39 Ito T, Ando H, Suzuki T, Ogura T, Hotta K, Imamura Y, et al. Identification of a primary target of thalidomide teratogenicity. *Science*. 2010 Mar;327(5971):1345–50.
- 40 Zhu YX, Kortuem KM, Stewart AK. Molecular mechanism of action of immune-modulatory drugs thalidomide, lenalidomide and pomalidomide in multiple myeloma. *Leuk Lymphoma*. 2013 Apr;54(4):683–7.
- 41 Krönke J, Hurst SN, Ebert BL. Lenalidomide induces degradation of IKZF1 and IKZF3. *Oncotarget*. 2014 Jul;3(7):e941742.
- 42 Georgopoulos K, Winandy S, Avitahl N. The role of the Ikaros gene in lymphocyte development and homeostasis. *Annu Rev Immunol*. 1997;15(1):155–76.
- 43 Lopez-Girona A, Heintel D, Zhang LH, Mendy D, Gaidarova S, Brady H, et al. Lenalidomide downregulates the cell survival factor, interferon regulatory factor-4, providing a potential mechanistic link for predicting response. *Br J Haematol*. 2011 Aug;154(3): 325–36.
- 44 Stannard JN, Kahlenberg JM. Cutaneous lupus erythematosus: updates on pathogenesis and associations with systemic lupus. *Curr Opin Rheumatol*. 2016 Sep;28(5):453–9.
- 45 Szczęch J, Samotij D, Werth VP, Reich A. Trigger factors of cutaneous lupus erythematosus: a review of current literature. *Lupus*. 2017 Jul;26(8):791–807.
- 46 Solé C, Gimenez-Barcons M, Ferrer B, Ordi-Ros J, Cortés-Hernández J. Microarray study reveals a transforming growth factor-beta-dependent mechanism of fibrosis in discoid lupus erythematosus. *Br J Dermatol*. 2016 Aug;175(2):302–13.
- 47 Toberer F, Sykora J, Göttel D, Hartschuh W, Werchau S, Enk A, et al. Apoptotic signal molecules in skin biopsies of cutaneous lupus erythematosus: analysis using tissue microarray. *Exp Dermatol*. 2013 Oct;22(10):656–9.
- 48 Dey-Rao R, Smith JR, Chow S, Sinha AA. Differential gene expression analysis in CCLE lesions provides new insights regarding the genetics basis of skin vs. systemic disease. *Genomics*. 2014 Aug;104(2):144–55.
- 49 Dey-Rao R, Sinha AA. Genome-wide transcriptional profiling of chronic cutaneous lupus erythematosus (CCLE) peripheral blood identifies systemic alterations relevant to the skin manifestation. *Genomics*. 2015 Feb;105(2):90–100.
- 50 Solé C, Domingo S, Ferrer B, Moliné T, Ordi-Ros J, Cortés-Hernández J. MicroRNA expression profiling identifies miR-31 and miR-485-3p as regulators in the pathogenesis of discoid cutaneous lupus. *J Invest Dermatol*. 2019 Jan;139(1):51–61.
- 51 Aringer M, Smolen JS. Efficacy and safety of TNF-blocker therapy in systemic lupus erythematosus. *Expert Opin Drug Saf*. 2008 Jul; 7(4):411–9.
- 52 Bhattacharya SN, Chattopadhyaya D, Saha K. Tumor necrosis factor: status in reactions in leprosy before and after treatment. *Int J Dermatol*. 1993 Jun;32(6):436–9.
- 53 He Y, Sawalha AH. Drug-induced lupus erythematosus: an update on drugs and mechanisms. *Curr Opin Rheumatol*. 2018 Sep;30(5):490–7.
- 54 Lesiak A, Narbutt J, Kobos J, Kordek R, Sysa-Jedrzejowska A, Norval M, et al. Systematic administration of chloroquine in discoid lupus erythematosus reduces skin lesions via inhibition of angiogenesis. *Clin Exp Dermatol*. 2009 Jul;34(5):570–5.
- 55 Cleaver N, Ramirez J, Gildenberg S. Cutaneous lupus erythematosus in a patient undergoing intravitreal bevacizumab injections: case report and review of the literature. *J Drugs Dermatol*. 2013 Sep;12(9):1052–5.
- 56 Galustian C, Meyer B, Labarthe MC, Dredge K, Klaschka D, Henry J, et al. The anti-cancer agents lenalidomide and pomalidomide inhibit the proliferation and function of T regulatory cells. *Cancer Immunol Immunother*. 2009 Jul;58(7):1033–45.
- 57 Skórka K, Bhattacharya N, Własiuk P, Kowal M, Mertens D, Dmoszyńska A, et al. Thalidomide regulation of NF-kB proteins limits Tregs activity in chronic lymphocytic leukemia. *Adv Clin Exp Med*. 2014 Jan-Feb;23(1): 25–32.

- 58 Hu SJ, Wen LL, Hu X, Yin XY, Cui Y, Yang S, et al. IKZF1: a critical role in the pathogenesis of systemic lupus erythematosus? *Mod Rheumatol*. 2013 Mar;23(2):205–9.
