The Course and Outcomes of Covid-19 in Patients with Anca-associated Systemic Vasculitis, Receiving Biological Therapy (Rituximab, Mepolizumab): the Results of the First 8 Months of the Pandemic

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Objective. Currently, the issues of the effect of anti-B cell therapy or inhibitor of interleukin 5 on the risk of COVID-19 infecting and outcomes in patients with ANCA-associated vasculitis (AAV) has not been completely studied. We present an analysis of the COVID-19 course and outcomes in AAV patients treated with rituximab or mepolizumab from one rheumatology center registry.
Methods. From November 11 to November 15, 2020, a cross-sectional study was conducted using telephone and online surveys, and information was collected from all 128 AAV patients treated with rituximab in V.A. Nasonova Research Institute of Rheumatology. Patients mean age was 51 (20–81) years, 61.7% were women. Granulomatosis with polyangiitis (GPA) was diagnosed in 58 patients, microscopic polyangiitis (MPA) – in 38, eosinophilic granulomatosis with polyangiitis (EGPA) – in 24 (including 54.2% of ANCA-negative cases), and AAV with uncertain nosological affiliation – in 8 patients. Due to the disease activity or a high risk of AAV recurrence during the pandemic rituximab was prescribed in 60/126 (47.6%) patients, and mepolizumab – in 6 cases.
Results. In the spring of the pandemic (until May 2020), the incidence of COVID-19 in AAV patients treated with rituximab was 4.3%, the disease course was relatively favorable. All patients recovered. At month 3–6, antibodies to SARS-CoV-2 IgG persisted in only 1 out of 4 patients. Since September 2020, the incidence has increased 3-fold, with a more severe course of COVID-19. In total, in the period until November 11, 2020, COVID-19 was diagnosed in 17.2% (22/128); the mean age of patients was 55 (25–81) years; 54.5% were women. 21/22 patients were on rituximab therapy, 2 patients had mepolizumab therapy (including 1 case after previous rituximab therapy). COVID-19 incidence was lower in patients with GPA (15.5%) vs MPA and EGPA (21.1% and 20.8% respectively). The mortality rate was 13.6%, including 2 patients with MPA and 1 patient with GPA. When analyzing the 5-year survival rate according to the registry of AAV patients treated with rituximab, prognosis worsening was noted; in 2020 there were 3 deaths due to COVID-19, in the previous 5 years – only 2 deaths.
Discussion. Taking into account the fact the mechanisms of AAV and severe COVID-19 are largely synergistic (primarily in the context of microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome as manifestation of the acute inflammatory syndrome), the activity of AAV can potentially contribute to the disease onset and a severe course of COVID-19. Given the previously published information on the use of rituximab during the COVID-19 pandemic for various diseases, it seems that B cell depletion, without reducing the risk of infection, may have a protective effect with regard to the risk of severe/catastrophic COVID-19, which, however, can be insufficient in AAV patients. Further analysis of COVID-19 cases in patients with AAV and other immuno-inflammatory rheumatic diseases is exceptionally important.
Keywords: COVID-19, rituximab, mepolizumab, B-cells, interleukin-5, ANCA-associated vasculitis, granulomatosis with polyangiitis, microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis
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ТЕЧЕНИЕ И ИСХОДЫ COVID-19 У ПАЦИЕНТОВ С АНЦА-АССОЦИИРОВАННЫМИ СИСТЕМНЫМИ ВАСКУЛИТАМИ, ПОЛУЧАЮЩИХ ЛЕЧЕНИЕ ГЕННО-ИНЖЕНЕРНЫМИ БИОЛОГИЧЕСКИМИ ПРЕПАРАТАМИ (РИТУКСИМАБ, МЕПОЛИЗУМАБ): ИТОГИ ПЕРВЫХ 8 МЕСЯЦЕВ ПАНДЕМИИ

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В настоящее время вопросы влияния терапии генно-инженерными биологическими препаратами на риск инфицирования и исходы COVID-19 у пациентов с АНЦА-ассоциированными системными васкулитами (АНЦА-СВ) окончательно не решены; опубликованные наблюдения немногочисленны. Накопленные в настоящее время данные свидетельствуют о возможном синергизме патологических механизмов АНЦА-СВ и COVID-19 тяжелого течения, прежде всего в контексте синдрома обструктивного тромбовоспаления сосудов микроциркуляции легких как проявления острого воспалительного синдрома при COVID-19. Случаи COVID-19 у пациентов с АНЦА-СВ, получающих анти-В-клеточную терапию ритуксимабом или лечение антагонистом интерлейкина 5 меполизумабом, требуют всестороннего анализа.

