

Thalidomide: focus on its employment in rheumatologic diseases

A. Ossandon, E.A.M. Cassarà, R. Priori, G. Valesini

Dipartimento di Terapia Medica, Cattedra di Reumatologia, Università degli Studi di Roma "La Sapienza", Rome, Italy.

Alejandra Ossandon, MD; Emanuele Antonio Maria Cassarà, MD; Roberta Priori, MD; Guido Valesini, MD, Professor of Rheumatology.

Please address correspondence and reprint requests to: Prof. Guido Valesini, Dipartimento di Terapia Medica, Cattedra di Reumatologia, Università degli Studi di Roma "La Sapienza", Policlinico Umberto I, 00161 Rome, Italy.

E-mail: guido.valesini@uniroma1.it

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ABSTRACT

Thalidomide is an immunomodulatory agent; although its mechanisms of action are not fully understood, many authors have described its anti-inflammatory and immunosuppressive properties. More interestingly, thalidomide has shown the ability to suppress tumor necrosis factor alpha (TNF α) production and to modify the expression of TNF α induced adhesion molecules on endothelial cells and on human leukocytes.

Thalidomide has been used in several diseases (i.e. dermatological, autoimmune, gastrointestinal). In this review we focus specifically on the use of this drug in disorders with rheumatological features such as lupus erythematosus, rheumatoid arthritis and Still's disease, ankylosing spondylitis, and Behçet's disease.

Despite its well known side effects, first of all peripheral nerve involvement and teratogenesis, which can be avoided by following strict guidelines, thalidomide could represent an alternative drug in some rheumatological conditions, particularly in patients who show resistance, contraindication or toxicity with other conventional treatments.

Introduction

There are few drugs known better for their chemical rather than for their commercial name: thalidomide (N-phtalimido-glutarimide) is one of them. The reason goes back to the dramatic discovery of its teratogenic effect in 1961 when, during a pediatric conference in Germany, the drug was associated with the presence of important malformations (phocomelia, microphthalmia, midline defects, and so on) in new-born children (1). In the same period several other reports confirmed this observation and thalidomide, introduced 5 years before for its sedative and ipnotic actions, was withdrawn from the world market place (1-3).

In 1965, Sheskin (4) reintroduced the drug for the treatment of reactive lepromatous leprosy, and thereafter several studies highlighted the benefits of thalidomide in various inflammatory diseases. Among thalidomide's mechanisms of action, anti-tumor necrosis factor alpha (anti-TNF) properties have been suggested. TNF plays a key role in the generation and maintenance of inflammation in various disorders, as demonstrated by the success obtained with specific anti-TNF drugs such as Infliximab and Etanercept in the treatment of rheumatoid arthritis (5), Crohn's disease (6) and Behçet's disease (7-11).

However, thalidomide has also shown efficacy in diseases where TNF does not seem to play a pathogenetic role. Thalidomide could represent an alternative therapeutic option in some rheumatologic diseases, particularly in patients who show resistance, contraindication or toxicity with other specific treatments. The interest on this drug is progressively growing, as it is also demonstrated by the recent publication of a book-length work on the matter (12).

Pharmacology

The empirical formula of thalidomide is C₁₃H₁₀N₂O₄ and its gram molecular weight is 258.2. Thalidomide is a crystalline powder soluble at 25°C in dimethyl sulfoxide and sparingly soluble in water and ethanol. Its bioavailability and the extent of plasma protein binding have not been determined in humans.

Little information is available regarding the metabolic route of thalidomide even if several metabolites are generated (13). The drug doesn't seem to induce or inhibit its own metabolism (14). Its half-life is approximately 5-7 hours. The pharmacokinetic of the drug in subjects with hepatic or renal dysfunction is not known.

Mechanism of action

Thalidomide is an immunomodulatory agent; although its mechanisms of action are not fully understood, many authors described its anti-inflammatory and immunosuppressive properties (Fig. 1). Thalidomide probably acts in several different ways which may explain the large variety of therapeutic results achieved with its use.

The anti-inflammatory properties, which may be useful in inflammatory diseases such as cutaneous lupus, may be in part explained by the ability of thalidomide to reduce chemotaxis of polymorphonucleates and monocyte phagocytosis (15, 16).

Thalidomide is also able to stabilize lysosomal membranes (17) and to inhibit the production of reactive oxygen species by PMN (18), thus preventing tissue damage (19). Since some studies reported contradictory observations (20) on this matter, it's difficult to establish a clear and predominant mechanism in the anti-inflammatory properties of this drug.

