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ORIGINAL ARTICLE

Thalidomide treatment in cutaneous lesions of systemic lupus erythematosus: a multicenter study in China

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Abstract Thalidomide is effective for treating severe cutaneous lupus patients. The aim of this study was to observe the optimum effective and maintenance doses of thalidomide to maximize clinical benefit and minimize side effects for patients with cutaneous lupus in China. Sixty-nine patients with lupus rash from eight hospitals in China were enrolled and treated with different doses of thalidomide. We started the dose of thalidomide at 25 mg daily and gradually increased administration dose once a week until erythema was markedly improved. The effective and maintenance doses were documented. The size of skin lesions was noted once a week. Systemic lupus erythematosus disease activity index (SLEDAI) score, levels of erythrocyte sedimentation rate (ESR), and serum TNF-α were measured before and after treatment. The remission rates were evaluated weekly until 8 weeks. Sixty-eight percent of patients showed an effective dose of 50 mg daily; another 13, 10, and 9 % of patients had an effective dose of 100, 75, and 25 mg daily, respectively. The maintenance dose was 50 mg daily for 71 % of the patients, and 100, 75, and 25 mg daily for 9, 14, and 6 % of the patients. SLEDAI score and serum ESR levels significantly decreased 4 weeks after thalidomide treatment. At the end of the fourth week, the rates of complete remission, partial remission, and no response were 56 % ($n=39$), 41 % ($n=28$), and 3 % ($n=2$). At the eighth week, the rate of total remission rose up to 100 %. The most common side effects were drowsiness and constipation. No peripheral neuropathy was observed in these patients. Thalidomide at a dose of 50 mg daily may offer a better benefit to risk ratio in the treatment of Chinese cutaneous lupus patients.

Keywords Cutaneous lupus · Optimum dose · Remission rate · Side effect · Thalidomide

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Introduction

Thalidomide (α-N-phthalimidoglutarimide) was initially used as an over-the-counter sedative in the treatment of morning sickness in pregnancy. Several years later, an Israeli physician named Sheskin reported that thalidomide could effectively treat erythema nodosum associated with leprosy [1]. Now it has been successfully used in several conditions, including erythema nodosum leprosum, rheumatoid arthritis, Behcet syndrome, multiple myeloma, wasting syndrome associated with human immunodeficiency virus infection, and graft-versus-host disease [2–7].

Thalidomide can inhibit the production of tumor necrosis factor-α (TNF-α), a key cytokine in mediating immunological

responses [8]. Since the reintroduction of thalidomide into clinical practice, several studies have demonstrated that it is effective in the treatment of severe cutaneous lupus, including systemic lupus erythematosus (SLE) with cutaneous features, discoid lupus erythematosus (DLE), and subacute cutaneous lupus erythematosus (SCLE), often in patients who were resistant to other therapies, including antimalarials, corticosteroids, and azathioprine [9–13]. Additionally, thalidomide could also effectively inhibit acute ultraviolet B erythema [14].

So far, there is no clinical experience for the application of thalidomide in cutaneous manifestation in Chinese SLE patients. So, the aim of this study is to present our experience of thalidomide's efficacy and safety in the treatment of cutaneous manifestations in lupus patients and to find out the effective and maintenance doses in Chinese patients.

Methods

Patients

Sixty-nine patients aged from 18 to 60 years old from eight hospitals in Jiangsu Province, China were enrolled, and all of them fulfilled the American College of Rheumatology (ACR) criteria for the diagnosis of SLE [15]. All patients had cutaneous manifestations, including DLE, butterfly erythema, and vasculitis on hands and legs, but not drug-induced rashes. Those with one of the following conditions were ruled out from this study: (1) pregnant, nursing women, or those who are thinking of being pregnant within 6 months; (2) patients with neuropathy, diabetes mellitus, or alcoholics; (3) people at the risk of thrombosis, who once had stroke or with positive anticardiolipin antibody (ACA); (4) patients with severe lupus, serious organ damages or dysfunction, such as neuropsychiatric systemic lupus erythematosus (NPSLE), severe cytopenia (white blood cells count less than 2000/μl, hemoglobin less than 6 g/dl, or platelet count less than 60,000/μl), moderate to severe pulmonary arterial hypertension, lung pulmonary disease, or renal dysfunction; (5) allergy to thalidomide therapy, for example, rash rapidly after treatment. During the medication period, patients were advised not to work at nights or drive.

