Artigo Original

Long-term thalidomide use in refractory cutaneous lesions of systemic lupus erythematosus

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SUMMARY – OBJECTIVE. To evaluate the efficacy of long-term thalidomide treatment in cutaneous lesions of systemic lupus erythematosus (SLE), not responsive to conventional therapy.

PATIENTS AND METHODS. Were selected 18 SLE patients (ACR criteria) with active cutaneous lesions not responsive to chloroquine, photoprotectors and low doses prednisone and who presented good response to thalidomide but relapsed after withdrawal of the drug. All female patients had no risk of pregnancy. Thalidomide was reintroduced and maintained at low dose (25-100mg/day) for a minimum of 6 months.

RESULTS. Eighteen patients (16 females) with mean age of 34.2yo (16-57y.o.) received thalidomide for 6-21 months (mean 8.5m). The mean dose of prednisone at beginning of study was 38.3 mg/d and at the end was 9.7mg/d ($p<0.05$). Complete remission of cutaneous lesions was observed in thirteen patients (72%) and partial remission in five (28%). Side effects observed were: drowsiness in eight patients, intestinal constipation in 5, transient oliguria in 1, paresthesia of hand with normal electromyography in another one. All side effects disappeared with reduction of thalidomide dose and no patient needed to stop treatment owing to side effect.

CONCLUSION. Thalidomide is a good alternative therapy to SLE patients with refractory cutaneous lesions and without any risk of pregnancy.

KEY WORDS: Thalidomide. Systemic lupus erythematosus. Cutaneous lesions. Treatment.

INTRODUCTION

Thalidomide (α [N-phthalimido]-glutaramide) was synthesized in 1956 and sold as a sedative until 1961, when it was withdrawn from the market due to high teratogenicity and after having caused more than 10,000 cases of malformed babies[1].

After withdrawal, thalidomide was used in many countries for the treatment of several inflammatory dermatoses such as lepra reaction[2,3], actinic prurigo[4], aphtae and aphtosis[5,6], pyoderma gangrenosum[7], Weber-Christian disease[8] prurigo nodularis[9] Langerhans cell histiocytosis[10] and discoid lupus erythematosus[11]. More recently, due to the immunomodulatory effect, thalidomide has been used to treat graft-versus-host disease[12] and patients with human immunodefficience virus[13].

Rubio & Gonzales in 1975[11] pioneered the use of thalidomide to treat patients with discoid lupus erythematosus (DLE), with good results. Thereafter, in literature, more than 200 patients with DLE have been treated with thalidomide, obtaining 90% of improvement. However, 70% of patients had recurrence of the lesions after stopping treatment[14-20]. Few cases of subacute cutaneous lupus erythematosus were treated with thalidomide with good results[21,22]. Only three patients with SLE were treated with thalidomide until 1993[23].

In 1993 we published the first paper showing good results using thalidomide in 23 patients with refractory cutaneous lesions to conventional treatment. Three patients had side effects needing to stop the drug. We found complete remission of cutaneous lesions in 18 out of 20 patients who could use thalidomide for more than one month, but we observed recurrence of lesions in thirty five percent of patients after stopping thalidomide [24].

This study aimed to evaluate the efficacy of long-term use of thalidomide in low doses to treat SLE patients with cutaneous lesions refractory to conventional therapy.

PATIENTS AND METHODS

Eighteen patients from Rheumatology Outpatient Clinic at Hospital São Paulo/UNIFESP entered this open trial, after prior approval by the Committee of Clinical Research Ethic Control *in anima nobile* at Hospital São Paulo/UNIFESP. The following inclusion criteria were used:1) four or more ACR criteria for SLE classification[25]; 2) cutaneous lesions refractory to conventional therapy (prednisone less than 0.5 mg/kg/day for at

least 1 month, chloroquine diphosphate at a dose of 4mg/kg/day for at least 3 months, photoprotector creams); 3) previous success with thalidomide therapy but with relapse after drug withdrawal;4) no risk for pregnancy; 5) agreement in participating in the study. The following exclusion criteria were used: 1) risk of pregnancy; 2) low capacity for comprehension of possible side effects; 3) use of thalidomide for less than 6 months.

All patients enrolled were informed about the nature of study, possible side effects (specially teratogenicity) and instructed not to give the drug to anyone else. Thalidomide in 100mg tablets was provided by the Health State Bureau of São Paulo. The reintroduced dose ranged from 100 to 300mg/day with gradual reduction depending on tolerance and clinical improvement. The prednisone dose was reduced as cutaneous lesions improved if the patient did not have other organs involvement.