Thalidomide was also shown to act by its influence on TNF, a cytokine involved in inflammatory as well as in immunological responses. Studies *in vitro* showed that thalidomide was able to inhibit selectively (21), but not completely (22), in a dose dependent manner, the production of TNF by monocytes *in vitro*, without any influence on

the production of IL-1, IL-6 and granulocyte/macrophage colony-stimulating factor. This specific cytokine inhibition is probably related to the ability of thalidomide to enhance the degradation of TNF mRNA reducing its half-life from 30 to 17 minutes, while not affecting other LPS-induced cytokines (23).

Thalidomide was also able to inhibit the expression of TNF induced adhesion molecules involved in the neutrophil-endothelial cell interactions during the adhesion cascade. In particular, the inhibition of the up-regulation of ICAM-1, VCAM-1 and E-selectin on human umbilical vein endothelial cells and of L-selectin on human leukocytes was demonstrated (24).

Moreover, thalidomide was also shown to affect the regulation of NF-KB, which is also involved in the activation of TNF and TNF genes (25).

In vivo, the action of thalidomide on TNF may be responsible for its efficacy in conditions where high serum levels of this cytokine have been demonstrated such as erythema nodosum leprosum. In these patients, treatment with thalidomide was followed by a decrease in the serum levels of TNF, accompanied by amelioration of symptoms, reduction of the dermal infiltration of PMN and T cells, and inhibition of the expression of ICAM-1 and MHC II antigens on epidermal keratinocytes

(26). Moreover, a 50-80% reduction of agonist-stimulated monocyte TNF secretion was demonstrated (21). Similarly, Tramontana and colleagues (27) pointed out a reduction of serum TNF levels after thalidomide treatment accompanied by accelerated weight gain in active tuberculosis patients. Conversely, in toxic epidermal necrolysis (28) or HIV-associated oral ulceration (29), serum levels of TNF increased during treatment with thalidomide, thus suggesting a complex mechanism of action of the drug whose effect *in vitro* does not always correspond to what actually happens *in vivo*. Finally, in SLE patients conflicting results (30-32) regarding the importance of serum TNF levels are available and tissue expression of the cytokine may be more relevant (33).

Thalidomide was able to inhibit *in vitro* lymphocyte proliferation induced by alloantigen, mitogen, and superantigen molecules (34, 35), though its action did not seem to be related to the inhibition of IL-2 production (36). Haslett and colleagues (37) showed potent co-stimulatory properties of thalidomide on primary human T cells *in vitro*. The effect of the drug was synergic with stimulation through the T cell receptor complex, obtaining an increase in IL-2 production and subsequent proliferation. The co-stimulatory effect was greater on CD8+ than on CD4+ subset, and CD8+ response was enhanced even in the absence of CD4+ T cells when stimulated by allogeneic dendritic cells. *In vivo*, in healthy male volunteers, thalidomide was able to alterate the ratio of circulating T-helper to T-suppressor cells, by diminishing the levels of the first ones and by increasing the second ones (38). Thalidomide probably plays an important role in the immune regulation of Th1 and Th2 subsets. In a comparative study with cyclosporin A, thalidomide was able to specifically enhance the production of Th2 cytokines such as IL-4 and IL-5 and to inhibit Th1 IFN- production in phytohaemoagglutinin stimulated human peripheral blood mononuclear cell (PBMC) cultures. In addition, thalidomide was able to switch the predominantly Th-1 response induced by stimulation of

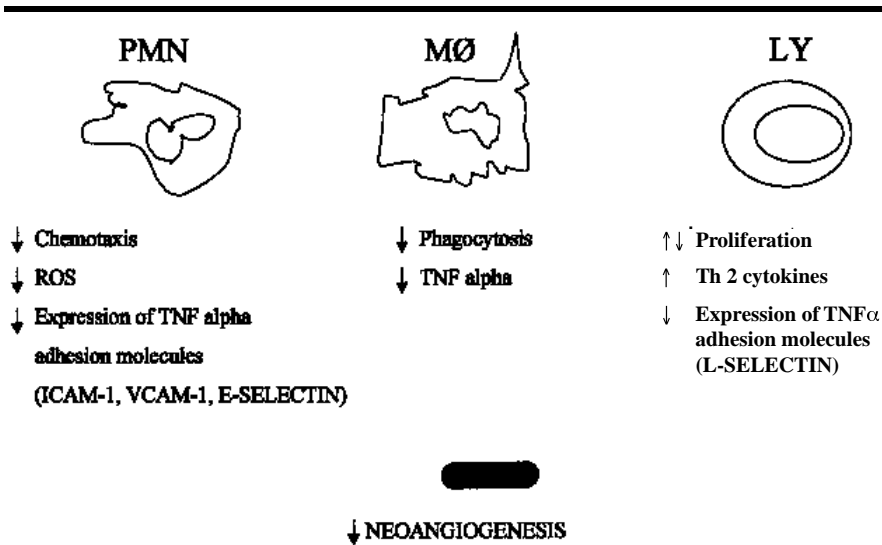


Fig. 1. *In vitro* actions of thalidomide. MØ= Macrophages; LY = Lymphocytes; PMN = Polymorphonucleates; ROS = Reactive oxygen species; TNF = Tumor necrosis factor; Th 2 = T helper 2.

