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EVALUATION OF THE EFFECTIVENESS OF TARGET THERAPY IN THE TREATMENT OF PATIENTS WITH POLYANGIITIS GRANULEMATOSIS

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Abstract

In recent years, EULAR, ERA-EDTA, European Vasculitis Society, British Society of Rheumatology, British Association of Rheumatologists have recommendations for PAG treatment. Due to the variety of clinical manifestations and the severity of the prognosis, it is always difficult to choose a treatment strategy for patients with PAG.

The need for timely diagnosis of PAG is determined by the need for early initiation of aggressive therapy. The main goal of therapy is to suppress the immunopathological reactions underlying the disease in order to achieve complete remission. In this article, we can witness the evaluation of the effectiveness of target therapy in the treatment of polyangiitis granulomatosis.

Keywords: granulomatosis with polyangiitis, treatment.

In recent decades, there have been significant changes in the goals of PAG therapy, from saving patients' lives to the modern concept of "Treat to target" therapy [2]. This allows for stable remission of PAG, reduction of side effects of treatment, control of comorbid pathology and high quality of life [1,4]. Expanding the potential targets of PAG therapy has been made possible largely by the emergence of innovative treatment strategies. Early detection of PAG progression and complications, at the same time, assessment of important relationships between clinical, biochemical and immunological manifestations of the disease, analysis and alternative of effective treatment methods are of particular importance [3]. Despite many scientific researches conducted in different countries of the world, the diagnosis and treatment of PAG, the development of principles for predicting the complications and consequences of the disease, and the identification of markers of its negative consequences remain an urgent problem.

Purpose: to evaluate the effectiveness of target therapy in the treatment of patients with granulomatosis with polyangiitis.

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Materials and methods: 60 patients with PAG who were treated in inpatient conditions in the rheumatology and cardiorheumatology departments of the multidisciplinary clinic of the Tashkent Medical Academy in 2018-2022 and were observed and treated in the outpatient department of the arthrological IADK department were taken as the object of the study.

As the subject of the study, patients' blood serum, x-ray and ultrasound methods, as well as materials for determining the level of disease activity (BVAS) and vasculitis damage index (VDI) were taken.

Research methods. The research used clinical questionnaire, laboratory analysis, immunological (ANTsA), bacteriological inoculation from the nasopharynx, BVAS and VDI indicators, instrumental (MSCT of the nasal cavities and lungs, X-ray examination) and statistical methods.

As induction therapy, all 60 patients received glucocorticoids, including 49 (81.6%) patients in excessively high doses ("pulse" therapy). The average starting dose of oral glucocorticoids was 30 mg/day for prednisolone. Glucocorticoids have been used in combination with cytostatic agents or genetically engineered biological drugs, particularly rituximab. Plasmapheresis was used in 11 (18.3%) patients together with the ongoing drug therapy.

We compared the results of treatment in patients with PAG of group I (localized) (n=29) and group II (diffuse) (n=31). To induce remission in group I, all patients received high doses of glucocorticosteroids (including intravenous pulse therapy during extremely high activity of vasculitis), which were used together with cyclophosphamide in the form of intravenous pulse therapy sessions at a dose of 800-1600 mg every 2-4 weeks.

Also in group II, all patients received high doses of glucocorticosteroids in combination with rituximab to induce remission (including intravenous pulse therapy during very high activity of vasculitis). Rituximab was administered as an intravenous infusion at a dose of 1000 mg, with a total of at least two infusions (standard total dose of 2000 mg). Prednisolone infusions at a dose of 120 mg were performed concurrently with rituximab infusions. Follow-up examinations were performed every 3 months thereafter.

BVAS and VDI indices were used for clinical assessment, which are used to evaluate the end point in clinical trials and to treat the main goal of treatment (Treat to target). To clarify BVAS and VDI, systematic objective and instrumental examinations of patients were carried out, including MSCT of the paranasal sinuses, orbit and chest organs. The list of necessary laboratory indicators included general blood and urine analysis, daily proteinuria, routine biochemical indicators and determination of serum protein fractions, CRO, ANTsA.

Results: After 3 months of treatment in both groups, vasculitis activity, EChT, C-reactive protein, and ANTsA titer decreased (Figure 1).