Treatment protocol

All enrolled patients were given thalidomide at a starting dose of 25 mg daily orally at bedtime. The maintenance administration dose would remain 25 mg daily if the rash was markedly ameliorated in a week, otherwise the dose would be gradually augmented to 50, 75, even 100 mg daily in the next weeks if new skin lesion appeared or no significant amelioration was obtained. Thalidomide could be tapered if patients had mild side effects or discontinued if they were still not tolerated to therapy. If thalidomide at a dose of 150 mg daily for 2 weeks was invalid, or severe adverse event occurred, the patient would be excluded from the study. All patients were followed up once a week until 8 weeks.

If patients were given steroid therapy or others, the dose of these drugs should not be increased overall experimental phase. Furthermore, any drugs, such as steroid and immunosuppressant, were not allowed to be newly added during the experimental process. Hydroxychloroquine sulfate was not allowed in this study. All the patients were recommended as normally to have sunscreen and avoid direct sunlight during the trial.

After 8 weeks, thalidomide was continued for those who had skin lesions that were not completely disappeared. And for those who had complete remission, thalidomide was tapered then discontinued. Others drugs, like hydroxychloroquine, were allowed to be added.

Clinical efficacy evaluation

All patients were followed up for 8 weeks. The effective dose and maintenance dose of thalidomide treatment were recorded. The definition of "effective dose" was the dose that thalidomide began to show clinical effect and amelioration of skin lesions. "Maintenance dose" was defined as the dose that thalidomide worked most effectively and showed least side effects. Before and at each visit time after thalidomide treatment, patients were allowed to see the clinicians at each center. The clinician took photos and measured the position, size, and character of skin lesions each time. Patients' objective reports were not convincing for measurement. If the patients were not able to come back for visit, they would be excluded from the trial.

SLEDAI scores and ESR levels for each patient before and 4 weeks after treatment were evaluated. Meanwhile, serum levels of TNF-α before and 4 weeks after thalidomide treatment were assayed by enzyme-linked immunosorbent assay (ELISA, eBioscience, USA). Clinical efficacy for cutaneous lesions was defined as complete remission (skin lesions totally disappeared or reduced more than 90 %), partial remission (the improvement was shown, but less than 90 %), and no response (no improvement of skin lesions).

Safety profile

Pregnancy test and contraception were checked before treatment. Blood and urine routine detection, liver, and renal functional index were examined before and 4–8 weeks after thalidomide treatment. The character, frequency, and severity of adverse events were recorded.

Statistical analysis

All the data were performed using SPSS version 13.0 (SPSS Inc, Chicago, IL). Continuous variables were described as

Table 1 Effective and maintenance doses of thalidomide ($n = 69$)

Percentage, % (n)	Doses of thalidomide			
	100 mg daily	75 mg daily	50 mg daily	25 mg daily
Effective dose	10 (7)	10 (7)	68 (47)	9 (6)
Maintenance dose	9 (6)	14 (10)	71 (49)	6 (4)

mean ± standard error mean and were compared by paired t test. A two-tailed P value of less than 0.05 was considered statistical significant.

Results

Effective and maintenance dose of thalidomide treatment

There were 6 male and 63 female patients in this cohort. Before thalidomide treatment, 48 patients had butterfly erythema, 9 patients had DLE, 12 patients had vasculitis on hands and/or legs, and 42 patients had photosensitivity. After thalidomide treatment, the effective dose was 50 mg daily for 68 % of the patients and 100, 75, and 25 mg daily for 13, 10, and 9 % of the patients, respectively. Seventy-one percent (71 %) of patients showed a maintenance dose of 50 mg daily, another 9, 14, and 6 % patients showed a maintenance dose of 100, 75, and 25 mg daily, respectively (Table 1).