PBMC by a recall antigen towards a Th-2 type response (39). These findings could partially account for thalidomide's action on cell-mediated autoimmune responses, and could be especially relevant for those diseases in which dysregulation of Th subpopulations has been demonstrated such as rheumatoid arthritis.

The study of Atra and colleagues (40) reported an effect of thalidomide on gammaglobulin levels, showing a significant decrease in 76.9% of the patients with systemic lupus erythematosus (SLE). In addition, Shannon *et al.* (41) described an inhibitory effect on IgM synthesis in a mouse model.

The controversial effects of thalidomide described so far at different levels of the immune response stress the need for further investigation under appropriate physico-chemical conditions.

Finally, thalidomide was able to inhibit angiogenesis, in a rabbit cornea model, induced by pharmacological doses of basic fibroblast growth factor (42) and by vascular endothelial growth factor (43). No results on generation of new blood vessels were obtained in solid tumours in mice (44). This diversity has been interpreted as a result of different species-specific metabolic activation of the drug (45).

Clinical use

Thalidomide has been used in various diseases (i.e. dermatological, autoimmune, gastrointestinal etc) as listed in Table I. In this review we will focus specifically on the use of this drug in disorders with rheumatological features.

Lupus erythematosus

The use of thalidomide was reported in all forms of cutaneous lupus erythematosus: the typical malar rash appearing during systemic lupus, the subacute lesion and the chronic discoid and profundus forms (Table II). A recent review published by Karim and colleagues (46) points out the role of thalidomide in this disease.

The first publication goes back to 1977 when Barba Rubio and colleagues (47) described 20 cases of chronic discoid lupus erythematosus (CDLE) treated with thalidomide at an initial dose of 300 mg/day, subsequently tapered to 25 mg/day. In 19 patients great clinical and histologic improvement in the cutaneous lesions was obtained. Side effects were limited to a slight somnolence in most but one patient that had to interrupt the treatment because of fever, arthralgia, nausea, cephalgia, vertigo and urticaria. In one woman treatment was started at 7 months of pregnancy without consequences on the new-born.

Subsequently, further series (48-52) ascertained the efficacy of thalidomide in subacute cutaneous lupus erythematosus (SCLE), CDLE, and lupus erythematosus profundus. Knop and colleagues (53) published the largest one in 1983. They treated 60 patients with CDLE resistant to other therapies (steroids, antimalarials and azathioprine) with a follow up of 2 years. Thalidomide was initially administered at doses of 400 mg BID and subsequently reduced upon response to a maintenance therapy of 50-100 mg a day. An improvement was obtained in 90% of

Table I. Some clinical conditions in which thalidomide has been successfully used.

Clinical disorders	References
Dermatological disorders	
Erythema nodosum leprosum	105,117
Oral and genital aphthosis	75, 77
Prurigo nodularis	118-120
Cutaneous lupus erythematosus	47-54
Pyoderma gangrenosum	121, 122
Sarcoidosis	123, 124
Toxic epidermal necrolysis	28
Autoimmune diseases	
Systemic lupus erythematosus	55, 56
Rheumatoid arthritis	66-68
Still disease	90
Ankylosing spondylitis	92
Systemic sclerosis	126
Graft versus host disease	126-28
Gastrointestinal diseases	
Crohn's disease	95
Ulcerative colitis	96
Infective diseases	
Leprosy	4
HIV associated proctitis	129
HIV aphthous ulcers	29, 130
Vasculitis	
Behçet's syndrome	75-89
Weber-Christian	93

the patients and a complete remission in 65%. After discontinuation of the drug a relapse was seen in 71% and a second re-treatment with thalidomide was needed. The authors suggested that the high frequency of peripheral neuropathy encountered (25%) could be attributed to the high dosages of the drug initially used.

In 1984, Grosshans and colleagues (54) reviewed 7 previous studies including a total of 156 CDLE patients treated with

Table II. Use of thalidomide in lupus erythematosus (with 20 patients).

N°	Study	Dosage	Cutaneous improvement#	Drop out (causes)	Neuropathy	Ref.
23	open	300 mg/day	20/20 (100%)*	3 (urticaria, drowsiness)	0	(40)
20	open	300 mg/day	19/19 (100%)	1 (vertigo, urticaria)	0	(47)
60	open	400 mg/BID	54/60 (90%)**	0	15/60	(53)
22	open	50-200 mg/day	17/17 (100%***)	5 (drowsiness, agitation, paresthesia)	0	(61)
22	open	100-300 mg/day	16/19 (84%****)	3 (vertigo, drowsiness, neuropathy)	1/22	(63)

#Calculated on patients who did not discontinue treatment.