Laboratory tests included full blood count, erythrocyte sedimentation rate, and urinalysis, performed every two months. Antinuclear antibodies were investigated at the beginning and at the end of the study by indirect immunofluorescence in mouse liver imprint. Antibodies to Sm, U1-RNP, SS-A/Ro, and SS-B/La were determined by double immunodifusion against calf spleen extract. Antibodies to native DNA were investigated by indirect immunofluorescence with *Crithidia luciliae as* substrate.

Statistical analysis for comparison of prednisone dose before and after long-term thalidomide therapy was performed by Wilcoxon's paired rank test. The significance level established was $p<0.05$.

RESULTS

Eighteen patients participated in this study. Sixteen were female and two male, twelve white and six non-white. The mean age was 34.2 y.o., ranging from 16 to 57 years, and the mean disease duration was 7 years, ranging from 1 to 15 years.

Table 1 shows the initial and the final doses of thalidomide and prednisone for each one of the patients. The total dose of thalidomide ranged from 13,500 to 69,000mg (mean of 29,200mg). The dose of prednisone at the beginning of the study ranged from zero to 80 mg/day (mean of 38,3mg/day) and at the end of the trial had a mean of 9,7mg/day (ranging from zero to 20mg/day). The prednisone dose reduction for the whole group was statistically significant ($p<0.05$). Seventeen patients could reduce prednisone dose after the use of thalidomide.

Table 1 – Thalidomide and corticosteroid dose at the onset and completion of the trial

Patients	Thalidomide Dose (mg/d)		Corticosteroid Dose (mg/d)	
	Initial	Final	Initial	Final
1	200	25	30	5
2	300	50	60	15
3	300	50	40	10
4	200	50	10	0
5	100	25	10	0
6	100	25	20	20
7	200	50	30	10
8	300	50	50	10
9	200	50	60	20
10	300	100	10	5
11	300	50	20	5
12	300	50	60	10
13	200	100	60	5
14	100	25	0	5
15	200	25	40	10
16	200	50	50	10
17	300	100	80	15
18	200	50	60	20
Average	222+-73.2	51+-25.1	38.3+-23.4	9.7+-6.3

Wilcoxon test: $p<0,05$.

All patients had previous treatment with thalidomide at 100 to 300mg/day, and presented recurrence of cutaneous lesions after stopping thalidomide. Then the drug was reintroduced with gradual reduction and maintenance at 25-100 mg/day, with mean of 51mg/day, taken at night. The duration of thalidomide use ranged from 6 to 21 months with mean of 8.5 months.

Table 2 shows the kind of cutaneous lesions and the antinuclear antibodies presented by the patients when entered this study, the therapeutic response, and the side effects observed during the use of thalidomide.

Complete remission of cutaneous lesion in 13 patients (72%) and partial remission in the other 5 patients (28%) was obtained with maintenance dose. Figures 1-4 depict some of the lesions before (A) and after (B) thalidomide.

Side effects observed were: drowsiness in 7 patients (39%) and intestinal constipation in 5 cases (27%). One patient (5.5%) referred transient oliguria that did not recur after reintroduction of the drug. One patient (5.5%) referred paresthesia in hands, with normal electromyography, that was controlled with dose reduction.

The laboratory tests did not show significant difference during the trial. Seven of the female patients had tuba ligature, one had tuba obstruction owing to tuberculosis, two had hyste-

Table 2 – Cutaneous lesion, antinuclear antibodies, responde and side effects observed in each patients in this study

Patients	Cutaneous lesion	Autoantibodies	Response	Side effects
1	Photosensibility, facial rash, vasculitis	a. SS-A/Ro	Partial	Drowsiness
2	Photosensibility, facial rash	a. SS-A/Ro, a. SS-B/La a. Sm, a.U1-RNP	Complete	Drowsiness
3	Photosensibility, facial rash, vasculitis Maculopapular rash	a. SS-A/Ro, a. Sm, a. U1-RNP	Partial	Drowsiness, constipation
4	Discoid lesion	a. SS-A/Ro	Partial	Drowsiness, constipation
5	Facial rash, maculopapular rash	a. U1-RNP	Complete	Drowsiness
6	Photosensibility, facial rash, vasculitis	a. Sm, a.U1-RNP	Complete	Absent
7	Subacute cutaneous lupus	a. SS-A/Ro, a.Sm, a.U1-RNP	Complete	Drowsiness, constipation
8	Photosensibility, facial rash, vascilitis	ANA*	Partial	Paresthesia of hands
9	Rash facial, vasculitis, maculopapular rash	a. SS-A/Ro	Complete	Constipation
10	Maculopapular rash	ANA*	Complete	Absent
11	Subacute cutaneous lupus	ANA*	Partial	Absent
12	Photosensibility, facial rash, maculopapular rash	a. Sm, a. U1-RNP	Complete	Absent
13	Diffuse cutaneous vasculitis, alopecia	a. Sm, a. U1-RNP	Complete	Constipation
14	Subacute cutaneous lupus	ANA*	Complete	Drowsiness
15	Discoid lesion	a. U1-RNP	Complete	Absent
16	Photosensibility, facial rash, maculopapular rash	a. U1-RNP	Complete	Absent
17	Maculopapular rash, palmar macules	ANA*	Complete	Absent
18	Maculopapular rash, vasculitis	a. SSA/Ro; a. u, RNP	Complete	Oliguria

*ANA positive, but, a. U1-RNP, a.SM, a.Ro/SS-A and a.La/SS-B negative.

rectomy, one was sterile, two were menopaused, and three did not have sexual activities.