Cutaneous efficacy of thalidomide treatment

At the end of the fourth week, the rates of complete remission, partial remission, and no response were 56 % (39/69), 41 % (28/69), and 3 % (2/69), respectively. The overall clinical remission rate was 97 % (66/69). We continued thalidomide

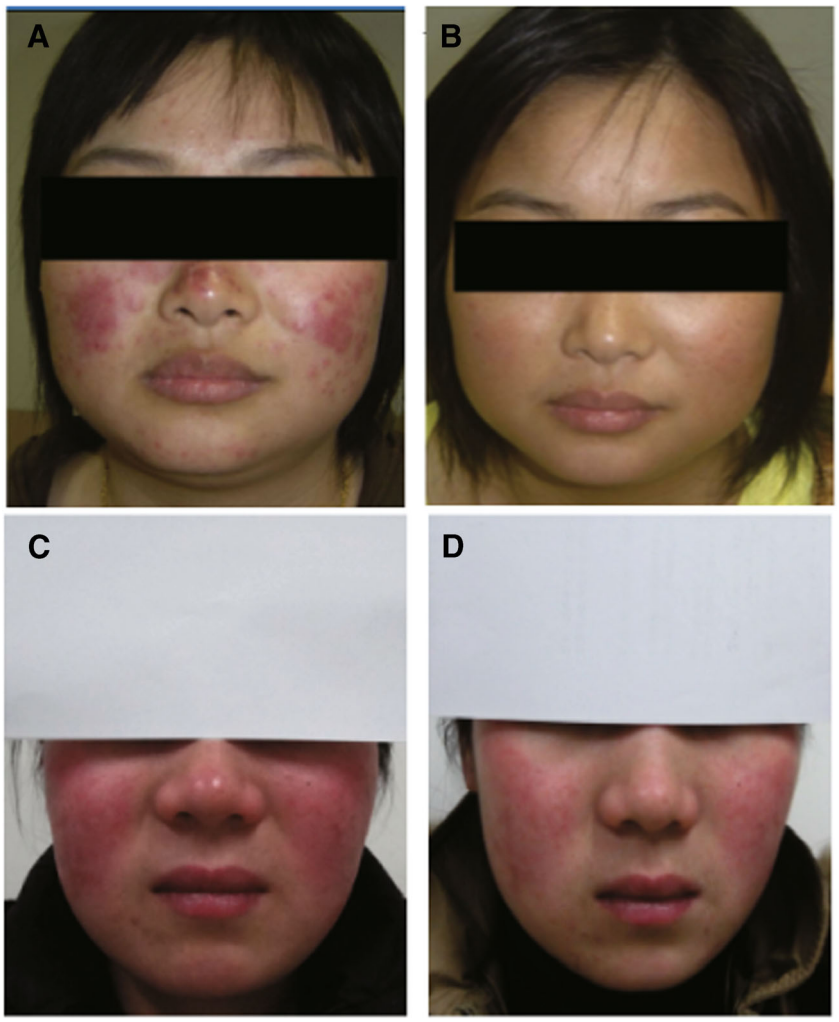

Fig. 1 Complete and partial cutaneous remission of lupus patient after thalidomide treatment. Erythema on the forehead and malar rash before (**a**) and 4 weeks (**b**) after thalidomide treatment, an example of complete remission. Malar rash before (**c**) and 4 weeks (**d**) after thalidomide treatment, an example of partial remission

treatment and followed up for 8 weeks and found the rates of complete remission and partial remission were up to 71 % (49/69) and 29 % (20/69), respectively. In Fig. 1, we showed 2 patients who achieved complete (1A-B) and partial (1C-D) remission of butterfly erythematosus, respectively. In Fig. 2, changes of DLE (2A), hands vasculitis (2B), and limb vasculitis (2C-D) were shown.

Disease activity index after thalidomide treatment

Besides the change of cutaneous manifestations, we also observed disease activity index and serum inflammatory parameters before and after thalidomide treatment. SLEDAI score significantly decreased 4 weeks after treatment (Fig. 3a). Additionally, levels of ESR were notably reduced at 4 weeks follow-up (Fig. 3b). Furthermore, we detected serum TNF-α levels before and 4 weeks after thalidomide treatment and found no significant changes (before: 4.37 ± 2.69 pg/ml, 4 weeks: 4.35 ± 1.75 pg/ml, $P > 0.05$).

