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Pre-exposure prophylaxis for COVID-19 with Tixagevimab/Cilgavimab in kidney transplant recipients in the Kraken variant (XBB.1.5) era: A Single-center Experience

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Pre-Exposure Prophylaxis for COVID-19 with Tixagevimab/Cilgavimab in Kidney Transplant Recipients in the Kraken Variant (XBB.1.5) Era: A Single-Center Experience

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Abstract: Pre-exposure prophylaxis for COVID-19 with Tixagevimab/Cilgavimab in immunocompromised patients has reduced the risk of breakthrough infection, disease, hospitalization, and COVID-19 related mortality. However, the advent of the Kraken variant (XBB.1.5) has limited the use of this monoclonal antibody, based on poor efficacy in *in vitro* studies The objective of the study was to evaluate the risk of breakthrough infection, symptomatic disease, hospitalization, intensive care admission and COVID-19 related death in kidney transplanted recipients receiving pre-exposure prophylaxis with Tixagevimab/Cilgavimab for COVID-19 in the era of the Kraken variant (XBB.1.5). In a prospective, observational study, we enrolled kidney transplant patients undergoing pre-exposure prophylaxis for COVID-19 with Tixagevimab/Cilgavimab at the Division of Infectious Diseases of Federico II University of Naples between February 2023 and August 2023. Each patient subsequently underwent a six-month follow-up with symptom monitoring and surveillance nasopharyngeal swab for SARS-CoV-2 RNA detection every 30 days, regardless of symptoms. Thirty-four kidney transplant patients were enrolled and in the follow-up period, only one tested positive for the nasopharyngeal swab for SARS-CoV-2 research with asymptomatic infection and virological recovery on the eighth day from the diagnosis of infection. Therefore, no patient developed disease and no patient needed hospitalization and no death occurred. No adverse drug reaction to Tixagevimab/Cilgavimab occurred. Our data, although derived from a limited and uncontrolled sample, show the potential of Tixagevimab/Cilgavimab as a valid and viable therapeutic strategy in pre-exposure prophylaxis for immunocompromised patients. These findings highlight the importance of conducting clinical studies on this topic.

Keywords: Tixagevimab/Cilgavimab; kidney transplantation; SARS-CoV-2; COVID-19; Kraken variant; XBB.1.5; pre-exposure prophylaxis; immunosuppressed patients

1. Introduction

Pre-exposure prophylaxis with the monoclonal antibodies Tixagevimab/Cilgavimab has been a key resource in the fight against COVID-19 (COronaVIrusDisease-2019), especially for immunocompromised patients, who present a lower response rate to vaccination than the general population [1,2,3,4]. It is noteworthy that immunosuppressed patients were poorly represented in the pivotal trial which assessed efficacy and safety of Tixagevimab/Cilgavimab as a pre-exposure prophylaxis [5,6]. Indeed, several studies have highlighted the efficacy and safety of this combination of monoclonal antibodies in preventing COVID-19 in immunocompromised patients [7]. Several studies conducted in the era of the Omicron variant showed that COVID-19 pre-exposure prophylaxis reduced the risk of breakthrough infection, hospitalization, intensive care admission and death by about 40%, 66% 80% and 90%, respectively [8]. However, in January2023, the FDA (Food and Drug Administration) blocked the use of Tixagevimab/Cilgavimab, as in vitro data showed that

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this combination was not able to neutralize the new subvariants of Omicron BQ .1, BQ.1.1, BF.7, BF.11, BA.5.2.6, BA.4.6, BA.2.75.2, XBB and XBB .1.5 (or Kraken) and therefore the drug would not have been effective against the new sublineages of SARS- CoV-2 [9,10]. Despite the FDA's decision, there have been no restrictions on the availability of Tixagevimab/Cilgavimab in Europe.

At present, clinical data of the efficacy of Tixagevimab/Cilgavimab as a pre-exposure prophylaxis during the Kraken variant era are lacking.

Aim of the present study was to evaluate the risk of breakthrough infection, symptomatic disease, hospitalization, intensive care admission and the risk of COVID-19 related mortality in kidney transplant recipients receiving pre-exposure prophylaxis for COVID-19 in the era of the Kraken variant (XBB.1.5).

2. Materials and Methods

In a prospective observational study, we enrolled kidney transplant patients undergoing COVID-19 pre-exposure prophylaxis with Tixagevimab/Cilgavimab (given intramuscularly at a single dose of 150 mg/150 mg) at the Division of Infectious Diseases of Federico II University of Naples from February 2023 to August 2023. During this time, the Kraken variant of SARS-CoV-2 increased up to become the prevalent one,

After Tixagevimab/Cilgavimab administration, every patient participated in a six-month follow-up period. This follow-up included weekly active calls to monitor the onset of symptoms, constant telephone availability for patients to make calls, and regular nasopharyngeal swab surveillance for SARS-CoV-2 RNA detection, regardless of the presence of symptoms. In case of reported suspicious symptoms, each patient was immediately subjected to a nasopharyngeal swab for SARS-CoV-2 RNA research.

In case of swab positivity, each isolated SARS-CoV-2 was subjected to typing for the identification of the variant and each patient was subjected to clinical monitoring to assess the evolution of the disease as well as clinical and virological outcome.

Diagnosis of SARS-CoV-2 infection was obtained by positivity to the rhino-oropharyngeal swab for SARS-CoV-2 RNA research by reverse transcription - polymerase chain reaction (RT-PCR). To describe the clinical status of SARS-CoV-2 infected patients we used the NIAID ACTT-1 (National Institute of Allergy and Infectious Diseases Adaptive COVID-19 Treatment Trial-1) Clinical Status Ordinal Scale [11].