*Complete remission in 90% and partial remission in 10%; **complete remission in 65% and partial remission in 25%; ***complete remission in 70.5% and partial remission in 29.5%; **** complete remission in 75% and partial remission in 11%.

thalidomide at various dosages (mean dose of 300 mg/day). Improvement was reported in 90% of the cases with 75% requiring a maintenance dose of 25-50 mg/day.

Interest in thalidomide subsided for many years until Bessis and colleagues (55) firstly reported a good clinical response in the cutaneous and articular features of 3 patients with SLE. Debate on scientific journals became hot again (56).

One year later, Atra and colleagues (40) confirmed the efficacy of thalidomide (initial dose of 300 mg/day for adults and 4 mg/kg/day for children) on 23 patients with SLE unresponsive to chloroquine, photoprotectors and corticosteroids. The type of cutaneous involvement ranged from maculopapular, vasculitis digitalis and/or palmus-plantaris, palmar erythema, bullous lesions, SCLE, discoid lesions, and photosensitivity. Remission was obtained in 90% of the patients within 30 days, while partial improvement was achieved in 10%. Other than a significant reduction in gammaglobulin levels ($p < 0.001$), no laboratory or clinical improvement in any other organ involvement was seen. The average decrease in the prednisone dose needed to control symptoms was significant ($p < 0.001$). Three patients dropped out because of severe urticaria and extreme drowsiness. The rest encountered tolerable side effects, the most frequent being drowsiness (52%) and abdominal distension or constipation (22%), subsequently controlled with dose reduction. Interestingly, they reported no neuropathy.

Later publications (57-61) confirmed the efficacy and safety of thalidomide in the treatment of various forms of cutaneous lupus erythematosus unresponsive to traditional drugs.

In 2000, Walchner and colleagues (62) reported their experience on 5 consecutive patients with SLE and 5 consecutive patients with cutaneous LE treated with thalidomide 100 mg/day for up to 2 years. They described regression of cutaneous lesions, regrowth of hair when alopecia and effluvium were present, increase in absolute peripheral lymphocyte count and decrease of anti double-stranded DNA and C-reactive

protein. Polyneuropathy appeared in 40% of the patients.

In the same year, Ordi-Ros and colleagues (63) reported their results on 22 patients with DLE, SCLE, lupus profundus and non-specific rash. Thalidomide was given at an initial dose of 100 mg/day subsequently diminished upon response. Complete remission was obtained in 75% of the patients, while a partial response was seen in 25% and no response in 16%. Sixty-five percent of the ones that underwent remission showed recurrence after thalidomide suspension. Among the side effects encountered, the authors addressed a high frequency of amenorrhea, which appeared during the first 4-5 months of treatment and resumed 2-3 months after the suspension of the drug.

Rheumatoid arthritis

TNF is thought to play an important role in the inflammatory processes of rheumatoid arthritis (RA) (64, 65). The cytokine seems to act through a cascade of secondary mediators involved in the recruitment of inflammatory cells, neoangiogenesis, synovocyte proliferation and joint destruction.

Compounds that antagonize TNF effects proved efficacious in controlling the disease and recently soluble TNF receptors and specific monoclonal antibodies entered the market place as new promising drugs for the treatment of RA, although they still are expensive (5).

The first work published on the use of thalidomide in RA is the one written by Gutierrez-Rodriguez and colleagues (66) in 1981. The authors reported the results obtained in two patients with longstanding definite RA, in whom the administration of thalidomide was followed after few weeks by clinical and laboratoristic remission, accompanied by a dramatic decrease of rheumatoid factor levels. Encouraged by these early findings, they treated 5 additional patients (67), and in 1989 they described the results obtained on a final number of 17 patients (16 females and 1 man) (68) with refractory or severe RA (mostly class III and IV). Two of these patients withdrew within the first 6 weeks of treatment due to side effects

(severe vomiting and drowsiness), 7 obtained complete remission, 5 partial remission (doses of 400-600 mg/day, duration of 7-38 weeks, mean 18.8 ± 8.8), 1 had marked amelioration of symptoms and 2 showed only an initial improvement (both with doses of 300 mg/day, duration of 62 and 65 weeks respectively). Rheumatoid factor became negative in 21% of the patients, decreased in 71% and remained unchanged in 7%. Rheumatoid nodules, present in 7 patients, decreased in size in 3 and disappeared in 4.

