Successful treatment with thalidomide for pemphigus vulgaris

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Abstract

Background: Pemphigus vulgaris (PV) is a potentially life-threatening mucocutaneous autoimmune blistering disease characterized by suprabasal acantholysis, causing painful mucocutaneous blisters and erosions. Current mainstay therapy for pemphigus is systemic corticosteroids in combination with or without immunosuppressive adjuvants, which may cause severe adverse effects and seriously impact on the quality of life in pemphigus patients. The objective of this study was to evaluate the efficacy and safety of thalidomide therapy in patients with PV.

Methods: This study examined six PV patients from June 5, 2017, to November 11, 2018, in the dermatology department of Peking Union Medical College Hospital. Treatment with thalidomide was applied at a dose of 50–100 mg/day for disease control.

Results: The mean age of the six patients (two male and four female patients) at the time of thalidomide therapy initiation was 50.2 years (range: 38–67 years), and the total duration of follow-up after thalidomide therapy was 13.2 months (range: 5–25 months). All patients responded favorably to thalidomide treatment, and three patients showed a dramatic reduction in anti-Dsg3 autoantibodies in the serologic examinations within 1 year. Five patients were found to have mucosal involvement. Mild adverse effects were noted in three patients, which could be managed after the application of symptomatic treatment and did not interfere with the pemphigus therapy.

Conclusion: These results demonstrate that thalidomide could be an effective and safe option for PV patients, especially those who are concerned about steroid-induced severe complications, and have mucosal diseases.

Keywords: pemphigus vulgaris, thalidomide, therapy

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Introduction

Pemphigus vulgaris (PV) is a chronic, autoimmune blistering disease that may affect the skin and mucous membranes, mediated primarily by circulating autoantibodies against desmogleins that are cell surface adhesion molecules on human keratinocytes. Binding of the autoantibodies to the desmogleins results in loss of cell–cell adhesion and blister formation in skin epidermis. The mainstay therapy for pemphigus is systemic corticosteroids, in combination with or without immunosuppressive adjuvants, which have remarkably decreased morbidity and mortality from pemphigus. However, prolonged corticosteroid therapy may lead to severe adverse effects and complications, such as infections, diabetes mellitus, hypertension, and osteoporosis that substantially contribute to morbidity and mortality from the disease. Interestingly, a certain number of patients tend to refuse to receive conventional therapy due to strong concerns about the potential adverse effects. These patients can be managed with alternative therapies, such as cyclophosphamide, plasmapheresis, intravenous immunoglobulins, my- cophenolate mofetil, and immunoadsorption. However, a considerable number of patients are resistant to these conventional treatments.
Recently, rituximab (a chimeric murine–human anti-CD20 monoclonal antibody) that targets pre-B and mature B lymphocytes, has been used to treat recalcitrant pemphigus patients. Rituximab induces a prolonged clinical remission.\(^2\) However, the high costs and limited knowledge of long-term adverse effects limit its use for pemphigus patients. Thus, the development of new optional therapies is always desired in spite of the novel emerging therapies in the investigational or clinical trials.\(^3\)

Thalidomide has been a valuable medication used to successfully treat a number of dermatological disorders,\(^4\) although the mechanism of action is unclear. Several sporadic case reports have also shown that thalidomide could be used for the management of pemphigus, including “Hailey-Hailey pemphigus”,\(^5\) cicatricial pemphigus,\(^6\) and PV.\(^7,8\) In this study, we report six cases of PV patients who refused corticosteroids therapies and other alternative therapies in our clinic due to concerns about the potentially severe adverse effects or complications. This study was approved by the Regional Ethics Committee of the Peking Union Medical University Hospital (approval number: S-K1030). All participants provided written informed consent prior to enrollment in the study, and written informed consent was obtained from the patients for the publication of this case report. Remarkably, the treatment of these patients with thalidomide achieved rapid disease control and complete remission of pemphigus lesions.

### Case presentation

#### Case 1

A 52-year-old male attended our dermatology department because of persistent bullae and erosions on his scalp (Figure 1a) and buccal mucosa for 6 months with progressive new lesions. Enzyme-linked immunosorbent assay (ELISA) testing revealed an anti-Dsg3 IgG autoantibody (Dsg3 AutoIgG) level of 90 U/ml (normal value < 20 U/ml), and indirect immunofluorescence (IIF) was positive for intercellular antibodies (titer 1:80). The patient was started on thalidomide at 50 mg/day. The scalp and oral lesions improved markedly over the next 2 months. Thalidomide was subsequently tapered to, and maintained at, 25 mg/day. The scalp lesions subsided completely within 1 year (Figure 1b), with Dsg3 AutoIgG and IIF becoming negative. The patient continues to show complete clinical remission over 1 year of follow up.