- 59 Manni M, Gupta S, Nixon BG, Weaver CT, Jessberger R, Pernis AB. IRF4-dependent and IRF4-independent pathways contribute to DC dysfunction in Lupus. *PLoS One*. 2015 Nov;10(11):e0141927.
- 60 Cummins DL, Gaspari AA. Photoprotection by thalidomide in patients with chronic cutaneous and systemic lupus erythematosus: discordant effects on minimal erythema dose and sunburn cell formation. *Br J Dermatol*. 2004 Aug;151(2):458–64.
- 61 Chasset F, Tounsi T, Cesbron E, Barbaud A, Francès C, Arnaud L. Efficacy and tolerance profile of thalidomide in cutaneous lupus erythematosus: A systematic review and meta-analysis. *J Am Acad Dermatol*. 2018 Feb; 78(2):342–350.e4.
- 62 Lenz W, Knapp K. Thalidomide embryopathy. *Arch Environ Health*. 1962 Aug;5(2): 100–5.
- 63 Ordi J, Cortes F, Martinez N, Mauri M, De Torres I, Vilardell M. Thalidomide induces amenorrhea in patients with lupus disease. *Arthritis Rheum*. 1998 Dec;41(12):2273–5.
- 64 Bennett CL, Schumock GT, Desai AA, Kwaan HC, Raisch DW, Newlin R, et al. Thalidomide-associated deep vein thrombosis and pulmonary embolism. *Am J Med*. 2002 Nov; 113(7):603–6.
- 65 Bishnoi A, Singh V, Handa S, Vinay K. Thalidomide and thromboprophylaxis for dermatologic indications: an unmet need for more evidence. *J Am Acad Dermatol*. 2018 Sep;79(3):e45–6.
- 66 Cesbron E, Bessis D, Jachiet M, Lipsker D, Cordel N, Bouaziz JD, et al.; Study Group of Systemic Diseases in Dermatology (Étude des Maladies Systémiques en Dermatologie). Risk of thromboembolic events in patients treated with thalidomide for cutaneous lupus erythematosus: A multicenter retrospective study. *J Am Acad Dermatol*. 2018 Jul;79(1):162–5.
- 67 Shah A, Albrecht J, Bonilla-Martinez Z, Okawa J, Rose M, Rosenbach M, et al. Lenalidomide for the treatment of resistant discoid lupus erythematosus. *Arch Dermatol*. 2009 Mar;145(3):303–6.
- 68 Cortés-Hernández J, Ávila G, Vilardell-Tarés M, Ordi-Ros J. Efficacy and safety of lenalidomide for refractory cutaneous lupus erythematosus. *Arthritis Res Ther*. 2012 Dec; 14(6):R265.
- 69 Braunstein I, Goodman NG, Rosenbach M, Okawa J, Shah A, Krathen M, et al. Lenalidomide therapy in treatment-refractory cutaneous lupus erythematosus: histologic and circulating leukocyte profile and potential risk of a systemic lupus flare. *J Am Acad Dermatol*. 2012 Apr;66(4):571–82.
- 70 Kindle SA, Wetter DA, Davis MD, Pittelkow MR, Scialis GF. Lenalidomide treatment of cutaneous lupus erythematosus: the Mayo Clinic experience. *Int J Dermatol*. 2016 Aug; 55(8):e431–9.
- 71 Fennira F, Chasset F, Soubrier M, Cordel N, Petit A, Francès C. Lenalidomide for refractory chronic and subacute cutaneous lupus erythematosus: 16 patients. *J Am Acad Dermatol*. 2016 Jun;74(6):1248–51.
- 72 Wu EY, Schanberg LE, Wershba EC, Rabinovich CE. Lenalidomide for refractory cutaneous manifestations of pediatric systemic lupus erythematosus. *Lupus*. 2017 May;26(6):646–9.
- 73 Werth V, Furie R, Gaudy A, Ye Y, Korish S, Delev N, et al. CC-220. Decreases B-Cell Subsets and Plasmacytoid Dendritic Cells in Systemic Lupus Erythematosus (SLE) Patients and Is Associated with Skin Improvement: Pharmacodynamic Results from a Phase IIa Proof of Concept Study [abstract]. *Arthritis Rheumatol*. Sept 2017; 69 (suppl 10).
- 74 Dauguet N, Fournié JJ, Poupot R, Poupot M. Lenalidomide down regulates the production of interferon-gamma and the expression of inhibitory cytotoxic receptors of human Natural Killer cells. *Cell Immunol*. 2010;264(2):163–70.
- 75 Nakayama Y, Kosek J, Capone L, Hur EM, Schafer PH, Ringheim GE. Aiolos overexpression in systemic lupus erythematosus B cell subtypes and BAFF-induced memory B cell differentiation are reduced by CC-220 modulation of cereblon activity. *J Immunol*. 2017 Oct;199(7):2388–407.
- 76 Gay F, Hayman SR, Lacy MQ, Buadi F, Gertz MA, Kumar S, et al. Lenalidomide plus dexamethasone versus thalidomide plus dexamethasone in newly diagnosed multiple myeloma: a comparative analysis of 411 patients. *Blood*. 2010 Feb;115(7):1343–50.