DOI: 10.15825/1995-1191-2023-1-7-14

EXPERIENCE IN THE USE OF NEUTRALIZING MONOCLONAL ANTIBODIES IN KIDNEY TRANSPLANT RECIPIENTS WITH COVID-19

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Therapy with neutralizing monoclonal antibodies (mAbs) is particularly relevant during COVID-19 outbreaks in patients at high risk of severe disease, including kidney transplant recipients (KTRs). **Objective:** to evaluate the efficacy and safety of neutralizing mAbs in KTRs with mild to moderate COVID-19. **Materials and methods.** The retrospective study included 99 KTRs who received inpatient treatment for COVID-19 between September 1 and December 31, 2021. Patients were 52.0 ± 11.5 years old (M, 47.5%). Bamlanivimab/etesevimab combination drug at a dose of 700/1400 mg was used as mAbs. To evaluate the efficacy of mAbs therapy, two groups of patients were identified. Group 1 consisted of 33 KTRs who received mAbs as one of the therapy components, while group 2 consisted of 66 patients who received no mAbs. Discharge from the hospital or death was considered as the endpoint of follow-up. **Results.** In group 1, after the use of mAb, progression of pulmonary process was observed less frequently than in the control group with CT1-2 transformation to CT3-4 (9.1% vs. 30.3%, respectively, $p < 0.01$). Group 1 KTRs differed significantly from group 2 – lower need for ICU and ventilator care (6.1% vs. 27.3% and 3% vs. 19.8%, respectively). The groups were comparable by sex, age, body mass index, Charlson Comorbidity Index (CCI) and time after kidney transplant (KTx) at the onset of the disease and by ıaseline blood biochemistry parameter values at the time of hospitalization. Only C-reactive protein (CRP) and fibrinogen values were higher in the non-mAbs patients who were hospitalized later in the course of the disease (7.7 ± 3.2 days versus 4.6 ± 1.6 days in group 1, $p < 0.001$). The frequency of prescription of other therapies did not differ between the compared groups. Use of mAbs significantly reduced mortality from 19.7% in KTRs in group 2 to 3% in group 1 without adverse effect on graft function. **Conclusion.** The use of mAbs therapy in the early stages of COVID-19 in KTRs is safe, it prevents severe COVID-19, and reduces the incidence of adverse outcomes.

Keywords: kidney transplant recipients, COVID-19, neutralizing monoclonal antibodies.

The rapid spread of the novel coronavirus infection (COVID-19), which quickly reached pandemic proportions with severe consequences [1], prompted the international medical research community to conduct intensive research aimed at finding effective treatment approaches. Various options for therapeutic [2–6] and preventive measures against SARS-CoV-2 infection were developed and introduced into clinical practice within an unprecedentedly short period. Many of these measures, according to phase 3 clinical trials, have demonstrated high efficacy [7–10]. Given the clinical experience gained during the pandemic, which indicated frequent cases of severe disease, the therapeutic potential of neutralizing monoclonal antibodies (mAbs) – recombinant immunoglobulins derived from B cells of convalescent patients or humanized mice – is of great interest [11].

As early as November 2020, the first mAbs were approved by the US Food and Drug Administration for emergency use in patients with mild to moderate SARS-CoV-2 infection in the prehospital phase [12, 13]. To date, the number of mAbs approved for COVID-19 treatment and prevention is steadily rising, and more are under development or clinical trials [14]. The main mechanism of action of neutralizing mAbs of the IgG1 subtype is aimed at blockade of various epitopes of receptor-binding domain (RBD) of the spike (S) protein SARS-CoV-2, preventing its interaction with angiotensin-converting enzyme 2 (ACE2) on target cells and thus preventing

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virus penetration into them. For therapeutic purposes, mAbs are used both as monotherapy (regdanvimab, sotrovimab, etc.) and in combination forms (bamlanivimab/etesevimab, casirivimab/imdevimab, AZD8895/AZD1061, etc.).