#### Case 2

A 39-year-old male presented with oral vesicles and blisters on his back persisting for 5 months. White vesicles were observed on the mucosae of the upper lip (Figure 1c). ELISA testing showed a Dsg1 AutoIgG level of 48 U/ml (normal value < 20 U/ml) and Dsg3 AutoIgG > 150 U/ml. The patient was treated with thalidomide at 100 mg/day, and topical corticosteroids on skin and mucosal lesions at the disease progression stage. After 6 weeks, the oral cavity lesions were improved (Figure 1d), and thalidomide was reduced to 50 mg/day. Dsg1 AutoIgG was decreased to 22 U/ml within 8 months, with no recurrence for more than 9 months.

#### Case 3

A 66-year-old female presented with a history of PV for 15 years, which had relapsed in the last 2 months. Dermatological examination showed bullae and erosions distributed widely on the trunk (Figure 1e) and oral mucosa. Intercellular deposits of IgG were detected with direct immunofluorescence (DIF). ELISA showed a Dsg1 AutoIgG level of 149 U/ml and a Dsg3 AutoIgG level of > 150 U/ml. IIF was positive (titer 1:1280). The patient was treated with thalidomide at 50 mg/day and topical corticosteroids on the trunk and oral mucosa. The dose of thalidomide was later increased to 100 mg/day to control disease activity. Five months later, the lesions both in the trunk and oral cavity were completely resolved (Figure 1f), albeit with no serologic change by ELISA. The patient continues to take thalidomide and is under follow up in our outpatient clinic.

#### Case 4

A 39-year-old female was seen at our clinic with a 2-month history of painful pustules in the frenulum. Subsequent workup, including skin biopsy and IIF (1:1280), was consistent with pemphigus vulgaris. After considering the risks associated with steroid use, the patient received the treatment with thalidomide at 50 mg/day. She exhibited resolution of the oral lesions, with IIF turning negative.
Case 5
A 67-year-old female presented with a chief complaint of blisters restricted to her left cheek and chest. She was previously misdiagnosed as having skin infections, and anti-infective therapy was ineffective. A skin biopsy from her face revealed a suprabasal cleft with acantholytic keratinocytes. ELISA testing revealed a Dsg3 AutoIgG level of 146 U/ml and IIF was positive (titer 1:80). After 6 months of thalidomide treatment at 50 mg/day, the patient was in clinical remission, with reduced Dsg3 antibodies of 29 U/ml. The patient’s skin condition has since remained stable.

Case 6
A 38-year-old female presented with persistent pustules in the oral cavity for 9 months, and difficulty in eating and swallowing. The biopsy specimen showed suprabasal acantholysis. Screening revealed that IIF was positive (titer 1:1280) and the Dsg3 AutoIgG level was >150 U/ml. The patient was treated with thalidomide at 50 mg/day. Within 1 month, the oral cavity lesions subsided and anti-Dsg3 was decreased to 140 U/ml. At 4 months of follow up, the patient showed no recurrence of mucosal lesions.

Figure 1. (a) Dark erythema on the scalp with effusion before treatment. (b) Complete clinical remission of skin lesions after 1 year of thalidomide treatment. (c) White vesicles and erosions on the mucosae of upper lip. (d) Reduction of mucosal lesions after 6 weeks of thalidomide treatment. (e) Dark erythema and erosions on the abdomen. (f) Improved skin lesions after thalidomide treatment.
Discussion

Prior studies have reported the therapeutic efficacy of thalidomide in the treatment of a variety of skin conditions. The effectiveness in treating pemphigoid, another antibody-mediated skin blistering disease, has also been recognized. However, few case reports of PV treated with thalidomide have been published. Here, we report six PV patients treated with thalidomide – to our knowledge the first and largest case series of patients. Interestingly, these patients were selected for study because of their serious concerns about corticosteroids-related complications. In our study, the total duration of follow up after thalidomide therapy was 13.2 months (range: 5–25 months). Treatment with thalidomide started at 50 mg/day led to marked improvement of mucocutaneous lesions, while in Case 3 it showed no benefit until the dosage was increased to 100 mg/day. Complete response was also observed in the patients initiated at 100 mg/day (Case 2). The treatment duration required for clinical remission might be variable, from 1.5 to 12 months (Table 1). After clinical remission, all patients accepted consolidation therapy on a maintenance basis of thalidomide at 25–50 mg/day. Our patients showed no relapse during the follow-up period, which is defined as appearance of at least three new lesions/month that do not heal spontaneously within 1 week.

Our patients had relatively mild disease with a Pemphigus disease area index (PDAI) score range from 1 to 24 (Table 1), indicating that thalidomide can be an optional therapy applicable for mild PV. Six cases with only mild disease were available for our case study potentially because they were more concerned about the long-term side effects by corticosteroids and would consider other treatments, while patients with severe disease are more ready to accept the first-line therapy after diagnosis. However, patients with severe PV could also be treated with thalidomide, which has led to long-term clinical remission in previous case reports.

