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EVALUATING THE EFFECTIVENESS OF TARGETED THERAPY IN THE TREATMENT OF PATIENTS WITH GRANULOMATOSIS WITH POLYANGIITIS

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Abstract
In recent years, several recommendations for the treatment of granulomatosis with polyangiitis (GPA) have been developed by major expert groups, including EULAR, ERA-EDTA, the European Vasculitis Society, the British Society for Rheumatology, and the British Association of Rheumatologists. Due to the clinical heterogeneity and the severity of prognosis, the management and treatment strategies for patients with GPA are often challenging. The necessity of early diagnosis of GPA is driven by the need to initiate aggressive therapy as early as possible. The main goal of therapy is to suppress the underlying immunopathological reactions in order to achieve complete remission. This article presents an evaluation of the effectiveness of targeted therapy in the treatment of granulomatosis with polyangiitis.

Keywords: Granulomatosis with polyangiitis, treatment.

Introduction

Over the past decade, the goals of GPA therapy have significantly shifted — from merely ensuring patient survival to aligning with the modern concept of "treat to target" [2]. This approach aims to achieve stable remission of GPA, minimize adverse effects of treatment, control comorbidities, and ensure a higher quality of life [1,4]. The expansion of potential therapeutic goals in GPA has largely been made possible due to the emergence of innovative treatment strategies. Identifying the progression and complications of granulomatosis with polyangiitis (GPA) at early stages — along with evaluating significant correlations between the clinical, biochemical, and immunological features of the

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disease — plays a crucial role in analyzing and optimizing treatment methods [3]. Despite numerous ongoing scientific studies around the world, challenges remain in the diagnosis and treatment of GPA, in developing principles for predicting disease complications and outcomes, and in identifying markers of adverse prognoses.

Objective:
To evaluate the effectiveness of targeted therapy in the treatment of patients with granulomatosis with polyangiitis (GPA).

Materials and Methods:
The study included 60 patients diagnosed with GPA who were treated either in inpatient settings at the Rheumatology and Cardiorheumatology Departments of the Tashkent Medical Academy Multidisciplinary Clinic, or observed in outpatient settings at the Arthrology Department of the Interregional Diagnostic and Advisory Center (IADC) between 2018 and 2024.
The study focused on analysis of patient serum, radiological and ultrasound imaging data, disease activity scores (BVAS – Birmingham Vasculitis Activity Score), and Vasculitis Damage Index (VDI) assessments.
The study employed clinical questionnaires, laboratory tests, immunological analysis (ANCA), bacteriological swabs from the nasopharynx, BVAS and VDI scores, as well as instrumental diagnostic methods such as high-resolution CT of the lungs and paranasal sinuses, X-ray examinations, and statistical analysis.

Results:
All 60 patients received induction therapy with glucocorticoids. Among them, 49 patients (81.6%) were treated with high-dose regimens ("pulse" therapy). The average initial oral dose of prednisolone was 30 mg/day. Glucocorticoids were administered in combination with cytotoxic agents or gene-engineered biological drugs, particularly rituximab. In addition, 11 patients (18.3%) underwent plasmapheresis alongside drug therapy.

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Comparison of Treatment Outcomes in GPA Patients Between Group I (Localized) and Group II (Generalized). We compared treatment outcomes in patients with GPA from Group I (localized, n=29) and Group II (generalized, n=31).

In Group I, all patients received high-dose glucocorticosteroids to induce remission (including pulse therapy administered intravenously during periods of high vasculitis activity). In addition, patients underwent pulse therapy with cyclophosphamide administered intravenously at doses of 800–1600 mg every 2–4 weeks.

In Group II, all patients also received high-dose glucocorticosteroids combined with rituximab to induce remission (again including intravenous pulse therapy during severe disease activity). Rituximab was administered as intravenous infusions at a dose of 1000 mg, with a minimum of two infusions (total standard dose: 2000 mg). Concurrently with rituximab infusions, prednisolone was administered intravenously at a dose of 120 mg. Follow-up assessments were conducted every three months.

Clinical assessment was carried out using the BVAS (Birmingham Vasculitis Activity Score) and VDI (Vasculitis Damage Index), both of which are widely used as outcome measures in clinical trials and to guide "Treat-to-Target" therapy approaches. To determine BVAS and VDI, patients underwent thorough clinical and instrumental evaluations, including high-resolution CT (HRCT) of the paranasal sinuses, orbits, and thoracic organs.