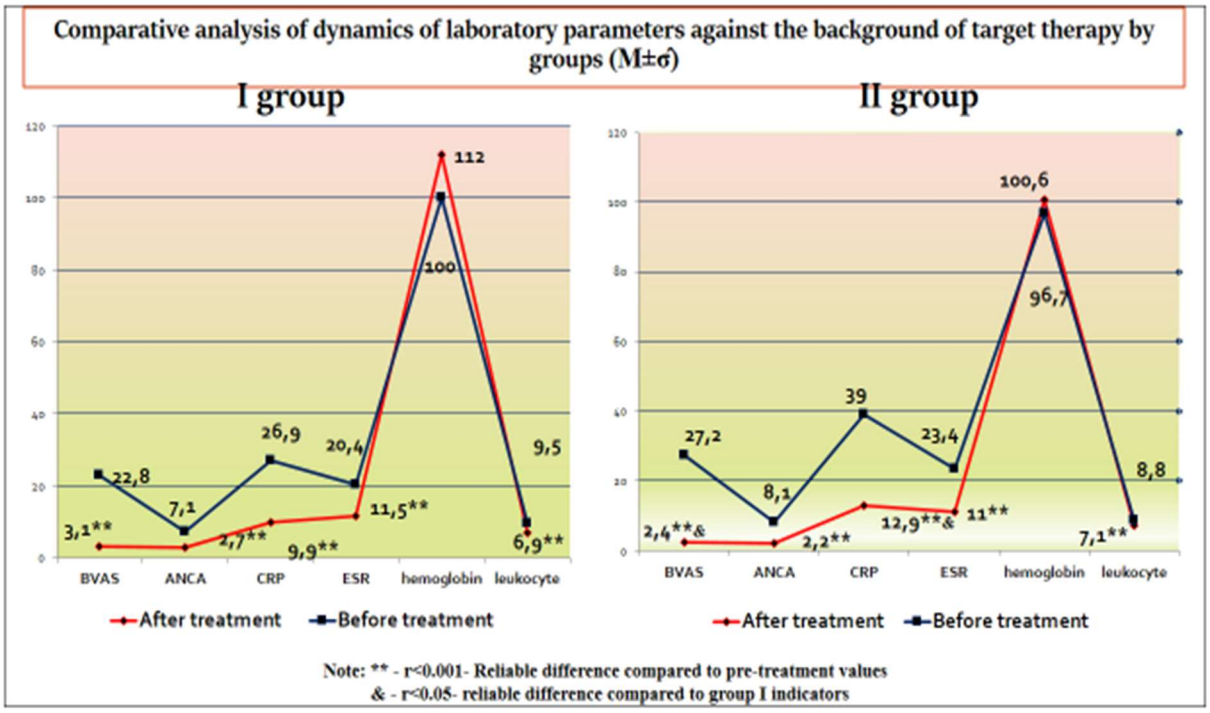

Figure 1.

A decrease in the clinical activity of PAG was manifested by a decrease in laboratory activity. According to the results of RF, CRO, ANCA, BVAS, Urea, Erythrocytes, Leukocytes, EChT, protein in urine, ALT analysis, statistically significant differences were found in two groups of patients (Tables 1 and 2).

Table 1

Indicators	1st 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
CFK	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 urine	0,05±0,05	0,03±0	<0,0005

Table 2

Indicators	**2nd 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
CFK	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 urine	0,05±0,02	0,04±0	0,011
RF	30,5±7,41	27,93±2,97	0,011
CRP	15,43±3,71	15,07±1,48	0,468
ANCA	20,15±8,9	21,7±3,71	0,106

In most cases, ANTsA was not detected in serum after the first course of RTM and was absent during the entire follow-up period. After the first course, a rapid and continuous decrease in serum CRO levels was observed. There was no significant increase in CRO in PAG relapses after remission induction by RTM. However, ECH decreased statistically significantly shortly after the first course of RTM, but then increased. Analysis of the dynamics of CRO, EChT and ANTsA was not evaluated as a predictor of PAG relapse (Figure 2).

