Therapeutic ladder for pemphigus vulgaris: Emphasis on achieving complete remission

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Background: Pemphigus vulgaris (PV) is a blistering autoimmune bullous disease that is usually fatal without proper treatment. There are no clear treatment guidelines for PV at this time.

Purpose: We suggest a standard treatment regimen for patients with PV based on the success of our treatment.

Methods: A retrospective chart review of 18 patients with PV was conducted to assess response to a similar approach using mycophenolate mofetil (MMF) and prednisone. Diagnosis was confirmed through routine histology, direct immunofluorescence, and indirect immunofluorescence, and patients were followed up for a total average of 35.2 months.

Results: We achieved complete disease control in 89% of patients using our treatment algorithm. Fourteen of 18 patients achieved complete disease control on therapy with prednisone and MMF. Three of the 4 patients who did not achieve control on MMF and prednisone went on to receive rituximab therapy, and two of those patients achieved disease control on rituximab. The average length of time from initiating therapy to 75% clearance of lesions was 4.5 months. Three of 18 patients were able to discontinue therapy after an average of 3 years and have remained in complete remission for more than 1 year.

Limitations: This was a retrospective chart review with a small patient sample size.

Conclusions: The combination therapy of MMF and prednisone is an effective treatment regimen to achieve rapid and complete control of PV. For those patients who fail treatment with MMF and prednisone, rituximab is an efficacious alternative therapy. (J Am Acad Dermatol 2011;64:490-4.)

Key words: blistering disease; mycophenolate mofetil; rituximab.

Pemphigus vulgaris (PV) is a rare autoimmune blistering disease that has nearly 100% mortality if left untreated.[1] Patients with PV have IgG antibodies to desmoglein and subsequently develop intraepidermal mucocutaneous blisters that easily rupture and leave patients susceptible to infection. The clinical diagnosis of PV can be confirmed in several ways: histologic findings of suprabasal acantholysis, direct immunofluorescence (DIF) showing intercellular deposits of IgG and C3, and evidence of circulating antibodies by indirect immunofluorescence (IIF) or enzyme-linked immunosorbent assay. There is no drug currently Food and Drug Administration approved for treatment of PV. PV has traditionally been treated with oral corticosteroids as this medication has the most evidence showing its efficacy.[1] Many physicians prescribe another

Abbreviations used:

DIF:	direct immunofluorescence
IIF:	indirect immunofluorescence
IVIG:	intravenous immunoglobulin
MMF:	mycophenolate mofetil
PV:	pemphigus vulgaris

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immunomodulator as adjuvant therapy to create a corticosteroid-sparing regimen.

Although a variety of adjuvant therapies have been used in PV, there are no randomized controlled trials showing one medication to be the most efficacious and safe. Most studies of PV treatments are small case series or case reports and lack long-term follow-up.[1] Mycophenolate mofetil (MMF) was recently shown to be more effective than azathioprine in maintaining disease control, with no difference in frequency of adverse effects.[2] MMF is currently in a phase III clinical trial to assess MMF's safety and efficacy for patients with PV.[3]

It is also unknown which patients will respond to a particular medication regimen. Previous studies have implicated initial disease severity and early response to therapy as being prognostic indicators.[4] IIF titers and enzyme-linked immunosorbent assay titers have been shown to mirror disease activity, decreasing as patients respond to therapy.[5-7] These titers have not previously been shown to predict a patient's response to their PV treatment regimen.

We sought to develop a therapeutic ladder for patients with PV in an effort to standardize treatment and to maximize remission rates. We developed the ladder outlined below and assessed its performance by reviewing the records of 18 patients with PV treated at our university medical center with this standard approach. We also looked at the IIF titers of our patients to determine if these titers could serve as a prognostic indicator for a patient's response to initial therapy.

CAPSULE SUMMARY

- There are no clear treatment guidelines for pemphigus vulgaris. We conducted a retrospective chart review to assess treatment consisting of mycophenolate mofetil and prednisone for patients with pemphigus vulgaris.
- Eighteen patients were followed for almost 3 years. We achieved complete disease control in 89% of patients using our treatment algorithm.
- Three of the 18 patients were able to discontinue therapy after 3 years and remained in complete remission for more than 1 year.

METHODS

Eighteen patients with a confirmed diagnosis of PV who presented to one investigator (J. L. J.) at our department of dermatology clinics between 2001 and 2007 were included in this institutional review board–approved retrospective chart review. Since their initial visit, patients were followed up for an average of 35.2 months (range 5-130 months) up to May 2009.

Fifteen of the 18 patients had their PV diagnosis confirmed by IIF, DIF, and histology at our institution. The 3 remaining patients had their PV diagnosis confirmed by IIF, DIF, and histology at outside institutions and IIF reconfirmed at our institution. Patient age, sex, disease distribution, histology, DIF results, IIF titers, date of diagnosis, date of remission, date of last follow-up, treatment, and dosages were recorded. Only patients with PV (not pemphigus foliaceous or paraneoplastic pemphigus) were included in this study. For the purposes of this study, we defined a patient as having complete control of disease activity when they had no active lesions or no development of new lesions.

All patients had diagnosis confirmed at first visit with IIF and by review of histology and DIF. A combination regimen of MMF and oral prednisone was started for all patients. Patients were then closely followed up in clinic and their treatment dosages modified until they achieved remission or failed to respond on MMF and prednisone within several months of initiating therapy. Patients who failed to achieve remission on MMF and prednisone were given the option to begin alternative treatment. Alternative treatments included cyclophosphamide, intravenous immunoglobulin (IVIG), or rituximab therapy. The occurrence of treatment side effects was monitored with serial laboratory work along with appropriate monitoring by their primary care physician, including osteoporosis prevention. Patients were educated on all medication side effects and were encouraged to read a brochure regarding the use of oral prednisone. Oral disease was controlled with treatment of secondary candidiasis and oral hygiene recommendations.

RESULTS

Clinical characteristics of study patients are as follows. The mean age of patients with PV in this study was 52 years (range 29-67 years). Ten of the patients were female and 8 were male. Twelve patients had both mucosal and skin involvement, and 6 had only severe mucosal involvement.

All patients included in this study had active PV when initially seen at our facility, and 14 of these patients had been on prior PV therapy (Table I). In all, 86% of patients on prior PV therapy and 75% of patient with no prior PV therapy achieved complete control of disease on MMF and prednisone (Table II).