The laboratory parameters assessed included:

Complete blood count (CBC) and urinalysis

24-hour proteinuria

Routine biochemical tests

Serum protein electrophoresis

C-reactive protein (CRP)

Anti-neutrophil cytoplasmic antibodies (ANCA)

In both groups, three months after the initiation of treatment, reductions were observed in vasculitis activity scores, erythrocyte sedimentation rate (ESR), CRP levels, and ANCA titers (Figure 1).

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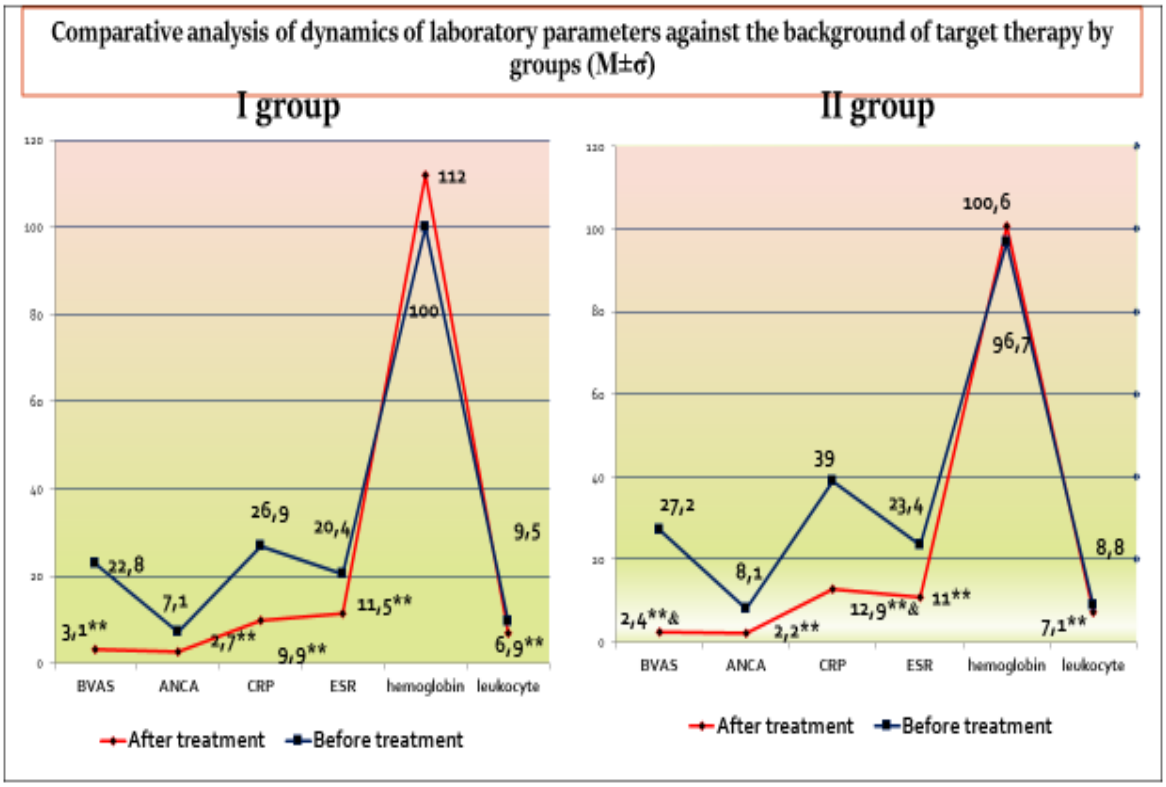

Figure 1.

The decrease in clinical activity of GPA was reflected by a parallel reduction in laboratory markers of disease activity. Based on the results of laboratory tests — including rheumatoid factor (RF), C-reactive protein (CRP), anti-neutrophil cytoplasmic antibodies (ANCA), Birmingham Vasculitis Activity Score (BVAS), blood urea, erythrocyte count, leukocyte count, erythrocyte sedimentation rate (ESR), urine protein levels, and alanine aminotransferase (ALT) — statistically significant differences were observed between the two patient groups (see Tables 1 and 2).