No other work had been published on the subject until 1996, when Huizinga and colleagues (69) described, in a phase I study, 12 patients treated with thalidomide 100 mg/day and pentoxifylline 400 mg/day for 12 weeks. Pentoxifylline was added for its supposed inhibition on TNF production (70) and moderate beneficial effect on rheumatoid disease activity (71). Despite 5 out of 9 patients (55%) that completed the study obtained a 20% reduction of the American College of Rheumatology improvement criteria, the authors concluded that the benefit/side effects ratio was unfavourable. Xerostomia, drowsiness, constipation, oedema, and dizziness were, in order of frequency, the major side effects encountered. Endotoxin-induced TNF production in whole blood cultures was reduced significantly ($P = 0.01$), but did not correlate to laboratory variables reflecting joint inflammation or clinical improvement. Thus, the authors questioned the validity of this parameter as a substitute index to determine thalidomide pharmacological efficacy.

More recently, Keesal and colleagues (72) treated 10 patients with refractory RA with incremental dosages of thalidomide up to 600 mg/day. They did not observe statistically significant improvement in any of the outcome measures, but concluded that the results could have been confounded by the fact that most of the patients had to interrupt the treatment because of the several side effects. Among them, reversible paresthesiae occurred in 4 patients, without changes of nerve conduction tests. Finally, Scoville (73) treated 10 female patients with RA in a 4-month open

Table III. Use of thalidomide in rheumatoid arthritis (with <10 patients).

N°	Study	Dosage	Improvement	Drop out (causes)	Neuro-pathy	Ref.
17	open	300-600 mg/day	7/15 complete remission 5/15 partial remission	2 (vomiting, drowsiness)	2/15	(68)
12	open	100 mg/day*	5/9 ACR-20%	3 (constipation, rash)	0	(69)

*Combined with pentoxifylline 400 mg/TID

trial with thalidomide (maximum doses of 150 mg/day slowly increased) and methotrexate (MTX) (minimum stable doses of 15 mg/wk). Five of 7 patients showed an amelioration in the ACR 20 criteria (3 responders and 2 partial responders). The single variables used did not show a statistically significant improvement. Paresthesias appeared in 60% of patients and resolved when thalidomide doses were reduced. Two patients withdrew because of drowsiness and one due to nausea induced by MTX. The authors suggested that combination therapy with MTX could allow a reduction of the doses of thalidomide used for RA in previous studies with fewer side effects.

In juvenile RA, Lehman and colleagues (74) reported two cases, resistant to several immunomodulatory drugs including etanercept, the anti-TNF recombinant receptor, which finally responded to thalidomide 2.5-3 mg/kg/day.

In conclusion, the indication for the use of thalidomide in RA is still under debate. Table III summarizes the most significant studies on the subject. Considering the good results obtained with the new biologic anti-TNF compounds, larger clinical trials designed to assess the role of thalidomide in the management of this disease are needed.

Behçet's disease

Behçet's disease (BD) is a chronic and relapsing systemic vasculitis originally described as a triad of oral and genital ulcers associated with uveitis. Many other organs may be involved: the joints, the gastrointestinal tract and the central nervous system. There is no consensus on the treatment of BD, which is generally based on the severity of the disease (75).

In 1982, after the report (76) on the efficacy of thalidomide in recurrent necrotic and giant mucocutaneous aphthae and aphthosis, Saylan and colleagues (77) treated 22 BD patients with orogenital lesions. Thalidomide was administered at the dose of 400 mg/day for the first 5 days, then reduced to 200 mg/day for 15-60 days. While the effect on oral and genital ulcers was seen almost immediately in all patients, no effect was observed on ocular manifestations, although in some patients thalidomide was used as a steroid sparing agent during attacks. Interestingly two patients experienced erythema nodosum while on treatment. Months later, Torras and colleagues (78) reported similar results in the mucocutaneous lesions of 9 BD patients treated with thalidomide for 4 years. They also described a beneficial effect of the drug on ocular involvement. In 1986, Hamza (79) reviewed the data of 30 BD patients in whom thalidomide

was efficacious on several manifestations of the disease including orogenital lesions, erythema nodosum, necrotic pseudofolliculitis and arthritis. Uveitis improved in 3 patients, was stable in 4 and worsened in 4.

In a patient with BD occasionally associated with palmoplantar pustulosis, the administration of thalidomide at 200 mg/day, tapered to 100 mg/day after two months, resulted in a complete remission of both manifestations (80). Larsson (81) reported successful treatment of severe BD associated colitis in a patient in whom high doses of oral and intravenous steroids combined with parental nutrition were ineffective. Thalidomide was introduced as a last resource before colectomy at the dose of 300 mg/day, subsequently reduced to 200 mg/day after 2 weeks, and to 100 mg/day after another week. The water-like diarrhoea and rectal bleeding disappeared the day after the administration of the drug. The mucosa of the rectum, which previously showed aphtous ulcers, fresh blood and mucosal oedema on rectoscopy, gradually normalized allowing reduction of steroids.