Based on the experience with the use of mAbs in HIV patients, in which, similarly to COVID-19, there is a high frequency of virus mutations, it has been suggested that a combination of mAbs binding non-overlapping epitopes in the SARS-CoV-2 S protein reduces the likelihood of simultaneous failure of individual antibodies making such antibody cocktails. Thus, prophylactic and therapeutic use of casirivimab/imdevimab combination, tested on animals and confirmed in clinical practice, allows maintaining the neutralizing ability in many known mutations in the S protein, reducing the degree of viremia as well as the frequency and severity of pulmonary lesions compared to placebo [15–18]. In view of these data, the use of mAbs is particularly relevant for the treatment of patients at increased risk of severe disease with an adverse outcome, which include kidney transplant recipients [19–21].

The results of one of the first studies on the use of mAbs in 25 solid organ transplant recipients with COVID-19 showed that no deterioration was observed in any case and no inpatient treatment was required [22]. In another observation, after administration of sotrovimab, COVID-19 progression was observed in only 1 of 51 recipients; there were no deaths [23]. The use of bamlanivimab and casirivimab/imdevimab in patients after solid organ transplantation with mild to moderate SARS-CoV-2 infection also reduced the rate of hospitalizations compared to recipients who did not receive mAbs (15.3% vs 8.7%, respectively). However, the differences did not reach statistical significance. As in previous publications, no deaths were observed in the study group, unlike in the control group [24]. Taking into account the absence of similar studies in Russian practice to date, it is reasonable to evaluate the results of mAbs therapy in the Russian population of KTx recipients, which, thanks to the project (initiated by the Moscow Health Department) on the use of mAbs in the most vulnerable patient groups, has recently been introduced in the treatment regimens of SARS-CoV-2 infection in patients after KTx.

The aim of this study was to evaluate the efficacy and safety of mAbs for COVID-19 in KTRs.

MATERIALS AND METHODS

The retrospective study included 99 KTRs hospitalized for COVID-19 from September 1 to December 31, 2021 at the Department of Nephrology and Kidney Transplant Pathology, City Clinical Hospital No. 52, Moscow. The hospital was reassigned during the pandemic to provide medical care for COVID-19 patients. Patients' age was 52.0 ± 11.5 years (M – 47.5%), post KTx at the time of COVID-19 disease was 62.0 (28.0; 157.0) months. Distribution of patients according to the nature of the underlying disease that caused the end-stage chronic kidney disease (CKD) is shown in Table 1. SARS-CoV-2 infection was verified on the basis of RNA virus identification in nasopharyngeal and oropharyngeal smears by PCR and chest computed tomography (CT) data. Determination of IgM and IgG antibodies to new coronavirus antigens in the blood was an additional diagnostic method. Patients with severe COVID-19 (CT3–4) at the time of admission were not included in the study.

Table 1

Causes of end-stage CKD

Nosology	Number of patients	
	abs.	%
Chronic glomerulonephritis	48	48.5
Polycystic kidney disease	12	12.1
Systemic diseases	8	8.1
Diabetes mellitus (type 1/2)	7 (5/2)	7.1 (5.1/2.0)
Chronic pyelonephritis	6	6.1
Abnormal development of the urinary system	4	4.0
Kidney stones	3	3.0
High blood pressure	2	2.0
Thrombotic microangiopathy	1	1.0
Gout	1	1.0
Rheumatoid arthritis	1	1.0
Oncology	1	1.0
Nephropathy of unknown etiology	5	5.1
Total	99	100

In accordance with international guidelines [25] and Russian interim guidelines for the treatment of new coronavirus infection [26, 27], maintenance immunosuppression was modified in KTRs with a confirmed COVID-19: mycophenolic acid preparations were cancelled, calcineurin inhibitors were minimized, while increasing the prednisolone dose by 5–10 mg/day from the initial level. Target cyclosporine and tacrolimus levels were considered 30–50 ng/ml and 1.5–3 ng/ml, respectively.

COVID-19 complex therapy included antiviral drugs and anticoagulants.

