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CLINICAL COURSE AND APPROACHES TO THERAPY IN KIDNEY TRANSPLANT RECIPIENTS WITH THE NOVEL COVID-19 DISEASE

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The COVID-19 pandemic has had global consequences due to the wide spread of the infection in the world, lack of currently proven effective therapy, resistance to treatment in a significant proportion of those affected and, as a result, high mortality, especially among high-risk groups. Kidney transplant recipients with coronavirus-induced pneumonia are among the most problematic categories of patients. This patient cohort experiences a severe form of the disease, taking into account a combination of risk factors, such as long-term immunosuppression, comorbid background of patients, and consequences of chronic kidney disease. Difficulties in the management of recipients with COVID-19 are also down to the limitation of the use of drugs due to adverse drug-drug interactions. **Objective:** to analyze the course of COVID-19 disease in organ recipients, to assess the factors influencing the prognosis of the disease, and to optimize approaches to treatment of these patients. **Materials and methods.** During the period from April 15, 2020 to June 15, 2020, 68 people (38 men and 30 women) were hospitalized at our clinic. Their average age was 49.7 ± 9.2 years (22 to 70 years). COVID-19 diagnosis was verified by PCR. Multispiral computed tomography (MSCT) scans showed that in all cases, there were characteristic lung lesions of varying degrees of severity. **Results.** Out of the 68 people treated, 61 (89.8%) were discharged with recovery, 7 patients died. So, the mortality rate was 10.2%. This indicator did not depend on age and gender. First of all, mortality depended on the severity of lung lesions: at CT4 it was 43% (3/7), at CT3 – 11.1% (4/36), there were no deaths in patients with CT2. There was a 100% mortality among patients who received mechanical ventilation. Severity of graft dysfunction was also an important prognostic factor: with moderate dysfunction, this indicator was 8% (5/63), while with severe dysfunction it was 40% (2 out of 5). Besides, a more severe prognosis was observed in patients in the early post-transplant period: 5 patients out of the 7 who died of COVID-19 (71%) lived for less than a year after kidney allotransplantation (ATP). Mortality in this category of patients was 24%, while in the period from 1 to 5 years, this indicator was 13.6%; no deaths were recorded among patients with a period of over 5 years after ATP. All patients received antibacterial (levofloxacin or azithromycin) and antiviral (hydroxychloroquine) therapy. In all cases, the baseline immunosuppressive therapy (IST) was changed, including withdrawal of mycophenolic acid preparations, minimization of the calcineurin inhibitor dose (target concentration 1.5–3 ng/mL for tacrolimus and 30–50 ng/mL for cyclosporine), and increase in prednisolone dose by 5 mg relative to the current one. About 78% of cases received pathogenetic therapy with anti-interleukin monoclonal antibodies (mainly tocilizumab). These patients also received intravenous immunoglobulin at 10 g average dose. In severe COVID-19 accompanied in by clinical and laboratory signs of thrombotic microangiopathy 22% of cases, plasma exchange sessions and/or infusion of fresh frozen plasma and dose adjustment of low molecular weight heparins were performed. **Conclusion.** COVID-19-induced pneumonia in kidney transplant recipients is characterized by a high risk of progressive lung damage and respiratory failure. Mortality in COVID-19 is independent of gender and age, but correlates with post-transplantation period, severity of pneumonia, and severity of graft dysfunction. The need for mechanical ventilation is associated with an extremely unfavorable prognosis of the disease.

Keywords: COVID-19, pneumonia, kidney allotransplantation, kidney graft.

