Original Article

Assessment of the Therapeutic Benefit of Oral Prednisolone and Common Adjuvant Therapy in Stage II of Randomized Controlled Trial Study for Management of Pemphigus Vulgaris

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Abstract

Background: Pemphigus is an autoimmune blistering mucocutaneous disorder. Common treatments include corticosteroids and immunosuppressive drugs. This study aimed to assess the therapeutic effects of oral prednisolone along with the common adjuvant therapy in pemphigus vulgaris.

Methods: Eighty-seven patients with pemphigus vulgaris from the first stage of a previously randomized clinical trial were enrolled in the present non-blinded clinical trial. The patients were divided into four groups and treated accordingly with prednisolone alone (P; N = 23), prednisolone and azathioprine (P/A; N = 23), prednisolone and mycophenolate mofetil (P/M; N = 21), and prednisolone and cyclophosphamide (P/C; N = 20). These patients were followed-up for an extended one-year period.

Results: The primary localization of the recurrence occurred in the oral cavity of 7, 6, 2, and 5 patients in the P, P/A, P/M, and P/C groups, respectively. There was no significant difference between them (P = 0.40). The mean total dose of prednisolone administered in groups P, P/A, P/M, and P/C was accordingly 7.5, 8.4, 9.2, and 8.6 mg/day. Minor recurrence of the disease in the above-mentioned groups was observed in 7 (30.4%), 5 (21.7%), 6 (28.6%), and 7 (35.0%) of the patients, respectively. With regard to the minor recurrence of the disease, there was no significant difference among the four treatment groups (P = 0.80).

Conclusion: Since in this follow-up study no therapeutic benefit of oral prednisolone and common adjuvant therapy was found in terms of the number of minor and major recurrences, the extent to which treatment of PV can be improved upon treatment with these agents remains to be elucidated.

Keywords: Adjuvant drug therapy, pemphigus vulgaris, prednisolone, randomized controlled trial

Cite this article as: Esmaili N, Chams-Davatchi C, Valikhani M, Daneshpazhooh M, Toosi S, Karimi A, et al. Assessment of the therapeutic benefit of oral prednisolone and common adjuvant therapy in stage II of randomized controlled trial study for management of pemphigus vulgaris. *Arch Iran Med*. 2014; **17(9):** 626 – 628.

Introduction

Pemphigus is a severe, blistering mucocutaneous autoimmune disorder. Commonly used treatments include corticosteroids and immunosuppressive drugs.[1] There is still no standard treatment for pemphigus vulgaris (PV), and sufficient data is not available from randomized trials using different drugs and methods. Recently, newer agents such as intravenous immunoglobulin therapy, rituximab, immunoadsorption using the Globaffin adsorber system and immunoadsorption for rapid removal of desmoglein-reactive autoantibodies have been used.[2–5] 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.[6]

The aim of this work was to assess therapeutic effects of oral prednisolone along with common adjuvant therapies in the management of PV patients in stage II of a one-year randomized comparative study of efficacy and safety.

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Accepted for publication: 20 June 2014

Patients and Methods

This study was performed after the first stage of a randomized controlled open-label trial of four treatment regimens for PV.[7] After completion of the first stage of the study, the patients were followed for an additional one-year period. All patients were followed up at least once a month during one-year of tracking. Any incidence of adverse events during treatment and corresponding lesions were further evaluated by a complete physical examination and routine laboratory tests. Patients were divided into four groups: treated with prednisolone alone (P), prednisolone and azathioprine (P/A), prednisolone and mycophenolate mofetil (P/M), and prednisolone and cyclophosphamide (P/C). All patients were selected from the primary stage of the study and followed up for an extended one-year period for any events of minor and major recurrence and the variations in the dose of prednisolone. The study was approved by the ethics review board of the Tehran University of Medical Sciences. Informed written consent was taken from each patient.

Participants were subjected to a detailed review of their clinical

Table 1. Mean age, phenotypic characteristics of disease before treatment

Group	Number of Patients	Gender		Mean age (SD)	Mucosal	Skin and mucous membrane	Skin
		Female	Male				
P	23 (26.4%)	12 (52.2%)	11 (47.8%)	37.83 (14.44)	6 (26.1%)	16 (69.6%)	1 (4.3%)
P/A	23 (26.4%)	12 (52.2%)	11 (47.8%)	34.09 (11.06)	6 (26.1%)	16 (69.6%)	1 (4.3%)
P/M	21 (24.1%)	18 (85.7%)	3 (14.3%)	39.00 (12.53)	7 (33.3%)	12 (57.1%)	2 (9.5%)
P/C	20 (23.0%)	14 (70.0%)	6 (30.0%)	48.45 (8.89)	5 (25.0%)	15 (75.0%)	0 (0.0%)
Total	**87 (100%)**	**56 (64.4%)**	**31 (35.6%)**	**39.56 (12.88)**	**24 (27.6%)**	**59 (67.8%)**	**4 (4.6%)**

Table 2. Mean daily dose of prednisolone, prevalence of minor and major recurrence, side effects and primary localization of the recurrence in each group of patients

