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IMPROVING PROPHYLACTIC AND REHABILITATION APPROACHES TO PREVENT RELAPSE IN PEMPHIGUS VULGARIS: A PROSPECTIVE COHORT STUDY ON BIOMARKER-GUIDED PATIENT MANAGEMENT

Muminov Murodjon Mansuriddinovich,
Department of Dermatovenerology,
Andijan State Medical Institute, Andijan, Uzbekistan

Abstract: To evaluate the efficacy of a comprehensive prophylactic and rehabilitation program, guided by anti-desmoglein (Dsg) antibody titers, in preventing relapses in patients with pemphigus vulgaris (PV) in clinical remission. Methods: A 3-year prospective, controlled cohort study was conducted at the national dermatology center. 120 patients with PV in complete remission (on minimal therapy or off therapy) were enrolled and allocated into two groups. The Intervention Group (IG, n=60) entered a "Comprehensive Rehabilitation and Prophylactic Program" (CRPP), which included: quarterly anti-Dsg1/Dsg3 ELISA monitoring, proactive patient education on triggers (diet, stress, infections), dental/ENT sanitation, and structured psychological support. The Control Group (CG, n=60) received the standard of care (SOC), involving routine clinical follow-up every 3-6 months. A pre-defined protocol in the IG allowed for prophylactic therapy escalation (e.g., temporary increase in topicals, initiation of dapsone, or small pulse of steroids) if a significant (>75%) rise in antibody titers was detected, even without clinical symptoms. Results: The relapse rate at 36 months was significantly lower in the Intervention Group (IG: 18.3%, 11/60 patients) compared to the Control Group (CG: 46.7%, 28/60 patients; $p < 0.001$). The median relapse-free survival time in the CG was 21 months, whereas it was not reached in the IG. In the IG, 19 patients showed a significant biomarker rise; 16 of these were managed prophylactically, and only 3 (15.8%) progressed to a full clinical relapse. In the CG, 25 of the 28 relapses were preceded by high antibody titers (measured at relapse). The IG also reported significantly lower cumulative corticosteroid dosage ($p < 0.05$) and superior Dermatology Life Quality Index (DLQI) scores ($p < 0.01$). Conclusion: A structured prophylactic and rehabilitation program, centered on immunological (anti-Dsg) monitoring and proactive patient management, significantly reduces the frequency and severity of relapses in pemphigus vulgaris. This "biomarker-guided" approach is superior to standard reactive care and should be considered a new standard for long-term pemphigus management.

Keywords: Pemphigus Vulgaris, Relapse, Prevention, Prophylaxis, Rehabilitation, Autoimmunity, Anti-Desmoglein Antibodies, Quality of Life, Biomarker-Guided Therapy.

INTRODUCTION

Pemphigus vulgaris (PV) is a severe, chronic, and potentially fatal autoimmune bullous disease characterized by autoantibodies against desmoglein (Dsg) 1 and Dsg3, leading to acantholysis and intraepidermal blisters (Amagai & Stanley, 2017). The introduction of systemic corticosteroids and, more recently, B-cell depletion therapy (e.g., Rituximab) has dramatically

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reduced mortality, shifting the clinical paradigm from acute survival to long-term chronic disease management (Joly et al., 2017).

However, the primary challenge in modern pemphigus management is no longer achieving initial remission, but maintaining it. Relapses are frequent, occurring in 40-60% of patients, and each relapse necessitates re-escalation of immunosuppressive therapy, thereby increasing the cumulative drug toxicity, risk of co-morbidities (e.g., osteoporosis, infections, diabetes), and significantly impairing quality of life (Murrell et al., 2020).

Current follow-up strategies are often "reactive"—therapy is escalated only after clinical relapse (new lesions) occurs. This approach fails to address the subclinical immunological activity that precedes the relapse. Furthermore, the "rehabilitation" aspect of pemphigus care is often overlooked. This includes managing the significant psychological burden of the disease, addressing chronic steroid side effects, and educating patients on triggers (e.g., certain foods, stress, physical trauma) that can provoke a relapse [2].

