The Course of SARS-CoV-2 in a Patient After a Recent Kidney Transplant: A Literature Review on COVID-19 Therapy

Karolina Kędzierska-Kapuza*, Dorota Zielińska, Marta Matejak-Górska, and Marek Durlik

Department of Gastroenterological Surgery and Transplantology, Center of Postgraduate Medical Education in Warsaw, Warsaw, Poland

ABSTRACT

Background. Kidney transplant recipients are at high risk of severe complications and death due to coronavirus disease 2019 (COVID-19).

Methods. The first part of the article describes a case of COVID-19 in our patient after a recent kidney transplant. The second part of the article presents the outcome of literature search from multiple resources from April 2020 until March 2021. Abstracts were screened, followed by full-text review with data extraction. Part 2 discusses current treatment options of COVID-19, and part 3 refers to this treatment application in patients after solid organ transplant.

Results. We have summarized 45 studies from China, France, Italy, Spain, the United Kingdom, and the United States. Mortality rates from published studies were variable. Based on early data from Spain, 42% of patients who developed COVID-19 within 60 days of transplant died. According to results of the European Renal Association COVID-19 Database collaboration group, the 28-day COVID-19−related mortality is 21.3% for kidney transplant recipients, which is still markedly higher than what is observed in other populations. Acute kidney injury was common, and mycophenolate mofetil and mammalian target of rapamycin were discontinued in most patients.

Conclusions. Effective therapy has been sought since the outbreak of the pandemic, and at the same time intensive work has been done to produce a vaccine that could effectively protect against the disease. Summing up the efforts of numerous groups of researchers from around the world that have been continued since the beginning of 2020, we may assume the following:
(1) we still do not have causal drugs that would reduce severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication and allow its complete elimination, but antispike monoclonal antibodies against SARS-CoV-2 seem to be very promising, and (2) the withdrawal of antiproliferative and antimetabolic drugs and the continuation of steroids and calcineurin inhibitors is now a commonly accepted approach in patients after organ transplant.

FROM March 4, 2020 until March 8, 2021, the total number of coronavirus disease 2019 (COVID-19) cases in Poland reached over 1.8 million (1,801,083). According to the Polish Ministry of Health, over 45,000 infected patients died (45,317) and most of them had concurrent diseases [1]. The mortality rate in the Polish population is ~2.5%.

In 2020 a significant drop in solid organ transplantation occurred in Poland and worldwide. In 2020 in Poland, 1180 organ transplants were performed compared with 1473 in 2019 (−20%). The number of kidney transplants (KTxs) dropped by 21% (717 vs 907 in 2019), pancreas + KTxs dropped by 88% (4 vs 34 in 2019), liver transplants dropped by 20.7% (262 vs 330 in 2019), and lung transplants dropped by 10.5% (51 vs 57 in 2019); only the heart transplants number remained the same (145 vs 145).

The number of patients on waiting lists at the end of 2020 was 1806 compared with 1947 in the 2019 Polish Transplantation Coordinating Center (Poltransplant) database [2]. This change

*Address correspondence to Karolina Kędzierska-Kapuza, MD, PhD, Department of Gastroenterological Surgery and Transplantology, Center of Postgraduate Medical Education, 137 Wołoska St, Warsaw 02-507, Poland. Tel: 22 508 12 17; Fax: 22 508 12 66. E-mail: karolina.kedzierska@gmail.com

was probably caused by high mortality of patients on the waiting list because of COVID-19 or the lack of current tests qualifying for transplantation and the inability to perform them because of the situation of hospitals and outpatient clinics related to COVID-19. This resulted in patients dropping out of the active waiting list for transplantation (no data available).

There are no current official and published data on the mortality of patients after solid organ transplants in Poland. These data are still being collected in the Poltransplant database and may be published at the end of 2021 in the annual newsletter. According to results of the European Renal Association COVID-19 Database collaboration group, including the data of 22 patients from Poland, the 28-day COVID-19−related mortality is 21.3% for KTx recipients and 25.0% for patients on dialysis, which is markedly higher than what is observed in other populations [3].

MATERIALS AND METHODS

The first part of this article describes a case of COVID-19 in our patient after a recent KTx. The second part of the article presents the outcome of a literature search from multiple resources from April 2020 until March 2021. Abstracts were screened, followed by full-text review with data extraction. Part 2 discusses current treatment options of COVID-19 and refers to this treatment application in patients after solid organ transplant. We have summarized 45 studies from China, France, Italy, Spain, the United Kingdom, and the United States.

A 54-year-old patient with autosomal dominant polycystic kidney disease after left-sided nephrectomy had been on dialysis therapy through an arteriovenous fistula since 2017. The patient had a history of hypertension and a neurosurgery because of hemorrhage following a ruptured brain aneurysm, which was sealed with a vascular clamp in 2001. He received a transplant from a deceased donor with a simultaneous implantation of a JJ stent into the transplanted kidney (October 8, 2020).