Before thalidomide treatment, most patients were simultaneously given prednisone (5–15 mg daily), leflunomide (10–20 mg daily), or cyclophosphamide (0.6 g per month) for more than 3 months, but they did not respond to these therapies. During thalidomide treatment, these primary therapies

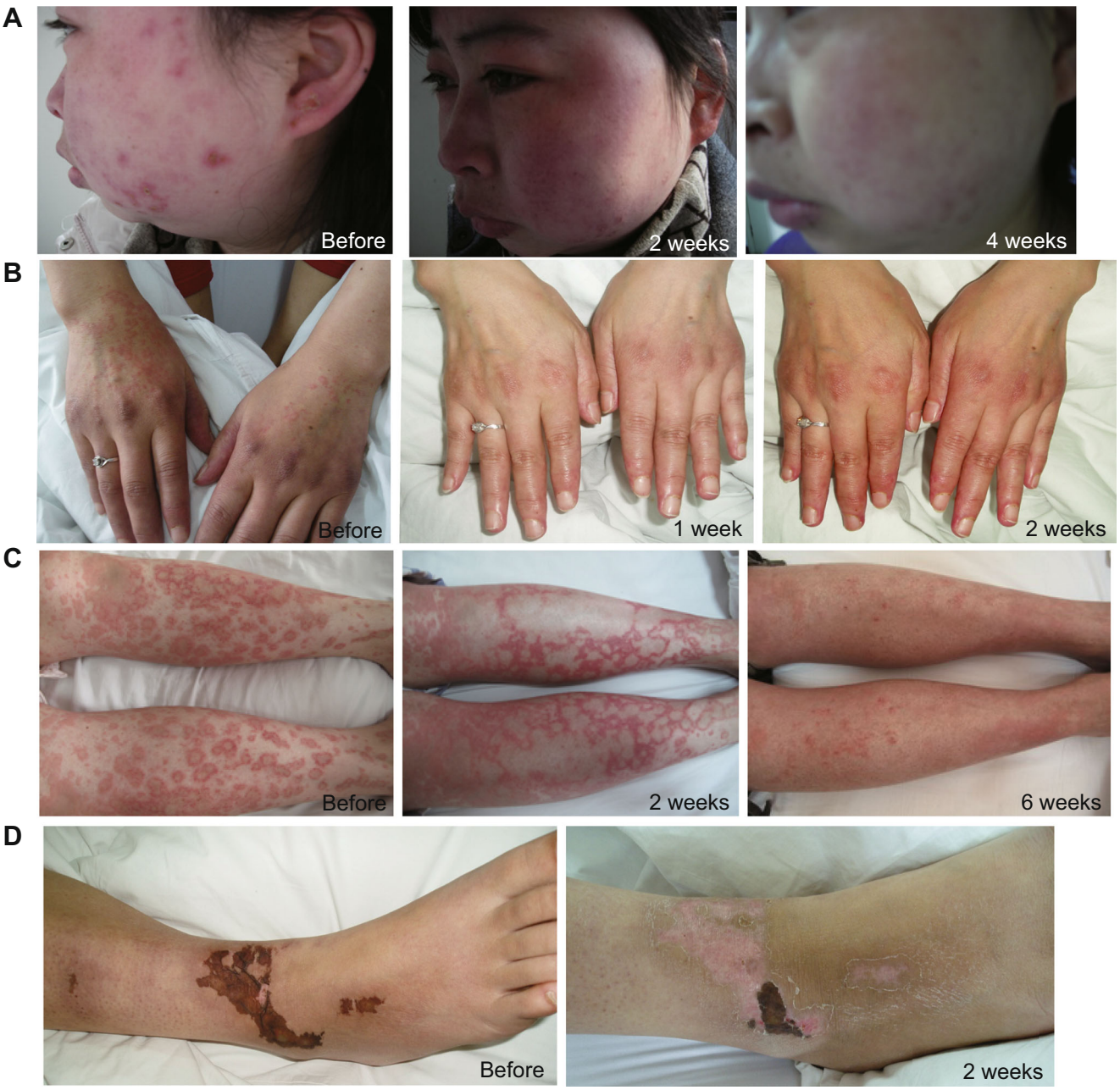

Fig. 2 Changes of discoid lupus erythematosus (**a**) and limb vasculitis (**b**–**d**) before and after thalidomide treatment