По итогам первых 8 месяцев пандемии COVID-19 представлены результаты анализа течения и исходов COVID-19, основанные на наблюдении 128 пациентов с АНЦА-СВ, получающих терапию генно-инженерными биологическими препаратами в ФГБНУ «Научно-исследовательский институт ревматологии им. В.А. Насоновой» (126 пациентов получали ритуксимаб, 6 – меполизумаб, в том числе 4 – после терапии ритуксимабом). Медиана возраста пациентов составила 51 (20–81) год; 61,7% – женщины. У 58 пациентов был диагностирован гранулематоз с полиангиитом (ГПА); у 38 – микроскопический полиангиит (МПА); у 24 – эозинофильный гранулематоз с полиангиитом (ЭГПА), в том числе у 54,2% из них – АНЦА-негативный вариант; у 8 пациентов – АНЦА-СВ с неопределенной нозологической принадлежностью. В период пандемии в связи с активностью или высоким риском рецидива АНЦА-СВ 47,6% (60/126) пациентам назначали ритуксимаб, в 6 случаях – меполизумаб.

В первые 3 месяца пандемии частота COVID-19 у пациентов с АНЦА-СВ, получавших лечение генно-инженерными биологическими препаратами, составила 4,3% (5/115); заболевание протекало относительно благополучно, во всех случаях наступило выздоровление. Через 3–6 месяцев антитела к коронавирусу IgG сохранялись только у 1 из 4 пациентов. С сентября 2020 г. отмечен рост заболеваемости в 3 раза, при этом наблюдалось более тяжелое течение заболевания.

За 8 месяцев пандемии COVID-19 диагностирован у 17,2% (22/128) пациентов; медиана возраста заболевших – 55 (25–81) лет; 54,5% – женщины. 21 из 22 пациентов получал ритуксимаб, 2/22 – меполизумаб (в том числе в 1 случае – после ритуксимаба). Частота COVID-19 была ниже при ГПА (15,5%), чем при МПА и ЭГПА (21,1% и 20,8% соответственно). Летальность составила 13,6%, включая 2 пациентов с МПА и 1 – с ГПА. При анализе выживаемости пациентов с АНЦА-СВ за последние 5 лет в группе, получавшей терапию ритуксимабом, отмечено ухудшение прогноза: в 2020 г. зарегистрированы 3 летальных исхода, обусловленных COVID-19, за 5 предшествующих лет было в общей сложности 2 летальных исхода.

Среди описанных в литературе 8 случаев АНЦА-СВ с COVID-19 на фоне лечения ритуксимабом обобщенная летальность составила 12,5%. Обсуждаются опубликованные сведения о применении ритуксимаба в период пандемии COVID-19 и вопросы влияния В-клеток и их деплеции на течение и исходы COVID-19. По-видимому, анти-В-клеточная терапия, не снижая риск инфицирования, способна оказывать протективный эффект в отношении тяжелого/катастрофического течения COVID-19, что тем не менее может оказаться недостаточным у пациентов с АНЦА-СВ в активной стадии заболевания на фоне полиорганного поражения.

Среди пациентов с ЭГПА и COVID-19 во всех случаях наступило выздоровление. Обсуждаются немногочисленные данные литературы, свидетельствующие о снижении тяжести течения COVID-19 у пациентов с бронхиальной астмой в результате лечения меполизумабом.

Исключительно важным является дальнейший анализ случаев COVID-19 у пациентов с АНЦА-СВ и другими иммуновоспалительными ревматическими заболеваниями, получающих лечение генно-инженерными биологическими препаратами.

Ключевые слова: COVID-19, ритуксимаб, меполизумаб, В-клетки, интерлейкин 5, АНЦА-ассоциированный системный васкулит, гранулематоз с полиангиитом, микроскопический полиангиит, эозинофильный гранулематоз с полиангиитом

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Currently, the issues of the anti-B cell therapy or inhibitor of interleukin 5 (IL-5) effect on the risk of infection and the outcomes of severe COVID-19 in patients with immunoinflammatory rheumatic diseases (IRDs), including ANCA-associated vasculitis (AAV), have not been thoroughly studied, and published observations are limited. Since the beginning of the COVID-19 pandemic, announced by WHO on March 11, 2020, there has been an extensive discussion about the safety of treatment with biologic disease-modifying antirheumatic drugs DMARDs (bDMARDs), primarily anti-B cell therapy, including recommendations on limiting the use of drugs with this mechanism of action. At the same time, during the COVID-19 pandemic, the risks of discontinuing bDMARDs cannot be ignored, as they can lead to progression or relapse of potentially life-threatening disease.