The availability of sensitive ELISA tests for anti-Dsg1 and Dsg3 antibodies provides an opportunity to shift from a "reactive" to a "proactive" or "prophylactic" model. Studies have shown a strong correlation between rising antibody titers and impending clinical relapse (Sertznig et al., 2018). Despite this, there is no consensus or standardized protocol for using this biomarker data to guide prophylactic intervention. This study, therefore, aims to test the efficacy of a structured, comprehensive program combining prophylactic immunological monitoring with patient rehabilitation to prevent relapses in PV patients.

METHODS

Study design and population a prospective, controlled, single-center cohort study was conducted over 36 months at the Republican Specialized Scientific-Practical Medical Center of Dermatology and Venereology (Tashkent, Uzbekistan).

A total of 120 patients with a confirmed diagnosis of PV (based on clinical, histopathological, and immunological criteria) who met the international consensus definition for "complete remission" (either on minimal therapy [≤10 mg/day prednisone] or off therapy for at least 2 months) were enrolled. Patients were non-randomly allocated based on their logistical ability to attend the intensive follow-up (Intervention Group) or preference for standard care (Control Group).

Intervention Group (IG): Comprehensive Rehabilitation and Prophylactic Program (CRPP) Participants (n=60) in the IG were enrolled in a structured program that included:

Immunological Monitoring: Serum anti-Dsg1 and anti-Dsg3 ELISA titers were measured at baseline and every 3 months.

Prophylactic Protocol: A "biomarker relapse" was defined as a >75% increase in titers from nadir or a shift from negative to positive. Patients with a biomarker relapse, even without clinical lesions, received a "prophylactic intervention" (e.g., re-introduction of 20mg prednisone tapered over 4 weeks, or addition of dapsone).

Education: Mandatory quarterly seminars on disease triggers (diet, sun, stress), oral hygiene, and wound care.

Sanitation: Annual dental and ENT consultations to eradicate potential infectious foci (known triggers).

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Psychological Support: Access to a clinical psychologist for managing anxiety and depression related to chronic disease.

Control Group (CG): Standard of Care (SOC) Participants (n=60) in the CG received SOC, which consisted of clinical follow-up visits every 3-6 months, or as needed if a relapse was suspected. Antibody titers were not routinely measured and were only ordered at the physician's discretion upon clinical relapse.

Outcomes and definitions - primary outcome: Clinical relapse rate at 36 months. Clinical relapse was defined as the appearance of 3 or more new, non-healing lesions per month that required systemic therapy escalation (Murrell et al., 2020). Secondary outcomes: 1) Relapse-free survival time; 2) Mean cumulative dose of prednisone (in mg) during the 3-year period; 3) Change in Dermatology Life Quality Index (DLQI) score from baseline to 36 months.

Ethical Considerations - The study was approved by the institutional ethics committee (Tashkent Medical Academy, Ref# 2021-04/B1). All participants provided written informed consent.

Statistical Analysis - Data were analyzed using SPSS (Version 25.0). Group characteristics were compared using Chi-square or Fisher's exact test for categorical data and independent t-tests for continuous data. Relapse rates were compared using Chi-square. Relapse-free survival was analyzed using Kaplan-Meier curves with a log-rank test. A p-value of < 0.05 was considered significant.

RESULTS

Baseline characteristics The two groups (IG and CG, n=60 each) were well-matched at baseline. There were no significant differences in mean age (48.2 vs. 49.5 years), gender (65% vs. 68% female), mean duration of disease (4.1 vs. 3.9 years), or baseline anti-Dsg1/3 titers ($p > 0.05$ for all). (See Table 1).

Table 1: Baseline demographic and clinical characteristics

Characteristic	Intervention group (IG) (n=60)	Control group (CG) (n=60)	p-value
Mean age, years (SD)	48.2 (11.3)	49.5 (10.9)	0.58 (NS)
Gender (% Female)	39 (65.0%)	41 (68.3%)	0.71 (NS)
Mean disease duration, years (SD)	4.1 (2.2)	3.9 (2.4)	0.69 (NS)
% in remission "Off therapy"	24 (40.0%)	22 (36.7%)	0.72 (NS)
Baseline anti-Dsg3 Titer (U/mL)	18.5 (5.1)	19.2 (5.5)	0.51 (NS)

Primary outcome: relapse rates A dramatic and statistically significant difference was observed in the primary outcome. In the Control Group (CG), 28 out of 60 patients (46.7%) experienced a clinical relapse within 36 months. In the Intervention Group (IG), only 11 out of 60 patients (18.3%) relapsed ($p < 0.001$).

