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Effectiveness of Target Therapy and its Complications in the Treatment of Polyangiitis Granulematosis

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Resume: In the treatment of polyangiitis granulomatosis (PAG), the selective recommendation of gene-engineered biological drugs, the application of a combination of glucocorticoids and immunodepressants allow to increase the effectiveness of treatment and have a positive effect on the outcome of the disease. Early detection of PAG progression and complications, at the same time, assessment of important connections between clinical, biochemical and immunological manifestations of the disease, analysis of effective treatment methods and alternatives are of particular importance.

Despite many scientific researches conducted in different countries of the world, diagnosis and treatment of PAG, development of principles for predicting the complications and consequences of the disease, and identification of markers of negative consequences remain an urgent problem.

Keywords: granulomatosis with polyangiitis, target therapy, complications.

In recent years, EULAR, ERA-EDTA, European Vasculitis Society, British Rheumatology Society, and British Rheumatological Association have recommended the treatment of PAG [3]. 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 [1]. 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 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 [2]. 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 [4]. 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 (CYPH) and other cytostatics [5].

In the treatment of PAG, GCS 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 GCS (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 [6]. Lower doses of Cyclophosphane are used when serum creatinine is increased or in elderly patients [7].

The duration of treatment with Cyclophosphane 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 Cyclophosphane should not exceed 25 g. The use of Cyclophosphane 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% [8].

At the same time, approximately 10% of patients are refractory to standard TsF therapy [3], the mortality rate in the first two years of treatment is very high (15-20%), 20% of patients with kidney damage develop end-stage CKD requiring hemodialysis.In addition, during therapy with other cytostatics and GCS, 35-65% of patients develop a relapse, which is possible even with high cumulative doses of Cyclophosphane. Therefore, according to S. Pagnoux and others. [9], against the background of standard treatment with Cyclophosphane, the risk of exacerbation in PAG was 64%, respectively.

Furthermore, 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 was included in the list of clinical research priorities [7].

Since 2001, rituximab, which causes depletion of SD20+-lymphocytes, shows efficacy for induction and maintenance therapy of ANCA-related vasculitis [10].Preliminary results were obtained mainly in patients with PAG who were refractory or contraindicated to Cyclophosphane[9].

After receiving the results of two international randomized clinical trials (RCTs) that showed the high efficacy and relative safety of RTM in PAG [11], taking into account the data of systematic reviews [12], RTM was included among the first-line drugs for PAG induction therapy together with Cyclophosphane [13].

The European Antirheumatic League (EULAR) recommendations for the treatment of ANTsA-related vasculitis published in 2016 showed that rituximab can be used not only in the presence of cyclophosphamide resistance, but also as a first-line drug [14]. RTM has been shown to be non-inferior to Cyclohosphane for induction of PAG remission [15], with the potential to be superior in disease relapse and long-term outcomes [16].

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 [5]. At the same time, treatment with Cyclophosphane 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 [18]. 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, higher doses of GKS can be administered intravenously to accelerate the treatment effect.The combination of Cyclophosphane 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) [19].

EULAR/ERA-EDTA experts recommend GCS in combination with methotrexate (MT) or MMF [20] for recurrent PAG without vital organ involvement. MT 20-25 mg may be effective in the absence of signs of renal damage [21], for example, non-destructive lesions of the ENT organs (without impaired sense of smell or deafness), nodules without signs of destruction and hemoptysis in the lung parenchyma, non-ulcerative skin changes, as well as when there are contraindications or the absence of the possibility to use Cyclophosphane or RTM [22].

At the same time, it is interesting to note that, according to RCT data, in a comparative follow-up of patients with PAG without severe renal damage for 18 months, the relapse-free period was longer as a result of treatment with TsF, and the survival was higher than in the MT group [23].

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 [20]. 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 PAG patients, mainly in patients with mild renal disease (creatinine <500 μmol), was lower when NT MMF was prescribed compared to TsF [24]. Since the renoprotective properties of MMF have been established, it may have some advantages in the treatment of patients with kidney damage [2].