Cases of COVID-19 in AAV patients treated with rituximab or mepolizumab are of significant interest and require comprehensive analysis. We present the results of the COVID-19 pandemic by the example of 128 patients included in the registry of AAV patients treated with rituximab or mepolizumab.

Methods

A cross-sectional study using telephone and online patient survey was conducted in 128 patients with AAV, who were under follow-up at the V.A. Nasonova Research Institute of Rheumatology and included in the registry of AAV patients treated with rituximab or . From November 11 to November 15, 2020, at the end of 8 months after the COVID-19 pandemic was announced, all patients were surveyed. Informed consents were received. Information on a specific form of disease, the severity of the AAV course and previous therapy was obtained from the registry database and patients' outpatient records. When diagnosing specific forms of AAV, surrogate criteria for granulomatosis and vasculitis were taken into account [1, 2]. ANCA overproduction was proven in all patients with a history of granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA); 54.2% patients with eosinophilic granulomatosis with polyangiitis (EGPA) were ANCA-negative.

When analyzing the results of the study, the following patients were found eligible for inclusion in the COVID-19 group: AAV patients treated with bDMARDs, with COVID-19 confirmed by PCR of the nasopharyngeal/oropharyngeal swab and/or by antibodies to coronavirus and/or patients hospitalized at a coronavirus in-patient department with diagnosed community-acquired pneumonia.

The study included 128 patients (58 with GPA, 38 with MPA, 24 with EGPA, 8 with an unspecified AAV); median age of 51 (20–81) years; 61.7% were women. The median duration of rituximab treatment was 49 (1–121) months; the total dose was 3.5 (0.5–9.5) g. In 20/126 (15.87%) cases, the interval between the last rituximab infusion and the beginning of the COVID-19 pandemic exceeded 12 months. During the COVID-19 pandemic, 60/126 (47.61%) patients with an active form of AAV or a high risk of recurrence with damage to vital organs received rituximab at a dose of 500 to 2000 mg, including 11 cases of first-prescribed rituximab. During the pandemic, the inhibitor of IL-5 mepolizumab was prescribed in 6 cases of EGPA.

All patients showed improvement or achieved remission of AAV as the result of rituximab or mepolizumab therapy. From March to November 2020, serious adverse reactions not associated with COVID-19 were limited to one case of bilateral pneumonia with negative PCR nasopharyngeal swab and the absence of antibodies to coronavirus; as a result of outpatient treatment, the patient recovered. This case was not included in the COVID-19 group because it did not meet the inclusion criteria.

Results

In the spring period of the pandemic (until May 2020), the incidence of COVID-19 in AAV patients treated with rituximab was 4.3% (5/115) with a relatively favorable course of the disease (Table 1). One patient had mild COVID-19 without clinical or radiological signs of lung damage, 2/5 (40%) of patients were hospitalized at the coronavirus in-patient department, but none of the cases required oxygen support, and all had a successful outcome (recovery). At month 3–6, antibodies to SARS-CoV-2 IgG persisted in only 1 out of 4 patients. There were no new cases of COVID-19 reported in the summer. Since September 2020, the incidence has increased 3-fold (Figure 1, Table 1), with a more severe course of COVID-19.

In total, in the period until November 11, 2020, COVID-19 was diagnosed in 17.2% (22/128) of AAV patients (9 with GPA, 8 with MPA, 5 with EGPA); the median age of patients was 55 (25–81) years; 54.5% were women. During the pandemic, 14/21 (66.66%) of COVID-19 patients received rituximab; two EGPA patient received mepolizumab (including 1 case after previous rituximab therapy). The incidence of COVID-19 in patients receiving rituximab during the pandemic (after March 11, 2020) was twice as high as in the rest of the patient group, amounting to 23.33% (14/60) and 10.60% (7/66), respectively. In cases of persistent remission of AAV with an interval of more than 12 months between the last infusion of rituximab and the beginning of the pandemic, the incidence of COVID-19 was 5% (1/20). No cases of infection with SARS-CoV-2 have been identified in the group of 6 patients who received the last infusion of rituximab more than 24 months before March 11, 2020.