Postema and colleagues (82) described another case that had partially responded to colchicine. Thalidomide at doses of 400 mg/day resolved the symptoms within 7 days. Although there are no controlled studies on the treatment of

Table IV. Use of thalidomide in Behçet's syndrome (with 20 patients).

N°	Study	Dosage (mg/day)	Mucocutaneous improvement	Drop out (cases)	Neuro-pathy	Ref.
22	open trial	400-200	100%	0	0	(77)
30	open	50-300	86.6% (26/30)* 20 completely 6 partially	0	0	(79)°
23	retrospective	200	73.9% ulcer free at 1 month 82.6% ulcer free at 2 months	n.s.	17.3%	(84)
95	double blind placebo-contr.	100-300	complete response in 7/63	4 (sedation, neuropathy)	6.3%	(89)

* Response on active buccal ulceration.

° Summarizes and reviews previously collected data from an open trial of thalidomide in 30 patients with BD: prospective study with open test.
n.s. = not specified.

BD colitis with thalidomide, these two reports seem particularly important considering that perforation complicates the disease in 40-50% of cases (83).

In 1994, Gardner-Medwin and colleagues (84) treated with thalidomide (200 mg/day) 59 patients with severe oral and genital ulcers, including 23 patients with BD. Within the first month of treatment, a complete resolution of the ulcers was observed in 73.9% of BD patients.

Thalidomide was efficacious in the treatment of pediatric BD, showing similar responses than those observed in adults (85-87). Moreover, a patient with neuro-BD (88) was successfully treated when thalidomide was added to a chlorambucil and prednisolone therapy, obtaining complete remission for a period of three years.

The first and only double-blind randomized placebo-controlled trial published on thalidomide's treatment of BD, was the one designed by Hamur-yudan and colleagues (89) in Turkey in 1998. Patients were enrolled consecutively between October 1993 and 1996 from the registry of the multidisciplinary Behcet's Syndrome Research Center. Ninety-five male patients with prevalent mucocutaneous lesions and without major organ involvement were randomized in three groups: 32 were treated with thalidomide 100 mg/day, 31 with 300 mg/day and 32 with placebo, for a period of 24 weeks. Presence of active eye inflammation and previous use of any immunosuppressive drug were among the exclusion criteria. A complete response was observed in 2 out of 32 patients treated with thalidomide 100 mg/day and in 5 out of 31 patients treated with 300 mg/day. No response was noted in the group receiving placebo. Moreover, patients treated with thalidomide (both doses) had fewer eye activations and lower extent of visual impairment than did those in the placebo group. At the end of the trial only 3 patients had developed poly-neuropathy. Other side effects encountered were sedation, fatigue and constipation. Table IV shows the data regarding the use of thalidomide in this disease.

Anecdotal reports

Still's disease

Stambe and colleagues (90) described the case of a 44-year-old woman with a 4-year history of resistant adult-onset Still's disease. Before the introduction of thalidomide (200 mg/day, tapered to 100 mg/day over 2 weeks) she had been unable to reduce her daily 30 mg prednisolone therapy despite the association with azathioprine and pentoxifylline. After introducing the drug, she not only had a marked clinical improvement and remained free of symptoms for 6 months, but was also able to reduce prednisolone to 7.5 mg/day and to suspend pentoxifylline. Interestingly, the proportion of stimulated TNF α -producing cells detected by fluorescence-activated-cell sorting fell from 42.7% before treatment to 1.4%.

Ankylosing spondylitis

The rationale for the use of thalidomide in ankylosing spondylitis (SA) (91) is related to the suggestion that TNF may be involved in the pathogenesis of SA.

Breban and colleagues (92) described 2 young patients affected by SA, resistant to previous treatment with non-steroid anti-inflammatory drugs and sulfasalazine. One of the patients had also received pulse methylprednisolone, methotrexate, intramuscular gold, bromocriptine, and local corticosteroid injections without being able to control the disease. Both patients had severe involvement of the axial skeleton and peripheral joints and persistently elevated erythrocyte sedimentation rate and C-reactive protein. Thalidomide (300 mg/day) induced frank improvement of both clinical and biologic parameters, leading to a progressive remission of the disease. Discontinuation of the drug in one of the patients was followed, on two occasions, by a rapid reappearance of symptoms. Remission was obtained again with reintroduction of the drug.

Weber Christian's disease

Weber-Christian disease is an idiopathic disorder characterized by a relapsing non-suppurative nodular panniculitis with a lobular subcutaneous fat distribution of acute inflammation and with

occasional visceral fat involvement.

