Randomized controlled open-label trial of four treatment regimens for pemphigus vulgaris

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Background: Pemphigus is a severe autoimmune blistering disease affecting the skin and mucosa. Mortality is high in the absence of treatment. Nowadays, treatment is based mainly on corticosteroids and cytotoxic drugs; however, because of the rarity of the disease worldwide, there is not yet a standard treatment based on randomized controlled trials, and the treatment used is based mainly on the experience of experts.

Objective: The aim of this study was to compare the efficacy and safety of 4 treatment regimens for pemphigus vulgaris: prednisolone alone, prednisolone plus azathioprine, prednisolone plus mycophenolate mofetil, and prednisolone plus intravenous cyclophosphamide pulse therapy.

Methods: One hundred twenty new cases of pemphigus vulgaris were enrolled. These patients were randomly allocated into 1 of 4 treatment groups (each comprising 30 patients) and received prednisolone (P), prednisolone and azathioprine (P/A), prednisolone and mycophenolate mofetil (P/MM), and prednisolone and intravenous cyclophosphamide pulse therapy (P/PC). They were followed up for 1 year at the Pemphigus Research Unit.

Results: In groups P, P/A, P/MM, and P/PC, 23 (76.5%), 24 (80%), 21 (70%), and 22 (73.3%) of the patients, respectively, followed the regimen for the full 1-year period. The mean total dose of prednisolone administered in groups P, P/A, P/MM, and P/PC was 11631 mg (standard deviation [SD] = 7742), 7712 mg (SD = 955), 9798 mg (SD = 3995), and 8276 mg (SD = 810), respectively. The mean total dose of prednisolone in group P (prednisolone alone) was 11,631 mg, The mean total dose of prednisolone in the 3 cytotoxic groups was 8652 mg. By using analysis of variance, the difference was statistically significant (P = .047). In the cytotoxic groups, there was a significant difference between the P/A and P/MM groups (P = .007), but not between P/A and P/PC (P = .971), and P/MM and P/PC (P = .670). Side effects were not significantly different among the 4 groups.

Limitations: Larger sample sizes and blind design are suggested for future studies.

Conclusion: The efficacy of prednisolone is enhanced when it is combined with a cytotoxic drug. The most efficacious cytotoxic drug to reduce steroid was found to be azathioprine, followed by cyclophosphamide (pulse therapy), and mycophenolate mofetil. (J Am Acad Dermatol 2007;57:622-8.)

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Supported by a grant from the vice chancellor of research at Tehran University of Medical Sciences.
Conflicts of interest: None declared.
Accepted for publication May 16, 2007.
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Published online July 24, 2007.
0190-9622/$32.00
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doi:10.1016/j.jaad.2007.05.024

Pemphigus is a severe, potentially life-threatening autoimmune blistering mucocutaneous disease with mortality and morbidity. Treatments consist mostly of the use of corticosteroid and immunosuppressive drugs. There is not yet a standard treatment for this disease, and insufficient data are available from randomized trials using different drugs and methods because of the rarity of the disease in the world.

In the past, prednisolone was the treatment of choice. Later, combination therapy in which prednisolone was associated with other immunosuppressive

Abbreviations used:

P: prednisolone
P/A: prednisolone plus azathioprine
P/MM: prednisolone plus mycophenolate mofetil
P/PC: prednisolone plus intravenous cyclophosphamide pulse therapy
PV: pemphigus vulgaris

agents was tested; in particular, azathioprine, cyclophosphamide, mycophenolate mofetil, dapsone, gold salts, methotrexate, cyclosporine, chlorambucil, dexamethasone plus cyclophosphamide pulse therapy, immunoablative therapy, plasmapheresis, and extracorporeal photochemotherapy were used. Recently, newer agents such as intravenous immunoglobulin therapy,[1-5] rituximab (an anti-CD20 chimeric monoclonal antibody),[6,7] immunoadsorption using the Globaffin adsorber system, and immunoadsorption for rapid removal of desmoglein-reactive autoantibodies have been used.[8,9]

The diversity of these drugs and treatment methods, together with their specific side effects, are indicative of the difficulty involved in choosing a suitable treatment for pemphigus today. In practice, the chosen therapy depends greatly on the experience of experts in different parts of the world.[10]

The aim of this randomized study was to compare the efficacy and safety of 4 treatment regimens for pemphigus vulgaris (PV): prednisolone alone, prednisolone plus azathioprine, prednisolone plus mycophenolate mofetil, and prednisolone plus pulsed therapy cyclophosphamide.

PATIENTS AND METHODS

Selection of patients

From January 2004 to December 2005, 140 new patients with PV were consecutively assessed for their eligibility to participate in this randomized, nonblinded clinical trial. Inclusion criteria were (1) confirmed pemphigus vulgaris: diagnosis was based on typical clinical manifestations, histologic pattern of the lesions, and direct immunofluorescence; (2) all selected patients had to be new cases, which had not been previously treated with prednisolone or immunosuppressive drugs; (3) no contraindications for cytotoxic drugs; and (4) no pregnancy or lactation. The study was approved by the ethics review board of Tehran University of Medical Sciences. An informed written consent was taken from each patient. Participants were subjected to a detailed review of their clinical history (age, sex, duration of disease, first anatomic site affected at the onset of the disease), drug intake, complete physical examination, routine laboratory tests, chest radiography, and bone densitometry. Patients were hospitalized (1 to 4 weeks) at the beginning of the treatment. They were then followed up regularly, once a week for 1 month, and then once a month for 1 year.

Treatment

Participants were randomly allocated to 1 of 4 treatment groups: prednisolone (P), prednisolone and azathioprine (P/A), prednisolone and mycophenolate mofetil (P/MM), prednisolone and pulse cyclophosphamide (P/PC). Group (P) was treated with 2 mg/kg per day of prednisolone. Group (P/A) was treated with 2 mg/kg per day of prednisolone and 2.5 mg/kg per day of azathioprine for the first 2 months, which was then reduced to 50 mg/d for the rest of the study period. Group (P/MM) was treated with 2 mg/kg per day of prednisolone and 2 g/d of mycophenolate mofetil for 1 year. Group (P/PC) was treated with 2 mg/kg per day of prednisolone, together with a monthly dose of 1000 mg of intravenous pulse therapy cyclophosphamide for the first 6 months, followed by a 1000-mg bimonthly dosage of the same treatment for the following 6 months. None of the patients was given more than 120 mg of prednisolone daily, whatever his or her weight. All patients received prophylaxis or treatment for corticosteroid-induced osteoporosis.

As soon as new blisters stopped appearing and old lesions dried, the steroid dosage was reduced to two thirds of the initial value. In the absence of new lesions, the daily prednisolone dosage was tapered by 5 mg every 3 days, until the dosage of 30 mg/d was reached. This dosage was then further reduced by 1.25 mg (1/4 of a 5-mg tablet) weekly for 2 months, then again by the same amount every 2 weeks for 2 months, and finally by the same amount once a month, until a dosage of 7.5 mg/d was reached. This dosage was maintained until the end of the study.

Analysis

Patients were considered to be in a state of "partial response" when new lesions stopped appearing and preexisting erosions formed a crust. At this point we started tapering the steroid dosage to two thirds of its initial value (initial steroid tapering). "Complete response" was defined as lesion-free state, while the patient was receiving a minimum dose of steroid according to the treatment protocol. "Failure of treatment" was defined as 3 minor recurrences or 1 major recurrence. Minor recurrence corresponded to the appearance of less than 20 lesions on less than 3 sectors of the body, whereas a major recurrence was noted when more than 20 lesions appeared on 3 or more sectors of the body.

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