The course of SARS-CoV-2 in a patient after a recent kidney transplantation – a literature review on COVID-19 therapy

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Running title: SARS-CoV-2 therapy in a kidney transplant patient.

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

Methods: First part of the paper describes a case of COVID-19 in our patient after recent kidney transplantation. Second and third part of the paper is an outcome of literature search from multiple resources from April 2020 till March 2021. Abstracts were screened, followed by full-text review with data extraction. Part two discusses current treatment options of COVID-19 and part three refers to this treatment application in patients after solid organ transplantation.

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

Conclusion: 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:

-We still do not have causal drugs that would reduce SARS-CoV-2 replication and allow its complete elimination, but anti-spike monoclonal antibodies against SARS-CoV-2 seem to be very promising.

-The withdrawal of antiproliferative and antimetabolic drugs and the continuation of steroids and CNI inhibitors is nowadays a commonly accepted approach in patients after an organ transplantation.

Key words: COVID-19, antiviral treatment, infection and infectious agents: viral, delayed graft function (DGF), drug interaction, immunosuppressant, tacrolimus, anti-spike monoclonal antibodies,

Introduction

Since March 4, 2020, untill March 8, 2021 the total number of cases in Poland reached over 1.8 million (1.801.083). According to the Polish Ministry of Health, over 45 thousand infected patients died (45.317), and most of them had been suffering from concurrent diseases [i]. Mortality rate in Polish population is ~ 2,5%.

In 2020 significant drop in solid organ transplantation occured in Poland and worldwide. In 2020 in Poland a total number of 1180 organ transplantation was performed compared to 1473 in 2019 (-20%). Number of kidney transplantation dropped by 21 % (717 vs 907 in 2019), pancreas +kidney tx dropped by 88% (4 vs 34 in 2019) liver tx dropped by 20,7% (262 vs 330 in 2019), lung tx dropped by 10,5% (51 vs 57 in 2019) only heart tx number remained the same 145 vs 145.

The number of patiens on waiting list at the end of 2020 was 1806 compared to 1947 in 2019 Polish Transplantation Coordinating Center (Poltransplant) database [ii]. It was probably caused by high mortality of patiens on waiting list due to COVID-19 or the lack of current tests qualifying for transplantation and the inability to perform them, due to the situation of hospitals/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. This data is still being collected in Poltransplant database and may be published at the end of 2021 in the annual newsletter. According to results of the ERACODA collaboration group including data of 22 pts from Poland the 28-day COVID-19-related mortality is 21.3% in kidney transplant and 25.0% in dialysis patients, which is markedly higher than what is observed in other populations [iii].

Materials and Methods

First part of the paper describes a case of COVID-19 in our patient after recent kidney transplantation. Second part of the paper is an outcome of literature search from multiple resources from April 2020 till March 2021. Abstracts were screened, followed by full-text review with data extraction. Part two discusses current treatment options of COVID-19 and refers to this treatment application in patients

after solid organ transplantation. We have summarized 45 studies from China, France, Italy, Spain, United Kingdom, and United States.

A 54-year-old patient with autosomal dominant polycystic kidney disease (ADPKD) after left-sided nephrectomy had been on dialysis therapy through an arteriovenous fistula since 2017. The patient had a history of hypertension, a neurosurgery due to hemorrhage following a ruptured brain aneurysm, which was sealed with a vascular clamp in 2001. He received a transplant (Tx) from a deceased donor with a simultaneous implantation of a JJ stent into the transplanted kidney (08.10.2020).

The donor, 57, male, died due to 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, BMI 35.1. He had been receiving low doses of levonor at 0.07 ug/kg/min. The cultures were negative and the diuresis was 140 ml/hour (2300 ml daily). Donor was COVID-19 negative, staying in the „clean" part of ICU. The recommendations of the Polish Transplant Society issued in April 2020 prohibit organ donation from Covid-19 + patients. (Table 1). The harvested kidney was perfused on a pump. CIT was 32 hrs 20 min, WIT 20 min, with 5 HLA mismatches. The selection of a recipient with low-HLA compatibility (2 pts) was due to the fact that 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. Prior to the transplantation the patient underwent a protocol ruling out a SARS-CoV-2 infection, and a complete epidemiological history. He had a negative nasopharyngeal swab based on PCR. The chest radiograph excluded pneumonia and other pulmonary pathologies. Cold ischemia time (CIT) was prolonged, as 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 PCR SARS-CoV-2 result of the recipient. On 9th October 2020 the provincial governor decided to change the whole Hospital of the Ministry of the Interior and Administration into a tertiary hospital which provided services only to COVID-19 patients. Therefore, the patient was transferred to the Nephrology Department of the Infant Jesus Teaching Hospital, University Clinical Center on Day 8 after the transplantation.