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Table 1

Indicators	1-group (M±σ)		P
	Before treatment	After treatment	
RF	11,7±3,71	8±0,74	<0,0005
CRP	26,9±1,48	9,85±1,48	<0,0005
ANCA	8,09±2,97	2,16±0,74	<0,0005
BVAS	27,2±10,38	2,4±1,48	<0,0005
VDI	0,9±1,48	1,08±1,48	0,241
Urea	6,63±0,59	7,42±0,52	0,889
Creatinine	65,9±22,98	70,67±13,34	0,879
GFR	99,75±5,93	99,4±2,97	0,839
Hemoglobin	96,65±15,57	100,6±3,71	<0,0005
Erythrocytes	3,27±0,52	3,58±0,52	<0,0005
Leukocytes	8,8±2,82	7,12±1,48	<0,0005
ESR	20,4±5,19	11,5±2,22	<0,0005
Erythrocytes in urine	6,25±5,19	2,65±2,97	0,689
Protein in the urine	0,05±0,05	0,03±0	<0,0005

Table 2

Indicators	2 - group (M±σ)		P
	Before treatment	After treatment	
RF	10,15±4,45	7,35±1,48	0,001
CRP	39,58±11,86	12,93±2,97	<0,0005
ANCA	6,65±6,35	2,44±1,91	<0,0005
BVAS	22,85±4,45	3,08±2,97	<0,0005
VDI	0,6±0	0,48±0	0,233
Urea	6,9±1,33	6,93±0,89	0,003
Creatinine	73,71±10,3	73,45±9,64	0,052
GFR	93,4±11,12	93,25±5,93	0,737
Hemoglobin	95,55±21,5	105,43±17,79	0,095
Erythrocytes	3,38±0,67	3,67±0,37	<0,0005
Leukocytes	9,31±3,56	6,87±1,41	0,019
ESR	23,18±5,93	11,1±2,97	<0,0005
Erythrocytes in urine	4,65±1,48	2±0	0,975
Protein in the urine	0,05±0,02	0,04±0	0,011

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In most cases, ANCA was not detected in the serum after the first course of RTX, and it remained absent throughout the entire follow-up period. A rapid and sustained decrease in serum CRP levels was observed after the first course. Following remission induction with RTX, no significant increase in CRP was observed during GPA relapses. At the same time, ESR significantly decreased shortly after the first course of RTX but later increased. The dynamics of CRP, ESR, and ANCA were not assessed as predictors of GPA relapse (Figure 2).

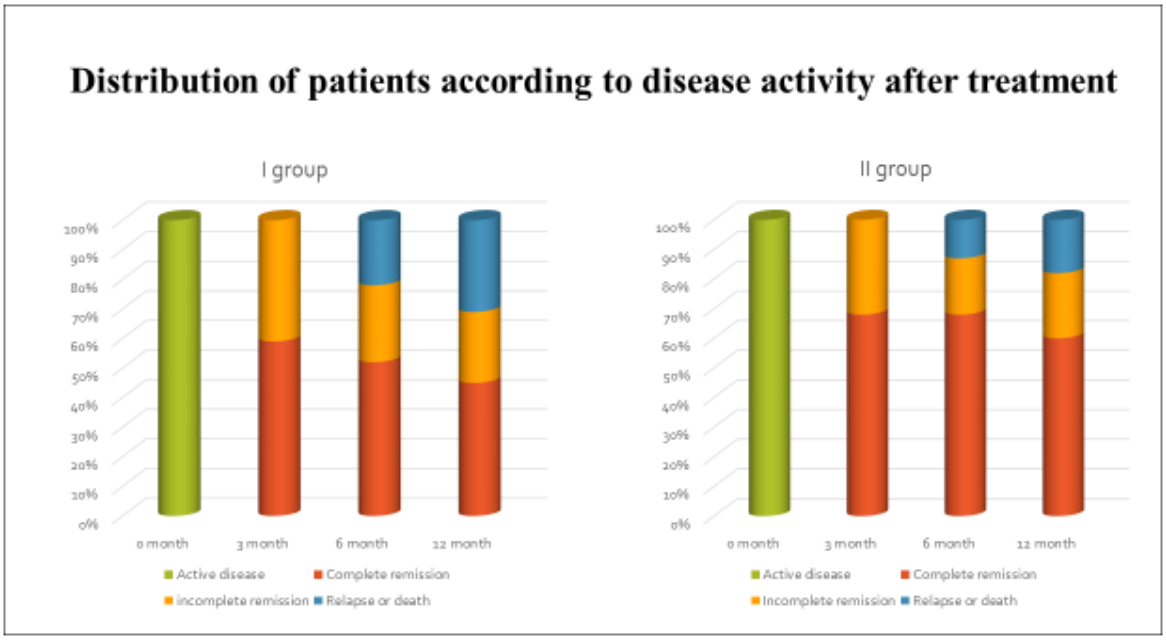

Figure 2.