3. Results

We enrolled 34 kidney transplant patients. All patients were on treatment with immunosuppressant agents upon enrollment. Anagraphic and clinical variables are summarized in Table 1.

Table 1. Characteristics of enrolled patients.

Age (years), median, (IQR)	*47 (24-66)*
Gender	
M	*13 (38%)*
F	*21 (62%)*
SARS-CoV-2 infection	*1 (3%)*
Asymptomatic	*1 (100%)*
COVID-19	*0*
Hospitalization	***0***
Intensive care admission	***0***
Death	***0***

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Type of transplant	
Kidney transplant	*34 (100%)*
Time from transplant (months), mean (IQR)	*17 (6-233)*
Immunosuppressive therapy at diagnosis	*17 (52%)*
Tacrolimus-Mycophenolate-Steroids	*9 (27%)*
Tacrolimus-Everolimus-Steroids	*4 (12%)*
Cyclosporine-Mycophenolate-Steroids	*1 (3%)*
Tacrolimus-Mycophenolate	*2 (6%)*
Tacrolimus-Steroids	
COVID-19 vaccination	
Yes	*32 (94%)*
No	*2 (6%)*

IQR: InterQuartile Range.

Thirty-two patients (94%) were vaccinated for COVID-19 (30 with mRNA BNT162b2 (Pfizer-BioNTech) and 2 with mRNA-1273 (Moderna)). Most patients (75%) had received 3 doses of vaccine, while 19% had received 4 doses and the remaining 6% had received less than 3 doses. (Table 1)

At the time of Tixagevimab/Cilgavimab administration, all patients had a negative rhino-oropharyngeal swab for SARS-CoV-2 research of the last 48 hours and all patients were asymptomatic due to suspected COVID-19.

No allergic reaction or other adverse events were noticed during the infusion.

During the post-administration Tixagevimab/Cilgavimab follow-up, with a median of 5 months of follow-up for each patient, only one patient tested positive for the nasopharyngeal swab for SARS-CoV-2 RNA research. In particular, a 48-year-old male patient, 13 months after transplantation and with 4 doses of anti-COVID-19 vaccine (with mRNA BNT162b2 (Pfizer-BioNTech)), was positive for the surveillance nasopharyngeal swab for SARS-CoV-2 RNA research 30 days after the administration of the monoclonal antibody. This patient was found to be asymptomatic and achieved virological recovery 8 days after the first positive finding. This SARS-CoV-2 was subjected to typing, with identification of the Kraken variant (XXB 1.5). No patients developed disease and no patients needed hospitalization and no death occurred.

4. Discussion

Although based on a limited sample, our study shows that Tixagevimab/Cilgavimab could be a promising and feasible therapeutic approach for pre-exposure prophylaxis in immunocompromised patients, even in the era of the Kraken variant. It is noteworthy that Tixagevimab/Cilgavimab is currently the only monoclonal-antibody based therapeutic option to be used in pre-exposure prophylaxis against COVID-19 [7,8].

Moreover, our study highlights that clinical data may be discordant from in vitro data [8]. Indeed, to our best knowledge, there are no clinical studies that have evaluated the efficacy of Tixagevimab/Cilgavimab as pre-exposure prophylaxis in the era of the Kraken variant. All data, in fact, refer to studies carried out before January 2023.

Our real-life study shows that Tixagevimab/Cilgavimab administration as pre-exposure prophylaxis in immunosuppressed patients was associated with a very low rate of infection and null rate of complications, even during the period characterized by high circulation of the Kraken variant a strain against which this monoclonal antibody combination has no in vitro neutralizing activity.

We underline that the only patient who tested positive had an asymptomatic disease and underwent a virological recovery after only 8 days, despite the state of immunocompromise.

An intriguing interpretation of our study is that a dissociation between in vitro results and clinical efficacy is possible in this setting. Indeed, a similar story happened with the monoclonal antibody sotrovimab in which the in vitro poor activity on some omicron subvariants did not correspond to the good clinical efficacy in several cohorts in preventing severe disease during circulation of the same variants [12,13,14].

5. Conclusions

In conclusion, Tixagevimab/Cilgavimab could currently represent a valid option in COVID-19 pre-exposure prophylaxis in immunocompromised patients, even during the circulation of the Kraken variant waiting for new therapeutic possibilities in this area.

Author Contributions: P.B. participated in substantial contributions to the conception, design of the work, the acquisition, analysis and interpretation of data for the work. R.C. conceived idea with analysis and participated in interpretation of the literature, drafting the article, approving the final version to be published and is accountable for the accuracy/integrity of the content. F.S. participated in revising the initial draft of the article and approving the final version to be. A.P. participated in drafting the article, and approving the final version to be published. E.S. participated in analysis and interpretation of data for the work. P.R. participated in the acquisition and analysis of data for the work. E.T. participated in design of the work and interpretation of data for the work. A.D.A. participated in approving the final version to be published and is accountable for the accuracy/integrity of the content. M.S. participated in analysis and interpretation of the literature, drafting the article, and approving the final version to be published. E.Z. participated in revising the initial draft of the article and approving the final version to be published. G.I. participated in substantial contributions to the conception, design of the work, the acquisition, analysis and interpretation of data for the work, approving the final version to be published.

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Data Availability Statement: We encourage all authors of articles published in MDPI journals to share their research data. In this section, please provide details regarding where data supporting reported results can be found, including links to publicly archived datasets analyzed or generated during the study. Where no new data were created, or where data is unavailable due to privacy or ethical restrictions, a statement is still required. Suggested Data Availability Statements are available in section "MDPI Research Data Policies" at https://www.mdpi.com/ethics.

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

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