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 with acute tubular necrosis (ATN; a biopsy was not performed) and delayed graft function (DGF) – the patient required dialyses until discharge. During hospitalization in the Nephrology Department of University Clinical Center the patient was also diagnosed with 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 30th October 2020 (day 23 after transplantation) 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 CT which revealed lesions typical of COVID-19: all lobes of both lungs presented irregular areas of reduced transparency, i.e. "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 approx. 40% of the volume of both lungs. The patient's MEWS score was 1 point. MEWS score assesses: age=54, O2 saturation=95%, oxygen use-no, respiratory rate-12/min, heart rate 76/min, systolic blood pressure 130 mmHg, body temperature 37,1, consciousness- yes. Figure 2.

Due to a tender, palpable fluid collection around the postoperative wound, two incisions were performed in the area, and a partially hemolyzed hematoma (clots and liquid matter) were evacuated. MMF was discontinued, the dose of tacrolimus was reduced to obtain the level of 8.6 ng/ml. The following treatment was introduced: Dexaven 1x6 mg intravenously, broad spectrum antibiotics – piperacillin/tazobactam 3x4.5g intravenously. Subsequently, due to the fact that the cultures sampled from the collection were positive for *Enterococcus faecium* HLAR+ VRE it was changed into Vankocin 2x1 g intravenously with the monitoring of vancomycin level in blood serum. Moreover, the patient was administered low molecular weight heparin as prophylaxis, valganciclovir, trimethoprim/sulfamethoxazole. Hypertension was controlled with one drug – amlodipine. The patient was not administered Remdesivir nor Tocilizumab, because Tocilizumab is recommended only in individuals with severe course and cytokine storm phase with marked elevation of inflammatory cytokines and other markers (CRP, PCT, IL-6, d-dimers, LDH, ferritin, troponin, NT-pro BNP).

According to our clinical and laboratory asessment (Table 2 figure 2) patien's condition was fair and he did not fell into cytokine storm phase of the COVID-19 disease. His newly-diagnosed drug-induced diabetes was treated with insulin followed by sulfonylurea derivatives 1x1 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 transplantation with nadir creatinine at 0.94 mg/dl (Table 2).

Whether the patient underwent an organ transplantation or not, the course of SARS-CoV-2 infection is relatively similar with clinical and therapeutic implications as presented in Figure 1 modified from Siddiqi et al.[iv]

1. **Inhibiting SARS-CoV-2 entry into cells**

a. Baricitinib, a JAK-kinase inhibitor, has 2 targets: it inhibits SARS-CoV-2 virus entry into the cell and the cytokine storm phase. Adaptive Covid-19 Treatment (ACCT-2) study[v], which included the co-treatment 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/kaletra.[vi]

b. Nafamostat mesylate: SARS-Cov-2 enters the lung cells via binding to ACE-2 and the activation of TMPRSS2 protease. Therefore, it may be the target of antiviral treatment. TMPRSS2 inhibitors prevented SARS-CoV-2 entry into cells *in vitro*. Nafamostat, being the strongest of those inhibitors, is used as an antithrombotic and anti-pancreatitis agent. It was approved in the treatment of cystic fibrosis, as its mucolytic properties may prevent the deterioration of pulmonary function via inhibiting respiratory infections. The RACONA study is going to test a hypothesis that nafamostat is useful in COVID-19-related pulmonary involvement, as COVID-19 is associated with the activation of the coagulation cascade, pulmonary embolism and bacterial superinfections.[vii]