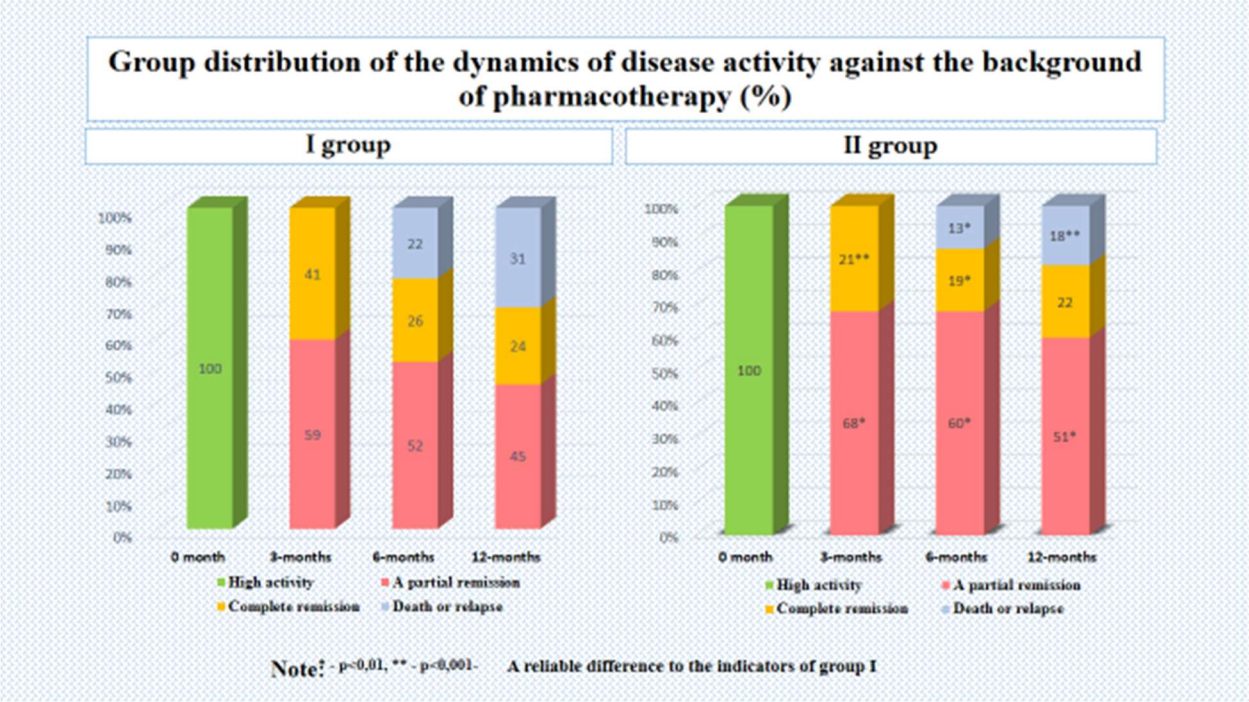

Figure 2.

In the 1st group, after 3 months, 59% (17) had a complete remission, 41% (10) had a partial remission of the disease. After 6 months, 22%, i.e. 4 out of 6 patients, the initially achieved remission turned out to be unstable and recurrence of vasculitis was observed, 2 patients died due to infectious complications; After 12 months, in 31% (9) of 6 patients, initially achieved remission turned out to be unstable and recurrence of vasculitis developed, infectious complications were observed in 3 patients; In the 2nd group, after 3 months, the condition of all patients improved: that is, 68% (21) had a complete remission, 32% (10) had a partial remission of the disease. After 6 months, in 13% (4) patients, the initially achieved remission turned out to be unstable and a severe recurrence of vasculitis developed, resulting in death in one patient; three patients were given repeated courses of rituximab at a schedule of 1000 mg with an interval of two weeks, which made it possible to achieve complete remission without increasing the dose of glucocorticoids. Therefore, we recommended rituximab 500-1000 mg every 6 months for patients without recurrence.

All patients were receiving combination immunosuppressive therapy at initiation of rituximab treatment. Cytostatic drugs at the time of rituximab administration are shown in Figure 3.