The only case reported in literature on the use of thalidomide in Weber-Christian's disease is the one published in 1977 by Eravelli and colleagues (93). They described the case of a young woman who had experienced in the previous three years repeated relapses of the disease, with increased severity and duration, whenever steroids were reduced or stopped. Cyclophosphamide was tried, but not tolerated. After beginning thalidomide at 300 mg/day, she experienced rapid improvement of symptoms and was able to stop fluocortolone after two weeks. Thalidomide was reduced to 200 mg/day after 3 weeks, to 100 mg/day after 10 weeks and stopped after 13 weeks with her lesions steadily regressing. She had no relapses throughout the 13 months of follow-up.

Inflammatory bowel diseases

Although inflammatory bowel diseases (IBD) are not rheumatologic disorders, we have included them in the present review because not rarely they present rheumatologic features with articular and spondylitic involvement. The use of thalidomide in Crohn's disease has only been described to date in non-controlled experience. Indeed, since treatment with the new biological anti-TNF compounds showed promising results in these patients (6, 94), thalidomide, known for its anti-TNF action, could represent an interesting therapeutic tool for this pathology.

Facchini and colleagues (95) recently published an interesting report on the use of thalidomide in children and young adults with Crohn's disease. The authors selected 5 patients intolerant, resistant or ready for surgical intervention, and treated them with thalidomide 1.5-2 mg/kg/day for 19-24 months. After 3 months of treatment there was a reduction of the mean Pediatric Crohn's Disease Activity Index from 36.9 to 2.5 and of the modified Harvey-Bradshaw scores from 8.5 to 0.75. Moreover, steroids, initially administered at 35 mg/day, were tapered and discontinued within 3 months. Long-standing remission was obtained in 4 patients, while the fifth one had to stop the drug after 1

week because of distal paresthesia. The first use of thalidomide in chronic ulcerative colitis goes back to 1979. Waters and colleagues (96) described the case of a 28-year old woman with a four and a half-year history of continuous abdominal pain, blood and mucus diarrhoea, resistant to corticosteroids and sulfasalazine. After beginning thalidomide at 300 mg/day, increased after 5 weeks to 400 mg/day, she obtained sustained clinical remission and was able to suspend the rest of the therapy and to decrease thalidomide to 200 mg/day without experiencing clinical relapse. Her colonoscopy looked normal and biopsy showed only little chronic inflammation with severe mucosal atrophy and epithelial hyperplasia. Morning joint pain and stiffness persisted. Bauditz and colleagues (97) published recently a 12 week open label study on 10 cases of therapy refractory IBD (9 with Crohn's disease and one with chronic ulcerative colitis). Four patients achieved remission, 3 had to stop the treatment because of sedation and the others had a significant decrease in disease activity. Thalidomide was also able to decrease the production of TNF and IL-12 in the PBMC of the patients after treatment and, in a dose dependent manner, in short term cultures of stimulated colonic lamina propria mononuclear cells.

Side effects

Neuropathy

Thalidomide neurotoxicity was reported even before than its teratogenic effect (98, 99). The drug is able to induce a sensitive polyneuropathy, primarily localized in upper and lower limbs. The mechanisms by which the damage to the nerve is produced are still partially unknown, but potentially irreversible (100).

The incidence of this side effect varies greatly in different series and although no clear correlation has been found with the dose and duration of therapy, a higher rate of incidence in patients treated with higher dosages has been reported (40, 72).

In a recent retrospective study Ochonisky and colleagues (100) reviewed the files of 42 patients treated with thalido-

midomide for different disorders. Among them, 21% presented a clear diagnosis of neuropathy due to the presence of both clinical and electrophysiologic abnormalities, while 28% showed just either one of the two. Female and elderly patients showed greater risk, but no correlation was found with daily dose or duration of treatment. The authors concluded that the incidence of thalidomide induced neuropathy could be estimated between 21% and 50% and that individual susceptibility could play an important role.

Different diseases seem also to influence the susceptibility to thalidomide nervous noxious action. In erythema nodosum leprosum (102), for example, the incidence of polyneuropathy is extremely low, in CDLE seems close to 28% (53) and in prurigo nodularis reaches almost 100% (103).