In KTRs with early hospitalization ≤7 days from the onset of the disease, neutralizing mAbs (combination of bamlanivimab and etesevimab at a dose of 700/1400 mg) was added to the basic therapy. In cases of severe systemic inflammatory response, monoclonal antibodies to interleukin receptors (IL6, less often IL1β, IL17) or Janus kinase inhibitors and/or dexamethasone were used. Antibiotics, IV immunoglobulin, and plasma exchange/plasma infusions were administered as indicated.

To evaluate the effectiveness of mAbs therapy, two groups of patients were identified. Group 1 consisted of 33 KTRs who received mAbs as one of the first components of COVID-19 therapy, group 2 (control) included 66 patients for whom no antibody cocktail was used for

treatment. In the compared groups, such parameters as patients' age, time since KTx at the time of SARS-CoV-2 infection, time from COVID-19 onset to hospitalization, its duration, body mass index (BMI), CCI, character of lung lesion dynamics (according to CT data), initial laboratory indicators and frequency of other immunomodulatory therapy were evaluated. Renal graft function was determined by creatinine plasma levels.

The patient was discharged from the hospital or died at the end point of follow-up.

Statistical analysis

When distribution of continuous variables was normal, the mean values were calculated, and in cases of irregular distribution, the median was calculated. Comparative analysis of averages was performed using Student's t-test. Categorical variables were expressed as numbers or percentages and their differences were assessed by Pearson's χ^2 method. When comparing variables, differences were considered significant at $p < 0.05$. SPSS software package (version 22) was used for statistical data processing.

RESULTS

In 95 of 99 (96%) KTRs, COVID-19 was diagnosed by identifying SARS-CoV-2, and only in 4 patients was the diagnosis based on detection of IgM class of antibodies to the virus antigen with corresponding clinical and laboratory manifestations of the disease. All patients had a characteristic picture of viral pneumonia according to chest CT scans. The study and control groups were comparable by sex, age, BMI, CCI, and time after KTx by the onset of the disease (Table 2). However, KTRs in group 2 who were not treated with neutralizing antibodies were hospitalized later than group 1 patients.

Most of the biochemical blood parameters that were examined on admission to the hospital, including creatinine levels, indicating the state of transplanted kidney, did not differ in the compared groups. The exceptions were CRP and fibrinogen levels, which were significantly higher in group 2 patients (Table 3).

The course of the disease was more favorable in patients who received mAbs. They had a higher level of oxygen saturation and required oxygen support less frequently (Table 4). In this group, progression of pulmonary process with transformation of CT1–2 into CT3–4 was detected only in 9.1% of KTRs. In the group of patients who did not receive neutralizing antibodies, it was detected in almost one-third of cases ($p < 0.01$).

Mortality was 3% (1 of 33 KTRs) and 19.7% (13 of 66 patients) in group 1 and group 2, respectively, $p < 0.03$. The main cause of death was acute respiratory dis-

Table 2

Comparative characteristics of the two groups

Parameters	Group 1 (mAbs+), n = 33 (100%)	Group 2 (mAbs–), n = 66 (100%)	p
Gender (M), n	14 (42.4%)	38 (57.6%)	NS
Age, g; M ± SD	50.9 ± 10.9	52.5 ± 11.8	NS
BMI, M ± SD	25.5 ± 5.5	24.9 ± 5.9	NS
CCI, M ± SD	3.8 ± 1.7	4.2 ± 1.9	NS
Time since KTx, months, Me (25%; 75%).	43.0 (21.5; 120.5)	93.5 (36.8; 163.0)	NS
Duration of illness before hospitalization, days; M ± SD	4.6 ± 1.6	7.7 ± 3.2	0.001

Note: NS, no statistically significant difference ($p > 0.05$) between groups.

