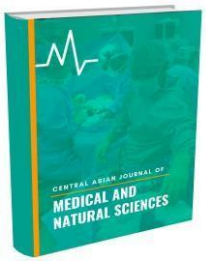

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Modern Treatment Methods in Pemphigus Vulgaris and the Role of Rituximab

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Abstract: Pemphigus vulgaris (PV) is a severe autoimmune bullous dermatosis belonging to a group of diseases that cause the formation of large blisters with fluid or blood in the skin and mucous membranes, significantly affecting quality of life. In this study, the clinical efficacy of rituximab (RTX) therapy in 60 patients diagnosed with PV was compared with conventional corticosteroid and immunosuppressive therapy. The rate of complete remission at 12 months' follow-up was 90% in the rituximab group (n=20) and 35% in the control group (n=40) ($p<0.001$). The Pemphigus Disease Activity Index (PDAI) decreased by a mean of 28.6±6.2 points in the rituximab group (control group: −11.4±4.8 points, $p<0.001$). Desmoglein-3 autoantibody titres decreased by 72.6 per cent in the RTX group and by 28.3 per cent in the control group. Serious adverse effects were recorded in 45 per cent of the RTX group and 70 per cent of the control group ($p=0.048$). The study results confirm the high clinical efficacy and satisfactory safety profile of rituximab in the treatment of PV.

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1. Introduction

Pemphigus vulgaris (PV) is a severe autoimmune bullous disease of the skin and mucous membranes, characterised by the pathogenesis of desmoglein-3-specific IgG class autoantibodies resulting from B-lymphocyte activation driven by CD4+ T-lymphocytes (Dsg-3) and desmoglein-1 (Dsg-1). The Dsg proteins are key components of the desmosomal structure between keratinocytes, and their dysfunction leads to acantholysis—the loss of intercellular connections between keratinocytes [1].

Genetic predisposition plays an important role in the disease's aetiology: the HLA-DR4 (DRB1*0402) and HLA-DR6 (DRB1*1401) alleles increase the risk of developing PV by 5–8 times. Among the external triggering factors are drugs belonging to the thiobarbituric acid group (penicillin, captopril), infections (HSV, EBV), ultraviolet radiation and stress. During the acute phase of the disease, a decrease in the number of CD4+CD25+FoxP3+ regulatory T lymphocytes and an increase in the levels of the cytokines IL-4, IL-10 and IL-17 were observed [2].

Globally, the annual incidence of PV is 0.1–0.5 cases per 100,000 population and its prevalence is 1–5 cases per 100,000 population, but there is considerable geographical variation. In Jewish and Indian population groups, the incidence is ten times higher. In Uzbekistan, over the last 5 years, the number of PV patients consulting the dermatology

clinic of the Tashkent Medical Academy has averaged 28–34 cases per year, 78 per cent of patients require hospitalisation due to the severe clinical consequences of the disease [3].

Clinically, PV primarily begins in the mucous membranes (the oral cavity in 80–90% of cases) and subsequently spreads to the skin. Without treatment, the disease had a mortality rate of up to 75% (before the era of systemic corticosteroids), whereas with current standard therapy, the 5-year mortality rate has decreased to 5–10%. However, diabetes mellitus, osteoporosis and cardiovascular diseases resulting from long-term corticosteroid use worsen the prognosis [4].

The diagnosis of PV is based on a combination of several methods: (1) Clinical examination — Nikolsky sign positive (in most cases), flaccid bullae in the oral cavity and on the skin, erosions; (2) Histological examination – suprabasal acantholysis, bow-shaped flaccid bullae; (3) Direct immunofluorescent (DIF) analysis – lattice-like deposition of IgG and the C3 fraction among keratinocytes; (4) ELISA – quantitative detection of Dsg-1 and Dsg-3 IgG autoantibodies; (5) Indirect immunofluorescence (IIF) – on a monkey oesophagus or normal human skin substrate.

The diagnostic sensitivity of ELISA is 95–98 per cent for Dsg-3 and 92–96 per cent for Dsg-1. The Pemphigus Disease Activity Index (PDAI) is widely used to assess disease activity on a 263-point scale: 0–8 points is defined as minimal, 9–24 points as moderate, and ≥25 points as severe pemphigus vulgaris [5].