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 FDA (August 2020).[viii] 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.[ix] 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.[x] A randomized Dutch study was conducted in July 2020. It included 86 individuals. However, it was discontinued, as prior to plasma administration the patient had had their own neutralizing antibodies.[xi] The latest study (PLACID) showed no beneficial effects associated with the use of convalescent plasma. It was a "real world" study which 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.[xii] Another randomized placebo-controlled study published in November 2020 in NEJM demonstrated that convalescent plasma did not protect COVID-19 patients and those with COVID-19-related pneumonia from death. Furthermore, it did not alleviate the course of the disease.[xiii]

d. Monoclonal antibodies (bamlanivimab/etesevimab and casirivimab/imdevimab) are potent anti-spike 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 to 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% (5/309) compared to 6.3% (9/143) who received placebo [xiv] [xv] On 09/02/2021 FDA authorized monoclonal antibodies for treatment of COVID-19 (Eli Lilly) [xvi]. In the statement issued by 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 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" [xvii] Likewise, casirivimab/imdesivimab 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 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% (8/434) compared to 4% (10/231) who received placebo. Based on those results FDA issued on 21/11/2020 an emergency use authorization (EUA) for casirivimab and imdevimab (REGEN-COV) 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. [xviii], [xix]

On 05/March/2021 The European Medicines Agency (EMA) announced, that a drug from the US company Eli Lilly, a combination of two preparations, bamlanivimab and etesevimab and based on monoclonal antibody therapy, can be used to treat Covid-19 in Europe.[xx]

2. **Inhibiting viral replication**

Remdesivir interferes with viral RNA polymerases in order 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.[xxi] Its effectiveness was confirmed in the first studies from March 2020 by Holshue M et al.[xxii] and April 2020 by Grein et al.[xxiii] Adaptive Covid-19 Treatment Trial (ACTT-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.[xxiv]

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 to 79 in the placebo group.[xxv]

The largest randomized study – WHO Solidarity trial results was published in October 2020. It included 405 hospitals, 11266 patients with 2750 treated with Remdesivir. It demonstrated a negligible or no effect on the mortality or the introduction of ventilation.[xxvi] The drug is expensive and, currently, it is unavailable because of delivery problems.

3. **Inhibiting COVID-19 cytokine storm**

a. Tocilizumab: It was first recommended by Chinese researchers in March 2020.[xxvii] A study by Rosas et al.[xxviii] included 425 patients who were randomized (2:1). Tocilizumab improved neither the clinical status not mortality rates. Its potential benefits were noted as regards shortening the duration of hospital stay and the hospitalization in ICU. A Polish study by Tomasiewicz K 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 [xxix].

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.[xxx]

c. Heparin – its role is to lower blood clotting in severe cases of COVID-19. The effectiveness was confirmed in COVID-19 patients.[xxxi], [xxxii]

d. Adalimumab (a TNF alpha inhibitor) lowers the production of TNF alpha 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 COVID-19 patients.[xxxiii]

e. Fluvoxamine, a selective serotonin reuptake inhibitor (SSRI), decreases the inflammatory response during cytokine storm through the S1R-IRE1 (a chaperone protein) pathway. A randomized study included 152 patients. The status of six patients deteriorated in the placebo group, while nobody's status deteriorated in SSRI group.[xxxiv]

Discussion

The population of post-transplantation patients is specific, as the clinical course of COVID-19 is much more severe in transplant recipients and hemodialysis patients than in the remaining COVID-19 patients. An observational study by Arenas et al. conducted in spring 2020 showed that the incidence of COVID-19 was 3.2% in kidney transplant (KTx) recipients and 3.6% in hemodialysis (HD) patients. The results of RT-PCR test were positive in 34 (26 KTx and 8 HD) and negative in 27 patients (14 KTx and 13 HD). The comparison between COVID-19 positive and 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 LDH and CRP, the necessity of hospitalization (100% vs. 63%, respectively), the use of noninvasive mechanical ventilation (36% vs. 11%, respectively) and high mortality (38% vs. 0%, $p<0.001$). The death rates were 42% in the kidney transplant recipient group and 37.5% in hemodialysis patient group.[xxxv]

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%, while in those infected with SARS-CoV-2 it was 16/66 (24%), including 11/15 (73%) in the ICU. Acute kidney injury developed in 28 (42%) kidney recipients with 7 requiring renal replacement therapy.[xxxvi] Elias et al. proposed the discontinuation of treatment with antiproliferative drugs (38/61 - 62%). Antimetabolite drugs were discontinued in all ICU patients. Tacrolimus (4-6 ng/ml) or CsA (400-600

ng/ml) and prednisone were continued. CNI was discontinued in only 2 recipients. Immunosuppression was completely withdrawn in only 2 severely ill patients [36]. A description a series of 4 cases of early COVID-19 after transplantation from Poland revealed a relatively low symptomatic clinical course and positive outcome of this disease. [xxxvii] All of them received inducton therapy with anti IL-2 monoclonal antibodies, but no one received antiviral therapy (Remdesivir) or anti-Sars-Cov2 monoclonal antibodies. One of four patients died due to other post-transplant complications leading to septic shock, which were not directly related to COVID-19 infection.