In Group 1, after 3 months, complete remission was observed in 59% (17 patients), and partial remission in 41% (10 patients). After 6 months, remission initially achieved proved to be unstable in 22% (4 out of 6 patients), and vasculitis relapse occurred; 2 patients died due to infectious complications. After 12 months, remission was unstable in 31% (6 out of 9 patients), and vasculitis relapse developed; infectious complications were observed in 3 patients.

In Group 2, after 3 months, improvement was noted in all patients: 68% (21 patients) achieved complete remission, and 32% (10 patients) achieved partial remission. After 6 months, remission initially achieved was unstable in 13% (4 patients), and severe relapse of vasculitis developed; one patient died. Three

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patients received repeated rituximab infusions (1000 mg with a two-week interval), which allowed achieving complete remission again without increasing the glucocorticoid dose. Therefore, we recommend administering rituximab at a dose of 500–1000 mg every 6 months, even in the absence of clinical relapse. At the initiation of rituximab treatment, all patients were receiving combined immunosuppressive therapy.

As a result of the treatment, steroid dependence was eliminated in the majority of patients. Thus, if the average daily dose of glucocorticoids before rituximab administration was 40 mg (38.2 ± 22.4 mg/day), it was later reduced by at least 5 mg in 15 patients (75%) after the treatment course — without using other immunosuppressive drugs.

In recent years, several recommendations for the treatment of GPA have been developed by European and American specialists, including EULAR, ERA-EDTA, the European Vasculitis Society, the British Society for Rheumatology, and the British Association of Rheumatologists [5–8].

Due to the clinical heterogeneity and severity of prognosis, managing and selecting treatment strategies for patients with GPA remains challenging [10].

Early diagnosis of GPA is essential, as it allows timely initiation of aggressive therapy. The primary goal of treatment is to suppress the underlying immunopathological reactions to achieve complete remission.

The treatment is divided into three phases:

1. Remission induction – a short course of aggressive therapy;
2. Remission maintenance – long-term immunosuppressive therapy;
3. Relapse treatment [9,11].

Over the past decade, the goals of GPA therapy have significantly shifted from merely ensuring survival to the modern "treat-to-target" approach [12–15]. This strategy allows for the achievement of sustained remission, reduction in adverse treatment effects, control of comorbid conditions, and improved quality of life.

The expansion of potential treatment targets for GPA has become possible primarily due to the development of innovative treatment strategies.

The commonly accepted induction regimen includes high-dose glucocorticosteroids (GCS), cyclophosphamide (CYC), and other cytostatic

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drugs [16]. In GPA treatment, GCS are administered in combination with CYC in the form of intravenous pulse therapy (15 mg/kg every 2 weeks for 1–3 doses, then every 3 weeks), or orally at 2 mg/kg/day (not exceeding 200 mg/day) for 3–12 months. High-dose GCS (1 mg/kg/day, not exceeding 80 mg/day) are initially used, and the prednisone dose is gradually tapered to 7.5–10 mg after 12 weeks of therapy [17].In cases of elevated serum creatinine or in elderly patients, lower doses of CYC are applied [18].

The average duration of CYC treatment is about 6 months, as long-term use is associated with a high frequency of adverse effects—primarily infections. The total cumulative dose of CYC should not exceed 25 g. The use of CYC has been shown to significantly improve survival, with 5-year survival rates reaching 82%, according to long-term follow-up data [19].

At the same time, approximately 10% of patients are refractory to standard cyclophosphamide (CYC) therapy [20], and the mortality rate during the first two years of treatment remains significantly high (15–20%). In 20% of patients with renal involvement, end-stage renal disease (ESRD) requiring hemodialysis develops. Furthermore, during therapy with other cytostatics and glucocorticoids (GCs), relapses occur in 35–65% of patients, even at high cumulative doses of CYC. According to S. Pagnoux et al. [21], the relapse risk in patients with GPA under standard CYC-based therapy was 64%.