Group	P	P/A	P/M	P/C	*P-value*
Mean prednisolone (mg), (SD)	7.5 (4.9)	8.4 (4.4)	9.2 (4.1)	8.6 (4.6)	0.21
Minor Recurrence (%)	7 (30.4%)	5 (21.7%)	6 (28.6%)	7 (35.0%)	0.80
Major Recurrence (%)	2 (8.7%)	1 (4.3%)	2 (9.5%)	1 (5.0%)	-
Number of patients Showed side effects (%)	3 (13.0%)	9 (39.1%)	4 (19.0%)	9 (45.0%)	0.057
Primary localization of the recurrence					0.40
Oral cavity	7	6	2	5	
Eye	---	---	1	---	
Scalp	---	---	2	---	
Skin of head and neck	---	---	---	1	

history (age, sex, duration of disease, and first anatomic site affected at the onset of the disease), drug intake, complete physical examination, and routine laboratory tests. A 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.

Obtained data were subjected to statistical analysis by SPSS 18, using Chi-square test for categorical variables and analysis of variance (ANOVA) for continuous variables. Fisher's exact test was used when necessary.

Results

Of the 120 patients admitted to the study of Chams-Davatchi, et al.[7] 90 were enrolled in the second stage of the study and 87 remained in the study. The 87 patients comprised 23 (26.4%) individuals in group P, 23 (26.4%) in group P/A, 21 (24.1%) patients in group P/M, and 20 (23.0%) in group P/C, (Table 1).

There were 56 women (64.4%) and 31 men (35.6%), yielding a female to male ratio of 1.8:1. The mean age of the patients was 39.56 (12.88) years, (Table 1). With regard to age and sex, there was no significant difference between the four groups ($P = 0.17$). The clinical forms of PV observed in the patients were mucosal (24 patients; 27.6%), skin and mucous membrane (59 patients; 67.8%), and skin phenotypes (4 patients; 4.6%), (Table 1). There were no significant differences among the patient phenotypes in the 4 groups ($P = 0.96$). The primary localization of the recurrence was the oral cavity in 7 patients of group P and 6 patient of group P/A. In group P/M, recurrence was seen in the oral cavity of 2 patients, the eye of 1 patient, and the scalp of 2 patients (Table 2). In group P/C, the recurrence was seen in the oral cavity of 5 patients and on the skin of the head and neck of 1 patient. The difference between the primary localization of recurrence in the oral cavity and the four treatment groups was not significant ($P = 0.40$). Minor recurrence was observed in groups P, P/A, P/M, and P/C in 7 (30.4%), 5 (21.7%), 6 (28.6%), and 7 (35.0%) patients, respectively, (Table 2). With regard to the incidence of minor recurrence, there was no significant difference between the four groups ($P = 0.80$). Major recurrence was observed in 2 (8.7%), 1 (4.3%), 2 (9.5%), and 1 (5.0%) patients from groups P, P/A, P/M, and P/C, respectively (Table 2). The mean daily dose of prednisolone was 7.9 mg (±4.9), 8.4 mg (±4.4), 9.2 mg (±4.1), and 8.6 mg (±4.6) in P, P/A, P/M and P/C groups, respectively, (Table 2). The difference between prednisolone doses among the four treatment groups was not significant ($P = 0.21$).

Discussion

PV, as an autoimmune mucocutaneous disease, creates bullous lesions in mucous and cutaneous membranes by producing IgG autoantibodies against keratinocytes antigens.[8] Similar to other autoimmune diseases, if not promptly treated, the process of PV would be progressive providing the opportunity for the spreading of epitopes and rendering the disease significantly more difficult to control.[7,9] It seems that adequate treatment at the onset of the disease leads to better outcomes in terms of controlling the disease and preventing recurrences. The main object in pemphigus treatment is development of low steroid regimens or an intervention without using systemic corticosteroid therapy. Due to the rarity of the disease (i.e. PV), the number of participants is quite low in most clinical trials; thus, many variations may be observed between same treatment regimens in different studies.[10] In this follow-up study (following the first stage of the study by Chams-Davatchi, et al.[7]), we observed no significant difference among the four treatment groups in terms of the number of minor recurrences of the disease. Since the total number of the major recurrence of the disease was small, it was not possible to compare the four groups with each other and we hesitate to give any comment in this regard. Although mycophenolate mofetilcould may be better in terms of controlling the autoimmune mechanism and lowering pemphigus antibody titers,[6] the same findings were not found in the present study, at least in case of the minor and major

recurrence rate. The mean daily dose of prednisolone (even a high dose of 9.2 mg/day in the P/M group) had no significant effect in cases of the appearance of minor recurrence. Correspondingly, appearance of primary localization of recurrence in the oral cavity and occurrence of side effects throughout the treatment was not associated with the four groups. In conclusion, in the primary stage of this clinical trial, the most efficacious cytotoxic drug to reduce steroid was found to be azathioprine, followed by pulse cyclophosphamide, and then mycophenolate mofetil.[7] However, in the current study, it seems that differences have emerged during the extended follow-up period. Further studies are recommended to evaluate different protocols in treatment of PV patients with longer follow-up periods.

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