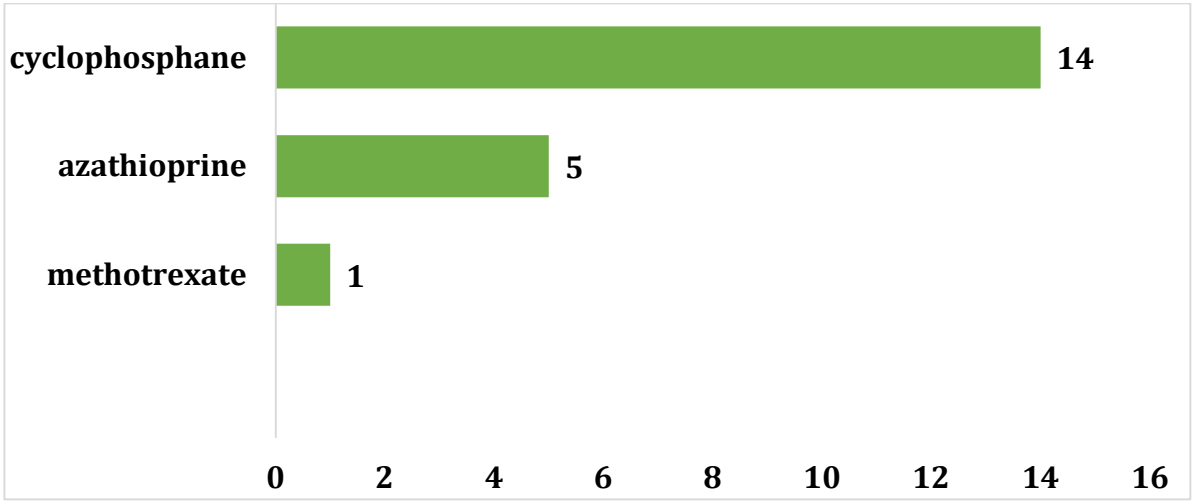

Figure 3. Number of patients receiving cytostatic drugs at the time of prescribing rituximab

As a result of treatment, elimination of steroid dependence was achieved in most patients. Thus, if the average dose of glucocorticoids before rituximab was 40 mg/day (38.2 ± 22.4 mg/day), then it was reduced to at least 5 mg after a course of treatment in 15 patients (75%) — without using other immunosuppressive drugs (Fig. 3.23) (differences are statistically reliable, r<0.01) (Fig. 4).