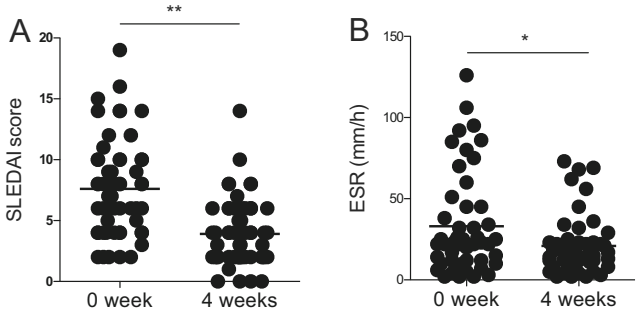

Fig. 3 Disease activity index before and after thalidomide treatment. Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (**a**) and erythrocyte sedimentation rate (ESR) (**b**) levels before and 4 weeks after thalidomide treatment. *$P < 0.05$ and **$P < 0.01$

were not allowed to be replaced and should be kept at the same dose as before, or discontinued due to inefficacy, to exclude the effect of these drugs. No deterioration was noticed in other clinical features, such as proteinuria, leukopenia, necrosis of the femoral head, and ischemic bowel necrosis.

Safety profile

The most common side effects were drowsiness and constipation. Six patients suffered mild drowsiness at a dose of 75 to 100 mg daily of thalidomide. The dose was tapered to 50 and 75 mg daily for 3 patients and drowsiness disappeared. Four patients suffered constipation at a dose of 100 mg daily. Then, 1 patient ameliorated after taking lactulose, and the dose of thalidomide remained at 100 mg daily. Another patient also took lactulose, and the dose was tapered to 75 mg daily, then constipation ameliorated. The dose of thalidomide was tapered to 50 and 75 mg daily, respectively for the other 2 patients and constipation disappeared. Abdominal pain appeared in 1 patient at a dose of 75 mg daily, which was alleviated by acid-suppressive drugs and protection of gastric mucosa. Leukopenia occurred in 1 patient at a dose of 50 mg daily and was reversed by oral berbamine hydrochloride for 2 weeks. All the adverse events were resolved after appropriate treatment, and thalidomide was continued (Table 2). No peripheral neuropathy or thrombotic events occurred.

Discussion

Many drugs have been applied in the treatment of cutaneous lupus erythematosus, such as corticosteroid, hydroxychloroquine, mycophenolate mofetil, methotrexate, azathioprine, cyclosporine, leflunomide, cyclophosphamide, and TNF-α antagonist [16–19]. Patients receiving immunosupressive drugs above are at a high risk of developing serious infectious complications, and thalidomide is safer and more attainable compared with other drugs. Thalidomide could induce a faster clinical response (cutaneous as well as systemic) compared with prenisolone and had fewer relapses and a longer period of remission than prednisolone [18]. Therefore, the purpose of this study is to explore the effect of thalidomide in improving cutaneous lupus for Chinese patients and to find out optimal dose of thalidomide treatment.

Early in most western countries, thalidomide was given at a starting dose of 100–400 mg daily and then reduced to 50 mg daily or less after clinical improvement [20–24]. There were clear dose-dependent effects [23]. However, thalidomide treatment at 100 mg daily for 3 months caused important adverse events so that they discontinued the therapy [25]. The side effects of thalidomide in these studies were much more and severe, including peripheral neuropathy and drowsiness. Compared with people in western countries, Chinese people have decreased size and body weight, which might need fewer doses of drugs to achieve a good clinical response. Therefore, in the present study, we used thalidomide at the starting dose of 25 mg daily, and then regulated the dose according to patients' clinical response as well as side effects. When followed up for 8 weeks, the maximum ratio of effective and maintenance dose of thalidomide were both at 50 mg daily. It was similar to the result reported in England that using starting dose of 50–100 mg daily, and maintaining dose of 25–50 mg daily were effective in controlling refractory disfiguring rash [26, 27]. At the same time, most patients (65 %) were quickly responsive to thalidomide at the first week, and the dose was much lower than Brazilian experiences [22].