INTRODUCTION

The new coronavirus infection of 2019 COVID-19 (SARS-CoV-2) has been declared a pandemic [2] and has had global consequences due to the widespread infection worldwide, lack of currently proven effective therapy, and resistance to treatment among a large proportion of the patients and, as a result, high mortality rate worldwide. The most serious threat from COVID-19 is in the high-risk patients. One of the most problematic categories of patients is renal transplant recipients with

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coronavirus pneumonia. It is assumed that immunosuppression worsens the course of the disease, exacerbating the severity of the process, and it is characterized by rapid progression of viral infection to pneumonia in organ transplant recipients. Optimal therapeutic approaches have not yet been developed. This remains a pressing issue and the subject of discussions by various specialists. The severity of prognosis of the disease in this patient cohort also depends on pronounced comorbid background (diabetes mellitus, arterial hypertension, cardiovascular disease, consequences of chronic kidney disease and pathogenetic therapy) in the vast majority of kidney transplant recipients. Difficulties in the management of transplant recipients with COVID-19 are also due to the limitation of the use of drugs as a result of adverse drug-drug interactions.

Currently, large-scale studies on the follow-up for this group of patients are lacking and are limited to registration of a series of cases at various clinics. According to the largest series reported to date in Europe and the United States, mortality ranged from 23% to 28% [1, 5–8], versus 5% mortality in the general population of patients infected with COVID-19 [5], and higher than the COVID-19 mortality among hospitalized severe non-transplant patients, which is 21% [9]. Interestingly, none of the series reported acute rejection and graft loss as a result of reduced immunosuppression [1, 5–8]. Various immunosuppressive therapy management strategies, based on stepwise reduction of immunosuppression depending on the severity of the disease, have been presented in reports.

The main pathogenetic mechanism of severe lung injury and development of a "cytokine storm" is attributed to a maladaptive immune response, which is particularly important in immunocompromised transplant patients. Treatment for COVID-19 is based on antiviral drugs that inhibit SARS-CoV-2 proliferation and on immunomodulatory drugs that inhibit the "cytokine storm" causing acute respiratory distress syndrome (ARDS) and life-threatening respiratory failure [3, 4]. Tocilizumab is currently the most popular treatment used to counteract hyperinflationary syndrome causing respiratory compromise [1, 10]. Also, vascular endothelial cell injury, which may be the cause of thrombotic microangiopathies (TMA), has recently received increasing attention in pathogenesis. In this regard, there are more and more publications on the use of plasma exchange, plasma infusions and eculizumab in the treatment of severe cases of COVID-19 complicated by TMA [11–14].

Our study was aimed at studying the characteristics of inpatient management of kidney transplant recipients with pneumonia caused by SARS-CoV-2. In this study, we included hospitalized renal transplant recipients with verified new coronavirus infection, pneumonia (PCR, MSCT). The aim of the study was to analyze the course of COVID-19 in organ transplant recipients, to assess the factors affecting the prognosis of the disease, and to optimize treatment approaches for these patients.

MATERIALS AND METHODS

From April 15, 2020 to June 15, 2020, 68 people (38 men and 30 women) were treated in our hospital. The mean age was 49.7 ± 9.2 years (22 to 70 years).

The post-kidney ATP period varied widely (from 1.5 months to 24 years) and averaged 62.6 ± 72.7 months. In 21 people (30.9%), the post-kidney ATP period did not exceed 1 year (13 of them had just a 3-month period). It ranged from 1 to 5 years, 5 to 10 years and over 10 years for 22 patients (32%), 14 patients (20.5%) and 11 patients (16%) respectively.

The majority of patients, 63 of 68 (92.6%), had moderate graft dysfunction not exceeding 200 μmol/L at the time of hospitalization. Dysfunction was severe (more than 400 μmol/L) in 5 (7.4%) cases and required renal replacement therapy. Plasma creatinine levels averaged 168.6 ± 92.7 μmol/L.

Immunosuppressive therapy (IST) at the time of hospitalization included prednisolone, mycophenolic acid preparations and calcineurin inhibitors (tacrolimus 91%, cyclosporine 9%). COVID-19 diagnosis was verified by PCR. MSCT revealed characteristic lung lesions of varying severity in all cases: CT grade 2 was diagnosed in 25 patients (37%); CT grade 3 in 36 patients (53%), and CT grade 4 in 7 patients (10%). Patients with CT grades 3 and 4 had progressive respiratory insufficiency and needed oxygen support.