The donor (aged 57 years; male) died of an intracranial trauma. His last creatinine record was 0.58 mg/dL (on the day of harvesting). He was obese (114 kg), his height was 180 cm, and his body mass index (calculated as weight in kilograms divided by height in meters squared) was 35.1. He had been receiving low doses of levonor (norepinephrine) at 0.07 μg/kg/min. The bacterial cultures were negative, and the diuresis was 140 mL/hour (2300 mL daily). The donor was COVID-19 negative and stayed in the "clean" part of the intensive care unit (ICU). The recommendations of the Polish Transplant Society issued in April 2020 prohibit organ donation from COVID-19−positive patients (Table 1). The harvested kidney was perfused on a pump. Cold ischemia time was 32 hours 20 minutes, warm ischemia time was 20 minutes, with 5 HLA mismatches. The selection of a recipient with low-HLA antigen compatibility (2 patients) was because patients with higher scores did not consent to undergo a surgery because of the epidemic situation, 2 persons had an infection, and 1 person was waiting for a transplant from a living consanguineous donor. Before the transplant the patient underwent a protocol ruling out a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and a complete epidemiologic history. He had a nasopharyngeal swab negative for SARS-CoV-2 based on polymerase chain reaction (PCR). The chest radiograph excluded pneumonia and other pulmonary pathologies. Cold ischemia time was prolonged because it was impossible to harvest lymph nodes for typing in the donor's hospital (the surgical team was quarantined), and it took a long time to obtain the recipient's PCR SARS-CoV-2 result. On October 9, 2020, the

Table 1. Parameters of the Kidney Transplant Recipient and Donor During the Qualification for the Procedure

Parameters	Donor	Recipient
Sex	Male	Male
Age, y	57	54
BMI	35.1	21.8
Cause of death/renal failure	Intracranial trauma	Adult polycystic kidney disease
Creatinine level, mg/dL	0.58	11
Pressor drugs, μg/kg/min	Levonor 0.07	NA
Hourly/daily diuresis, mL	140/2300	0/0
HLA	A 2, lack of antigene (−), B 18,51, DR 11,13	A 1, 29 B 44, 71 DR 7, 15
CMV IgG/IgM	Positive/negative	Positive/negative
PRA	NA	PRA maximum 7 PRA last 0

BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CMV, cytomegalovirus; NA, not applicable; PRA, panel-reactive antibody.

provincial governor decided to change the whole Hospital of the Ministry of the Interior and Administration into a tertiary hospital that provided services only to patients with COVID-19. Therefore, the patient was transferred to the Nephrology Department of the Infant Jesus Teaching Hospital, University Clinical Center on day 8 after transplant.

During the hospitalization in the Department of Gastroenterological Surgery and Transplantology of the Central Clinical Hospital of the Ministry of the Interior and Administration, the patient was diagnosed as having acute tubular necrosis (biopsy was not performed) and delayed graft function; the patient required dialyses until discharge. During hospitalization in the Nephrology Department of University Clinical Center, the patient was also diagnosed as having a SARS-CoV-2 infection. The patient was transferred back to the Department of Gastroenterological Surgery and Transplantology of the Central Clinical Hospital of the Ministry of the Interior and Administration on October 30, 2020, (day 23 after transplant) with the suspicion of a hematoma in the area of the transplanted kidney concomitant with SARS-CoV-2 infection. On admission the patient underwent chest computed tomography, which revealed lesions typical of COVID-19: all lobes of both lungs presented irregular areas of reduced transparency, that is, ground-glass opacity located mainly in peripheral regions. Inferiorly and dorsally, the lesions were continuous with more consolidated streaky opacities, which were estimated to affect approximately 40% of the volume of both lungs. The patient's Modified Early Warning Score (MEWS) was 1 point. MEWS assesses the following: age, 54 years; O_2 saturation, 95%; oxygen use, no; respiratory rate, 12/min; heart rate, 76/min; systolic blood pressure, 130 mm Hg; body temperature, 37.1°C; consciousness, yes (Fig 1).

Because of a tender, palpable fluid collection around the postoperative wound, 2 incisions were performed in the area, and a partially hemolyzed hematoma (clots and liquid matter) was evacuated. Mycophenolate mofetil (MMF) was discontinued, and the dose of tacrolimus was reduced to obtain the level of 8.6 ng/mL. The following treatment was introduced: dexamethasone 1 × 6 mg intravenously and broad-spectrum antibiotics piperacillin/tazobactam 3 × 4.5g intravenously. Subsequently, because of the cultures sampled from the collection were positive for *Enterococcus faecium* high-level aminoglycoside resistance plus vancomycin-resistant enterococci, it was changed into vancomycin 2 × 1 g intravenously with the monitoring of vancomycin level in blood serum. Moreover, the patient was given low-molecular-weight heparin as prophylaxis,
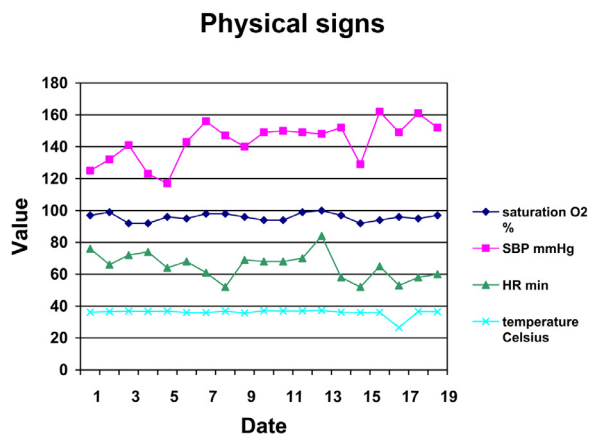
Physical signs

Fig 1. Patient's vital signs from the time of COVID-19 diagnosis until discharge (10/30/2020-11/18/2020). COVID-19, coronavirus disease 2019; HR, heart rate; SBP, systolic blood pressure.

valganciclovir, and trimethoprim/sulfamethoxazole. Hypertension was controlled with 1 drug, amlodipine. The patient was not given remdesivir or tocilizumab because tocilizumab is recommended only in individuals with severe course and cytokine storm phase with marked elevation of inflammatory cytokines and other markers (C-reactive protein, procalcitonin, interleukin (IL) 6, D-dimers, lactate dehydrogenase, ferritin, troponin, N-terminal pro-B-type natriuretic peptide). According to our clinical and laboratory assessment (Table 2, Fig 1) the patient's condition was fair, and he did not fall into cytokine storm phase of the COVID-19 disease. His newly diagnosed drug-induced diabetes was treated with insulin followed by sulfonylurea derivatives 1 × 1 orally. During the whole hospitalization in the Department, the patient was respiratorily and cardiovascularly stable; he received passive oxygen therapy via a nasal cannula. He was discharged on day 40 after transplant with nadir creatinine at 0.94 mg/dL (Table 2).