It has been reported that there was no obvious association between thalidomide dose and remission rate [23]. Here, we found that the remission rates were gradually increased in a time-dependent manner, especially the rate of complete remission, which was 56 % at the fourth week and then rose up to 71 % at the 8th week. The total remission rate rose to 100 % at

Table 2 Side effects after thalidomide treatment

Side effects	Incidence rate	Degree	Treatment	Results
Drowsiness	8.6 % (6/69)	Mild	NA	Resolved
Constipation	5.8 % (4/69)	Mild	Lactulose oral for 2 patients	Resolved
Abdominal pain	1.4 % (1/69)	Moderate	Omeprazole and talcid oral	Resolved
Leukocytopenia	1.4 % (1/69)	Mild	Berbamine hydrochloride oral	Resolved

the eighth week. So according to these therapeutic effects, low dose of thalidomide (50 mg daily) was still valid, and the remission rate was close to those of moderate and large dose treatment [9, 23]. For example, Barba et al. reported that thalidomide could treat chronic discoid erythema to attain clinical remission (19/20), and only 1 patient had to stop using thalidomide due to its side effects [20]. In addition, 60 patients with erythema, who were resistant to prednisone, antimalarials, and azathioprine, were treated by thalidomide, and the remission was up to 90 % [9]. In Brazilian, long-term thalidomide treatment ameliorated refractory cutaneous lupus erythematosus up to 98.9 % [22], suggesting a good clinical efficacy of thalidomide in treating lupus erythematosus.

Meanwhile, SLEDAI score and ESR levels for patients were notably decreased after low dose thalidomide treatment for 4 weeks, indicating that thalidomide might relieve disease activity, not just erythema related with SLE. As Walchner et al. reported that thalidomide therapy could improve lupus disease, such as proteinuria, the level of anti-double-strand DNA antibodies, CRP, even hair loss [21], indicating the obvious therapeutic effect of thalidomide in lupus patients. The therapeutic mechanism of thalidomide might be associated with inhibition of tumor necrosis factor-α (TNF-α) production [28]. However, we examined the level of TNF-α in the serum of patients, but found no significant decrease after thalidomide treatment. Zampieri et al. reported in 2006 that TNF-α accumulated in lesion skin tissues from patients with SCLE, but not in non-lesion skin [29], which suggested that thalidomide might improve erythema through inhibiting TNF-α production in skin tissues but not in serum, or inhibiting TNF-α migration from serum to local skin lesions. On the other hand, in vitro study showed thalidomide administration could cause a decrease in type 1 cytokines (interleukin 2 and interferon gamma) and an increase in type 2 cytokines (interleukin 4 and interleukin 5) [30], so the underling mechanisms of thalidomide treatment in lupus patients need further investigations.

The common side effects in our study were drowsiness and constipation, similar to the results in other studies [22, 27, 31]. Thalidomide was reported to cause peripheral neuropathy such as paralysis, paresthesia, pain, and so on [32]. And no correlation was reported between the age of the patients and the occurrence of peripheral neuropathy [27]. But in the current study, peripheral neuropathy was not observed in patients receiving thalidomide, which might be closely related to the dose or the duration of thalidomide therapy. If treatment time needs to be extended, we should follow up the advert events frequently, especially neuropathy.

As we all know, patients who are pregnant or thinking of being pregnant within 6 months are not allowed to use thalidomide. Severe teratogenesis appeared in the first trimester of thalidomide treatment, which might be the result of abnormal angiogenesis during fatal development [31, 33]. Some studies reported that thalidomide could cause severe thrombosis [34, 35], and it also could motivate antiphospholipid syndrome [36], so patients with positive anticardiolipin antibodies were excluded in this study. Low starting dose treatment is as effective as that of moderate or large dose therapy, but the side effect is greatly reduced.

Conclusion

For Chinese patients with cutaneous lupus, the effective and maintenance dose is 50 mg daily, and the dose of thalidomide could be gradually increased to 100 mg daily within 8 weeks.

Compliance with ethical standards

Financial and competing interests disclosure The study was supported by the National Natural Science Foundation of China (NO. 81273304, NO. 81401347), Jiangsu Provincial Natural Science Foundation (BK20140098), Jiangsu Provincial Health Department Foundation (Q201411), and The Scientific Research Project of Nanjing Municipal Health Bureau (YKK14067). The authors have no financial/other relationships such as consultancies, employment, expert testimony, honoraria, speakers bureaus, retainers, stock options, or ownership.

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