Table 3

Comparison of laboratory parameters in the analyzed groups

Parameters	Group 1 (mAbs+), n = 33	Group 2 (mAbs–), n = 66	p
Leukocytes, 10^9/L	5.9 ± 2.8	6.3 ± 2.9	NS
Lymphocytes, 10^9/L	1.0 ± 0.5	0.9 ± 0.5	NS
Platelets, 10^9/L	136.9 ± 44.4	129.5 ± 59.8	NS
Creatinine, μmol/L	162.0 ± 66.2	188.9 ± 86.4	NS
AST, IU/L	27.8 ± 12.4	29.9 ± 14.5	NS
ALT, IU/L	23.9 ± 15.7	20.9 ± 14.3	NS
LDH, IU/L	272.5 ± 102.4	274.6 ± 104.3	NS
Fibrinogen, g/L	5.0 ± 1.3	5.8 ± 1.6	0.01
D-dimer, ng/ml	269.5 (155.3; 470.0)	234.0 (129.0; 514.5)	NS
CRP, mg/L	18.2 (4.9; 46.5)	34.0 (10.4; 84.9)	0.02
Procalcitonin, ng/ml	0.2 (0.1; 0.4)	0.4 (0.3; 1.1)	NS

Note: NS, no statistically significant difference ($p > 0.05$) between groups.

tress syndrome (ARDS). At the same time, in group 1, ARDS developed in a patient with a history of severe complications, who had suffered acute humoral rejection less than a month before the onset of COVID-19. It was treated with anti-crisis therapy with plasmapheresis, immunoglobulin, and rituximab. In group 2, 6 of 12 KTRs had ARDS aggravated by pulmonary embolism (1 person), sepsis/multiple organ dysfunction syndrome (MODS) (2 persons), and hemorrhagic syndrome (3 persons); cardiac arrest was the cause of death in 1 case.

The study and control groups were comparable in terms of frequency of prescription of other immunobiological drugs (Table 5), which excluded the possibility of them having some influence on the outcome of mAbs treatment. Therapeutic plasma exchange (TPE) was used more frequently in patients who did not receive neutralizing antibodies.

Renal graft function in the compared groups did not differ both at the hospitalization stage and by the end of follow-up. Plasma creatinine levels decreased in all KTRs against the background of minimizing the dose of calcineurin inhibitors: in group 1 from 162.0 ± 66.2 μmol/L at hospital admission to 133.2 ± 46.0 μmol/L at the end of treatment ($p < 0.01$), and in group 2 from 188.9 ± 86.4 μmol/L to 151.1 ± 82.8 μmol/L, respectively ($p < 0.01$).

No serious adverse events were observed during therapy with neutralizing antibodies.

DISCUSSION

KTRs who receive continuous immunosuppressive therapy to maintain graft function are generally recognized to have a high rate of SARS-CoV-2 infection, a propensity for a more severe COVID-19 [23, 24, 29] and an inadequate response to vaccine prophylaxis even when using booster doses of vaccines [28–30]. The risk of COVID-19-associated death in this patient cohort doubles compared to patients without transplantation after adjustment for age, body mass index, and comorbidities [31]. In view of the above, drugs capable of inhibiting disease progression in its early stages, which include neutralizing mAbs, are considered a priority for the treatment of patients with a prognostically unfavorable outcome of the new coronavirus infection.

According to a number of studies, the use of mAbs in KTRs in the first 7 days of the disease reduces the viral load, the frequency of severe COVID-19 and, accordingly, the need for inpatient treatment [16, 32–35]. For instance, in a study by Wang A.X. et al. [36], mAbs therapy at the outpatient stage more than halved the need for hospitalization compared to the control group (14.5% vs. 30.8%, respectively). The authors compared the intensity of passive immunity after administration of bamlanivimab and casirivimab/imdevimab with the natural immunity that forms after COVID-19, based on quantitative analysis to assess the blocking activity of anti-SARS-CoV-2 class IgG. Almost all KTRs who received mAbs had a 90%–100% activity level for these antibodies early after administration and remained high for the next 3 months. In the comparison group, the vast majority of patients had low neutralizing antibody activity both early and in the long-term period after COVID-19 (less than 49%), which seems to be the reason for more frequent disease progression and the need for hospitalization in these patients [36].