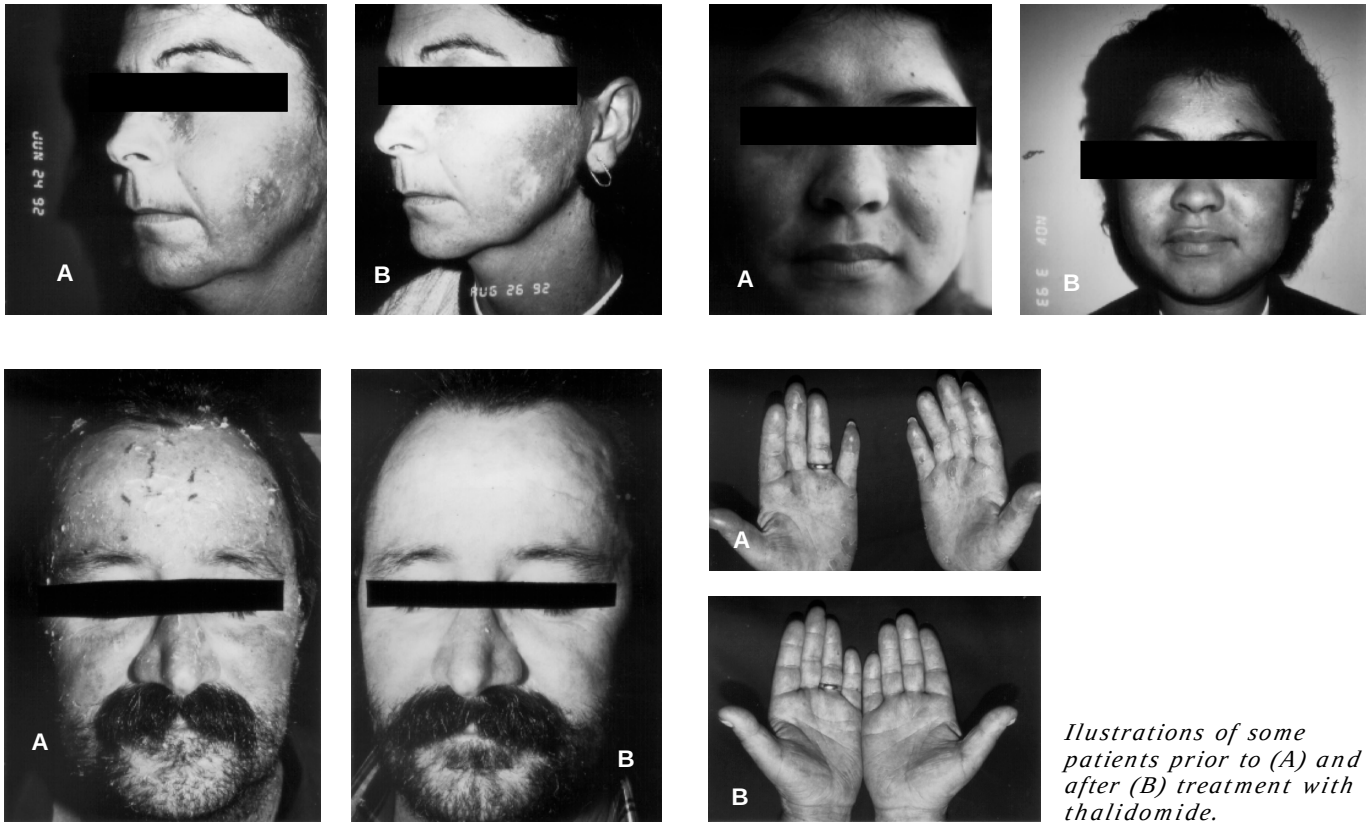
DISCUSSION

As observed in discoid lupus erythematosus, the use of thalidomide, improves the majority of cutaneous lesions of SLE, but, the recurrence after withdrawal was frequently observed in our cases. On the other hand, the reintroduction and maintainance of low dose of thalidomide was sufficient to control the lesion in these patients.