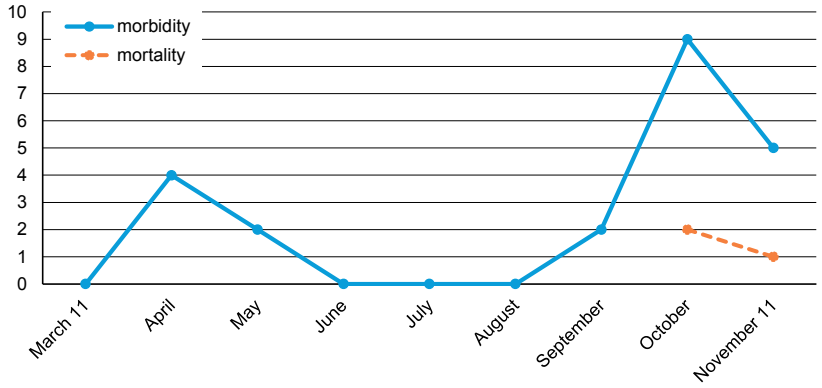

Fig. 1. *COVID-19 Incidence and Mortality in AAV patients, Our Own Results*

Table 1. *Course and Outcomes of COVID-19 in 21 AAV patients Treated with Rituximab or Mepolizumab, According to Our Own Observation*

No.	Month of COVID-19 disease	Sex/ Age, years	AAV diagnosis ANCA specificity	GEBD		COVID-19 diagnosis (PCR swab, SARS-CoV-2 antibodies)	Lung damage	Extrapulmonary manifestations of COVID-19	COVID-19 course/ outcome
				TD, g	Duration of rituximab therapy prior to COVID-19, mo				
1	April	m/49	GPA ANCA +	5	64	PCR +	CT 2–3		Hospitalization/ Recovery
2	April	f/59	GPA aPR3	1	46	PCR + antibodies +	CT 2	diarrhea	Hospitalization/ Recovery
3	April	f/69	MPA aPR3	2.5	17	PCR - antibodies +	CT 0	conjunctivitis	Mild disease/ Recovery
4	April	m/37	GPA aPR3	2	4	PCR +	CT 3 SpO_2 94%	nausea	Hospitalization, severe disease/ Recovery
5	May	m/56	EGPA ANCA –	Mepolizumab		antibodies +	no data		Mild disease/ Recovery
6	May	m/42	MPA aPR3	4.5	74	PCR +	CT 2		Moderate disease/ Recovery
7	September	m/55	EGPA aMPO	2	17	PCR +	no data	conjunctivitis, diarrhea	Mild disease/ Recovery
8	September	f/47	EGPA aMPO	6	35	PCR +	CT 2	myalgias	Hospitalization/ Recovery
9	October	f/50	MPA aMPO	3.5	27	no data	CT 4 SpO_2 73%		Hospitalization in a coronavirus hospital, severe disease, mechanical ventilation/ Exitus
10	October	f/36	EGPA ANCA –	4.5	53	PCR +	CT 2 concomitant bacterial pneumonia		Hospitalization, complicated disease/ Improvement
11	October	m/69	MPA aPR3	6	81	PCR +	CT 4		Hospitalization, severe disease, mechanical ventilation/Exitus
12	October	f/43	MPA aMPO	3	121	PCR +	Bilateral pneumonia		Moderate disease/ Recovery
13	October	f/56	GPA aPR3	3.5	91	PCR +	Pneumonia		Hospitalization in coronavirus hospital/Exitus (cause: HF)
14	October	m/61	GPA aPR3	9	91	PCR – antibodies –	CT 2 SpO_2 94%		Hospitalization in coronavirus hospital/ Recovery
15	October	m/33	GPA ANCA +	5	46	PCR +	no data	diarrhea	Mild disease/ Recovery
16	October	f/25	GPA aPR3	2.5	13	PCR +	no data		Mild disease/ Recovery
17	October	f/81	MPA aPR3	3	58	PCR +	CT 0	transient CVA	Hospitalization at coronavirus in-patient department/ Recovery
18	November	m/67	EGPA aMPO	2.5	20	PCR +	CT 1		Moderate disease/ Recovery
19	November	f/64	EGPA ANCA –	4	37	PCR +	CT 3 SpO2 72%		Hospitalization, severe disease, IL-6 inhibitor/ Recovery
				Mepolizumab					
20	November	f/68	GPA aPR3	3	4	PCR + antibodies –	CT 3–4 SpO_2 70%		Hospitalization, severe disease, IL-6 inhibitor/ Recovery
21	November	f/54	GPA aMPO	0.5	1.5	antibodies +	CT 1		Mild disease/ recovery
22	November	f/74	MPA aMPO	5.5	90		CT 2	conjunctivitis, myalgias	Moderate disease/ Improvement

Note: *GPA – granulomatosis with polyangiitis, MPA – microscopic polyangiitis, EGPA – eosinophilic granulomatosis with polyangiitis, aPR3 – antibodies to proteinase 3, aMPO – antibodies to myeloperoxidase, TD – total dose of rituximab, CVA – cerebrovascular accident, HF – heart failure*