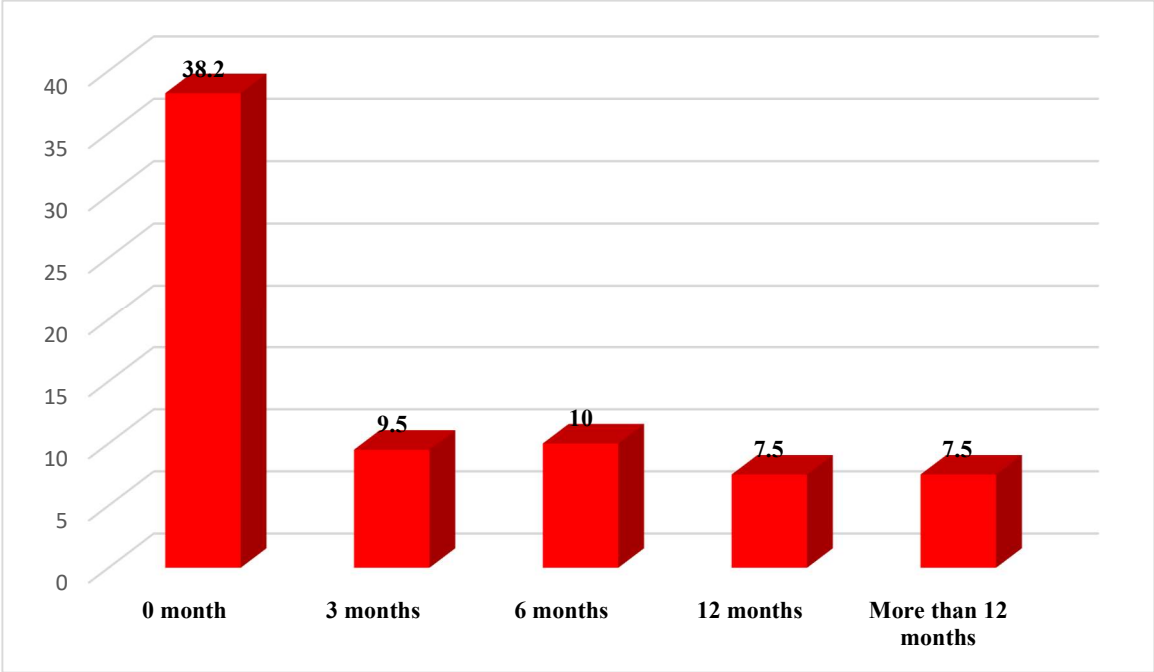

Figure 4. Dynamics of mean prednisolone dose (mg/day) after treatment with rituximab.

In recent years, EULAR, ERA-EDTA, European Vasculitis Society, British Rheumatology Society, and British Rheumatological Association have recommended the treatment of PAG [5-8].

Due to the variety of clinical manifestations and the severity of the prognosis, it is always difficult to choose the management and treatment tactics of patients with PAG [10].

The need for timely diagnosis of PAG is determined by the need for early initiation of aggressive therapy. The main goal of therapy is to suppress the immunopathological reactions underlying the

disease to achieve complete remission. Treatment is divided into three stages: induction of remission (a short course of aggressive therapy), maintenance of remission (long-term therapy with immunosuppressants), treatment of relapse [9,11].

In recent decades, there have been significant changes in the goals of PAG therapy, from saving patients' lives to the modern concept of "Treat to target" treatment [12-15]. This allows for stable remission of PAG, reduction of side effects of treatment, control of comorbid pathology and high quality of life. Expanding the potential targets of PAG therapy has been made possible largely by the emergence of innovative treatment strategies.

The generally accepted induction regimen includes the administration of high doses of glucocorticosteroids (GCs), cyclophosphane (TsF) and other cytostatics [16].

In the treatment of PAG, GKS combined with cyclophosphamide as intravenous pulse therapy 15 mg/kg every 2 weeks 1-3 times, then every 3 weeks or orally 2 mg/kg/day (no more than 200 mg/kg) 3-12 prescribed during the month. High doses of GKS (1 mg/kg per day, no more than 80 mg per day) are accepted, the dose of prednisolone is gradually reduced to 7.5-10 mg after 12 weeks of treatment [17]. Lower doses of TsF are used when serum creatinine is increased or in elderly patients [18].

The duration of treatment with TsF is on average 6 months, since long-term use is associated with a high frequency of side effects, primarily infectious, the total cumulative dose of TsF should not exceed 25 g. The use of TsF undoubtedly contributes to a significant increase in survival, according to the results of long-term follow-up, the five-year survival rate of patients reaches 82% [19].

At the same time, approximately 10% of patients are refractory to standard TsF therapy [20], the mortality rate in the first two years of treatment is very high (15-20%), 20% of patients with kidney damage develop end-stage SBE requiring hemodialysis. In addition, during therapy with other cytostatics and GKS, 35-65% of patients develop a relapse, which is possible even with high cumulative doses of TsF. Thus, according to S. Pagnoux et al. [21], against the background of standard treatment with TsF, the risk of exacerbation in PAG was 64%, respectively.

Thus, the introduction of cyclophosphamide into practice gave the opportunity to achieve remission in the majority of patients with PAG, but it was not a reason to stop further research for an effective and safe therapy. This led to a change in the strategic goal of PAG therapy - to achieve a complete stable remission with a decrease in the number of side effects (primarily infectious). In 2007, in order to study and implement new treatment methods that significantly improve the prognosis of PAG, EULAR clinical research was included in the priority list [22].

Since 2001, rituximab, which causes depletion of SD20+-lymphocytes, shows efficacy for induction and maintenance therapy of ANTsA-related vasculitis [23]. Preliminary results were obtained mainly in patients with PAG who were refractory or contraindicated to TsF [24].

After receiving the results of two international randomized clinical trials (RCTs) that showed the high efficacy and relative safety of RTM in PAG [25], taking into account the data of systematic reviews [5], RTM together with TsF was included among the first-line drugs for PAG induction therapy [26].