Decribed in our report patient did not receive inducton therapy with anti IL-2 monoclonal antibodies. The use of induction therapy shows great differences between countries and transplant centers. It is emphasized that the decision to use induction and its type should be individualized based on the risk-benefit profile of the transplant recipient. Recipient was assessed as a patient of low immunological risk [Caucasian, PRA = 0, first transplant, blood group compatibility, recipient with an average age of 54 (i.e. neither< 30 nor > 60 years old)]. Such recipient, in accordance with the guidelines of the Polish Society of Transplantation, has no indications for induction with monoclonal antibodies.[xxxviii] According to the authors (Opelz 2016), induction treatment should only be given to high-risk recipients, low-risk recipients do not show additional benefits. [xxxix]The present patient was asymptomatic. His MEWS score was 1 point. His chest CT revealed a reduced transparency, i.e. “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 approx. 40% of the volume of both lungs. We lowered the dose of tacrolimus administered to the patient. The level of the drug 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 2x1.5 mg.

Other authors described a patient with a recent kidney transplantation 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 a biopsy). DSA 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 transplantation should be aware of dangers associated with SARS-CoV-2 infection.[xl]

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.[xli] 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.[xlii] 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 liver recipients (15.1%), 57 (11.8%) heart recipients and 30 (6.2%) lung recipients. Furthermore, no differences were reported as regards 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, while the intensity of immunosuppression had no significant effect on their survival.

In a prospective study Rinaldi et al. demonstrated that all kinds of superinfections (CMV, bacterial, fungal) occurred more commonly in transplant recipients (24 individuals) than in the general population (861 patients) (50% vs. 15.5%, $p<0.001$). Immunosuppression was modified in all recipients. mTORi was discontinued in all patients, MMF in all but 1, CNI – in 19 out of 21 recipients.[xliii]

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

Anti-spike monoclonal antibodies against SARS-CoV-2 seem to be very promising therapy especially in immunocompromised patients. One must remember, that treatment with anti SARS- Cov-2 monoclonal antibodies recently approved by 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 (BMI) ≥35, chronic kidney disease, diabetes mellitus, immunocompromising condition, currently receiving immunosuppressive treatment, aged ≥65 years or aged ≥55 years, and having cardiovascular disease, or hypertension, or chronic obstructive pulmonary disease or another chronic respiratory disease. In the studies described above (14-15), the number of participants was small, and only a limited number of clinical events (e.g., 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 (dialysis pts with end stage renal disease? patients after organ or bone marrow transplantation??) in which the potential benefit will be the greatest.

Some questions still remain unanswered: When should antimetabolite or antiproliferative drugs be re-introduced in convalescents? What CNI dose should be used in such patients? Is two-drug (e.g. steroids and CNI) therapy sufficient? Hopefully, answers to those questions will be available in the literature soon.

Proposal of treatment regimen in patients after a kidney transplantation

1. Reduced immunosuppressive treatment

- discontinue MMF, discontinue mTOR,
- a recent transplantation → dexamethasone max 12 mg for 10 days, tacrolimus at a dose adjusted to the level of the drug (6-8 ng/ml),
- a non-recent transplantation (e.g. a kidney transplanted a year or longer before) → dexamethasone 1x6 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 1x2 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 GFR <30 ml/min/1.73 m2 – 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 IV 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, e.g. chronic kidney disease, without anti-SARS-CoC-2 antibodies produced.
- Anti-spike monoclonal antibodies against SARS-CoV-2 seem to be very promising therapy, need further evaluation in clinical trials

Additionally it is possible to:

- Measure the level of vitamin 25(OH) D3 or 1.25 OG D3 → vitamin D3 supplementation or alfacalcidol 1x1.0 ug orally,
- Vitamin C 2x1 g intravenously,
- Zinc – 70 mg daily in divided doses, orally.

