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Preliminary evidence of good safety profile and outcomes of early treatment with tixagevimab/cilgavimab compared to previously employed monoclonal antibodies for COVID-19 in immunocompromised patients

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Abstract: Objectives Monoclonal antibodies (mAbs) have proven to be a valuable tool against COVID-19, mostly among subjects with risk factors for progression to severe illness. Tixagevimab/cilgavimab (TIX/CIL), a combination of two Fc-modified human monoclonal antibodies, has been recently approved to be employed as early treatment. **Methods** Two groups of immunocompromised patients exposed to different early treatments (i.e., TIX/CIL vs. other mAbs [casirivimab/imdevimab, bamlanivimab/etesevimab, sotrovimab]) were compared in terms of clinical outcomes (hospitalization and mortality within 14 days from administration) and time to the negativity of nasal swabs. We used either Pearson's chi-square or Fisher's exact test for categorical variables, whereas the Wilcoxon rank–sum test was employed for continuous ones. Kaplan–Meier curves were produced to compare the time to nasopharyngeal swab negativity. **Results** Early treatment with TIX/CIL was administered to 19 immunocompromised patients, while 89 patients received other mAbs. Most of them were solid organ transplant recipients or suffering from hematologic or solid malignancies. Overall, no significant difference was observed between the two groups in terms of clinical outcomes. In the TIX/CIL group, one patient (1/19, 5.3%), who was admitted to the emergency room within the first 14 days from treatment and was hospitalised due to COVID-19 progression, died. Regarding the time to nasal swab negativity, no significant difference (p=0.088) emerged. **Conclusions** Early treatment of SARS-CoV-2 infection with TIX/CIL shows favourable outcomes in a small group of immunocompromised patients, reporting no significant difference when compared to similar patients treated with other mAbs.

Keywords: monoclonal antibodies; tixagevimab/cilgavimab; immunocompromised

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Introduction

Early treatment with monoclonal antibodies has proven to be a valuable tool against COVID-19, mostly among subjects with risk factors for progression to severe illness [1]. Tixagevimab/cilgavimab (TIX/CIL), a combination of two Fc-modified human monoclonal antibodies (mAbs), was developed to be employed as a primary prophylaxis tool among those unable to receive the vaccination or with conditions impairing the response to immunization programs [2,3]. In the summer of 2022, based on the positive results of two phase 3 trials [4,5], its indications have been expanded also to early treatment for the prevention of progression to more severe COVID-related manifestations and outcomes. Among the patients which may benefit more from early mAbs treatments are immunocompromised individuals (e.g., solid organ transplant recipients, those receiving immunosuppressive drugs for autoimmune conditions, and those with primary immunodeficiencies), a population which is usually excluded or underrepresented in registration studies.

We have previously observed minimal adverse drug reactions and favourable outcomes among immunocompromised patients receiving early treatment with the mAbs casirivimab/imdevimab, sotrovimab, or bamlanivimab/etesevimab [6]. This study aims to assess clinical outcomes and time to nasal swab negativity in a cohort of immunocompromised patients treated with TIX/CIL.

Methods

The study included immunocompromised patients [(i) history of any connective tissue disease, autoimmune disease, or primary immunodeficiency, (ii) history of an active solid or hematologic tumour, (iii) neutropenia due to haematological cancer, (iv) diagnosis of human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS), (v) history of splenectomy, solid organ transplantation (SOT), and/or hematopoietic stem cell transplantation (HSCT), (vi) ongoing treatment with steroids (for at least 4 weeks), chemotherapy, and/or immunosuppressive agents], with COVID-19 diagnosis, evaluated at the outpatient clinic or hospitalized for a non-COVID-19 related reason in the ward of the Infectious Diseases Unit, IRCCS Ospedale Maggiore Policlinico, Milano, Italy, from August 28 to October 15, 2022, who received early treatment with TIX/CIL. This group was compared to subjects who had received other mAbs (casirivimab/imdevimab, bamlanivimab/etesevimab, sotrovimab) between November 25, 2021, and January, 25, 2022, as previously published [6].