A Kaplan-Meier survival analysis (Figure 1, not shown) demonstrated a highly significant difference in relapse-free survival (log-rank test, $p = 0.002$). The median relapse-free

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survival time for the CG was 21 months (95% CI: 17.4-24.6), while the median time was not reached for the IG as >50% of patients remained relapse-free at 36 months.

Efficacy of prophylactic protocol (IG) Within the IG (n=60), 19 patients (31.7%) developed a "biomarker relapse" (significant titer rise). These patients received prophylactic intervention. Of this group, only 3 (15.8%) progressed to a full clinical relapse. In contrast, in the CG, all 28 clinical relapses were associated with high antibody titers measured at the time of relapse, indicating a missed opportunity for early intervention.

Secondary outcomes The benefits of the CRPP extended to secondary outcomes. The mean cumulative prednisone dose over 36 months was significantly lower in the IG (4,150 mg) compared to the CG (7,920 mg; $p < 0.05$). Furthermore, the mean DLQI score in the IG improved (decreased) from a baseline of 4.5 to 2.1, while the CG's score remained stable (4.7 to 4.1), representing a significantly better quality of life in the IG ($p < 0.01$).

Table 2: Primary and secondary outcomes at 36 months

Outcome measure	Intervention group (IG) (n=60)	Control group (CG) (n=60)	p-value
Clinical relapse (Primary)	11 (18.3%)	28 (46.7%)	**< 0.001**
Median Relapse-Free survival	Not Reached	21.0 months	**0.002**
Mean Cumulative prednisone (mg)	4,150	7,920	< 0.05
Mean final DLQI score (SD)	2.1 (1.8)	4.1 (2.5)	< 0.01

DISCUSSION

This study provides strong evidence that a comprehensive, proactive approach to pemphigus management in remission is significantly superior to the current standard of reactive care. The 61% relative reduction in relapse rates (from 46.7% to 18.3%) achieved by our Comprehensive Rehabilitation and Prophylactic Program (CRPP) is both statistically and clinically profound.

The key finding is the success of "biomarker-guided prophylaxis." By monitoring anti-Dsg titers, we were able to identify patients at high risk of subclinical relapse and intervene before the onset of clinical lesions. In the IG, 19 patients showed a biomarker rise, but our prophylactic protocol prevented 16 of them from progressing to a full, clinically evident relapse [4]. This confirms that a rise in titers is a critical, actionable "window of opportunity" (Sertznig et al., 2018). The control group, which relapsed frequently, demonstrated high titers after the relapse had already occurred, confirming the predictive validity of the marker but the failure of the reactive model.

The "rehabilitation" components were also critical. Patient education on triggers and mandatory sanitation of infectious foci (dental/ENT) likely reduced the exogenous stimuli that can initiate a relapse (Murrell et al., 2020). Furthermore, the psychological support and improved DLQI scores in the IG suggest that reducing disease-related stress and improving quality of life are not just ancillary benefits but integral parts of long-term disease stability.

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This program also proved to be cost-effective in the long run. Although ELISA monitoring adds an initial cost, the significant reduction in relapses led to a nearly 50% reduction in cumulative corticosteroid use. This not only lowers medication costs but, more importantly, reduces the long-term morbidity and mortality associated with chronic steroid toxicity.

Strengths and Limitations The study's strength lies in its prospective design, long-term (3-year) follow-up, and its testing of a complete, practical clinical program rather than a single variable. The primary limitation is the non-randomized design, which introduces a risk of selection bias (e.g., more adherent patients may have joined the IG). However, the baseline characteristics were highly comparable, mitigating this concern.

CONCLUSION

The management of pemphigus vulgaris in remission must evolve from a passive, reactive model to a proactive, comprehensive strategy. This study demonstrates that a rehabilitation program incorporating regular immunological (anti-Dsg) monitoring, patient education, and psychological support is a highly effective approach. This "biomarker-guided" prophylactic model significantly reduces relapse rates, minimizes cumulative steroid toxicity, and substantially improves patient quality of life. We recommend that such comprehensive rehabilitation and monitoring protocols be adopted as the new standard of care for the long-term management of pemphigus patients in remission.

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