Whether the patient underwent an organ transplant or not, the course of SARS-CoV-2 infection is relatively similar with clinical and therapeutic implications as presented in Fig 2 modified from Siddiqi et al [4].

1. Inhibiting SARS-CoV-2 entry into cells

a. Baricitinib, a janus-activated kinase inhibitor, has 2 targets: it inhibits SARS-CoV-2 entry into the cell and the cytokine storm phase. Adaptive COVID-19 Treatment 2 study [5], which included the cotreatment with remdesivir or remdesivir alone was conducted in over 1000 patients. Convalescence was obtained 1 day earlier in case of the baricitinib arm. However, complete results of the study are still unknown. A small randomized study (Italy, 24 participants) demonstrated the effectiveness of baricitinib and lopinavir/ritonavir [6].

b. Nafamostat mesylate: SARS-CoV-2 enters the lung cells via binding to angiotensin-converting enzyme 2 and the activation of transmembrane serine protease 2. Therefore, it may be the target of antiviral treatment. Transmembrane serine protease 2 inhibitors prevented SARS-CoV-2 entry into cells in vitro. Nafamostat, being the strongest of those inhibitors, is used as an antithrombotic and antipancreatitis agent. It

was approved in the treatment of cystic fibrosis because its mucolytic properties may prevent the deterioration of pulmonary function via inhibiting respiratory infections. The Randomized Clinical Trial in COVID-19 Patients to Assess the Efficacy of the Transmembrane Protease Serine 2 Inhibitor Nafamostat study is going to test a hypothesis that nafamostat is useful in COVID-19−related pulmonary involvement because COVID-19 is associated with the activation of the coagulation cascade, pulmonary embolism, and bacterial superinfections [7].

c. Convalescent plasma: plasma collected from successfully cured patients provides neutralizing antibodies against SARS-CoV-2. The effectiveness was proved and the therapy was accepted by the U.S. Food and Drug Administration (FDA) (August 2020) [8]. Over 35,000 patients were examined with no significant complications reported (also by the Polish Society of Epidemiologists and Contagious Disease Specialists). The research is scarce. A Chinese observational study from April 2020 included 6 patients in whom the use of plasma was beneficial [9]. Another randomized study from China was discontinued. The authors included 103 patients, but a positive effect of plasma was not confirmed in severely ill patients [10]. A randomized Dutch study was conducted in July 2020. It included 86 individuals. However, it was discontinued because prior to plasma administration the patients had their own neutralizing antibodies [11]. The latest study (PLACID) showed no beneficial effects associated with the use of convalescent plasma. It was a "real world" study that also qualified individuals with concomitant diseases. A very interesting editorial comment on the publication drew attention to the fact that the procoagulatory activity of the serum removed the beneficial influence of antibodies neutralizing the virus [12]. Another randomized placebo-controlled study published in November 2020 in the *New England Journal of Medicine* demonstrated that convalescent plasma did not protect patients with COVID-19 and those with COVID-19−related pneumonia from death. Furthermore, it did not alleviate the course of the disease [13].

d. Monoclonal antibodies (bamlanivimab/etesevimab and casirivimab/imdevimab) are potent antispike neutralizing monoclonal antibodies that bind with high affinity to the receptor-binding domain of SARS-CoV-2. The BLAZE-1 and BLAZE-4 trials compared bamlanivimab and bamlanivimab/etesevimab with placebo in outpatients with mild to moderate COVID-19 infection. Bamlanivimab's main clinical endpoint was the percentage of patients who were hospitalized by day 29 of follow-up. The rate of hospitalization for patients who received bamlanivimab was 1.6% (5 of 309) compared with 6.3% (9 of 143) who received placebo [14,15]. On February 9, 2021, the FDA authorized monoclonal antibodies for the treatment of COVID-19 (Eli Lilly) [16]. In the statement issued by the FDA we learned that, "Based on the review of the data from the Phase 2/3 BLAZE-1 trial (NCT04427501), [. . .] and Phase 2 BLAZE-4 trial (NCT04634409), [. . .] it is reasonable to believe that bamlanivimab and etesevimab administered together may be effective for the treatment of mild to moderate COVID-19 in

Table 2. Biochemical Parameters in the Described Patient

Parameters	10/8/20	10/15/20	10/30/20	11/5/20	11/17/20
CRP, mg/L	1.4	41.9	46.3	20	5.4
PCT, ng/mL	————-	————-	0.07	0.1	0.12
IL-6, pg/mL	————-	————-	————-	118	6.3
D-dimers, μg/L feu	————-	————-	————	1193	4310
Creatinine, mg/dL	11	7.41	1.29	1.5	1.07
eGFR, mL/min	5	7	58	49	76
WBC, 10^3/uL	10.47	7.69	4.35	7.41	7.11
Lymphocytes, 10^3/uL	0.95	5.2	0.37	0.56	0.7
Neutrophils, 10^3/uL	8.96	0.92	3.64	6.53	5.41
Tacrolimus, ng/mL	—————	9.8	17.6	8.6	3.8
SARS-CoV-2 IgG, AU/mL	—————	————	————	————	58.1 (positive $\geq$ 15)
SARS-COV-2 IgM, AU/mL	—————	—————	————	————-	21.9 (positive $\geq$ 1.1)

CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; IL, interleukin; PCT, procalcitonin; SARS-COV-2, severe acute respiratory syndrome coronavirus 2; WBC, white blood cell.

adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization, and that, when used under the conditions described in this authorization, the known and potential benefits of bamlanivimab and etesevimab administered together outweigh the known and potential risks of such products" [17]. Likewise, casirivimab/imdevimab are monoclonal antibodies that work in a similar fashion to neutralize the spike protein of COVID-19. R10933-10987-COV-2067 was a randomized, double-blinded, placebo-controlled clinical trial studying casirivimab and
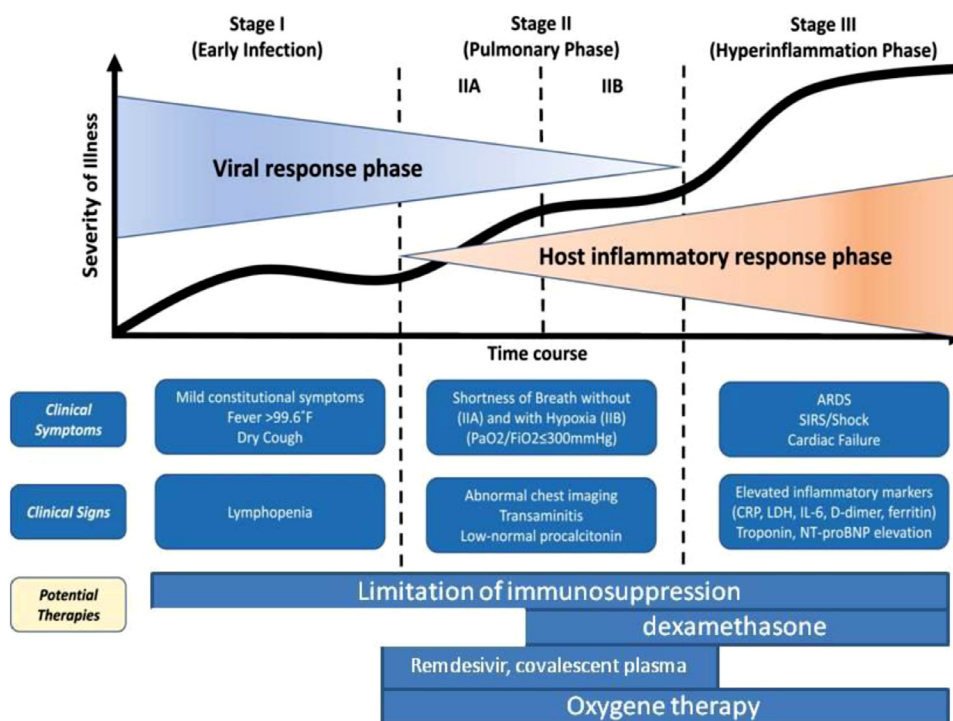

Fig 2. Classification of COVID-19 disease states and potential therapeutic targets. The figure shows 3 escalating stages of COVID-19 disease progression, with accompanying symptoms, and potential phase-specific drugs (modified from Siddiqi et al [4]). ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; IL, interleukin; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SIRS, systemic inflammatory response syndrome.

imdevimab for the treatment of adult outpatients with mild to moderate COVID-19. Casirivimab/imdevimab's main clinical endpoint was the percentage of patients who were hospitalized by day 29 of follow-up. The rate of hospitalization for patients who received casirivimab/imdevimab was 2% (8 of 434) compared with 4% (10 of 231) who received placebo. Based on those results the FDA issued on November 21, 2020 an emergency use authorization (EUA) for casirivimab and imdevimab to be administered together for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age or older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing and who are at high risk for progressing to severe COVID-19 [18,19].

On March 5, 2021, the European Medicines Agency announced that a drug from the United States company Eli Lilly, a combination of 2 preparations, bamlanivimab and etesevimab and based on monoclonal antibody therapy, can be used to treat COVID-19 in Europe [20].

2. Inhibiting viral replication

Remdesivir interferes with viral RNA polymerases to inhibit viral replication. It was previously used in the treatment of Ebola virus. Remdesivir demonstrated its effectiveness as early as at the beginning of the pandemic. It was also the first drug officially registered by the FDA in May 2020 in the treatment of COVID-19 [21]. Its effectiveness was confirmed in the first studies from March 2020 by Holshue et al [22] and April 2020 by Grein et al [23]. Adaptive COVID-19 Treatment Trial 1 is the largest study conducted so far. It included 541 patients in the drug arm and 521 in the placebo arm. It demonstrated that remdesivir shortened the time necessary to regain health [24].

A Polish STARSTer study (Flisiak et al) is waiting for a publication in the *Lancet*.

Not all randomized studies showed the effectiveness of this drug. In a study from April 2020 Yeming Wang reported the shorter duration of clinical manifestations in 158 patients using the drug compared with 79 in the placebo group [25].

The largest randomized study, World Health Organization Solidarity trial results, was published in October 2020. It included 405 hospitals and 11,266 patients with 2750 treated with remdesivir. It demonstrated a negligible or no effect on the mortality or the introduction of ventilation [26]. The drug is expensive and, currently, it is unavailable because of delivery problems.

