Brief Report

Preexposure Prophylaxis against COVID-19 with Tixagevimab/Cilgavimab in Slovenian National Cohort of Kidney Transplant Recipients

Špela Borštnar [1,2*], Miha Arnol [1,2], Željka Večerić Haler[1,2] and Gregor Mlinšek [1,2]

1. Department of Nephrology, University Medical Center Ljubljana, Zaloška 7, 1000 Ljubljana
2. Faculty of Medicine, University of Ljubljana, Korytkova 2, 1000 Ljubljana

* Correspondence: spela.borstnar@kclj.si; Tel.: 0038615221543

Abstract: Tixagevimab/cilgavimab (TIXA/CILGA) was introduced in early 2022 as a promising new drug for pre-exposure prophylaxis against COVID-19 in immunocompromised patients. The aim of our study was to evaluate the efficacy and safety of TIXA/CILGA in a Slovenian national cohort of kidney transplant recipients as pre-exposure prophylaxis in the Omicron era. Demographic, clinical, laboratory, and therapeutic data were collected from electronic and paper medical records. Of the 106 patients who received TIXA/CILGA, 6 patients (5.7%) subsequently acquired SARS-CoV-2 breakthrough infection. The incidence of SARS-CoV-2 infection was only slightly lower compared with patients who did not receive TIXA/CILGA (7.0%). All patients who received TIXA/CILGA had a mild disease course, whereas 20% of patients who did not receive TIXA/CILGA required hospitalization and two patients died. Adverse effects most likely related to TIXA/CILGA occurred in 12% of patients, one of whom experienced deep vein thrombosis. None of the patients suffered acute myocardial infarction or cerebrovascular insult. Overall, the benefit of added protection for kidney transplant patients appears to outweigh the potential risk of adverse events and provide additional protection against severe COVID-19 protection.

Keywords: COVID 19; pre-exposure prophylaxis; kidney transplantation, tixagevimab/cilgavimab

1. Introduction

Kidney transplant recipients (KTRs), like all other immunocompromised patients, have a higher risk of developing more severe COVID-19 disease [1]. Although the majority of KTRs are vaccinated against COVID-19, these patients are more likely to have a poor response to the vaccine [2], and since COVID-19 has become a part of our daily lives, we are still looking for an effective drug that can reduce morbidity in our patients.

KTRs are also not always eligible for therapy with remdesivir due to estimated glomerular filtration rate below 30 ml/min, additionally they cannot receive nirmatrelvir/ritonavir due to interactions with immunosuppression [3,4]. Recombinant monoclonal antibodies are, apart from virostatic agents, an important therapeutic measure for COVID-19 [4]. Many of our patients received casirivimab/imdevimab or sotrovimab in the earlier course of COVID-19 pandemic. These monoclonal antibodies were applied as therapy only after obtaining positive polymerase chain reaction (PCR) test to SARS-CoV-2. With the development of tixagevimab/cilgavimab (TIXA/CILGA), however, pre-exposure prophylaxis became an important component of the care of KTRs. TIXA/CILGA - Evusheld®, a monoclonal antibody combination, was approved for pre-exposure prophylaxis of COVID-19 in high-risk adult patients with impaired vaccine response following results from the double-blind, placebo-controlled AZD7442 Phase III study (PROVENT) [5]. The aim of our study was to evaluate the efficacy and safety profile of TIXA/CILGA in Slovenian national cohort of KTRs.

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2. Materials and Methods

Slovenia, with a population of about two million, has a national kidney transplant center where all patients with transplanted kidneys (currently 801) are treated. About 45 to 60 new patients are transplanted annually. In 2020, 58 of our patients developed COVID-19, and the mortality rate was 10.3%; in 2021, 132 patients developed COVID-19, and the mortality rate was 8.3%. In 2022, 184 KTRs developed COVID-19 by October 31, and only two patients died with the disease. In Slovenia, TIXA/CILGA has been available since March 2022, and in May 2022, the drug was administered to the first KTR.

All of our outpatient KTRs who were more than one month after transplantation received a letter of invitation for TIXA/CILGA application with an explanation of the benefits but also possible cardiovascular (CV) risks. Those expressing interest in TIXA/CILGA, and being without CV risks, received the drug in the following days at our center. All patients who received TIXA/CILGA (150 mg TIXA and 150 mg CILGA - prophylaxis dose) from May 1 to October 31, 2022, were included in our historic cohort study.

Demographic, clinical, laboratory, and therapeutic data at the time of application were collected from hospital electronic and paper medical records and patient reports. We recorded adverse effects and COVID-19 breakthrough infections after TIXA/CILGA application confirmed by rapid antigen testing and/or PCR testing through November 14, 2022.