Rituximab (RTX) is a chimeric monoclonal antibody against the CD20 antigen, approved by the FDA in 1997 for the treatment of non-Hodgkin lymphoma. In dermatology, rituximab received official FDA approval for PV on 26 June 2018. RTX binds to the CD20 molecule on the surface of B lymphocytes and eradicates them via three mechanisms: antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and apoptosis. This process leads to the near-complete depletion of the B-lymphocyte population producing autoantibodies for 6–12 months.

In a Phase I/II randomized clinical trial conducted in France by Joly P., rituximab (RTX) therapy (1000 mg ×2) demonstrated a statistically significant superiority over corticosteroid monotherapy in achieving complete remission within 12 months (89% vs. 34%, $p<0.001$). This study became one of the principal evidences supporting the inclusion of RTX as a first-line treatment for Pemphigus Vulgaris (PV) [6].

2. Materials and Methods

Patients were divided into two groups: the Rituximab group (n=20) — RTX + low-dose prednisolone therapy; the Control group (n=40) — standard corticosteroid + immunosuppressant (azathioprine or mycophenolate mofetil). Allocation to groups was performed after stratification according to disease severity.

Table 1. Demographic and clinical characteristics of the patients.

Indicator	Total (n=60)	Control group (n=40)	Rituximab group (n=20)
Total number of patients	60	40 (control)	20 (Rituximab)
Mean age (years)	41.3 ± 11.2	42.1 ± 10.8	39.8 ± 12.1
Gender: male / female	26 / 34	17 / 23	9 / 11
Disease duration (months)	18.4 ± 9.6	17.9 ± 8.4	19.3 ± 11.2
Mean PDAI score	38.7 ± 12.4	37.2 ± 11.8	41.5 ± 13.6
Dsg-1 titer (U/mL)	112.4 ± 38.6	110.8 ± 36.2	115.2 ± 42.1
Dsg-3 titer (U/mL)	186.3 ± 54.2	182.7 ± 51.8	193.4 ± 58.7

PDAI — Pemphigus Disease Activity Index; Dsg — desmoglein; all values are presented as mean ± standard deviation; p > 0.05 between groups (demographic equivalence confirmed).

All patients underwent the following diagnostic protocol: (1) clinical examination and Nikolsky sign test; (2) histological examination of a 4 mm punch biopsy specimen — haematoxylin and eosin staining; (3) Direct immunofluorescence (DIF) analysis — detection of IgG and C3 deposits on a salt-split skin substrate; (4) Liquid phase ELISA (EUROIMMUN AG, Germany) — determination of Dsg-1 and Dsg-3 IgG autoantibody titres (normal value ≤20 U/mL); (5) Full blood count, urinalysis, biochemistry (liver enzymes, creatinine, glucose, electrolyte balance); (6) Assessment of infectious risk: Mantoux test, full blood count (FBC), HBsAg, anti-HCV, anti-HIV[7].

Disease activity was assessed every 4 weeks using the PDAI scale. Laboratory tests (ELISA) were repeated every 3 months. Clinical response criteria: complete remission (CR) — disappearance of all new lesions and healing of erosions; partial remission (PR) — a reduction in the number of new lesions by more than 50%; no response (NR) — stable or increased disease activity.

Table 2. Treatment regimens and dosing.

Drug / Dosage	Control group	Rituximab group	Maintenance therapy	Duration
Prednisolone (mg/kg/day)	1.0–1.5	1.0–1.5	0.5–1.0	6–12 months
Azathioprine (mg/day)	100–150	100–150	50–100	12–18 months
Mycophenolate mofetil (g/day)	2.0–3.0	2.0–3.0	1.0–2.0	12–24 months
Rituximab (mg/infusion)	—	1000 mg ×2	500 mg ×4	Weeks 0 and 2 / Weeks 0,1,2,3
Dexamethasone (mg/pulse)	100	100	—	3 days, once a month

RTX – Rituximab; pre-infusion premedication: methylprednisolone 100 mg IV, diphenhydramine 25 mg IM, paracetamol 1000 mg orally. Infusion duration 4–6 hours under monitoring.

Prior to rituximab infusion, all patients underwent latent tuberculosis screening (QuantiFERON-TB Gold, chest radiography). In cases of active latent tuberculosis, RTX was delayed by one month and isoniazid prophylaxis was initiated. During the RTX infusion and for one hour afterwards, vital signs (blood pressure, SpO2, pulse) were monitored.