In contrast to the above, in the present study, the results of mAbs were evaluated not in outpatients but in inpatients with KTRs. We, as well as other authors, con-

Table 4

Comparison of treatment outcomes in groups 1 and 2

Parameters	Group 1 (mAbs+), n = 33 (100%)	Group 2 (mAbs–), n = 66 (100%)	p
CT1–2 transformation to CT3–4	3 (9.1%)	20 (30.3%)	0.01
SpO_2, %; M ± SD	94.2 ± 6.0	87.1 ± 12.9	0.003
Need for oxygen support, n	6 (18.2%)	36 (54.5%)	0.001
Mechanical ventilation, n	1 (3%)	13 (19.8%)	0.025
Frequency of transfer to ICU, n	2 (6.1%)	18 (27.3%)	0.01
Length of hospital stay, n days; M ± SD	10.9 ± 6.1	14.8 ± 8.7	0.03

Table 5

Comparison of the frequency of prescription of immunomodulators and TPE

Therapy	Group 1 (mAbs+), n = 33 (100%)	Group 2 (mAbs–), n = 66 (100%)	p
IL-6 receptor blockers, n	30 (90.1%)	64 (97.0%)	NS
Dexamethasone, n	27 (81.8%)	55 (83.3%)	NS
Janus kinase inhibitors, n	20 (60.6%)	45 (68.2%)	NS
TPE, n	5 (15.2%)	27 (40.9%)	0.01

Note: NS, no statistically significant difference ($p > 0.05$) between groups.

firmed the positive effect of therapy with neutralizing antibodies against SARS-CoV-2 when administered early in the disease. In group 1 after bamlanivimab/etesevimab administration, an increase in the prevalence of pulmonary lesions, manifested by transformation of CTR1–2 into CTR3–4 (9.1% vs 30.3%, $p < 0.01$), was statistically significantly less frequent than in group 2 patients. KTRs in the study group were characterized by a higher level of oxygen saturation and correspondingly low need for oxygen support compared to the control group. As a consequence, group 1 less frequently required ICU treatment and ventilator use after mAbs administration than group 2 KTRs (6.1% vs. 27.3%, respectively, $p < 0.001$ and 3% vs. 19.8%, respectively, $p < 0.025$). At the same time, the compared groups were comparable by sex, age, BMI, CCI, and time since KTx by COVID-19 onset. They also did not differ in baseline blood biochemical parameters at the time of hospitalization. The exception was CRP and fibrinogen, which were higher in patients who received no mAbs therapy. This was most likely due to their later hospitalization from the onset of the first symptoms (7.7 ± 3.2 days versus 4.6 ± 1.6 days in Group 1, $p < 0.001$), which precluded the use of neutralizing antibodies in these KTRs in accordance with the selection criteria for treatment. This circumstance is an unconditional limitation in our study. Nevertheless, taking into account the comparability of the compared groups according to the main clinical parameters and the frequency of prescription of other immunomodulatory drugs, we believe that early use of antibody cocktails in KTRs with COVID-19 is effective. Therapy involving mAbs in these patients was associated with significantly lower mortality (3% in group 1 versus 19.7% in group 2). The findings are consistent with the results of a recently published meta-analysis that included 8 retrospective studies [37]. In a comparison of the mAbs+ ($n = 313$) and mAbs– ($n = 617$) patient groups, treatment with neutralizing antibodies was associated with both a reduced risk of severe disease (OR = 0.19, 95%CI: 0.08 to 0.42, $p < 0.0001$) and lower mortality from COVID-19 (OR = 0.16, 95%CI: 0.06 to 0.45, $p = 0.0005$).

CONCLUSION

Thus, neutralizing monoclonal antibody therapy administered early in COVID-19 demonstrates a favorable safety profile and high efficacy in KTRs. Early administration of mAbs prevents progression of pathological processes in the lungs, reducing the frequency of severe course and adverse outcomes. However, with accumulation of experience in the use of this group of drugs, the question about possible virus mutations against the background of treatment with neutralizing antibodies with the risk of disease recurrence is discussed more and more actively in the literature. The real effectiveness of reported prolonged action of some mAbs in preventing SARS-CoV-2 infection is also of interest. Answers to these and a number of other questions require further extensive research.

The authors declare no conflict of interest.

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The article was submitted to the journal on 08.09.2022