3. Results

3.1. Patients' characteristics at the time of TIXA/CILGA application

Through October 31, 2022, 106 patients with a transplanted kidney more than 1 month after transplantation received pre-exposure prophylaxis with TIXA/CILGA, 72 men and 34 women, with a mean age of 60 years (range, 20 to 82 years). At the time of TIXA/CILGA administration, the mean time since transplantation was 9 years (range 1 month to 25 years).

Most of our patients (59 patients, 56%) were treated with dual immunosuppressive therapy with calcineurin inhibitor and mycophenolic acid (mycophenolate mofetil (MMF) or mycophenolate sodium). Nineteen patients were also receiving methylprednisolone (MP). Nine patients were on calcineurin inhibitor and everolimus, 7 were receiving calcineurin inhibitor and MP, and 6 of them azathioprine in addition to calcineurin inhibitor. Two patients were receiving calcineurin inhibitor monotherapy; one patient was being treated with tacrolimus, azathioprine, and MP; one was treated with tacrolimus, azathioprine, and eculizumab; one patient with cyclosporine, MP, and everolimus; and one patient with belatacept, mycophenolate, and MP.

The mean serum creatinine concentration was 147 µmol/L (range, 63-808 µmol/L), and the mean glomerular filtration rate estimated with the CKD-EPI equation was 51 ml/min/1.73 m2 (4 to 90 ml/min/1.73 m^2). Three patients started hemodialysis treatment after receiving TIXA/CILGA, but this was expected because their renal function was gradually deteriorating already before treatment with monoclonal antibodies.

The control group (transplanted recipients who did not receive TIXA/CILGA) included 696 patients with a mean age of 56 years (range, 20 to 85 years). At the time of TIXA/CILGA administration, the mean time since transplantation was 10 years (range, 1 month to 38 years). The majority of these patients (52%) were treated with dual immunosuppressive therapy with calcineurin inhibitor and mycophenolic acid. 25% also received MP. 8% of patients were treated with a calcineurin inhibitor and everolimus, and another 15% of patients received other combination of immunosuppressive agents. The mean serum creatinine concentration was 122 µmol/L (range, 50-958 µmol/L), and the mean glomerular filtration rate, estimated using the CKD-EPI equation, was 59 ml/min/1.73 m^2 (5 to 90 ml/min/1.73 m2) (see Supplementary Material, Table S1).

3.2. COVID-19 and vaccination status

Regarding the COVID-19 status of our patients, 45% had no history of SARS-CoV-2 infection before TIXA/CILGA application. The same number of patients (45%) had recovered from COVID-19

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once, 8% had been infected twice. Only one patient had COVID-19 three times before receiving TIXA/CILGA antibodies.

Almost all of our patients had been vaccinated against COVID-19; only one patient had not been vaccinated because he had had severe adverse reactions to influenza vaccination in the past. No one received only one dose of the vaccine; 18% of patients were vaccinated twice and 64% of patients received the vaccine three times. Sixteen percent of patients received four doses of the vaccine before receiving TIXA/CILGA, and one patient received the vaccine five times before receiving TIXA/CILGA. Patients received vaccines developed by different companies, predominantly by Pfizer (Comirnaty).

After administration of TIXA/CILGA, an additional 25 patients were vaccinated a fourth time (so by November 14, a total of 39% of patients had been vaccinated four times), and one patient opted for a fifth vaccine dose (a total of two patients were vaccinated five times).

In the control group (patients without TIXA/CILGA), 52% of patients recovered once from COVID -19, 8% twice, and 1% even three times. 39% of patients did not relapse. 52% of patients were vaccinated three times against COVID -19, 22% twice, 8% four times, 2% once; 16% of patients were not vaccinated at all.

3.3. Efficacy of TIXA/CILGA on COVID-19 incidence

The average time from the application of TIXA/CILGA to the end of our observation period was 64 days (range 17 to 179 days). During this time, six patients (5.7%) became infected with SARS-CoV-2, as confirmed by nasopharyngeal swab test, either rapid antigen testing or PCR testing. The average time from TIXA/CILGA administration to positive test was 56 days. All patients with breakthrough infection had a mild form of the disease and did not require hospitalization.

