Immunologic prediction of relapse in patients with pemphigus vulgaris (PV) in clinical remission

Maryam Daneshpazhooh, MD,[a] Vahid Zafarmand Sedigh, MD,[a] Kamran Balighi, MD,[a] S. Hamed Hosseini, MD,[b] Ali Ramezani, MD,[a] Mohammad-Sadegh Kalantari, MD,[a] Narges Ghandi, MD,[a] Maryam Ghiasi, MD,[a] Azita Nikoo, MD,[c] and Cheyda Chams-Davatchi, MD[a]
Tehran, Iran

Background: Pemphigus vulgaris (PV) is characterized by multiple relapses, occurring especially in patients on minimal therapy or off therapy.

Objective: To identify immunologic predictors (anti-desmoglein [Dsg] 1 and 3 antibodies; direct immunofluorescence [DIF]) for relapse in PV patients.

Methods: Eighty-nine patients in complete clinical remission for at least 6 months and receiving less than or equal to 10 mg prednisolone daily and no immunosuppressive drugs were evaluated using DIF (n=89) and Dsg ELISA (n=46). They were followed until relapse or for at least 18 months.

Results: DIF was positive in 44 of 89 patients (49.5%); anti-Dsg 3 antibodies were detected in 18 of 46 patients (39.1%) and anti-Dsg 1 antibodies were detected in 4 of 46 patients (8.7%). Relapse occurred in 38 patients (42.7%). Mean relapse-free time was significantly shorter in anti-Dsg 3-positive patients compared to anti-Dsg 3- negative patients (P = .015) and in DIF-positive patients compared to DIF-negative patients (P = .047), but not in anti-Dsg 1- positive patients compared to anti-Dsg 1-negative patients (P = .501). Sensitivity and predictive values of neither of these tests were high.

Limitations: Small number of anti-Dsg 1-positive patients and use of conventional ELISA.

Conclusion: Positive anti-Dsg 3 ELISA and, to a lesser degree, positive DIF are predictors of relapse in PV patients in clinical remission. Decision on discontinuing treatment should be based on the results of these tests as well as on clinical findings. (J Am Acad Dermatol 2016;74:1160-5.)

Key words: anti-desmoglein 1; anti-desmoglein 3; clinical remission; direct immunofluorescence; pemphigus vulgaris; relapse; relapse-free time.

Pemphigus vulgaris (PV) is a chronic autoimmune disease characterized by blistering of the skin and/or mucosa and mediated by autoantibodies against desmoglein (Dsg)3 and to a lesser degree Dsg1.

Treatment of PV is largely based on systemic steroids and immunosuppressants, which had dramatically improved the prognosis of the disease.

Abbreviations used:

CI:	confidence interval
DIF:	direct immunofluorescence
Dsg:	desmoglein
ELISA:	enzyme-linked immunosorbent assay
NPV:	negative predictive value
PPV:	positive predictive value
PV:	pemphigus vulgaris

From the Autoimmune Bullous Diseases Research Center, Department of Dermatology,[a] School of Public Health,[b] and Department of Dermatopathology,[c] Tehran University of Medical Sciences.

Funding sources: None.
Conflicts of interest: None declared.
Accepted for publication October 25, 2015.

Reprint requests: Maryam Daneshpazhooh, MD, Autoimmune Bullous Diseases Research Center, Razi Hospital, Vahdate-Eslami Square, 11996 Tehran, Iran. E-mail: daneshpj@tums.ac.ir.

Published online February 17, 2016.
0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2015.10.051

However, complete remission on minimal or off therapy is always on the edge of relapse.

Although some authors rely on clinical findings alone for discontinuing treatment,[1] having a tool for reliable assessment of the immunologic remission would help physicians in making the right decision. Indirect immunofluorescence, direct immunofluorescence (DIF), and Dsg enzyme-linked immunosorbent assay (ELISA) are available options suggested in different guidelines.[1,2] Although indirect immunofluorescence has been shown to be of less value in this setting,[3-5] only a limited number of studies, mostly without adequate follow-up, are available for DIF[6-8] and Dsg ELISA.[9] Our aim was to evaluate the predictive value of Dsg1 and Dsg3 ELISA and DIF for relapse in patients with PV in clinical remission.