Thus, the introduction of cyclophosphamide into clinical practice enabled remission in the majority of patients with GPA. However, this was not sufficient to discontinue further research for effective and safe treatment. This led to a shift in the strategic goal of GPA therapy — achieving sustained and complete remission while reducing the number of adverse effects, particularly infections. In 2007, the European League Against Rheumatism (EULAR) included the study and implementation of new therapies that significantly improve the prognosis of GPA into its list of top-priority clinical research directions [22].

Since 2001, rituximab — a drug that induces CD20+ lymphocyte depletion — has demonstrated efficacy for both induction and maintenance therapy of ANCA-associated vasculitis [23]. Initial results were obtained mainly in GPA patients who were refractory to or had contraindications for CYC therapy [24].

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Following the results of two international randomized controlled trials (RCTs) that demonstrated the high efficacy and relative safety of rituximab in GPA [25], and based on data from systematic reviews [5], rituximab was included as a first-line option for induction therapy of GPA alongside cyclophosphamide [26].
The 2016 EULAR recommendations for the treatment of ANCA-associated vasculitis stated that rituximab may be used not only in cases of cyclophosphamide resistance but also as a first-line agent [27]. Rituximab was shown to be no less effective than cyclophosphamide in inducing remission of GPA [8], and it holds potential superiority in preventing relapses and achieving long-term outcomes [15].
Glucocorticoid monotherapy does not significantly affect the prognosis of GPA, with survival rarely exceeding three years in patients treated with steroids alone [7]. Therefore, high-dose glucocorticoids are administered in combination with either CYC or rituximab as an essential component of combination therapy [17].

In cases of relapsing vasculitis or CYC-refractory disease, rituximab is prescribed at a dose of 375 mg/m² weekly for 4 weeks, or 1000 mg twice at a 2-week interval. Methotrexate (25–30 mg/week) and mycophenolate mofetil (1 g/day) may be considered as alternative induction therapies in cases of low disease activity and low risk of severe organ damage [24]. During rituximab treatment, glucocorticoids are recommended at a dose of 1 mg/kg/day (not exceeding 80 mg/day), and the dose of prednisone is gradually tapered to 7.5–10 mg after 12 weeks of therapy. High-dose intravenous glucocorticoids may be used during the initial rituximab course to accelerate treatment efficacy.Avoiding the combination of cyclophosphamide (CYC) and rituximab (RTX) is generally recommended. However, in severe cases of the disease and when rapid therapeutic effect is needed, a combination of standard-dose RTX and CYC may be used for one or several months. RTX treatment is often combined with azathioprine (AZA) or mycophenolate mofetil (MMF) [18].
EULAR/ERA-EDTA experts recommend glucocorticoids (GCs) in combination with methotrexate (MTX) or MMF [28] for relapsing GPA without life-threatening organ involvement. MTX at a dose of 20–25 mg per week can be

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effective in the absence of renal involvement [29], such as non-destructive ENT lesions (without anosmia or deafness), non-cavitating pulmonary nodules without hemoptysis, and non-ulcerative skin lesions. This option is also suitable when CYC or RTX are contraindicated or unavailable [30].

However, it is important to note that according to randomized controlled trial (RCT) data, in a comparative 18-month follow-up of patients with GPA without severe renal damage, CYC therapy was associated with longer relapse-free periods and higher survival rates than MTX therapy [6].

The efficacy of MMF in GPA is supported by RCT results, which demonstrate that MMF is not inferior to CYC for inducing remission, including in patients with renal involvement [32]. MMF is initially prescribed at a dose of 1 g/day, which is later increased to 2 g/day. According to recently published two-year follow-up data, in patients with GPA—primarily those with mild renal disease (creatinine <500 μmol/L)—induction therapy with MMF was associated with lower nephrotoxicity compared to CYC [31]. Given the identified renoprotective properties of MMF, it may offer certain advantages in treating patients with renal involvement [7].

In cases of prolonged low disease activity in GPA, or in patients with secondary immunodeficiency due to long-term immunosuppressive therapy and superimposed infectious complications, intravenous immunoglobulin (IVIG) administration (0.4 g/kg/day for 5 days) may be effective. This approach has been validated by RCTs. Serum Ig levels should be monitored prior to initiating IVIG therapy [33]. In patients with selective IgA deficiency, IVIG administration may provoke anaphylactic reactions. Hyperglobulinemia may lead to increased blood viscosity.