The duration of hospitalization varied from 8 to 31 days, averaging 14.1 ± 5.9 days.

RESULTS

Of the 68 people, 61 (89.8%) recovered and were discharged, 7 patients died. The mortality rate was 10.2%. This indicator did not depend on age and sex. First of all, mortality depended on the severity of pulmonary involvement: 43% (3/7) CT4 and 11.1% (4/36) CT3 patients died. There were no deaths among CT2 patients (Fig. 1). Among the patients on mechanical ventilation, the mortality rate was 100%.

Severity of graft dysfunction was also an important prognostic factor: 8% (5/63) in moderate dysfunction against 40% (2/5) in severe dysfunction. During hospitalization, 20 patients with moderate dysfunction developed acute renal injury, followed by restoration of graft function to baseline in 15 cases out of 20, while 5 cases of progressive dysfunction within the framework of multiple organ failure ended in death. The average creatinine level at the time of hospitalization was 222.3 ± 118.4 μmol/L (median 185 μmol/L), which turned out to be significantly higher than in those who recovered (401.3 ± 291.8 μmol/L (median 322 μmol/L) (Fig. 2)

In addition, a more severe prognosis was observed in patients in the early post-kidney ATP period: in 5 out

of 7 patients who died from COVID-19 (71%), the post-kidney ATP period was less than a year. So, the mortality rate in patients in the early stages after kidney ATP (less than 12 months) was 24% (of the total number of treated patients). In the period from 1 to 5 years, mortality was 13.6%. There were no deaths among patients whose post-kidney ATP period was more than 5 years (Fig. 3). However, for more than 10 years, there were more often severe bacterial complications after COVID-19, which is probably due to long-term immunosuppression.

Based on the experience of our center, we developed an internal protocol for the treatment of kidney transplant recipients with COVID-19.

In all cases, the baseline immunosuppressive therapy (IST) was changed, including withdrawal of mycophenolic acid preparations, minimization of the dose of calcineurin inhibitors (target concentration of 1.5–3 ng/mL for tacrolimus and 30–50 ng/mL for cyclosporine), and increasing prednisolone dose by 5 mg relative to the current dosage.

During hospitalization, it was noteworthy that 30% of patients showed high tacrolimus levels against a background of usual dosages of the drug. At the same time, only half of them had diarrhea. In the remaining 15%, increased tacrolimus levels did not correlate with diarrheal syndrome. In 12% of patients, temporary withdrawal of calcineurin inhibitors was required (for 2–3 days).

All patients were prescribed antibiotic therapy: initial therapy with levofloxacin or azithromycin, with subsequent adjustment depending on the effectiveness of therapy and data from microbiological studies.

In all cases, antiviral therapy was also given: hydroxychloroquine in doses adjusted for renal function. In patients with a cardiac history and existing cardiac arrhythmias, hydroxychloroquine was administered without a loading dose.

We did not use ritonavir/lopinavir in renal transplant recipients due to adverse drug interactions with the main IST drugs (tacrolimus, cyclosporine).

Pathogenetic therapy with anti-interleukin monoclonal antibodies was administered in 53 patients (78%). Of these, 38 patients (72%) received tocilizumab, 8 (15%) received sarilumab, 5 (9%) were administered with canakinumab, while 2 (4%) got netakimab. At the same time, the tocilizumab dose was reduced taking into account the ongoing baseline immunosuppressive therapy. In most cases (79.5%), the dose did not exceed 200 mg. In 14 patients (20.5%), the dose ranged from 240 to 600 mg. The choice of a drug, dose and additional administration was determined based on the severity of the clinical, laboratory and X-ray picture.

Also, intravenous immunoglobulin (average dose 10 g) was administered in all patients in order to correct their immunological status.