The first patient was a 67-year-old man, one year after kidney transplantation with tacrolimus and everolimus therapy. He had been vaccinated three times and had no previous COVID-19. He became infected 74 days after receiving TIXA/CILGA. The illness was mild (low fever, cough, malaise), he received remdesivir and recovered completely. The second patient, a 55-year-old man, received TIXA/CILGA 3 months after transplantation. At that time, he was being treated with tacrolimus and MMF. He previously had COVID-19 and had been vaccinated three times. Four months after TIXA/CILGA administration, he developed symptoms of respiratory infection (cough, low-grade fever, and runny nose). After a positive PCR test for COVID-19, we treated him with remdesivir. The third patient was a 58-year-old woman who had had a transplanted kidney for 13 years and was receiving tacrolimus and MMF. She had already been vaccinated four times and recovered from COVID-19 once. She newly became infected with SARS-CoV-2 only 1 week after TIXA/CILGA application. Again, the disease was mild, and she received no additional antiviral therapy. The fourth patient was a 60-year-old woman who had previously been vaccinated twice and recovered twice from COVID-19 and received TIXA/CILGA 8 months after kidney transplantation. She was being treated with tacrolimus, MP, and eculizumab, meaning that she was severely immunosuppressed. Thirty-eight days after TIXA/CILGA, she became positive for SARS-CoV-2 for the third time. Sars-CoV-2 infection was incidentally confirmed by routine testing during hospitalization and was asymptomatic. Remdesivir was not administered because of poor kidney function. Leucopenia with neutropenia were attributed to severe concurrent cytomegalovirus infection. The fifth patient was a 75-year-old man with a transplanted kidney who had been treated with tacrolimus and MP for three years. He had been vaccinated four times and had not previously had COVID-19. 59 days after receiving TIXA/CILGA, he became ill with high fever and cough for several days. He did not inform his physician, so he did not receive further treatment for SARS-CoV-2. The sixth patient was a 64-year-old woman who was being treated with cyclosporine and MMF 18 years after transplantation. She received three doses of the vaccine against COVID-19. She was positive for the first time 36 days after receiving TIXA/CILGA, and the disease manifested as cough and muscle pain. She also received remdesivir.

Of the 696 KTRs who did not receive TIXA/CILGA pre-exposure prophylaxis, 49 (7.0%) developed COVID-19 during the same period, compared with 6 of 106 patients who received TIXA/CILGA (ARR 1.38%, 95% confidence interval: [-3.41%, 6.17%]; RRR 19.6%, 95% confidence

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interval: [-83%, 65%]). 10 of these 49 patients (20%) required hospitalization, and two patients (4%) died from complications of COVID-19. Of the patients with a more severe course of COVID-19, three of 10 had not been vaccinated, but the two patients who died were vaccinated and also received remdesivir. This group of patients was on average four years younger than the group of patients who received TIXA/CILGA (54 years versus 60 years), and the mean time after transplantation was similar (10 years versus 9 years in the TIXA/CILGA group).

3.4. Efficacy of TIXA/CILGA on COVID-19 humoral response

We did not systematically survey anti-SARS-CoV-2 spike protein S1 antibodies in BAU/ml in all 106 TIXA/CILGA recipients. However, in 5 patients BAU/ml were determined before and 10-23 days after TIXA/CILGA application. All these patients had antibodies before the use of TIXA/CILGA (after vaccinations and/or after recovery from COVID -19). We observed a significant increase in BAU/ml in all 5 patients (Table 1), none of whom had COVID -19 after TIXA/CILGA administration.

Table 1. Increase of anti-SARS-CoV-2 Spike protein S1 antibodies after tixagevimab/cilgavimab (TIXA/CILGA) administration.

Patient	Vaccinated before TIXA/CILGA	Recovered form COVID-19 before TIXA/CILGA	anti-SARS-CoV-2 Spike protein S1 antibodies (BAU/ml) before TIXA/CILGA	Days between TIXA/CILGA, and antibodies determination	anti-SARS-CoV-2 Spike protein S1 antibodies (BAU/ml) after TIXA/CILGA	Relative increase (%)
1	3x	1x	1250	23	4521	261
2	3x	0x	10399	11	15383	52
3	3x	1x	1797	9	3433	91
4	2x	1x	5776	14	9148	58
5	3x	2x	7880	14	> 25000	>217

3.5. Adverse effects of TIXA/CILGA

We analyzed the occurrence of adverse events during a period up to 6 months after the use of TIXA/CILGA, paying particular attention to CV and/or thromboembolic events. No adverse effects occurred in 82% of patients during the observation period. 12% of patients experienced adverse effects that were most likely related to TIXA/CILGA. 6% of patients experienced some form of discomfort after administration of the drug, but this was unlikely to be related to the medication. None of the 106 patients experienced acute myocardial infarction or cerebrovascular insult after TIXA/CILGA administration. One patient experienced deep vein thrombosis (popliteal vein and deep femoral vein) 10 days after prophylactic use of TIXA/CILGA. There were no precipitating factors (malignancy, recent surgery, injury, or other) at the time of the event. He had a similar event 10 years ago, but at that time the thrombosis was related to a recent surgery and postoperative complications. The most common side effect was pain and redness at the injection site for several days in 7% of patients. Other side effects are listed in Table 2. We did not observe any increase in serum creatinine concentration in any of the patients, which would occur after the use of TIXA/CILGA and would not have had other reasons for worsening renal function.