Plasmapheresis (PLEX) is used in cases of severe renal failure (serum creatinine >500 μmol/L), in patients who have undergone allotransplantation with severe graft dysfunction, or in alveolar hemorrhage, including during disease onset or relapse [34]. According to RCTs, combining standard pathogenetic therapy with PLEX in cases of severe renal involvement can reduce the risk of progression to end-stage renal disease within 12 months by up to 24%. However, it does not improve overall survival [9].

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Currently, there are no established recommendations for the use of antiplatelet or anticoagulant therapy in GPA [5].

If clinical and laboratory remission is achieved with induction therapy for ≥2 years, methylprednisolone is prescribed at a daily dose of 6–8 mg in combination with one of the following drugs [8]:

1. Rituximab 1 g every 4–6 months (most effective and prevents relapse);
2. Azathioprine (2 mg/kg/day), methotrexate (25–30 mg/week), or leflunomide (20 mg/day).

In patients who have achieved sustained disease remission for one year while on maintenance therapy, it is recommended to first taper the glucocorticoid (GC) dose, followed by gradual reduction or discontinuation of immunosuppressive therapy [6].

The addition of trimethoprim/sulfamethoxazole (800/160 mg twice daily) may reduce the risk of GPA relapse [3], although trimethoprim/sulfamethoxazole monotherapy is not used for maintaining remission. In patients with upper respiratory tract involvement and documented Staphylococcus aureus colonization, topical antibiotics such as mupirocin are prescribed. Furthermore, to prevent Pneumocystis jirovecii infection, long-term prophylaxis with trimethoprim/sulfamethoxazole at a dose of 800/160 mg daily or 400/80 mg daily is recommended [6].

Due to the long-term risk of GPA relapse, regular follow-up after achieving remission is necessary, according to UK guidelines — initially after 3 months, then every 6 months, and annually if stable long-term remission is maintained [2].

Treatment of GPA relapse sometimes requires re-initiation of induction therapy, particularly when the relapse presents more severely than previous flares. In cases of severe, life-threatening, or organ-threatening relapses, glucocorticoids should be used in combination with either CYC or RTX, as in initial disease onset [3].

For mild relapses, temporary escalation of GC dose may be effective in many cases.However,relapses tend to recur afterward. Therefore, when intensifying therapy, the addition of cytotoxic agents or genetically engineered biologic drugs (GEBPs) is preferable [35].

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There is evidence that in patients experiencing their first relapse of high-activity GPA after remission induced by CYC, switching to RTX is more effective and cost-efficient than reintroducing CYC. In patients with a high cumulative CYC dose, relapse is considered a valid indication for RTX. The preference for RTX in such cases reflects its better safety profile compared to CYC, especially in those with concurrent infections. In certain scenarios, RTX offers additional advantages — for example, in women of reproductive age [10].

Treatment of recurrent transplant glomerulonephritis (GN) is a challenging task, as there are no universally accepted treatment protocols. According to R. Nachman et al., standard induction therapy with high doses of glucocorticosteroids (GCS) and cyclophosphamide (CYC) allows disease activity control in approximately 69% of such cases [13]. There are only isolated reports of the effective use of rituximab (RTX) [22].

In patients with granulomatosis with polyangiitis (GPA), reconstructive ENT surgery is only feasible during the inactive phase of the disease and in highly specialized centers [5].

Thus, despite significant advances in the treatment of GPA in recent years, it still remains a difficult task, requiring individualized approaches for each specific case.

Immunosuppressive therapy significantly improves the prognosis for patients with GPA; however, treatment is associated with a higher risk of severe infectious complications. Infections are one of the leading causes of morbidity and mortality in GPA. According to the literature, severe infections requiring hospitalization occur in 26–31% of patients, with one-third of these infections affecting the lungs or upper respiratory tract [14].

Within just the first year of standard therapy, serious adverse effects are observed in every fourth patient. Approximately one-third of all GPA-related deaths are associated with long-term CYC therapy, particularly due to infections. Leukopenia is considered a predictor of poor outcomes in such cases [32].

Conclusion: In both localized and systemic forms of GPA, targeted therapy with pulse administration of cyclophosphamide and methylprednisolone leads to reduced disease activity and lower BVAS scores. In patients refractory to standard

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therapy, rituximab use enables achieving full or partial remission, while simultaneously reducing the need for glucocorticosteroids and lowering the risk of steroid-related adverse effects.

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