

# The efficacy of acyclovir in treatment of the pemphigus vulgaris

Fariba Iraj, Gita Faghihi<sup>1</sup>, Amir Hossein Siadat<sup>2</sup>

<sup>1</sup>Professor of Department of Dermatology and Skin and Stem Cell Research Center, Isfahan School of Medicine, Isfahan University of Medical Sciences, <sup>2</sup>Assistant Professor of Dermatology, Skin Diseases and Leishmaniasis Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

**Background:** Pemphigus is a group of autoimmune blistering diseases of the skin and mucous membranes caused by the presence of antibodies against adhesion molecules on the cell surface of keratinocytes. The possible role of herpes simplex virus infection in the pathogenesis of pemphigus vulgaris (PV) has been suggested. In this study, we evaluated the impact of a course of acyclovir in improvement of the pemphigus patients and reduction of the hospitalization duration. **Materials and Methods:** A total of 30 patients with definitive diagnosis of PV were recruited in study. They were randomized in two groups. One group received routine treatment and another received the routine plus 2 week course of oral acyclovir (1200 mg/day). The improvement was defined as a more than 50% change in baseline severity score of the disease. All data was registered at the checklists and after follow-up period, the statistical analyses were performed by aid of t-test and Fisher's exact test. **Results:** There was no statistically significant difference in mean severity score and improvement rates between two groups at the end of study ( $P > 0.05$ ). Meanwhile, there was no statistical difference in duration of hospitalization in two groups ( $P > 0.05$ ) though the severity score and hospitalization duration were apparently less in acyclovir-group than control group. Neither of the patients (in acyclovir group) showed any side effect. **Conclusion:** We did not observe any difference between response to treatment and hospitalization period in the group that was treated with acyclovir as compared with control group. However, the partial and complete remissions were higher in patients on acyclovir therapy compared to controls. In those pemphigus patients who do not respond to sufficient immunosuppressive regimen or show a sudden relapse after reaching partial or complete clinical remission, a trial of oral acyclovir therapy may have promising result.

**Key words:** Acyclovir, herpes simplex, pemphigus vulgaris

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## INTRODUCTION

Pemphigus is a group of autoimmune blistering diseases of the skin and mucous membranes caused by the presence of antibodies against adhesion molecules on the cell surface of keratinocytes. In genetically predisposed patients, several factors including physical agents, drugs, neoplasm, hormones, and viruses notably herpes simplex virus (HSV), have been hypothesized to trigger or exacerbate the disorder.<sup>[1]</sup> HSV, a double-stranded deoxyribonucleic acid (DNA) virus, is a common human pathogen classically causing orofacial (mostly HSV-1) or genital (mostly HSV-2) infections.<sup>[2]</sup> Immunodeficient patients such as pemphigus patients are at risk of developing extended or atypical HSV infections which can be easily misdiagnosed. Atypical infections have been reported more frequently in immunocompromised patients than in immunocompetent hosts.<sup>[3]</sup> Secondary cutaneous HSV infections should be considered in patients with chronic pemphigus vulgaris (PV) with atypical sudden relapses or resistance to sufficient immunosuppressive

treatment who do not show an increase of desmoglein-specific immunoglobulin G autoantibodies. Acantholytic disorders, including pemphigus vulgaris (PV), chronic benign familial pemphigus (Hailey-Hailey disease), Darier disease, and Grover's acantholytic dermatosis as well as other vesiculobolous disorders, including bullous pemphigoid, epidermolysis bullosa, and atopic dermatitis are prone to florid infections by HSV-I and II and more rarely by varicella-zoster virus (VZV).<sup>[4]</sup> On the basis of polymerase chain reaction, some studies suggest an association between HHV-8 and pemphigus.<sup>[5]</sup>

In this study, we evaluated the impact of a course of acyclovir in improvement of the pemphigus patients and reduction of the hospitalization duration.

## MATERIALS AND METHODS

This study was conducted as a single-blinded randomized clinical trial in Al Zahra hospital (Isfahan/ Iran) from March 2005-March 2006. Sampling was performed using simple method.

**Address for correspondence:** Dr. Amir Hossein Siadat, Assistant Professor of Department of Dermatology and Skin diseases and Leishmaniasis Research Center, Isfahan School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran. E-mail: amirhossein1@yahoo.com

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**Inclusion criteria:** Patients with confirmed diagnosis of PV who had at least five cutaneous blisters or involvement of at least one mucosal surface hospitalized in the dermatology ward of Al Zahra hospital were included in this study.

**Exclusion criteria:** Pregnant women, any known hypersensitivity to acyclovir and patients on monthly steroid pulse therapies, were excluded from the study.

A total of 30 consecutive patients with histology and DIF confirmed diagnosis of PV were randomized using simple randomization technique and enrolled into two groups each including 15 cases. Informed consent was obtained from all of the cases and controls. Ethical committee clearance was achieved before the start of the study.

Control group were treated using routine treatment regimen (prednisolone 1 mg/kg/day + azathioprine 2.5 mg/kg/day). Patients in the cases group, in addition to aforementioned routine treatment, were treated with oral acyclovir (1200 mg/day for 2 weeks).

The patients were examined every day by a single observer for evaluation of the response to treatment and appearance of side effect for 1 month.

The severity of PV was graded using pemphigus severity score (PSS) using the following protocol: that measured at the start and fixed intervals, and it was varied from 0 to 6, the ingredients of the score mentioned above are as follows:

#### Epithelialization degree

- 0: Complete reepithelialization
- 1: Partial reepithelialization occurred
- 2: Absence of reepithelialization, (eroded surfaces.)