CAPSULE SUMMARY

- Direct immunofluorescence and desmoglein antibodies may remain positive in patients with pemphigus vulgaris in clinical remission.
- Positive desmoglein 3 enzyme-linked immunosorbent assay and, to a lesser degree, positive direct immunofluorescence are predictors of relapse.
- These tests can help determine when discontinuation of treatment may be considered.

METHODS

This follow-up study was conducted at Autoimmune Bullous Diseases Research Center, Razi Hospital, Tehran, Iran, from 2008 until 2012. The study was exempted from approval by the institutional review board. In all, 89 patients with PV, who were in complete clinical remission (absence of new or established lesions) off therapy or on minimal therapy (≤10 mg prednisolone, daily; with no adjuvant drug) at least for the preceding 6 months (range, 6–72; mean ± SD, 23.8 ± 15.8 months) were included in the study. The initial diagnosis of the disease was based on clinical, histologic (the presence of suprabasal cleft and acantholysis), and DIF (the presence of intercellular epithelial IgG and/or C3 deposits) factors. These patients had already participated in 2 previous process-research studies for evaluation of immunologic remission[10,11] and had undergone DIF of normal-appearing skin or mucosa (89 cases) and Dsg1 and Dsg3 ELISA (46 cases). The presence of intercellular epithelial deposits of IgG and/or C3 was defined as positive DIF. For anti-Dsg1 and anti-Dsg3, commercially available Dsg1/Dsg3 ELISA tests (EUROIMMUN Medizinische Labordiagnostika AG, Lübeck, Germany) were performed according to the manufacturer's instructions and a value higher than the cutoff point of 20 U/mL was considered positive. Patients were followed up for at least 18 months or until relapse. Data about age, sex, the phenotype of the disease (mucocutaneous, mucosal, or cutaneous PV), duration of the disease, duration of remission, and last dose of prednisolone were recorded. All patients were also instructed to present to the clinics in case of relapse. The primary end point was a flare of the disease, as defined by the appearance of any new lesion.

Quantitative variables were presented as mean ± SD, and qualitative variables as frequency and percentage. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were also calculated. The Kaplan-Meier method was used for estimation of relapse-free survival in DIF, anti-Dsg1, and anti-Dsg3 groups, and the log rank test for between-group comparison. As the status of DIF, anti-Dsg1, and anti-Dsg3 were highly correlated, multivariate analysis was excluded. Two-tailed *P* value less than .05 was considered statistically significant.

RESULTS

A total of 89 patients with PV (32 men, 57 women; mean age 48.2 ± 12.9 years) were included in the study. Five patients were in complete remission off therapy and the remaining 84 were on minimal corticosteroid therapy (≤10 mg/d prednisolone; mean dose 4.5 ± 2 mg/d) for an average duration of 23.8 ± 15.8 (range 6-72) months. Baseline characteristics of the study patients are presented in Table I.

Mean follow-up time was 27.9 (SD 14.7; range 2-59) months. Relapse occurred in 38 patients (42.7%). Relapse occurred in 23 of 44 DIF-positives (52.3%) and 15 of 45 DIF-negatives (33.3%); in 10 of 18 anti-Dsg3-positives (55.5%) and 7 of 28 anti-Dsg3-negatives (25.0%); and in 2 of 4 anti-Dsg1-positives (50%) and 15 of 42 anti-Dsg1-negatives (35.7%) (Table II).

Sensitivity, specificity, PPV, and NPV of DIF for relapse were 0.61 (95% confidence interval [CI] 0.43-0.76), 0.73 (95% CI 0.57-0.86), 0.68 (95% CI 0.50-0.83), and 0.67 (95% CI 0.51-0.80), respectively. Sensitivity, specificity, PPV, and NPV of anti-Dsg3 for relapse were 0.59 (95% CI 0.33-0.82), 0.72 (95% CI 0.53-0.87), 0.56 (95% CI 0.31-0.79), and 0.75 (95% CI 0.55-0.89), respectively. For anti-Dsg1, sensitivity,