1. Inhibiting COVID-19 cytokine storm

a. Tocilizumab was first recommended by Chinese researchers in March 2020 [27]. A study by Rosas et al [28] included 425 patients who were randomized (2:1). Tocilizumab improved neither the clinical status not mortality rates. Its potential benefits were noted regarding shortening the duration of hospital stay and the hospitalization in the ICU. A Polish study by Tomasiewicz was conducted in a small group of 28 individuals. The results were very good, with the rapid improvement of the clinical status of the patients [29].

b. Dexamethasone has multidirectional properties, such as the suppression of proinflammatory cytokine formation. According to recommendations it was effective, which was shown in the recovery study involving its use for 10 days at a dose of 6 mg intravenously in patients requiring oxygen therapy and mechanical ventilation [30].

c. Heparin's role is to lower blood clotting in severe cases of COVID-19. The effectiveness was confirmed in patients with COVID-19 [31,32].

d. Adalimumab (a tumor necrosis factor α inhibitor) lowers the production of tumor necrosis factor α molecule during cytokine storm phase. It has been used for many years in rheumatoid arthritis. It diminished the progression to severe or critical state or death in patients with COVID-19 [33].

e. Fluvoxamine, a selective serotonin reuptake inhibitor, decreases the inflammatory response during cytokine storm through the S1R-IRE1 (a chaperone protein) pathway. A randomized study included 152 patients. The status of 6 patients deteriorated in the placebo group, whereas no patient's status deteriorated in the selective serotonin reuptake inhibitor group [34].

DISCUSSION

The population of patients posttransplant is specific because the clinical course of COVID-19 is much more severe in transplant recipients and patients on hemodialysis (HD) than in the remaining patients with COVID-19. An observational study by Arenas et al conducted in spring 2020 showed that the incidence of COVID-19 was 3.2% in KTx recipients and 3.6% in patients on HD. The results of reverse transcriptase−PCR tests were positive in 34 patients (26 KTx, 8 HD) and negative in 27 patients (14 KTx, 13 HD). The comparison between COVID-19−positive and COVID-19−negative patients showed the following results: a higher occurrence of typical manifestations of a viral infection (cough, dyspnea, weakness, muscle soreness), pneumonia (88.2% vs 14.3%, respectively), high lactate dehydrogenase and C-reactive protein, the necessity of hospitalization (100% vs 63%, respectively), the use of noninvasive mechanical ventilation (36% vs 11%, respectively), and high mortality (38% vs 0%, $P < .001$). The death rates were 42% in the KTx group and 37.5% in the HD group [35].

Similar observations were made by researchers from Paris, who emphasized high COVID-19−related mortality in kidney recipients. All-population mortality in the group of recipients was 1%, but in those infected with SARS-CoV-2 it was 16 of 66 (24%), including 11 of 15 (73%) in the ICU. Acute kidney injury developed in 28 (42%) kidney recipients, with 7 requiring renal replacement therapy [36]. Elias et al proposed the discontinuation of treatment with antiproliferative drugs (38 of 61, 62%). Antimetabolite drugs were discontinued in all ICU patients. Tacrolimus (4-6 ng/mL) or cyclosporine (400-600 ng/mL) and prednisone were continued. Calcineurin inhibitor (CNI) was discontinued in only 2 recipients. Immunosuppression was completely withdrawn in only 2 severely ill patients [36]. A description of 4 cases of early COVID-19 after transplant from Poland revealed a relatively low symptomatic clinical course and positive outcome of this disease [37]. All of them received induction therapy with anti-IL-2 monoclonal antibodies, but no one received antiviral therapy (remdesivir) or anti−SARS-CoV-2 monoclonal antibodies. One of 4 patients

died of other posttransplant complications leading to septic shock, which were not directly related to COVID−19 infection.

The patient described in our report did not receive induction therapy with anti−IL-2 monoclonal antibodies. The use of induction therapy shows great differences between countries and transplant centers. The decision to use induction and its type should be individualized based on the risk-benefit profile of the transplant recipient. The recipient was assessed as a patient of low immunologic risk (White, panel-reactive antibody = 0, first transplant, blood group compatibility, recipient with an average age of 54 years, ie, neither <30 nor >60 years old). Such a recipient, in accordance with the guidelines of the Polish Society of Transplantation, has no indications for induction with monoclonal antibodies [38]. According to Opelz et al, induction treatment should only be given to high-risk recipients; low-risk recipients do not show additional benefits [39]. The present patient was asymptomatic. His MEWS score was 1 point. His chest computed tomography revealed a reduced transparency, that is, ground-glass opacity located mainly in peripheral regions. Inferiorly and dorsally, the lesions were continuous with more consolidated streaky opacities, which were estimated to affect approximately 40% of the volume of both lungs. We lowered the dose of tacrolimus administered to the patient. The drug level was monitored until 8.6 ng/mL was reached. At discharge the level was 3.8 ng/mL. The definitive dose of tacrolimus was increased to 2 × 1.5 mg.

Other authors described a patient with a recent KTx and a severe course of COVID-19. Drug interactions with azithromycin and a high level of tacrolimus contributed to the development of acute kidney injury in the transplanted organ. Immunosuppressive drugs were completely withdrawn when the patient was staying in the ICU. As a result, the patient developed acute graft rejection (confirmed with biopsy). Donor-specific antibodies were present in the serum. The authors demonstrated that SARS-CoV-2 infection in the early period after KTx may have a negative effect on the function of the transplanted organ. Patients consenting to an organ transplant should be aware of dangers associated with SARS-CoV-2 infection [40].