Conclusion

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:

-We still do not have causal drugs that would reduce SARS-CoV-2 replication and allow its complete elimination, but anti-spike monoclonal antibodies against SARS-CoV-2 seem to be very promising.

-The withdrawal of antiproliferative and antimetabolic drugs and the continuation of steroids and CNI inhibitors is nowadays a commonly accepted approach in patients after an organ transplantation.

Conflict of interest statement: the results presented in this paper have not been published previously in whole or part, except in abstract format.

Figure 1. 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.)

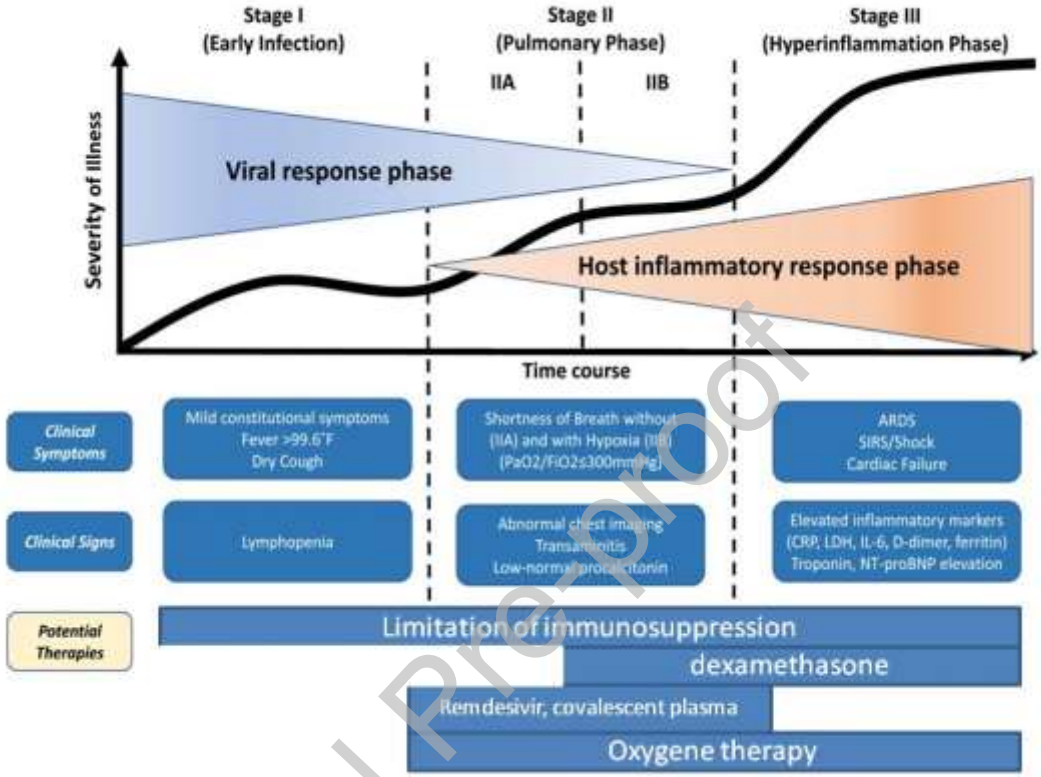

Figure 2. Patients's vital signs from the time of COVID-19 diagnosis until discharge (30.10.2020-18.11.2020).