12/21 (57.1%) of COVID-19 patients received rituximab were hospitalized, 8 (66.6%) of them had a decrease in SpO_2 within 70%–94% and required oxygen support. In 3/21 (14.3%), the severe course of COVID-19 led to a fatal outcome; all of them were treated with rituximab (1 with GPA and 2 with MPA; 2 women, 1 man; age 50; 56; 69 years); the information about treatment for COVID-19 was incomplete or absent. In 2 out of 3 patients who died from COVID-19 had incomplete remission of AAV; they were admitted to hospital at late stage with extensive lung damage and pronounced symptoms of respiratory failure. In another fatal case, there was a relapse of AAV; no information on the course of COVID-19 or the treatment was received; SARS-CoV-2 infection was confirmed by PCR; congestive heart failure was specified as the cause of death. Among the patients with EGPA and COVID-19, all recovered.

The incidence of COVID-19 against the background of bDMARDs therapy in GPA patients (15.5%) was lower than in MPA or EGPA patients (21.1% and 20.8%, respectively). The mortality rate in GPA patients is lower than in MPA patients (11.11% and 25.0%, respectively). When analyzing the 5-year survival rate according to the registry of AAV patients treated with rituximab, prognosis worsening was noted; in 2020, 3 deaths were due to COVID-19, while in the previous 5 years there were only 2 deaths which were caused by acute myocardium infarction in an 82-year-old patient with GPA and by multiple organ failure in a 46-year-old patient with a 23-year history of severe refractory GPA (Figure 2).

Discussion

During the COVID-19 pandemic, the issues of treatment of AAV group diseases are becoming especially relevant. All specific forms of AAV are characterized by a high incidence of damage to the respiratory system, upper respiratory tract (58%–96%), bronchi and lungs (65%–100%), with a tendency to relapse [2, 3]. Thus, necrotizing inflammation of the barrier organs (upper respiratory tract, lungs), the main entry point of coronavirus, along with corneal cells, intestinal mucosa, and other organs, creates significant prerequisites for susceptibility to COVID-19 infection [4]. An additional factor is immunosuppressive therapy prescribed to all AAV patients at the induction and maintenance stages of treatment, which may contribute to the development of secondary immunodeficiency disorder with an increased risk of serious infections, primarily respiratory infections.

Another aspect that increases interest in AAV in the context of coronavirus infection (Table 2) is the similarity of the current understanding of the pathological processes characterizing AAV [3] and COVID-19, primarily in the context of the new concept of microvascular COVID-19 Lung vessels Obstructive Thromboinflammatory Syndrome (MicroCLOTS) as a manifestation of acute inflammatory syndrome in severe/catastrophic COVID-19 with damage to lungs and various other organs [5, 6]. Similarly to AAV [3], the significance of pathological activation of the B cell link of immunity and hyperproduction of antibodies (antibodies to SARS-CoV-2, autoantibodies to interferon) [7–13], alternative and lectin pathways of complement [14, 15], neutrophils [4, 16–19] is discussed in the context of pathogenesis of severe COVID-19. Extrapulmonary localization of lesions of the microvascular way with the involvement of the nervous system, myocardium, kidneys, skin [6, 7, 20–29] is possible in COVID-19. There are literature data on the development of vasculitis, Kawasaki syndrome, and other autoimmune and autoinflammatory diseases in children with COVID-19 [30, 31]. The possibility of destructive lung damage in COVID-19 should be noted [32]. In addition, in recent years, therapeutic approaches have been increasingly converging, with prescription of glucocorticoids, bDMARDs, primarily inhibitors of proinflammatory cytokines, in severe/catastrophic COVID-19. There are reports on the effective use of the antagonist of the C5 complement component eculizumab, cyclosporine [3, 32–34]. Thus, in AAV patients infected with coronavirus, co-progression of two disorders with synergistic mechanisms with an associated increase in the risk of poor prognosis is possible.