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Table 2. Adverse effects after tixagevimab/cilgavimab (TIXA/CILGA) administration.

Patient	Adverse effect	Onset time after TIXA/CILGA	Duration of adverse effect	Likelihood of relation to TIXA/CILGA
1	Pain at the injection site, leg cramp	Couple of hours	Couple of days	Yes
2	Malaise, diarrhea, fatigue	Couple of hours	10 days	Yes
3	Pain at the injection site, headache, nausea	Couple of hours	Couple of days, headache ongoing	Yes
4	Headache	Couple of hours	One day	Yes
5	Stomach pain	Couple of hours	One day	Yes
6	Pain at the injection site	Couple of hours	5 days	Yes
7	Pain at the injection site	Couple of hours	One day	Yes
8	Joint pain	Couple of hours	7 days	Yes
9	Pain at the injection site	Couple of hours	One day	Yes
10	Deep vein thrombosis	10 days	---	Yes
11	Headache	Couple of hours	Couple of days	Yes
12	Pain at the injection site	Couple of hours	One day	Yes
13	Pain at the injection site, joint pains	Couple of hours	Two days	Yes
14	Newly diagnosed “shadow” in lungs	One month	Ongoing	No
15	Dizziness	1 week	Couple of days	No
16	Leucopenia	1 month after	One month	No
17	Worse pain in heels	Couple of hours	Ongoing	No
18	Diarrhea	14 days	10 days	No
19	Fever, malaise, cough	3 days	10 days (parainfluenza was isolated)	No

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4. Discussion

TIXA/CILGA has been shown to reduce the risk of SARS-CoV-2 infection in unvaccinated individuals during the B.1.1.7 (alpha) and B.1.617.2 (delta) waves [5], but limited data were available to date on its efficacy and safety in vaccinated, severely immunocompromised patients (including solid organ transplant recipients (SOTRs)) during the Omicron wave.

The neutralizing monoclonal antibody combination TIXA/CILGA at a dosage of 300 mg proved effective against SARS-CoV-2 infection in vaccinated KTRs during the Omicron wave in Slovenia. Although the incidence of COVID-19 infection was not significantly lower in KTRs receiving TIXA/CILGA (ie, 5.7% of KTRs who received TIXA/CILGA developed COVID-19 after administration, compared with 7.0% of patients who did not receive TIXA/CILGA), it is important to emphasize that all infected patients who received pre-exposure prophylaxis with TIXA/CILGA had an asymptomatic or mild form of the disease and did not require hospitalization, compared with 20% of KTRs with a moderate-to-severe course of SARS-CoV-2 infection who did not receive TIXA/CILGA prophylaxis. Two patients who were not treated with TIXA/CILGA unfortunately died, although they were vaccinated and also received remdesivir.

Our data are consistent with previous findings by Al Jurdi et al, who reported breakthrough of SARS-CoV-2 infection in 5% of 222 vaccinated SOTRs who received pre-exposure prophylaxis with TIXA/CILGA compared with 14% of SOTRs in the control group who were vaccinated but did not receive TIXA/CILGA [6]. Similar results on the clinical efficacy of the TIXA/CILGA monoclonal antibody combination as pre-exposure prophylaxis against the BA.1 and BA.2 SARS-CoV-2 Omicron sublines were most recently reported in 1112 immunocompromised patients abroad in France (46% of them were KTRs), where the breakthrough rate of SARS-CoV-2 infection was 4.4% [7]. Among infected patients 88% had a mild form, whereas 12% of patients had a moderate-to-severe form. Two thirds of these were KTRs. One of these patients died. In our patient cohort, which was much smaller, no TIXA/CILGA recipient had moderate-to-severe disease course and no patient died.