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 [25]. 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 cases of severe renal failure (blood creatinine > 500 μmol/l), severe graft dysfunction or alveolar hemorrhage in allotransplant patients, PAG debut or relapse [10]. 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 [26].

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 [2]:

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

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 [24]. While the addition of trimethoprim/sulfamethoxazole (800/160 mg twice daily) has been reported to reduce the risk of PAG relapse [27], trimethoprim/sulfamethoxazole monotherapy is not used to maintain remission. Topical antibiotics (mupirocin) are prescribed to patients with upper respiratory tract infections and Staphylococcus aureus. Additionally, trimethoprim/sulfamethoxazole 800/160 mg daily or 400/80 mg daily long-term is given to prevent Pneumocystis jirovecii infection [28].

As the risk of relapse of PAG remains in the long term, after achieving remission, according to the recommendation of British experts, the condition of patients should be regularly monitored,initially after 3 months, then every 6 months, then annually if long-term stable remission is maintained [29].

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 PAG debut, GKS is used in combination with Cyclophosphane or RTM [30].

For non-severe relapses of PAG, a temporary increase in the dose of GCS can be effective in most cases, but later relapses usually recur, so cytostatics or gene-engineered biological drugs (GIBD) are preferable when intensifying treatment [31].

There is evidence that adding RTM is more effective and more cost-effective than resuming Cyclophosphane for patients with first relapse of PAG after induction of remission by Cyclophosphane. 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 Cyclophosphane 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 [32].

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., in 69% of such cases, GN activity can be controlled [5], there are only observations of the effective use of RTM [6].

Reconstructive surgery in ENT organs in patients with PAG is possible only in the inactive stage of the disease and in highly specialized centers [7]. Also, 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.

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 [33].

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].

In a study of 255 patients with the onset of PAG with a mean follow-up of 6.4 years, compared with a control population, mortality in patients with PAG was ninefold increased in the first year of the disease due to infections, PAG activity, and renal failure, especially in patients over 65 years of age, and mortality was significantly higher at the next 5-year follow-up. decreased and increased again after 10-15 years [34].

In addition, patients have an increased risk of developing lymphoma and bladder cancer, due to the harmful effect of Cyclophosphane on the bladder mucosa, which was determined to be dependent on the cumulative dose of Cyclophosphane. Therefore, the risk of bladder cancer increases when the dose of Cyclophosphane exceeds 30 g [5].

The most common infectious complications develop during induction of remission, which is associated with high intensity of immunosuppressive therapy. In the long-term EUGVAS study, 24% of patients with PAG developed infectious complications during the first year after diagnosis, and mortality from infections during 1-year follow-up was 5.6% [11].In a French study, infectious complications were found in 39.6% of patients within the first year after the diagnosis of PAG [7]. The study also revealed a statistically significant direct relationship between the cumulative dose of cyclophosphamide and the frequency of the development of infectious complications in the early stages of the disease. The dose of glucocorticosteroids (GCS) is also a risk factor for the development of infectious complications. In a French study, serious infectious complications occurred during treatment with GCS (variable doses) in 89% of cases, and in previous studies, a decrease in the dose of GCS was associated with a decrease in the frequency of infections [8].

The incidence of infectious complications was compared in two studies comparing the safety of rituximab and cyclophosphamide for induction of remission in patients with PAG with a similar dosing regimen of GCS [9].

Among infectious complications of immunosuppressive therapy (up to 62% of all episodes), bacterial infections predominate, including pneumonia (39% of all episodes), soft tissue infections, and disseminated septicemia [35].

The main causative agents of respiratory tract infections are Streptococcus pneumoniae, Haemophilus influenzae, Pseudomonas aeruginosa and Staphylococcus aureus [8].