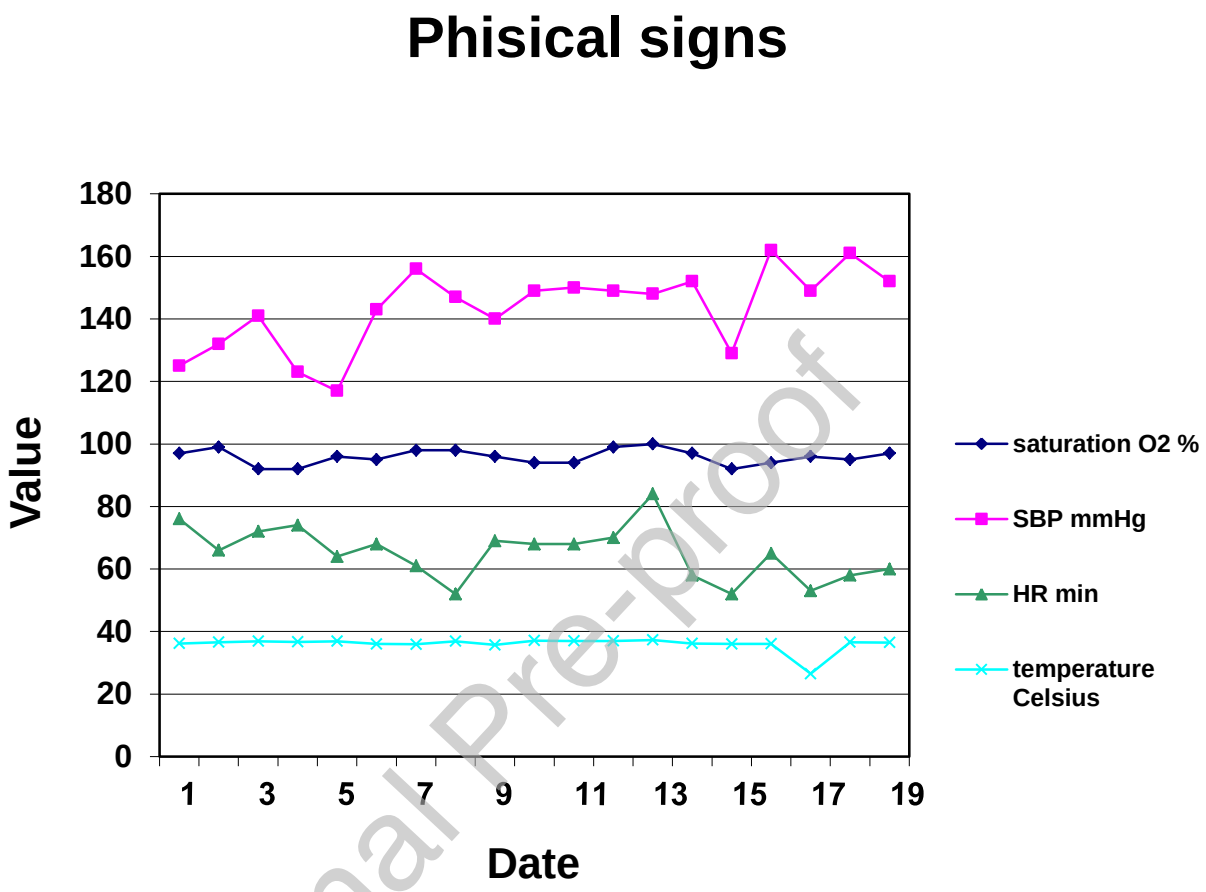

Table 1. Parameters of the kidney transplant recipient and donor during the qualification for the procedure.

	Donor	**Recipient**
Gender	male	male
Age	57	54
BMI	35.1	21.8
Cause of death / renal failure	Intracranial trauma	Adult polycystic kidney disease
Creatinine level	0.58 mg/dl	11 mg/dl
Pressor drugs	levonor 0.07 ug/kg/min	N/A
Hourly / daily diuresis	140 ml / 2300 ml	0 ml / 0 ml
HLA	A 2,-, B18,51, DR 11,13	A 1, 29 B 44, 71 DR 7, 15
CMV IgG/IgM	positive/negative	positive/negative
PRA	N/A	PRA max 7 PRA last 0

Table 2. Biochemical parameters in the described patient

	8.10.20	15.10.20	30.10.20	5.11.20	17.11.20
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 ug/l feu	----------	----------	----------	1193	4310
creatinine mg/dl	11	7.41	1.29	1.5	1.07
e-GFR ml/min	5	7	58	49	76
WBC 10^3/ul	10.47	7.69	4.35	7.41	7.11
Lymph. 10^3/ul	0.95	5.2	0.37	0.56	0.7
Neutro. 10^3/ul	8.96	0.92	3.64	6.53	5.41
Tac. ng/ml	----------	9.8	17.6	8.6	3.8
SARS-COV2 IgG	----------	----------	----------	----------	58.1 (positive >= 15) [AU/ml]
SARS-COV2 IgM	----------	----------	----------	----------	21.9 (positive >=1,1) [AU/ml]

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