The studies have shown, that the TIXA/CILGA maintain neutralization against the majority of Omicron sublineages [8,9], but there is loss of neutralization against BA.4.6 [9,10]. Beside BA.4.6. variant, variants BA.2.75.2, BA.5.2.6, BF.7, BQ.1, and BQ.1.1 are also likely to be resistant to TIXA/CILGA [11]. Major limitation of our historic cohort study is that we did not subanalyze the positive PCR tests of patients with breakthrough infection and did not specify the subvariant of SARS-CoV-2 virus. However, this observational study was performed before Slovenian National Laboratory of Health, Environment and Food started reporting newer SARS-CoV-2 subvariants capable of neutralization escape [12]. Not earlier as of early December 2022, BQ subvariants thought to be resistant to TIXA/CILGA were present in 50% of SARS-CoV-2 infected patients in Slovenia [12].

In our patient cohort, adverse events occurred somewhat more frequently than reported in previous studies of immunocompromised subjects [6,7], but were mostly mild and related to pain and redness at the injection site that persisted for only several days. There was no significant deterioration in renal function or liver function tests during the observed post-exposure period to TIXA/CILGA.

Because of financial constraints, we could not determine the anti-SARS-CoV-2 spike protein S1 antibody concentration in all patients after TIXA/CILGA application, but only in 5 patients. All of them already had high antibody concentration before TIXA/CILGA application. Because TIXA/CILGA showed lower neutralizing activity against Omicron sublineages compared with previous SARS-CoV-2 variants of concern, high antibody concentration appeared reasonable to potentially confer higher antiviral protection to patients. Some studies reported arbitrary concentrations below which immunocompetent patients are not adequately protected against SARS-CoV-2 infection [13], but some other studies did not confirm this or their "effective" antibody concentration was different [14-16]. With data in Table 1, we aimed to show the increase in antibody concentration after administration of TIXA/CILGA (which does not necessarily mean adequate protection against infection, but represents a higher probability that the patient will not be infected with COVID -19).

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According to previous studies, rates of serious adverse events were generally similar between the TIXA/CILGA and placebo groups [5,6]. There was, however, some concern because in the PROVENT study, a higher proportion of subjects receiving TIXA/CILGA (0.6%) compared with placebo (0.2%) reported serious cardiac adverse events [5]. None of the cardiac events (including myocardial infarction, arrhythmias, and heart failure) were reported in our cohort, although the cohort was of comparable age and had similar CV risk factors (chronic kidney disease, arterial hypertension, diabetes mellitus) as the patients in PROVENT study. The absence of serious cardiac adverse events in our patients may be due to our decision not to use TIXA/CILGA in patients who have had a myocardial infarction, other forms of ischemic heart disease, cardiac arrhythmias, or symptomatic heart failure in the past year. There was only one individual with deep vein thrombosis that occurred 10 days after TIXA/CILGA pre-exposure prophylaxis and could not be associated with any other possible triggers.

We had expected that the highest breakthrough rate of SARS-CoV-2 infection would occur in the patients receiving triple immunosuppression, but this was not the case. Only one of the six patients received triple immunosuppression (tacrolimus, MP, and eculizumab), whereas the other five patients received double. However, three of these patients also received MMF, which suppresses B and T cell replication and makes patients more susceptible to infection.

Apart from the fact that most patients with breakthrough infection were diagnosed with a rapid antigen test or real-time reverse transcriptase PCR which were performed in laboratories outside the hospital and did not provide variant data, our study has several other limitations. First, the follow-up period after TIXA/CILGA administration was relatively short. We were not able to extend the observation period because of the emergence of new dominant variants in our country against which TIXA/CILGA is not effective. The follow-up was also not the same for all patients, as not all patients received TIXA/CILGA at once, but over several months. This means that the rate of breakthrough infections is probably underestimated. In addition, our rate of COVID-19 may have been undervalued because of possible missed asymptomatic cases. No systematic follow up with PCR was included in our study. However, it is unlikely that moderate-to-severe forms were missed because these patients are centrally recorded and we had access to their medical records when they were in the hospital. Pre-exposure prophylaxis was offered to all KTRs in our country, so the study was not comparative. However, we do provided data on infection rates in KTRs who did not receive TIXA/CILGA prophylaxis.

5. Conclusions

Our study reveals a low rate of breakthrough COVID-19 infections and mild disease course in vaccinated KTRs treated with pre-exposure prophylaxis with TIXA/CILGA monoclonal antibodies in the Omicron era. Adverse events occurred infrequently and were mild. In addition, no serious CV adverse events were noted. Overall, the benefit of additional protection for KTRs appears to outweigh the potential risk for adverse events.

Supplementary Materials: Table S1. Patients' demographic and baseline characteristics.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and was approved by the National Ethics Committee (approval number 0120-208/2020/6).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Not applicable.

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Conflicts of Interest: The authors declare no conflict of interest.

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