Reports on COVID-19 disease in AAV patients treated with rituximab are few in number. The available literature describes 8 cases (Table 3) [35-40]; the total mortality rate was 12.5%. According to our observation, similar results were obtained: of 21 AAV patients with COVID-19 disease (9 with GPA, 8 with MPA, 4 with EGPA) 12 (57%) were hospitalized at the coronavirus in-patient department; 8 of them required oxygen support; the mortality rate was 14.3%. It should be noted

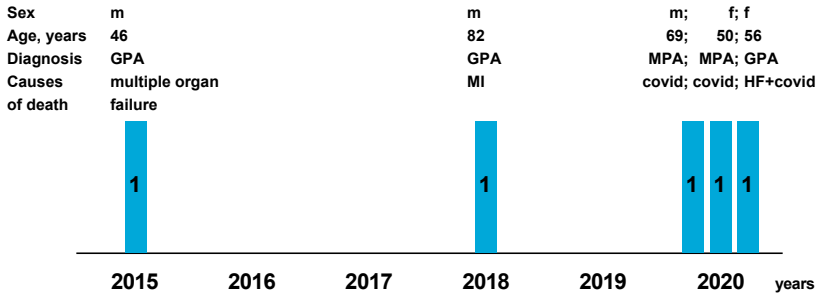

Fig. 2. *The 5-year survival rate according to the registry of AAV patients treated with rituximab (n=128).*

Note: *GPA – granulomatosis with polyangiitis, MPA – microscopic polyangiitis, MI – acute myocardial infarction, HF - heart failure.*

Table 2. *Comparison of AAV and Severe COVID-19*

Parameter	AAV	Severe COVID-19
Lung damage	High frequency of lung damage in all forms of AAV (65–100%). GPA is characterized by pulmonary infiltrates with destruction and formation of cavities, MPA – by hemorrhagic alveolitis, and EGPA – by bronchial asthma and eosinophilic pneumonia	Viral pneumonia is the main clinical manifestation that determines the prognosis. Possibly destructive lung damage
Damage to other organs	Typically affects the upper and lower airways and kidneys. Other organs and systems can be involved	Possible extrapulmonary localization of the lesion, including the nervous system, kidneys, myocardium, and other organs
Vascular involvement	Systemic necrotizing vasculitis with predominant lesion of small vessels. In the active phase, hypercoagulation	Obstructive thrombus inflammation of the microcirculation vessels of the lungs and extrapulmonary vessels. Increased incidence of Kawasaki syndrome during the COVID-19 pandemic
Inflammation	High or very high. Characterized by an increase in the level of CRP, ESR, blood platelets	Very high in severe cases. Characterized by an increase in the level of CRP, interleukin-6, blood ferritin
Autoantibodies	ANCA pathogenetic role	Dominant extrafollicular B cell responses. Positive correlation between SARS-CoV-2 antibody titer and the clinical severity of COVID-19. In severe COVID-19, high titers of IFN-α2 and/or IFN-ω autoantibodies
Neutrophil	Neutrophils are the most important effector cells in the pathogenesis	Changes in the morphology of neutrophils were noted. Netosis, the release of serine proteases from neutrophils promote the activation of the complement system, hypercoagulation, endotheliitis, the production of pro-inflammatory cytokines. In severe cases, an increase in the number of neutrophils in the blood and the amount of bronchoalveolar lavage fluid
Complement	Complement is crucial in the pathogenesis. A clinical study has proven the efficacy of the C5a receptor antagonist Avacopan	Activation of alternative and lectin complement pathways. Eculizumab, C5 complement component anatagonist, has been reported to be effective in severe COVID-19
Treatment	Cytostatics, rituximab, glucocorticoids. In the active phase, anticoagulants	Anticoagulants. In severe cases, glucocorticoids, pro-inflammatory cytokine antagonists, JAK inhibitors, cyclosporine
Prognosis	Serious	High mortality rate in severe/catastrophic COVID-19

Table 3. *Incidence and Severity of COVID-19 in AAV Patients Treated With Rituximab, According to the Literature [35–40]*

Authors	Diagnosis, number of patients	COVID-19 severity Outcomes
Kant S., et al. [35]	1 – GPA	Mild disease Recovery
Schramm M., et al. [36]	1 – EGPA	Pneumonia, oxygen support (3 days) Recovery
Suárez-Díaz S., et al. [37]	1 – MPA	Mild disease Recovery
Fallet B., et al. [38]	1 – GPA	Bilateral pneumonia Recovery
Guilpain P., et al. [39]	1 – GPA	Bilateral pneumonia, mechanical ventilation Recovery
Loarce-Martos J., et al. [40]	3 – AAV	1/3 – death
Total	**8 – AAV**	**1/8 (12.5%) – death**

that according to our own data, 2 out of 3 patients with fatal outcomes were hospitalized late; and there is no information about the course of COVID-19 and the treatment for the third fatal case.