In 1994, Gardner-Medwin and colleagues (84) published a retrospective study on the use of sensory nerve action potential (SNAP) amplitude measurements for the early detection of thalidomide neuropathy. Fifty-nine patients with different disorders, who had in common severe oral and/or genital ulceration, were treated with thalidomide at initial doses of 200 mg/day, subsequently reduced to a maintenance therapy of 7-200 mg/day over a period of 8-3369 days. Total SNAP amplitudes of three different nerves (median, radial and sural) were measured at baseline and every six months or after each 10 g of thalidomide. Eight out of 59 patients (13.5%) complained of paraesthesiae, while 8 out of 59 were classified as having a subclinical neuropathy since they showed a decreased of 42.6 - 69% in SNAP amplitudes baseline measurements without complaining any symptoms. No patient with a decrease of less than 42% developed symptoms. After discontinuing thalidomide most patients, but not all, showed an improvement of symptoms and of SNAP amplitudes. No clear correlation was found between the rate of deterioration of SNAP measurements and the dose or duration of therapy.

Teratogenesis

The other major side effect of thalido-

midomide, unfortunately sadly famous, results from the action of the drug on the development of mesenchymal tissues, primarily the bone and the gastrointestinal system. The major susceptibility of the fetus seems to be between the 34th and the 50th day after conception (103) and a single dose of 100 mg is enough to generate the damage.

In 1961, Lentz (3) and McBride (2) were the first to report congenital abnormalities related to the use of thalidomide. At that time they estimated an incidence of birth defects of around 20%. Indeed, after its approval in Europe in 1957 (105), thalidomide was considered responsible for the birth of 10,000 - 20,000 new-borns with congenital abnormalities (106).

This tremendous effect led to a profound modification of laws regarding the approval of drugs entering the market place (107). In particular, since thalidomide effects revealed to be species-specific, compulsory tests to reveal drugs potential teratogenesis in different animal models before administration to humans were introduced (108).

A mutagenic effect of thalidomide was advocated by some. In particular McBride (109) described two cases of children with the same birth defects of their fathers, victims of teratogen thalidomide. Although literature seems controversial on this topic, two recent reports (110, 111) advocated the safety of the drug and excluded its responsibility in developing second-generation defects.

Other side effects

Various side effects involving different organs have been described (112). Fortunately they are usually mild and infrequent. Among them, somnolence, dizziness and rash are the most commonly reported and in the majority of cases do not need discontinuation of the drug. Regarding sedation, a good advice is to administer the drug at night before sleeping.

Flageul and colleagues (113) recently proposed thalidomide as a potential thrombotic precipitating agent in high-risk patients. They reported the cases of 5 patients with different predisposing

factors (anti-phospholipid and/or anti-cardiolipin antibodies, trauma), with no previous history of thrombosis, in which the first vascular event occurred few days to 3 months after the introduction of thalidomide. The authors suggested that an interaction between thalidomide effects on the expression of adhesion molecules on different cell types and anti-phospholipid and anti-cardiolipin antibodies could predispose to the thrombotic event.

Guidelines for prescribing and monitoring thalidomide treatment

In 1994, Powell and colleagues (114) published in the UK a guideline for the clinical use and dispensing of thalidomide. The authors gave detailed information about the compulsory prescription of the drug, only on a 'named patient' basis, by hospital-based physicians with necessary expertise in its use and the resources to detect subclinical neuropathy.

In 1999 Celgene Corporation (115) (Warren, New Jersey) developed a program called STEPS (System for Thalidomide Education and Prescribing Safety) to which any physician or pharmacist has to register and comply in order to receive the drug from the company. A signed informed consent has to be filled out by both patient and doctor, and the latter has to give full comprehensive information on thalidomide side effects, especially regarding neuropathy and teratogenesis.

In particular, childbearing potential women must agree to abstain from sexual-intercourse or to use two reliable birth control methods, and men must always use latex condoms, since it is unknown whether thalidomide is present in the ejaculate.

Patients need to be evaluated every month for the first three months of treatment and periodically thereafter, and to be questioned about the appearance of numbness, tingling or pain in both hands and feet. Periodical monitoring of sensory nerve action potential (SNAPS) amplitudes on at least three different nerves (median, radial and sural) is necessary for the early discovery of neurotoxicity and permits to suspend the drug before the manifestation

of symptoms, allowing better chances for recovery. A fall from the baseline summated score, with an equal weighting for each nerve > 40%, is considered as significant. Reintroduction of the drug can be considered with extreme precaution only if there is a return to the baseline status.

Rao and colleagues (116) recently suggested the introduction of motor nerve conduction velocity as another useful tool for detecting early neuropathy.

Conclusions

From the experience acquired so far, thalidomide seems a useful drug for many disorders. Unfortunately, most of the studies on thalidomide are "open" and not placebo-controlled. Results reported in literature need further evaluation and the involvement of a larger number of patients. Nevertheless, the striking results described by some authors should be taken in consideration.

Its administration should be restricted to patients resistant to other safer traditional drugs or when their side effects have precluded their use. Teratogenesis and neurotoxicity can be greatly avoided by careful monitoring and accurate choice of patients by the physician.

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