Among the causative agents of opportunistic infections in patients with PAG, Pneumocystis jirovecii (old name Pneumocystis carinii) is the most common (0.85-12.00%). In patients receiving

immunosuppressive therapy, P. jiroveci infection is more aggressive and has a worse outcome than AIDS-related cases. According to different authors, R. Juravecci 14 to 64% of patients who developed jiroveci infection received long-term therapy with high doses of GCS (more than 3 months) and cyclophosphamide. However, the frequency of pneumocystis pneumonia in the group of patients who received oral cyclophosphamide was higher than in the group of patients who received Cyclophosphane in the form of intravenous infusion (30.4% and 11.1%, respectively) [7]. Because of the high risk of developing an infection caused by Pneumocystis jiroveci, co-trimoxazole/trimethoprim is recommended for all patients treated with Cyclophosphane [36].

It is possible that V-cells also play an important role in protection against P. jirovecii, since pneumocystis pneumonia has been observed in patients receiving rituximab [37].

Tuberculosis is a rare but potentially fatal complication of immunosuppressive therapy in patients with PAG. In most cases, the cause is reactivation of latent M. tuberculosis infection. High rate of TB reactivation observed in early studies of NOF inhibitors in patients with rheumatoid arthritis and therefore the practice of examining each patient to rule out the risk of TB reactivation was introduced in all systemic diseases, including vasculitis [16].

Viral infections are the second most frequent in patients with PAG and account for up to 35.8% of all infectious complications. Reactivation of the chickenpox virus, which is not life-threatening, but can be complicated by the development of neuralgia from herpes, is observed in 13-24% of patients. Reactivation of latent cytomegalovirus infection is less common in patients with PAG and accounts for 7.5% of the total number of infectious complications [37].

Hepatitis V reactivation associated with rituximab treatment has been reported in large studies of patients with rheumatoid arthritis [4]. In this regard, before starting therapy with rituximab, patients are screened early for hepatitis V and C, and patients with a history of infection or an active process are indicated for full serological monitoring and determination of the dynamics of the viral load during treatment.

Disseminated forms of fungal infections in patients with PAG are rare but characterized by high mortality. The oropharyngeal form of candidiasis caused by C. albicans is one of the common complications of GCS therapy.

The development of fungal infection is life-threatening, but the disseminated form of candidiasis is very rare [9].

During combined therapy with glucocorticoids and cytostatics, 30 (28.6%) patients developed infectious complications: 17 had respiratory tract infections (mainly pneumonia, including 3 pneumocystis pneumonias and purulent bronchitis, tuberculosis infection was not detected), 8 had herpes virus infections , mainly V. zoster, development of sepsis from an unspecified focus in 2 people. In 1 person - reactivation of chronic viral infection of hepatitis C, in 8 patients infections of various locations (urine, skin, etc.) were detected.

RTM was characterized by relatively good treatment safety. The frequency of infusion reactions (itching, rash, urticaria) was 6.5%, their severity was reduced by slowing down the rate of administration of RTM and prescribing antihistamines, in no case was it necessary to cancel treatment with RTM. The most common serious infectious side effects (10%) were pulmonary lesions occurring within 6 (1.5-6) months after the first or second course of RTM, with pneumonia in combination with neutropenia in three of six cases. As well as , RTM showed superior efficacy in PAG with a treatment safety profile. At the same time, against the background of the introduction of innovative RTM therapy, the problem of the risk of recurrence of PAG was not fully resolved (the recurrence rate was 13%).