In the study by J. Loarce-Martos et al. [40], other IRDs were considered along with AAV; a total of 76 patients receiving rituximab therapy, with COVID-19 diagnosed in 13 (17.1%), including 3 cases of AAV, 5 cases of rheumatoid arthritis, 2 cases of Sjogren's syndrome and 2 cases of systemic lupus erythematosus. Eight of the COVID-19 patients (61.5%) were hospitalized, five of them required oxygen support or mechanical ventilation, and 3 (23%) cases were fatal (AAV, rheumatoid arthritis, systemic lupus erythematosus). E. Favalli et al. [41] also provided information about patients with IRDs (AAV were not included in the study) who received anti-B cell therapy with rituximab (n=5) or belimumab (n=18). In one case of systemic scleroderma, COVID-19 was diagnosed during treatment with rituximab; hospitalization and mechanical ventilation were required; the outcome was fatal.

Interestingly, two reports on the incidence of COVID-19 in AAV patients in the spring period of the pandemic [35, 42] were relatively favorable, which is

consistent with our data for this period (the incidence of COVID-19 until May 2020 was 3.5%). From April 8 to May 29, 2020, S. Banerjee et al. [42] conducted an online survey in 662 patients in North America with various forms of AV, including 460 AAV patients, of whom 225 received rituximab treatment (73% during pandemic). At the same time, in the general AV group, coronavirus infection was diagnosed in 1% of patients based on the results of a laboratory test for SARS-CoV-2 (n=5) or clinical signs of COVID-19 (n=2); the incidence of AAV in the patients was not given. It should be noted that 30% (20/66) of patients with signs of a respiratory infection were unable to get tested to confirm COVID-19. In a pooled study by 2 US and UK centers [35], from May 1 to July 23, 2020, a telephone survey was conducted in 206 AAV patients (mean age 64 years, 51% were women), of whom 158 received rituximab treatment, including 48.7% during the pandemic, which corresponds to the characteristics of own cohort (mean age 51 years, 61.7% were women, 47.6% were having rituximab treatment during the pandemic). 6% of patients had symptoms of COVID-19, 2% had contact with a person with COVID-19 disease. Of 10 patients tested by PCR (4 patients with asymptomatic COVID-19, 6 patients – with symptomatic), only 3 were diagnosed with SARS-CoV-2, of whom one was treated with rituximab; in that case, SARS-CoV-2 was diagnosed 24 hours after rituximab administration, with no serious manifestations of COVID-19; no hospitalization was required. Thus, in this study, the incidence of COVID-19 in AAV patients did not differ significantly from the general population (1.4% and 1.2%, respectively), and in the rituximab group it was 0.6%. At the same time, during this period, a relapse of AAV was diagnosed in 6% (12/206) of patients. According to the authors, the risk of relapse is likely to significantly outweigh the risk of COVID-19, therefore reduction of immunosuppressive therapy during the pandemic is not indicated.

The data accumulated in the literature suggest a possible protective effect of B cell depletion induced by rituximab therapy. It was noted that in severe COVID-19, immune disorders were accompanied by activation of the extrafollicular pathway of the B cell response, associated with the overproduction of pro-inflammatory mediators and autoantibodies [9, 10]. An experiment on animals found that antibodies to the SARS-CoV-2 spike protein could provoke severe acute lung injury, promoting the recruitment of monocytes/macrophages, stimulating the production of MCP-1 (monocyte chemoattractant protein-1), IL-8, and also suppressing repair mechanisms [43]. It was shown that the serum of patients with COVID-19 in vitro could induce netosis, which was considered as a marker of endothelitis and severe disease [44]. A possibility of cross-interaction of antibodies to the spike protein, the anti-SARS-CoV-2 nucleoprotein, with human antigens, including nuclear and mitochondrial antigens was demonstrated [45]. Several studies have shown that COVID-19 patients have a correlation between the titer of SARS-CoV-2 antibodies and the clinical severity of the disease [7, 8, 10, 11], with high titer of total SARS-CoV-2 antibodies associated with poor prognosis (p=0.004) [11]. Interestingly, in 10% of patients with severe COVID-19, high titers of autoantibodies to type 1 interferon (α2 and/or ω) are detected in the blood serum, which are not detected in mild or asymptomatic COVID-19 [13].