The recommendations of the European Antirheumatic League (EULAR) for the treatment of ANTsA-related vasculitis published in 2016 indicated that rituximab can be used not only in the presence of cyclophosphamide resistance, but also as a first-line drug [27]. RTM has been shown to be non-inferior

to TsF for induction of PAG remission [8], with the potential to be superior in disease relapse and long-term outcomes [15].

GKS monotherapy does not significantly affect the outcome of PAG, with this therapy, the survival time of patients with PAG does not exceed three years [7]. At the same time, treatment with TsF and RTM is combined with the appointment of GKC in high doses as an integral part of combined therapy [17]

In cyclophosphamide-refractory, recurrent vasculitis, rituximab is prescribed at 375 mg/m2 per week for 4 weeks or 1000 mg twice with an interval of 2 weeks. Methotrexate (25-30 mg/week) and mycophenolate mofetil (1 g/day) are considered as alternative induction therapy when the disease activity is low and the risk of developing severe organ damage is not high [24]. In the treatment of RTM, GKS is recommended at a dose of 1 mg / kg per day (not more than 80 mg per day), the dose of prednisolone is gradually reduced to 7.5-10 mg after 12 weeks of treatment. During the first course of RTM, high doses of GKS can be administered intravenously to accelerate the treatment effect. The combination of TsF and RTM should be avoided, but in severe cases of the disease and to accelerate the therapeutic effect, a combination of RTM and TsF in a standard dose is used for one or several months. RTM treatment is often combined with azathioprine (AZA) or mycophenolmofetil (MMF) [18].

EULAR/ERA-EDTA experts recommend GKC in combination with methotrexate (MT) or MMF [28] for recurrent PAG without vital organ involvement. MT at a dose of 20-25 mg per week can be effective in the absence of signs of kidney damage [29], for example, non-destructive damage of the ENT organs (without impaired sense of smell or deafness), nodules in the lung parenchyma without signs of destruction and hemoptysis, non-ulcerative skin changes, as well as , when there are contraindications for the use of TsF or RTM or the lack of opportunity [30].

At the same time, it should be noted that, according to RCT data, in the comparative follow-up of patients with PAG without severe kidney damage for 18 months, the relapse-free period as a result of TsF treatment was longer, and the survival was higher than in the MT group [6].

The efficacy of MMF in PAG is confirmed by RCT results, according to which MMF is not inferior to TsF in induction of primary remission, including in patients with kidney damage [32]. MMF is initially prescribed at a dose of 1 g per day, then the dose is increased to 2 g per day. According to a recently published two-year follow-up, the effectiveness of induction therapy with MMF in patients with PAG, mainly in patients with mild renal disease (creatinine <500 μmol), was lower when NT MMF was prescribed compared to TsF [31]. Since the renoprotective properties of MMF have been established, it may have some advantages in the treatment of patients with kidney damage [7].

In cases of secondary immunodeficiency as a result of immunosuppressive therapy, when the low activity of PAG persists for a long time, the addition of infectious NT, intravenous injection of human Ig (0.4 g/kg per day for 5 days) can be effective, which is confirmed by RCT. Serum Ig levels should be monitored before initiating Ig therapy [33]. Selective IgA deficiency can lead to an anaphylactic reaction when intravenous Ig is administered, and hyperglobulinemia can lead to a state of increased blood viscosity.

Plasmapheresis (PAF) is used in severe renal failure (blood creatinine > 500 μmol/l), severe graft dysfunction or alveolar hemorrhage in allotransplant patients, and PAG debut or relapse [34]. According to the results of an RCT in severe renal impairment, the combination of standard pathogenetic therapy and PAF reduces the risk of progression to end-stage renal failure by 24% within 12 months, but does not improve the overall survival of patients [9].

Currently, there are no significant recommendations for the use of antiaggregant or anticoagulant therapy in PAG [5].

If clinical-laboratory remission is achieved with the help of induction therapy ≥ 2 years - methylprednisolone is prescribed in a dose of 6-8 mg per day with one of the following drugs [8]:

1) rituximab 1 g every 4-6 months (most effective and prevents recurrence);

2) azathioprine (2 mg/kg per day), methotrexate (25-30 mg per week), leflunamide (20 mg per day).