Some authors suggested that immunosuppression reduction did not seem necessary in all kidney recipients with active COVID-19 because transplant recipients with COVID-19 produced the immune response to SARS-CoV-2 [41]. Our patient also produced a normal level of anti−SARS-CoV-2 antibodies, both IgG and IgM.

Similar conclusions regarding the lack of effect of combination immunosuppression on mortality were reached by Kates et al [42]. In their multicenter study of American organ recipients with COVID-19, they assessed the risk factors and 28-day mortality in hospitalized patients. They retrieved the data of 482 organ recipients with COVID-19 from over 50 transplantology centers. The data included 318 (66%) kidney or kidney and pancreas recipients, 73 (15.1%) liver recipients, 57 (11.8%) heart recipients, and 30 (6.2%) lung recipients. Furthermore, no differences were reported regarding mortality depending on the number of immunosuppressive drugs (1, 2, or 3) the patients received. The authors concluded that age and concomitant

diseases were associated with COVID-19 mortality in transplant recipients, whereas the intensity of immunosuppression had no significant effect on their survival.

In a prospective study Rinaldi et al demonstrated that all kinds of superinfections (cytomegalovirus, bacterial, fungal) occurred more commonly in transplant recipients (24 individuals) than in the general population (861 patients) (50% vs 15.5%, P < .001). Immunosuppression was modified in all recipients. Mammalian target of rapamycin inhibitor was discontinued in all patients, MMF in all but 1, and CNI in 19 of 21 recipients [43].

No experience or randomized studies are available regarding convalescent plasma administration to patients posttransplant. Anecdotal evidence was provided for 3 cases (3 patients after KTx) in which the administration of convalescent plasma led to a positive effect [44] and for a 70-year-old Chinese patient after KTx [45]. In our case it was decided not to administer plasma because the patient produced anti−SARS-CoV-2 antibodies and we were anxious about possible procoagulatory effect of plasma.

Antispike monoclonal antibodies against SARS-CoV-2 seem to be a very promising therapy, especially in immunocompromised patients. Treatment with anti−SARS-CoV-2 monoclonal antibodies recently approved by the FDA has several limitations. The FDA EUAs allow for the use of bamlanivimab plus etesevimab or casirivimab plus imdevimab for the treatment of mild to moderate COVID-19 in nonhospitalized adults and children and who are at high risk for progressing to severe COVID-19 and/or hospitalization. High-risk criteria specified in the EUA are body mass index ≥35, chronic kidney disease, diabetes mellitus, immunocompromising condition, currently receiving immunosuppressive treatment, aged ≥65 years or aged ≥55 years, cardiovascular disease, hypertension, chronic obstructive pulmonary disease, or another chronic respiratory disease. In the studies described previously [14,15], the number of participants was small, and only a limited number of clinical events (eg, hospitalizations or emergency department visits) were reported. Given the low number of clinical events, it is difficult to draw definitive conclusions about the efficacy of these anti−SARS-CoV-2 antibodies. Additional clinical trial data are needed to provide further evidence on the safety and efficacy of these agents and to identify the populations (possibly patients on dialysis with end-stage renal disease, patients after organ or bone marrow transplant) in which the potential benefit will be the greatest.

Some questions still remain unanswered: When should antimetabolite or antiproliferative drugs be reintroduced in convalescents? What CNI dose should be used in such patients? Is 2-drug (eg, steroids and CNI) therapy sufficient? We hope answers to those questions will be available in the literature soon.

Proposed treatment regimen in patients after KTx

1. Reduced immunosuppressive treatment

- discontinue MMF, discontinue mammalian target of rapamycin,
- a recent transplant: dexamethasone maximum 12 mg for 10 days, tacrolimus at a dose adjusted to the level of the drug (6-8 ng/mL),

- a nonrecent transplant (eg, a KTx a year or longer before): dexamethasone 1×6 mg for 10 days, tacrolimus at a dose adjusted to the level of the drug (6-8 ng/mL), 6 mg of dexamethasone = 40 mg of prednisolone,
- enoxaparin sodium at a dose of 0.4-0.6 mL subcutaneously or nadroparin calcium 0.3-0.5 mL subcutaneously; to be controlled, if D-dimers increase the patient should receive a therapeutic dose,
- antibiotic therapy (in case of a high risk of a superinfection): ceftriaxone 1×2 g intravenously once a day and azithromycin 500 mg orally for 6 days,
- good hydration of the patient, minimum 3000-3500 mL orally and/or intravenously (in total),
- the administration of remdesivir is justified only during the viremic phase (the first week after the infection was confirmed during the viral replication phase): the dose of 200 mg on day 1, then 100 mg for 4 days; if glomerular filtration rate <30 mL/min/1.73 m^2 it should be discontinued,
- tocilizumab in individuals with an increased level of IL-6 (to be administered in the severe course, cytokine storm phase): intravenously 8 mg/kg, administration via an intravenous pump for 1 hour; the second dose may be administered during 2 days; the patient should be observed, administration only after ruling out an active bacterial and viral infection, IL-6 should be monitored (a characteristic increase even >600 ng/mL receptor blockade),
- plasma: no data in patients with KTx, "an act of despair" in patients with chronic diseases, for example, chronic kidney disease, without anti−SARS-CoV-2 antibodies produced,
- antispike monoclonal antibodies against SARS-CoV-2 seem to be very promising therapy, need further evaluation in clinical trials.