In a number of patients (22%), mostly with severe COVID-19, there were clinical and laboratory signs of

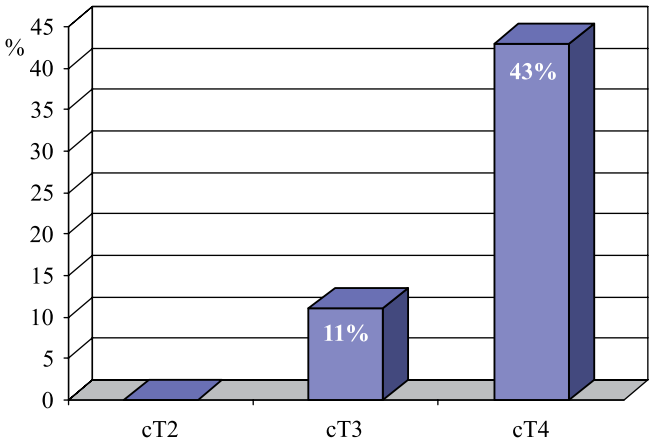

Fig. 1. Mortality depending on the severity of pulmonary involvement

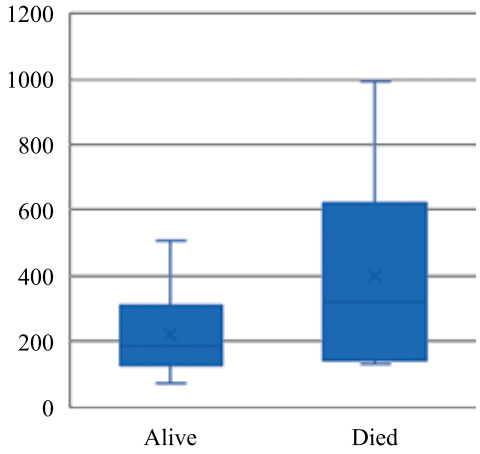

Fig. 2. Creatinine levels in surviving and deceased COVID-19 patients

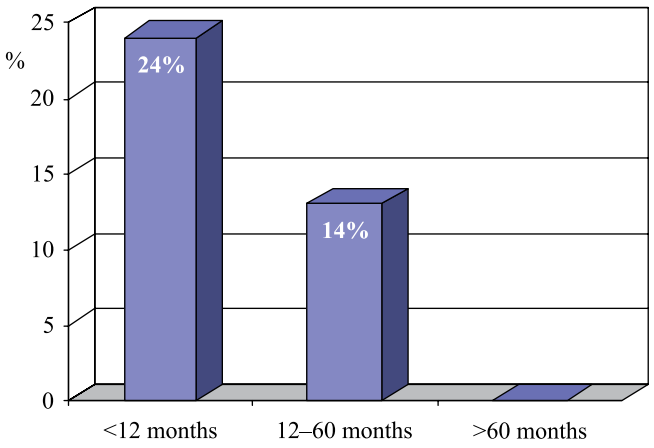

Fig. 3 Mortality depending on the post-kidney ATP period

thrombotic microangiopathy (anemia, thrombocytopenia, increased lactate dehydrogenase (LDH), D-dimer, organ ischemic disorders). Therefore, sessions of plasma exchange and/or FFP infusion were carried out as a pathogenetic therapy. The dose of low molecular weight heparin (LMWHs) was also adjusted. Against this back-

ground, regression of secondary TMA manifestations was observed in the majority of patients.

CONCLUSION

COVID-19-induced pneumonia is characterized by a high risk of progressive lung injury and respiratory failure. Mortality in COVID-19 does not depend on sex and age. However, it correlates with the post-transplant period, severity of pneumonia and severity of graft dysfunction. Transfer to mechanical ventilation is associated with an extremely unfavorable prognosis of the disease. The following categories of patients presented the greatest difficulty for management: patients in the early period after kidney ATP and patients with severe graft dysfunction due to a high risk of death, as well as patients with a post-transplantation period of more than 10 years due to a high risk of complications on the background of prolonged immunosuppressive therapy and severe comorbidity.