It is recommended to first reduce the dose of GCS, and then reduce or cancel immunosuppressive therapy in patients with a permanent remission of the disease for a year against the background of maintenance therapy [6].

Although the addition of trimethoprim/sulfamethoxazole (800/160 mg twice daily) has been reported to reduce the risk of PAG relapse [3], trimethoprim/sulfamethoxazole monotherapy is not used to maintain remission. Topical antibiotics (mupirocin) are prescribed for patients with upper respiratory tract infections and Staphylococcus aureus. In addition, trimethoprim/sulfamethoxazole 800/160 mg daily or 400/80 mg daily long-term is given to prevent Pneumocystis jirovecii infection [6].

As the risk of recurrence of PAG remains in the long term, after achieving remission, according to the recommendation of British experts, the condition of patients should be monitored regularly, first after 3 months, then every 6 months, and annually if a long-term stable remission is maintained [2].

In the treatment of relapse of PAG, it is sometimes necessary to re-introduce induction therapy in the later stages of the disease. In cases of serious relapses that are life-threatening or damage vital organs, as in the case of PAG debut, GKS is used in combination with TsF or RTM [3].

For non-severe relapses of PAG, a temporary increase in the dose of GKC can be effective in most cases, but later relapses usually recur, so cytostatics or gene-engineered biological drugs (GIBP) are preferable when intensifying treatment [35].

There is evidence that adding RTM is more effective and more cost-effective than resuming TsF for patients with first relapse of PAG after induction of remission by TsF. Relapse of PAG in patients with a high cumulative dose of cyclophosphamide is also considered an indication for RTM. The possibility of prescribing RTM when using a high cumulative dose of TsF or in patients with concomitant infections reflects the opinion that RTM has a better safety profile than TsF. In some cases, RTM may have additional benefits, such as in women of reproductive age [10].

Treatment of recurrent transplant glomerulonephritis (GN) is a difficult task, as there are no generally accepted treatment regimens. Standard induction therapy with high doses of GKS and TsF, R. According to Nachman et al., 69% of such cases allow control of GN activity [13], there are only observations of effective use of RTM [22].

Reconstructive surgery in ENT organs in patients with PAG is possible only in the inactive stage of the disease and in highly specialized centers [5].

Thus, despite significant progress in the treatment of PAG in recent years, it still remains a difficult task and requires an individual solution in each specific case. 57 (60%) of 60 patients received maintenance therapy. All patients received GKS to maintain disease remission, the average duration of admission was 28 (1; 217) months. To maintain remission, azathioprine was used in 32 (53.3%) patients, cyclophosphamide in 12 (20%), rituximab in 16 (26.6%), monotherapy with steroids in 2 (3.3%). In addition, 56 (93.3%) patients received trimethoprim/sulfamethoxazole (biseptol 960 mg) for a long time to prevent opportunistic infection.

The mean cumulative dose of cyclophosphamide during the follow-up period was 9.69 g (0.4; 200). By the end of the follow-up, 48 (80%) patients had disease remission, 12 (20%) had signs of vasculitis activity, 8 patients had relapsed disease, and the rest had "smoky" signs of vasculitis activity (minimally manifested urinary syndrome, arthralgias).

Immunosuppressive therapy significantly improves the prognosis of patients with PAG, but treatment is associated with an increased risk of severe infectious complications. Infections are a major cause of morbidity and mortality in patients with PAG. According to the literature, serious infectious complications requiring hospitalization develop in 26-31% of patients, and in one third of them, the focus of infection is located in the lungs or upper respiratory tract [14].

In the first year of standard therapy alone, serious side effects occur in every fourth patient, approximately one-third of the total number of PAG deaths are long-term TsF therapy, primarily infections, with leukopenia being a predictor of adverse outcome [32].

Conclusion Pulse therapy with cyclophosphamide and methylprednisolone in targeted treatment of localized and diffuse types of PAG leads to a decrease in disease activity and BVAS indicators. The use of rituximab in patients refractory to standard therapy makes it possible to achieve complete or partial remission of the disease and, at the same time, to reduce the need for glucocorticosteroids and the side effects that develop under their influence.

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