Additionally it is possible to do the following:

- Measure the level of vitamin 25(OH) D3 (25-hydroxyvitamin D) or 1.25 OH D3 (1,25-dihydroxyvitamin D), vitamin D3 supplementation or alfacalcidol 1×1.0 ug orally,
- vitamin C 2×1 g intravenously,
- zinc 70 mg daily in divided doses, orally.

CONCLUSIONS

Effective therapy has been sought since the outbreak of the pandemic, and at the same time intensive work has been underway to produce a vaccine that could effectively protect against the disease. Summing up the efforts of numerous groups of researchers from around the world that have been continued since the beginning of 2020, we may assume the following:

(1) We still do not have causal drugs that would reduce SARS-CoV-2 replication and allow its complete elimination, but antispike monoclonal antibodies against SARS-CoV-2 seem to be very promising, and (2) the withdrawal of antiproliferative and antimetabolic drugs and the continuation of steroids and CNIs is now a commonly accepted approach in patients after an organ transplant.

REFERENCES

[1] Statista. Coronavirus (COVID-19) deaths worldwide per one million population as of March 23, 2021, by country. https://www.statista.com/statistics/1104709/coronavirus-deaths-worldwide-per-million-inhabitants/. [accessed 08.03.2021].

[2] Poltransplant. Statistics 2020, http://www.poltransplant.org.pl/statystyka_2020.html. 2020. [accessed 08.03.2021].

[3] Hilbrands LB, Duivenvoorden R, Vart P, Franssen CFM, Hemmelder MH, Jager KJ, et al. COVID-19-related mortality in kidney transplant and dialysis patients: results of the ERACODA collaboration. Nephrol Dial Transplant 2020;35:1973–83. doi: 10.1093/ndt/gfaa261.

[4] Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. J Heart Lung Transplant 2020;39:405–7. doi: 10.1016/j.healun.2020.03.012.

[5] Adaptive COVID-19 Treatment Trial 2 ClinicalTrials.gov Identifier: NCT04401579.

[6] Cantini F, Niccoli L, Matarrese D, Nicastri E, Stobbione P, Goletti D. Baricitinib therapy in COVID-19: a pilot study on safety and clinical impact. J Infect 2020;81:318–56.

[7] Efficacy of Nafamostat in COVID-19 Patients (RACONA Study) (RACONA) ClinicalTrials.gov Identifier: NCT04352400.

[8] US Food and Drug Administration. FDA issues emergency use authorization for convalescent plasma as potential promising COVID-19 treatment, another achievement in administration's fight against pandemic. https://www.fda.gov/news-events/press-announcements/fda-issues-emergency-use-authorization-convalescent-plasma-potential-promising-covid-19-treatment. [accessed 26.03.2021].

[9] Ye M, Fu D, Ren Y, Wang F, Wang D, Zhang F, et al. Treatment with convalescent plasma for COVID-19 patients in Wuhan. China. J Med Virol 2020;92:1890–901. doi: 10.1002/jmv.25882.

[10] Li L, Zhang W, Hu Y, Tong X, Zheng S, Yang J, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. JAMA 2020;324:460–70 Erratum in: JAMA 2020;324:519.

[11] Gharbharan A, Jordans CCE, Geurtesvankessel C, den Hollander JG, Faiz Karim, Mollema FPM, et al. Convalescent plasma for COVID-19. A randomized clinical trial [e-pub ahead of print]. medRxiv doi:10.1101/2020.07.01.20139857, [accessed 22.02.2021].

[12] Pathak EB. Convalescent plasma is ineffective for COVID-19. BMJ 2020;371:m4072.

[13] Simonovich VA, Burgos Pratx LD, Scibona P, Beruto MV, Vallone MG, Vázquez C, et al. A randomized trial of convalescent plasma in COVID-19 severe pneumonia. N Engl J Med 2021;384:619–29. doi: 10.1056/NEJMoa 2031304.

[14] Chen P, Nirula A, Heller B, Gottlieb RL, Boscia J, Morris J, et al. SARS-CoV-2 Neutralizing antibody LY-CoV555 in outpatients with COVID-19. N Engl J Med 2021;384:229–37. doi: 10.1056/NEJMoa2029849.

[15] Gottlieb RL, Nirula A, Chen P, et al. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: a randomized clinical trial. JAMA 2021;325:632–44. doi: 10.1001/jama.2021.0202.

[16] US Food and Drug Administration. Coronavirus (COVID-19) update: FDA authorizes monoclonal antibodies for treatment of COVID-19. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibodies-treatment-covid-19-0. [accessed 08.03.2021].

[17] US Food and Drug Administration. Emergency use authorization 094. https://www.fda.gov/media/145801/download. [accessed 08.03.2021].

[18] US Food and Drug Administration. Coronavirus (COVID-19) update: FDA authorizes monoclonal antibodies for treatment of COVID-19. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibodies-treatment-covid-19. [accessed 15.04.2021].

[19] US Food and Drug Administration. Regeneron Pharmaceuticals, Inc, https://www.fda.gov/media/143891/download. 2020. [accessed 08.03.2021].

[20] European Medicines Agency. EMA issues advice on use of antibody combination (bamlanivimab /etesevimab). https://www.ema.europa.eu/en/news/ema-issues-advice-use-antibody-combination-bamlanivimab-etesevimab. [accessed 08.03.2021].

[21] Lamb YN. Remdesivir: first approval. Drugs 2020;80:1355–63. doi: 10.1056/NEJMoa2031304.