For quantitative variables, the Kolmogorov–Smirnov normality test was performed. Normally distributed data are expressed as mean ± standard deviation (M ± SD) and were compared using the Student's t-test (unpaired). Non-normally distributed variables were assessed using the Mann–Whitney U-test. Categorical variables were analysed with the Pearson chi-square test and Fisher's exact test. A p-value of <0.05 was considered statistically significant. The 95% confidence intervals (CI) for clinical response rates were calculated. Kaplan–Meier curves and the log-rank test were used for relapse analysis.

3. Results and Discussion

At the 12-month follow-up, a statistically significant difference in clinical efficacy was observed between the two groups. In the rituximab group (n=20), 18 patients (90%; 95% CI: 68.3–98.8%) achieved complete remission — a 2.6-fold higher rate compared with the control group (14 patients, 35%; 95% CI: 20.6–51.7%) (p<0.001). Partial remission was

observed in 10% (n=2) of patients in the RTX group and 40% (n=16) in the control group (p=0.018). In the control group, 25% (n=10) of patients showed no response to treatment and their therapy was changed; This was not observed in the RTX group [8].

Time to remission: 8.6±3.1 weeks in the RTX group (18.4±5.2 weeks in the control group), i.e., 2.1 times faster (p<0.001). At 12 months' follow-up, the relapse rate was 15% (n=3) in the RTX group and 52.5% (n=21) in the control group (p=0.003). Kaplan-Meier curve analysis confirmed the statistical superiority of the RTX group in relapse-free survival (log-rank χ^2=14.8, p<0.001) [9].

Table 3. Comparison of clinical and laboratory findings.

Indicator	Control group (n=40)	Rituximab group (n=20)
Clinical response	—	—
Complete remission (CR)	14 (35%)	18 (90%)
Partial remission (PR)	16 (40%)	2 (10%)
No response (NR)	10 (25%)	0 (0%)
Laboratory indicators	—	—
Relapse rate (12 months)	52.5%	15%
Mean reduction in PDAI score	−11.4 ± 4.8	−28.6 ± 6.2
Reduction in Dsg-3 titer (%)	−28.3%	−72.6%
Reduction in Dsg-1 titer (%)	−24.1%	−65.4%
Reduction of steroid dosage	38%	85%
Mean time to remission (weeks)	18.4 ± 5.2	8.6 ± 3.1

CR — complete remission; PR — partial remission; NR — no response; PDAI — Pemphigus Disease Activity Index; Dsg — desmoglein; Student's t-test (quantitative) and the chi-square test (categorical) were used.

Desmoglein-3 autoantibody titre (Dsg-3 IgG) in the RTX group fell from 193.4±58.7 U/mL to 52.8±18.4 U/mL—a 72.6% reduction (p<0.001). In the control group, the Dsg-3 titre fell from 182.7±51.8 U/mL to 131.0±44.2 U/mL (a 28.3% decrease, p<0.05). Concomitantly, the Dsg-1 IgG titre decreased by 65.4% in the RTX group (from 115.2±42.1 to 39.7±14.8 U/mL) and by 24.1% in the control group (from 110.8±36.2 to 84.1±28.6 U/mL) [10].

PDAI dynamics: in the RTX group, it decreased from a baseline of 41.5±13.6 points to 12.9±5.8 points (−28.6±6.2 points), whereas in the control group it decreased from 37.2±11.8 points to 25.8±9.4 points (−11.4±4.8 points). The difference between the groups was statistically significant (p<0.001, Cohen's d=2.74 — a very large effect size). The ability to reduce the steroid dose by more than 50 per cent was observed in 85% (n=17) of patients in the RTX group, and 38% (n=15) in the control group (p<0.001) [11].

Table 4. Comparison of adverse effects.

Type of adverse effect	Control group (n=40)	Rituximab group (n=20)
Infusion reactions	—	4 (20%)
Hyperglycemia	18 (45%)	6 (30%)
Infectious complications	12 (30%)	5 (25%)
Signs of osteoporosis	11 (27.5%)	3 (15%)
Arterial hypertension	9 (22.5%)	2 (10%)
Immunosuppressive complications	7 (17.5%)	2 (10%)
PML (Progressive Multifocal Leukoencephalopathy)	0 (0%)	0 (0%)
Total serious adverse effects	28 (70%)	9 (45%)

Serious adverse events – grade ≥3 events according to CTCAE v5.0; PML – progressive multifocal leukoencephalopathy.