Despite continuous interest in thalidomide, its mode of action is not totally known, with some studies with contradictory results. Thalidomide showed to inhibit IgM antibody formation in mice when fed before immunization with sheep erythrocytes[26] but, in experimental model of myasthenia gravis, it could not inhibit acethylcholine antibody formation[27]. The effect of thalidomide on chemotaxis and the capacity to generate superoxide anions of polymorphonuclear leukocytes is also contradictory[28]. More recently it was refered that thalidomide was associated with a decrease in CD4+ cells in 2 patients with erythema nodosum leprosum[29], but not in healthy volunteers[30]. Reduced expression of integrin receptors in CD4 cells during thalidomide treatment was observed in laboratory animals[31], but not in healthy volunteers[30]. Reduced expression of major histocompatibility complex class II antigens and ICAM-1 on keratinocytes from erythema nodosum leprosum lesions was observed during thalidomide treatment[32]. More recent studies have shown important role of TNF-α in the mode of action of thalidomide[28], and it may be due to increased degradation of TNF-α mRNA[32, 33].

In relation to side effect, the teratogenicity is the biggest problem, but it can be used in patients without risk of pregnancy, such as men, posmenopaused or sterile women. Neuropathy remains the major complication of treatment with thalidomide, and it is mainly sensory. However, weakness and signs of pyramidal tract involvement may occur. Sensory symptoms may persist, and sometimes get worsen, after withdrawal of the drug and the pathologic findings suggest axonal neuropathy[34]. Although the frequency and the severity of neuropathy are not always found to be related to total dosage[34], Wulff *et al.*, confirmed that the neuropathy began after a total of 40-50g of thalidomide in most patients[35].

Despite the increased use of thalidomide around the world, we worry about the possible side effects, mainly teratogenicity and neuropathy of this drug[36], but we believe that more than prohibit their production, the governments need to do more restrict laws to permit their use. We do not agree that in the risk-benefit evaluation forgets the great benefit that this drug gives to some patients. The careful use of thalidomide and the



Ilustrations of some patients prior to (A) and after (B) treatment with thalidomide.

search for derivatives with low toxicity seem important for many patients.

Evidently thalidomide is not a first choice to treat cutaneous lesions of SLE patients, but we concluded that it is a good alternative for cases refractory to traditional treatment and may be used in patients without any risk of pregnancy, whose use of high dose of steroids or immunosuppressive drugs bring many side effect without the improvement that we observed with thalidomide.

We would like to remember that although the cutaneous lesions of SLE do not carry risk of life, it may bring many problems to the patients, mainly for female patients, since the SLE cutaneous lesions affect mainly face and arm. The patients lose self-esteem and have problem in work or social inter-personal relation-ship, worsening her quality of life. It is very important to continue looking for alternative therapy for SLE patients with cutaneous lesions refractory to the conventional treatment.

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RESUMO

Uso da talidomida por tempo prolongado no tratamento das lesões cutâneas refratárias do lúpus eritematoso sistêmico

OBJETIVO. Avaliar a eficácia do uso prolongado de talidomida no tratamento das lesões cutâneas do lúpus eritematoso sistêmico (LES) refratárias ao tratamento convencional.

PACIENTES E MÉTODOS. Foram avaliados 18 pacientes (16 mulheres) com LES (critério do ACR) com lesões cutâneas ativas não-responsivas ao uso de cloroquina, fotoprotetores e prednisona em doses baixas, que haviam apresentado boa resposta ao uso de talidomida, mas tiveram reativação das lesões após sua suspensão. Todas as pacientes femininas não tinham nenhum risco de gravidez. Talidomida foi reintroduzida e mantida em doses baixas (25-100mg/dia) por no mínimo seis meses.

RESULTADOS. Dezoito pacientes (16 mulheres), com média de idade de 34,2 anos, receberam talidomida por 6 a 21 meses, com média de 8,5 meses. A dose média de prednisona, no início do estudo, foi de 38,3mg/dia e, no final, de 9,7 mg/dia (p<0,05). Remissão completa das lesões

cutâneas foram observadas em 13 pacientes (72%) e remissão parcial em cinco (28%). Os efeitos colaterais observados foram: sonolência em oito, obstipação intestinal em cinco, oligúria transitória em um, parestesia em mãos com eletromiografia normal em um. Todos os efeitos colaterais desapareceram com redução da dose de talidomida e nenhum paciente necessitou suspender seu uso devido aos efeitos colaterais.

CONCLUSÃO. A talidomida é uma boa alternativa terapêutica para pacientes com LES com lesões cutâneas refratárias ao tratamento convencional, e que não tenham nenhum risco de gravidez. [Rev Ass Med Brasil 1998; 44(4): 289-93.]

UNITERMOS: Talidomida. Lúpus eritematoso sistêmico. Lesões cutâneas. Tratamento.

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