There are reports on a relatively mild course of COVID-19 in cases of agammaglobulinemia with a lack of B-cells in the circulation (a total of 4 patients) [46, 47], while in general variable immunodeficiency with B lymphocyte dysfunction (5 patients in total) [46, 48] COVID-19 caused severe disease, with mechanical ventilation required in 4 cases and with 1 death. In two large cohort studies [49, 50], there were no fatal outcomes in patients with multiple sclerosis who received anti-B cell therapy (Table 4). R. Montero-Escribano et al. [49] analyzed 60 cases of multiple sclerosis while on anti-B cell therapy with rituximab (54 patients) or ocrelizumab (6 patients) and detected COVID-19 in 15% of patients (13% having rituximab therapy, 33% – ocrelizumab therapy); all cases were relatively mild, without complications or the need for oxygen support. Family members were infected in 17% of patients treated with rituximab without signs of COVID-19. F. Safavi et al. [50] presented information obtained in 1/3 of the followed-up patients with multiple sclerosis who filled the questionnaire (no diagnostic nasopharyngeal swab tests were performed), of whom 285 were treated with rituximab and 12 were treated with ocrelizumab. COVID-19 cases were reported in rituximab group (7.3%), while none were reported in patients treated with ocrelizumab. Among COVID-19 patients the hospitalization rate was 9.5%; none of them required oxygen

Table 4. *Incidence and Severity of COVID-19 in AAV Patients with Multiple Sclerosis* Who *Received Anti-B Cell Therapy, According to the Literature [49,50]*

Authors	Number of patients	Anti-B cell therapy	Number of patients with COVID-19 (%)	COVID-19 severity Outcomes
P.Montero-Escribano, et al [49]	60 – multiple sclerosis	54 – rituximab, 6 – ocrelizumab	9/60 (15%) rituximab: 7/54 (13%), ocrelizumab: 2/6 (33%)	Not need an oxygen support or mechanical ventilation 100% – recovery
F.Safavi, et al [50]	297 – multiple sclerosis (35,6% who filled the questionnaire)	285 – rituximab, 12 – ocrelizumab	21/297 (7,1%) rituximab: 21/285 (61,8%), ocrelizumab: 0/12 (0%)	2/21 (9,5%) – hospitalization, not need an oxygen support or mechanical ventilation 100% – recovery
Total			**30/357 (8,4%) rituximab: 28/339 (8%) ocrelizumab: 2/18 (11%)**	**100% – recovery**

support or mechanical ventilation; all patients recovered. The authors concluded that in patients with multiple sclerosis, bDMARDs-induced B-cell depletion may be protective against severe COVID-19 disease, while not reducing the risk of infection.

When discussing severe disease and outcomes of COVID-19 in AAV patients and other IRDs, it should be emphasized that AAV, systemic lupus erythematosus and systemic scleroderma are characterized by severe multiple organ damage with high immunoinflammatory activity. In systemic lupus erythematosus and systemic scleroderma, as in EGPA, off-label use of rituximab generally indicates severe and/or refractory disease, intolerance and/or contraindications for standard treatment methods. Most patients receiving rituximab during the pandemic have signs of active disease or a high risk of relapse. In addition, we noted the highest mortality associated with COVID-19 in MPA, the AAV variant with the most unfavorable prognosis [2].

This may explain the differences in the outcomes of COVID-19 while on anti-B cell therapy in IRDs, including AAV, and in patients with mono-organ lesions in multiple sclerosis or in agammaglobulinemia with no B-cells in circulation. It should be noted that during treatment with mepolizumab, the incidence of COVID-19 according to our own results in EGPA patients (two of 6 cases) also exceeded the published incidence rates of COVID-19 in patients with bronchial asthma treated with mepolizumab (0–2.3%) [51, 52].

Taking into account largely synergistic mechanisms of AAV and severe COVID-19, the persistence of AAV activity can potentially contribute to the disease and severe course of COVID-19. A decrease in the incidence of COVID-19 according to our data in the group of patients who did not receive rituximab in the last 12 months before the pandemic, as compared to those who received such treatment after March 2020 (5.0% and 23.3%, respectively), can be associated with persistent remission of AAV. Thus, anti-B cell therapy, without reducing the risk of infection, seems to have a protective effect against severe/catastrophic COVID-19, which, however, may be insufficient in AAV patients and other IRDs with active disease and multiple organ damage.

The presented data suggest that the information about AAV patients as cases requiring monitoring at the initial stages of coronavirus infection, before signs of pneumonia appear, as well as about the reduction of the established threshold for hospitalization in AAV patients and COVID-19, including cases where clinical manifestations, oximetry parameters and basic laboratory biomarkers do not warrant inpatient treatment, be included in guidelines on COVID-19. In addition, it should be noted that the risk of life-threatening complications during the progression or relapse of AAV may exceed the risks associated with COVID-19, and in the context of the widespread focus healthcare institution of on COVID-19, the diagnosis and treatment of AAV patients may face insurmountable barriers.

Research transparency

The study was not sponsored. Authors are fully responsible forsubmitting the final version of the manuscript for press.

Declaration on financial and other relationships

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