LIST OF REFERENCES USED

1. Gibb W. et al., 1986 Gibb W, Wiliams A. Nocardiosis mimicking Wegener's granulomatosis. Scand J Infect Dis 1986; 18:583-585.
2. Gibson A. The epidemiology of Wegener’s granulomatosis and microscopic polyangiitis in a Southern Hemisphere region / A. Gibson [et al.] // Rheumatology (Oxford). — 2006. — Vol. 45. — № 5. — P. 624–628.
3. Greco A. Clinic manifestations in granulomatosis with polyangiitis / A. Greco [et al.] // International journal of immunopathology and pharmacology. — 2016. — Vol. 29. — № 2. — P. 151–159.
4. Groot K. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody–associated vasculitis. A randomized trial / K. Groot [et al.] // Annals of internal medicine. — 2009. — Vol. 150. — № 10. — P. 670–680.
5. Girard C. Tracheobronchial stenoses in granulomatosis with polyangiitis (Wegener's): a report on 26 cases / C. Girard [et al.] // Medicine (Baltimore). — 2015. — Vol. 94. — № 32. — P. e1088.
6. Guerry M. Recommendations for the use of rituximab in anti-neutrophil cytoplasm antibody-associated vasculitis / M. Guerry [et al.] // Rheumatology (Oxford). — 2012. — Vol. 51. — № 4. — P. 634–643.
7. Guillevin L. A prospective, multicenter, randomized trial comparing steroids and pulse cyclophosphamide versus steroids and oral cyclophosphamide in the treatment of generalized Wegener's granulomatosis / L. Guillevin [et al.] // Arthritis and rheumatism. — 1997. — Vol. 40. — № 12. — P. 2187–2198.
8. Guillevin L. The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort / L. Guillevin [et al.] // Medicine (Baltimore). — 2011. — Vol. 90. — № 1. — P. 19–27.
9. Guillevin L. et al. A prospective, multicenter, randomized trial comparing steroids and pulse cyclophosphamide versus steroids and oral, 188 188. Guillevin L, Pagnoux C, Karras A, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. NEJM 2014;371(19):1771-80.
10. Harper L. Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up / L. Harper [et al.] // Annals of the rheumatic diseases. — 2012. — Vol. 71. — № 6. — P. 955–60.
11. Harper S.L., et al. Wegenerrs granulomatosis: the relationship between ocular and systemic disease J. Rheumatol. 2001. – №28. – P.1025−1026.
12. Hellmich B. EULAR recommendations for conducting clinical studies and/or clinical trials in systemic vasculitis: focus on anti-neutrophil cytoplasm antibody-associated vasculitis / B. Hellmich [et al.] // Annals of the rheumatic diseases. — 2007. — Vol. 66. — № 5. — P. 605–617.
13. Hermann J. Clinical interpretation of antineutrophil cytoplasmic antibodies: parvovirus B19 infection as a pitfall / J. Hermann [et al.] // Annals of the rheumatic diseases. — 2005. — Vol. 64. — № 4. — P. 641–643.
14. Hernández-Rodríguez J. Surgical Interventions and Local Therapy for Wegener's Granulomatosis / J. Hernández-Rodríguez, G. Hoffman, C. Koening // Current opinion in rheumatology. — 2010. — Vol. 22. — № 1. — P. 29–36.
15. Hoffman G. S. Wegener granulomatosis: An analysis of 158 patients / G. S. Hoffman [et al.] // Annals of internal medicine. — 1992. — Vol. 116. — № 6. — P. 488–498.