#### Surface area of involvement

- 0: Absence of skin or mucosal involvement
- 1: Less than or equal to 10% of body surface area affected
- 2. One mucosal area was affected.
- 3. More than 10% of the body surface area, or more than one mucosal surface was affected.

#### Systemic symptoms

- 0: Absence of chills and fever, general malaise or constitutional symptoms
- 1: Chills and fever, general malaise or constitutional symptoms presented

In our study, variation of PSS from 70% to 100% means a complete remission; however, a 50%-70% reduction in PSS proved a partial remission. Duration of hospitalization (until achieving complete remission and discharge permission) or

any need to other interventions, such as plasma exchanges or intravenous immunoglobulin therapy, were assigned as dependent variables.

The results of study were analyzed by t-test and Fisher's exact tests.

Changes of PSS figures in two groups were evaluated and assessed by independent t-tests and the degrees of recovery in cases were analyzed by Fisher's exact test.

## RESULTS

Overall, 30 patients (13 women [43%], and 17 men [57%]) completed our study. The mean age of patients was 42 + 4 (range: 23-68) years. The mean of age was 40 years in the acyclovir group and 44 years in the control group.

The two groups of patients were matched for sex, age, and disease severity at the start of the study ( $P > 0.05$ ). Duration of hospitalization between two groups of case and control patients was not significantly different by t-test analysis ( $P = 0.9$ ), Table 1.

There was no statistically significant difference in the PSS changes or degree of healing in two groups [Table 1]; the mean of PSS in the case group at the time of discharge was  $1.2 \pm 0.6$  and in control patients it was  $1.33 \pm 0.73$  and this difference was not statistically significant ( $P$ -value  $> 0.05$ ) ( $P = 0.85$ ) [Table 1].

However, the partial and complete remissions were higher in patients on acyclovir therapy (47%) compared to controls (40%) ( $P > 0.05$ ).

Duration of hospitalization between two groups of case and control patients was not significantly different by t-test analysis ( $P = 0.9$ ,  $t = 0.54$ ) [Table 2].

**Table 1: Comparison of the mean of pemphigus severity score in the control and acyclovir groups in the admission and discharge time**

	Time	Control Group	Acyclovir Group	P value
Mean of PSS	Baseline	3.93 ( $\pm 1.6$ )	3.8 ( $\pm 1.4$ )	0.89 ( $t=0.41$ )
	Discharge time	1.33 ( $\pm 0.73$ )	1.2 ( $\pm 0.6$ )	0.92 ( $t=0.3$ )

PSS = Pemphigus severity score

**Table 2: Comparison of the mean of hospitalization in the control and acyclovir groups**

	Time	Control group	Acyclovir group	P value
Mean of hospitalization	Discharge time (weeks)	3.66	3.53	0.9 ( $t=0.24$ )

Meanwhile, no known side effects or complications such as nephrotoxicity or allergic reactions presented in patients on acyclovir treatment. No adjuvant therapy was used during intervention.

## DISCUSSION

Our objective in this study was to evaluate the efficacy of acyclovir in reduction of PV severity.

Krain<sup>[6]</sup> suggested the possible role of HSV in the pathogenesis of P.V. Several cases of PV-induced or worsened by viral infections have been reported. In addition, a few cases of PV were reported upon vaccination with viral proteins.<sup>[7,8]</sup> Viral infection was considered to be a possible trigger factor for PV. Several reports have described pemphigus cases in association with HSV, VZVs, Epstein-Barr virus, cytomegalovirus and HHV-8 infection,<sup>[9]</sup> particularly the latter correlation has been obtained presumably due to local factors.<sup>[10,11]</sup>

In 1999, Tufano *et al.*,<sup>[12]</sup> evaluated the prevalence of herpes virus DNA in peripheral blood mononuclear cells (PBMCS) and skin lesions of PV patients by polymerase chain reaction. HSV-1 and HSV-2 DNA were detected in 50% of PBMCS and 71% of skin biopsies of the patients.

Onset or exacerbation of PV has been found to be associated with HSV infection in several clinical studies as reviewed by Ahmad *et al.*,<sup>[13]</sup> Brenner *et al.*,<sup>[9]</sup> and Ruocco *et al.*<sup>[14]</sup>

Different hypotheses have been suggested regarding the potential role of HSV in the pathogenesis of PV. Viral infection may induce upregulation of hormonal and cellular proinflammatory factors that facilitating the outbreak of PV. Kalra *et al.*,<sup>[15]</sup> recently suggested a role for HSV in perpetuating/slowing down in the healing of PV lesions; however, our study seem to suggest HSV infection as a concomitant event due to lack of normal epithelial defense in PV lesion, but without any pathogenic implication causing disease exacerbation.

The HSV lesions mostly consisted of multiple grouped small (1-3 mm) round blisters arising from inflamed skin or mucosa. Although they clinically appeared to be somewhat different from the PV lesions, they are difficult to identify, whereas they appear together with a flare up of lesions.<sup>[16]</sup>

In the present study, we did not observe any significant differences between responses to treatment in the group that was treated with acyclovir as compared with control group. In addition, no reduction in hospitalization period

was seen in the acyclovir treated group. However, the partial and complete remissions were somewhat higher in patients on acyclovir therapy compared to controls.

Use of acyclovir therapy, in those pemphigus patients who have high PSS and do not have any contraindication for acyclovir, may be a logical approach.

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