In the rituximab group, infusion reactions were recorded in four patients (20%): three cases were mild (erythema, tremor, fever), and one case was moderate (bronchospasm, promptly resolved with corticosteroids and antihistamines). None of these cases required discontinuation of RTX. Infectious complications were observed in 5 (25%) patients in the RTX group and 12 (30%) in the control group — mainly skin and mucous membrane infections (staphylococcal infection, candidiasis). Serious adverse events (CTCAE ≥3) were observed in 45 per cent of the RTX group and 70 per cent of the control group ($p = 0.048$). Progressive multifocal leukoencephalopathy (PML) related to immunosuppression was not observed in any patient [12].

The main clinical advantages of RTX are: (1) a high complete remission rate (70–90%); (2) rapid induction of remission (median 8–12 weeks); (3) prolonged remission duration — 6–18 months after a single treatment; (4) steroid-sparing effect (85% of patients able to taper their dose); (5) The rapid and profound reduction in autoantibody titres (Dsg-3) indicates a direct effect on the pathogenesis [13].

Limitations and challenges: the pricing issue – the cost of a single infusion of RTX in Uzbekistan is US$1,200–1,800, limiting its accessibility; the immunosuppression period (6–9 months) – increased risk of infection; infusion reactions (5–20%); vaccination issues due to B-lymphocyte depletion; (5) the need for a separate risk–benefit assessment in off-label use for PV. However, as acknowledged by Herbst A, the long-term safety profile of RTX in PV has been extensively studied, and the risk of PML in practice is very low (<0.1 cases per 100 patient-years) [14].

The future of biological therapy in the treatment of PV is developing along several lines. The first line of development is combination regimens of RTX: Mentink L.F. in the Netherlands is investigating a combination of RTX and the new biologic agent dupilumab. The second line of development is new anti-CD20 agents: ofatumumab and obinutuzumab, which exert more potent depletion than RTX. The third line is CAR-T therapy and Dsg-3-targeted plasma cell depletion, currently in Phase I trials. The fourth approach – efgartigimod (an FcRn inhibitor) – a drug that exerts its effect by completely eliminating IgG autoantibodies, demonstrated high efficacy in Phase III trials in 2023 [15], [16], [17].

According to OECD data, the biologic therapy market is projected to reach US$700 billion by 2030, of which biologic dermatology products will account for 15–18 per cent. This trend also creates opportunities for developing countries such as Uzbekistan to increase the affordability and availability of biosimilar RTX drugs [18].

In Uzbekistan, expanding RTX therapy to the treatment of PV faces several practical obstacles: (1) Financial: the cost of an RTX course (US$2,400–3,600) is high relative to the average salary. However, the availability of biosimilar RTX (Rituvel, Indian manufacture) in Uzbekistan since 2023 reduces the barrier by 40–50 per cent; (2) Personnel: specialised centres with infusion rooms and full monitoring capabilities are currently available in 4 regional centres and in Tashkent; (3) Protocols: The Ministry of Health of Uzbekistan issued a local clinical guideline in January 2024 authorising the use of biological therapy for PV (Instruction No. 18); (4) Monitoring: there is a sufficient number of medical laboratories for long-term ELISA monitoring of patients [19], [20].

4. Conclusion

This prospective clinical study, conducted on 60 patients with pemphigus vulgaris, demonstrated a statistically significant clinical superiority of rituximab over conventional corticosteroid therapy.

In the rituximab group (n=20), complete remission was achieved in 90% of patients within 8.6±3.1 weeks — a statistically significant advantage compared to the control group (35%, 18.4±5.2 weeks) ($p<0.001$).

Desmoglein-3 autoantibody titres decreased by 72.6% in the RTX group (28.3% in the control group), and PDAI fell by 28.6 points — confirming RTX's direct, profound effect on pathogenesis.

The relapse rate was 15% in the RTX group and 52.5% in the control group, and Kaplan–Meier analysis confirmed the statistical superiority of the RTX group in relapse-free survival (log-rank $p<0.001$).

Adverse event profile: serious complications occurred in 45% of the RTX group versus 70% of the control group ($p=0.048$) — the steroid-sparing effect of RTX significantly reduces long-term toxicity.

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