Most of our patients (5/6) were found to have mucosal involvement. Interestingly, two cases were reported to have mucosal lesions in oral mucosae and/or cervix, and these patients who were resistant to therapy with high-dose steroids responded well to thalidomide started at 100–200 mg/day. Thalidomide was also reported for the successful management of oral and genital ulcerations in various disorders. Additionally, complete remission was also reported in the control of aphthous stomatitis treated with thalidomide. These observations suggest that thalidomide could be valuable for PV, particularly with mucosal involvement.

The mechanism by which thalidomide leads to complete remission of pemphigus remains to be investigated. One possible mechanism of action is by inhibiting the production of inflammatory cytokines, including tumour necrosis factor- (TNF-). TNF- is highly expressed in skin lesions of patients with pemphigus, and serum levels appear to correlate with disease activity. Alternatively, thalidomide could regulate local immunity in the epidermis, which has been shown to play an essential role in pemphigus pathogenesis. Furthermore, thalidomide may also up-regulate desmoglein expression in epidermal keratinocytes, a mechanism compensating for desmoglein depletion.

Notably, only three patients showed a dramatic reduction of anti-Dsg3 autoantibodies in the serologic examinations within 1 year (Figure 2). Studies have demonstrated that ELISA scores fluctuated in parallel with disease activity, which could also be validated by our results. However, two of the six patients showed no change in anti-Dsg3 antibodies during clinical remission. Similar cases were also observed with high ELISA values during the quiescent disease period in some subsets of PV patients, supporting a direct regulation of local immunity or epidermal keratinocytes in addition to the systemic effects on the immune system by thalidomide.

The safety of thalidomide treatment is a matter of great concern. Aside from teratogenicity, common side effects include dizziness, constipation, tremor, mood changes, and peripheral neuropathy. We detailed thalidomide-associated adverse effects with every patient before our treatment. For sexually active patients, strict contraceptive measures were advised during the whole procedure. Thalidomide appeared well-tolerated in our case series, and no thromboembolic events or severe neurotoxicity was observed. Mild drowsiness was observed in two patients (33.3%), and constipation in one patient (16.7%). These could be managed with the symptomatic treatment,
| Case | Age/Gender | Disease history | Location | PDAI score | Histopathologic examination | DIF | Effective dose of thalidomide (mg/day) | Months to obtain clinical remission | Response to thalidomide | Follow-up months after therapy |
|------|------------|----------------|----------|------------|----------------------------|------|--------------------------------------|-----------------------------------|-----------------------------|-----------------------------|
| 1    | 52/M       | 6 months       | Scalp, buccal mucosa | 8          | Suprabasal cleft, acantholytic keratinocytes in blister fluid | IgG and C3 deposits in the epidermis | 50   | 12 | [-]→[-] [1 year] | 1:80→[-] [1 year] | 25 |
| 2    | 39/M       | 5 months       | Back, mucosa of upper lip | 7          | Acantholysis, suprabasal cleft | None | 100  | 1.5 | 48→22 [8 months] | >150→>150 [8 months] | 1:320 | 11 |
| 3    | 66/F       | 2 months       | Trunk, oral mucosa   | 24         | Suprabasal cleft, neutrophils, eosinophils and acantholytic keratinocytes in blister fluid | IgG and C3 deposits in the epidermis | 100  | 5  | 149 | >150→>150 [6 months] | 1:1280→[-] [6 months] | 13 |
| 4    | 39/F       | 2 months       | Frenulum   | 1           | Acantholysis, suprabasal cleft | IgG deposits in the epidermis | 50   | 3  | [-]→[-] [1 month] | [-]→[-] [1 month] | 1:1280→[-] [1 month] | 13 |
| 5    | 67/F       | 6 months       | Face, chest | 2           | Acantholysis, suprabasal cleft | None | 50   | 3  | [-]→[-] [3 months] | 146→29 [6 months] | 1:80→[-] [1 month] | 12 |
| 6    | 38/F       | 9 months       | Oral mucosa | 2           | Acantholysis | None | 50   | 1  | [-]→[-] [1 month] | >150→160 [1 month] | 1:1280 | 5 |

Clinical characteristics and treatment responses in our case series.
DIF, direct immunofluorescence; ELISA, enzyme-linked immunosorbent assay; F, female; IIF, indirect immunofluorescence; M, male; PDAI, pemphigus disease area index.
without dosage adjustments due to side effects. Nonetheless, careful follow up is essential for patients with long-term use of thalidomide.

The limitations of this study are the low number of patients treated and limited months to prove the continuous effects of thalidomide on PV.

Despite these limitations, our case series serves to further understanding of the treatment of PV.

Conclusion
In conclusion, our preliminary experiences have shown that an old medication, thalidomide, may represent a novel and effective option for pemphigus therapy, leading to rapid disease control and few adverse effects. Clinicians should consider using thalidomide as an alternative therapy for PV patients, especially those with mucosal diseases who refuse the proposal of systemic corticosteroid treatment due to strong concerns about potential corticosteroid-associated side effects.

Conflict of interest statement
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