16. Holle J.U. Prospective long-term follow-up of patients with localised Wegener's granulomatosis: does it occur as persistent disease stage? vasculitides / J. U. Holle [et al.] // Annals of the rheumatic diseases. — 2010. — Vol. 69. — № 11. — P. 1934–1939.
17. Holle J.U., Windmöller M., Lange C., Gross W.L., Herlyn K., and Csernok E. Toll-like receptor TLR2 and TLR9 ligation triggers neutrophil activation in granulomatosis with polyangiitis. // Rheumatol. Oxf. Engl. 2013. – P.257-266
18. Holle J.U., Gross W.L., Latza U., Nölle B., Ambrosch P., Heller M., et al. Improved outcome in 445 patients with Wegener's granulomatosis in a German vasculitis center over four decades. // Arthritis Rheum 2011. – №63. – P.257-66.
19. Holle J.U. Rituximab for refractory granulomatosis with polyangiitis (Wegener's granulomatosis): comparison of efficacy in granulomatous versus vasculitic manifestations / J. U. Holle [et al.] // Annals of the rheumatic diseases. — 2012. — Vol. 71. — № 3. — P. 327–333.
20. Hu W. Mycophenolate mofetil versus cyclophosphamide for inducing remission of ANCA vasculitis with moderate renal involvement / W. Hu [et al.] // Nephrology, dialysis, transplantation. — 2008. — Vol. 23. — № 4. — P. 1307–1312.
21. Hoffman G. S. Wegener granulomatosis: An analysis of 158 patients / G. S. Hoffman [et al.] // Annals of internal medicine. — 1992. — Vol. 116. — № 6. — P. 488–498.
22. Holle J.U. Prospective long-term follow-up of patients with localised Wegener's granulomatosis: does it occur as persistent disease stage? vasculitides / J. U. Holle [et al.] // Annals of the rheumatic diseases. — 2010. — Vol. 69. — № 11. — P. 1934–1939.
23. Holle J.U., Windmöller M., Lange C., Gross W.L., Herlyn K., and Csernok E. Toll-like receptor TLR2 and TLR9 ligation triggers neutrophil activation in granulomatosis with polyangiitis. // Rheumatol. Oxf. Engl. 2013. – P.257-266
24. Hugle B. et al. Pneumocystis jiroveci pneumonia following rituximab treatment in Wegener's granulomatosis. // Arthritis Care Res. 2010. – №62. – P.1661–1664.
25. IANNELLA G. et al. Granulomatosis with polyangiitis and facial palsy: Literature review and insight in the autoimmune pathogenesis. Autoimmun Rev, v. 15, n. 7, p. 621-31, Jul 2016. ISSN 1873-0183 (Electronic) 1568-9972 (Linking). Available at: < https://www.ncbi.nlm.nih.gov/pubmed/26851550 >
26. Jagiello P. New genomic region for Wegener's granulomatosis as revealed by an extended association screen with 202 apoptosis-related genes / P. Jagiello [et al.] // Human genetics. — 2004. — Vol. 114. — № 5. — P. 468–477.
27. Jayne D Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity / D. Jayne [et al.] // The Quarterly journal of medicine. — 2000. — Vol. 93. — № 7. — P. 433–439.
28. Jayne D Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis / D. Jayne [et al.] // Journal of the American Society of Nephrology. — 2007. — Vol. 18. — № 7. — P. 2180–2188.
29. Jones R. A randomised trial of mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis: "MYCYC". On behalf of the European vasculitis study group / R. Jones, M. Walsh // La Presse Médicale. — 2013. — Vol. 42. — № 4. — P. 678–679.
30. Jones R.B. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. / R. B. Jones, [et al.] // The New England journal of medicine. — 2010. — Vol. 363. — № 3. — P. 211–220. . 26. — № 10. — P. 3077–3079.
31. Kallenberg C.G. Key advances in the clinical approach to ANCA-associated vasculitis / C. G. Kallenberg // Nature Reviews Rheumatology. — 2014. — Vol. 10. — № 8. — P. 484–493.

32. Kamali S., Erer B., Artim-Esen A., Gul A., Ocal L., Konice M., Aral O., and Inanc M. Predictors of Damage and Survival in Patients with Wegener's Granulomatosis: Analysis of 50 Patients. // J Rheumatol 2010. – №37. – P.374–8; doi:10.3899/jrheum.090387

33. Kessenbrock K. Netting neutrophils in autoimmune small vessel vasculitis / K. Kessenbrock [et al.] // Nature Medicine. — 2009. — Vol. 15. — № 6. — P. 623–625.

34. Kitching A.R., Anders H-J., Basu N., et al. ANCA-associated vasculitis. Nat Rev Dis Prim. 2020. – №6. – P.71.

35. Knecht K., Mishriki Y.Y. More than a mouth ulcer: oral ulcer due to Wegener's granulomatosis. Postgrad Med 1999. – №105. – P.200-203.

36. Knight A. Urinary bladder cancer in Wegener’s granulomatosis: risks and relation to cyclophosphamide / A. Knight [et al.] // Annals of the rheumatic diseases. — 2004. — Vol. 63. — № 10. — P. 1307–1311.

37. Klemmer P.J. Plasmapheresis Therapy for Diffuse Alveolar Hemorrhage in Patients with Small-Vessel Vasculitis / P. J. Klemmer [et al.] // American journal of kidney diseases. — 2003. — Vol. 42. — № 6. — P. 1149–1153.