According to our experience in managing this patient cohort, COVID-19 therapy includes mandatory minimization of IST, and in moderate to severe course – administration of anti-interleukin drugs and immunoglobulin. If signs of secondary TMA appear, the use of plasma exchange and/or FFP infusion becomes effective. As in the general population, the use of LMWHs is recommended in renal transplant recipients. Thus, COVID-19 in renal transplant recipients is characterized by a greater severity of the infectious and inflammatory process against the background of immunosuppressive therapy compared to the general population of patients, frequent renal transplant dysfunction, and unstable levels of baseline immunosuppressants. Taking this into account, it is not advisable to use drugs that have pronounced interaction with baseline immunosuppressants (calcineurin inhibitors).

At present, the question on approaches to COVID-19 treatment in renal transplant recipients remains open and requires further study.

The authors declare no conflict of interest.

REFERENCES

1. How should I manage immunosuppression in a kidney transplant patient with COVID-19? An ERA-EDTA DESCARTES expert opinion. *Nephrol Dial Transplant*. 2020; 35: 899–904. doi: 10.1093/ndt/gfaa130 Advance Access publication 22 May 2020.
2. *Cucinotta D, Vanelli M*. WHO declares COVID-19 a pandemic. *Acta Biomed*. 2020; 91: 157–160.
3. *Barlow A, Landolf KM, Barlow B et al.* Review of emerging pharmacotherapy for the treatment of coronavirus disease 2019. *Pharmacotherapy*. 2020. doi: 10.1002/phar.2398.
4. *Sanders JM, Monogue ML, Jodlowski TZ et al.* Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. *JAMA*. 2020. doi: 10.1001/jama.2020.6019.
5. *Akalin E, Azzi Y, Bartash R et al.* Covid-19 and kidney transplantation. *N Engl J Med*. 2020. doi: 10.1056/NEJMc2011117.
6. *Pereira MR, Mohan S, Cohen DJ et al.* COVID-19 in-solid organ transplant recipients: initial report from the US epicenter. *Am J Transplant*. 2020. doi: 10.1111/ajt.15941.
7. *Fernandez-Ruiz M, Andres A, Loinaz C et al.* COVID-19 in solid organ transplant recipients: a single-center case series from Spain. *Am J Transplant*. 2020. doi: 10.1111/ajt.15929.
8. *Alberici FD, Delbarba E, Manenti C et al.* A single center observational study of the clinical characteristics and short-term outcome of 20 kidneytransplant patients admitted for SARS-CoV2 pneumonia. *Kidney Int*. 2020. doi: 10.1016/j.kint.2020.04.002.
9. *Richardson S, Hirsch JS, Narasimhan M et al.* Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA*. 2020. doi: 10.1001/jama.2020.6775.
10. *Zhang C, Wu Z, Li JW et al.* The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist tocilizumab may be the key to reduce the mortality. *Int J Antimicrob Agents*. 2020. doi: 10.1016/j.ijantimicag.2020.105954.
11. Application of plasma exchange in association with higher dose CVVH in Cytokine Storm Complicating COVID-19. *Journal of the Formosan Medical Association.* 2020; 119: 1116e1118.
12. *Risitano AM, Mastellos DC, Huber-Lang M, Yancopoulou D, Garlanda C, Ciceri F, Lambris JD.* Complement as a target in COVID-19? *Nat Rev Immunol*. 2020 Jun; 20 (6): 343–344.
13. *Diurno F, Numis FG, Porta G*. Eculizumab treatment in patients with COVID-19: preliminary results from real life ASL Napoli 2 Nord experience. *European Review for Medical and Pharmacological Sciences*. 2020; 24: 4040–4047.
14. *Keith P, Day M, Perkins L, Moyer L, Hewitt K, Wells A.* A novel treatment approach to the novel coronavirus: an argument for the use of therapeutic plasma exchange for fulminant COVID-19. *Critical Care*. 2020; 24: 128. https://doi.org/10.1186/s13054-020-2836-4.

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