[22] Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med 2020;382:929–36.

[23] Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate use of remdesivir for patients with severe COVID-19. N Engl J Med 2020;382:2327–36. doi: 10.1056/NEJMoa2001191.

[24] Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of COVID-19 - final report. N Engl J Med 2020;383:1813–26. doi: 10.1056/NEJMoa2007016.

[25] Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020;395:1569–78. doi: 10.1056/NEJMoa2007764.

[26] Pan H, Peto R, Karim QA, Alejandria M, Henao-Restrepo AM, García CH, et al. Repurposed antiviral drugs for Covid-19 - interim WHO solidarity trial results. N Engl J Med 2021;384:497–511.

[27] National Health and Family Planning Commission of China (NHPFC). Chinese clinical guidance for COVID-19 pneumonia diagnosis and treatment. 7th ed 2020.

[28] Rosas I, Bräu I, Waters M, Go RC, Hunter BD, Bhagani S, et al. Tocilizumab in hospitalized patients with COVID-19 pneumonia [e-pub ahead of print]. medRxiv doi:10.1101/2020.08.27.20183442, [accessed 22.02.2021].

[29] Tomasiewicz K, Piekarska A, Stempkowska-Rejek J, Serafińska S, Gawkowska A, Parczewski M, et al. Tocilizumab for patients with severe COVID-19: a retrospective, multi-center study. Expert Rev Anti Infect Ther 2021;19:93–100. doi: 10.1080/14787210.2020.1800453.

[30] Nuffield Department of Medicine Centre for Tropical Medicine and Global Health. No clinical benefit from use of lopinavir-ritonavir in hospitalised COVID-19 patients studied in RECOVERY. https://www.tropicalmedicine.ox.ac.uk/news/no-clinical-benefit-from-use-of-lopinavir-ritonavir-in-hospitalised-covid-19-patients-studied-in-recovery. [accessed 17.01.2021].

[31] Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020;18:844–7. doi: 10.1111/jth.14768.

[32] Yin S, Huang M, Li D, Tang N: Difference of coagulation features between severe pneumonia induced by SARS-CoV2 and non-SARS-CoV2 [e-pub ahead of print]. J Thromb Thrombolysis doi:10.1007/s11239-020-02105-8, [accessed 17.01.2021].

[33] Gianfrancesco M. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis 2020;79:859–66.

[34] Lenze EJ, Mattar C, Zorumski CF, Stevens A, Schweiger J, Nicol GE, et al. Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19: a randomized clinical trial. JAMA 2020;324:2292–300. doi: 10.1001/jama.2020.22760.

[35] Arenas MD, Crespo M, Pérez-Sáez MJ, Collado S, Redondo-Pachón D, Llinàs-Mallol L, et al. Clinical profiles in renal patients with COVID-19. J Clin Med 2020;9:E2665. doi: 10.3390/jcm9082665.

[36] Elias M, Pievani D, Randoux C, Louis K, Denis B, Delion A, et al. COVID-19 infection in kidney transplant recipients: disease incidence and clinical outcomes. J Am Soc Nephrol 2020;31:2413–23.

[37] Kolonko A, Dudzicz S, Wiecek A, Król R. COVID-19 infection in solid organ transplant recipients: a single-center experience with patients immediately after transplantation. Transpl Infect Dis 2021;23:e13381. doi: 10.1111/tid.13381.

[38] Durlik M, Przybyłowski P. Recommendations for immunosuppressive treatment after vascularized organ transplantation. Warsaw, Poland: Polish Transplant Society; 2018.

[39] Opelz G, Unterrainer C, Süsal C, Döhler B. Efficacy and safety of antibody induction therapy in the current era of kidney transplantation. Nephrol Dial Transplant 2016;31:1730–8. doi: 10.1093/ndt/gfw086.

[40] Del Bello A, Marion O, Sallusto F, Delas A, Esposito L, Doumerc N, et al. Kidney transplantation during the COVID-19 pandemic: potential long-term consequences of an early post-transplant infection [e-pub ahead of print]. Transpl Infect Dis doi:10.1111/tid.13446, [accessed 17.01.2021].

[41] Hartzell S, Bin S, Benedetti C, Haverly M, Gallon L, Zaza G, et al. Evidence of potent humoral immune activity in COVID19-infected kidney transplant recipients. Am J Transplant 2020;20:3149–61. doi: 10.1111/ajt.16261.

[42] Kates OS, Haydel BM, Florman SS, Rana MM, Chaudhry ZS, Ramesh MS, et al. COVID-19 in solid organ transplant: a multi-center cohort study [e-pub ahead of print]. Clin Infect Dis doi:10.1093/CID/CIAA1097, [accessed 17.01.2021].

[43] Rinaldi M, Bartoletti M, Bussini L, Pancaldi L, Pascale R, Comai G, et al. COVID-19 in solid organ transplant recipients: no difference in survival compared to general population. Transpl Infect Dis 2021;23:e13421.

[44] Naeem S, Gohh R, Bayliss G, Cosgrove C, Farmakiotis D, Merhi B, et al. Successful recovery from COVID-19 in three kidney transplant recipients who received convalescent plasma therapy. Transpl Infect Dis 2021;23:e13451. doi: 10.1111/tid.13451.

[45] Jiang J, Miao Y, Zhao Y, Lu X, Zhou P, Zhou X, et al. Convalescent plasma therapy: helpful treatment of COVID-19 in a kidney transplant recipient presenting with severe clinical manifestations and complex complications. Clin Transplant 2020;34:e14025. doi: 10.1111/ctr.14025s.