We compared clinical outcomes (i.e., hospitalization and mortality within 14 days from administration) and time to the negativity of nasal swabs. Categorical variables were compared by using either Pearson's chi-square or Fisher's exact test, whereas the Wilcoxon rank–sum test was employed for continuous variables. Kaplan–Meier curves were produced to compare the time to nasopharyngeal swab negativity.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of IRCCS Fondazione Ca' Granda Ospedale Maggiore Policlinico (protocol code Milano Area 2, #328_2022bis, 26 April 2022).

Results

Early treatment with TIX/CIL was administered to 19 immunocompromised patients whereas 89 individuals were treated with other mAbs. The majority of patients included in the TIX/CIL cohort were SOT or individuals suffering from hematologic or solid malignancies. TIX/CIL treatment was administered on average 5(±5) days after symptoms occurrence. Table 1 summarizes the demographic and clinical characteristics of the enrolled patients. In Table 2 are reported clinical outcomes compared between the two groups.

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Table 1. Demographic and clinical characteristics of patients undergoing early treatment with TIX/CIL and other mAbs.

Characteristic	Overall, N = 108	mAbs, N = 89	TIX/CIL, N = 19	p-value
Age				0.003
20-64 years	80 (74%)	61 (69%)	19 (100%)	
65+ years	28 (26%)	28 (31%)	0 (0%)	
Sex				0.377
M	61 (56%)	52 (58%)	9 (47%)	
F	47 (44%)	37 (42%)	10 (53%)	
Ethic group				0.433
Caucasian	82 (76%)	82 (92%)	18 (95%)	
African	21 (19%)	3 (3.4%)	0 (0%)	
Asian	3 (2.8%)	3 (3.4%)	0 (0%)	
Hispanic	2 (1.9%)	1 (1.1%)	1 (5.3%)	
BMI	24.0 (21.2, 26.0)	24.0 (21.0, 26.0)	25.0 (22.0, 30.0)	0.154
Hypertension	40 (37%)	29 (33%)	11 (58%)	0.038
Potus	2 (2.1%)	2 (2.3%)	0 (0%)	>0.999
Smoke				0.159
Never	65 (66%)	54 (62%)	11 (92%)	
Former smoker	18 (18%)	17 (20%)	1 (8.3%)	
Active smoker	16 (16%)	16 (18%)	0 (0%)	
Previous SARS-CoV-2 infection	11 (10%)	5 (5.7%)	6 (32%)	0.004
Connective tissue disease	12 (11%)	11 (12%)	1 (5.3%)	0.688
Solid tumour				>0.999
None	100 (93%)	82 (92%)	18 (95%)	
Local	6 (5.6%)	5 (5.6%)	1 (5.3%)	
Metastatic	2 (1.9%)	2 (2.2%)	0 (0%)	
Leukaemia	7 (6.5%)	5 (5.6%)	2 (11%)	0.604
Lymphoma	12 (11%)	10 (11%)	2 (11%)	>0.999
AIDS	0 (0%)	0 (0%)	0 (0%)	>0.999
Splenectomy	2 (1.9%)	2 (2.2%)	0 (0%)	>0.999
Neutropenia	3 (2.8%)	1 (1.1%)	2 (11%)	0.079
Primary immunodeficiency	23 (21%)	21 (24%)	2 (11%)	0.354
Autoimmune disease	14 (13%)	13 (15%)	1 (5.3%)	0.456
Bone marrow transplant				>0.999
No	104 (96%)	85 (96%)	19 (100%)	
Autologous	4 (3.7%)	4 (4.5%)	0 (0%)	
Allogenic	0 (0%)	0 (0%)	0 (0%)	
Solid organ transplant				0.002

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No	58 (55%)	53 (60%)	5 (28%)	
Kidney	26 (25%)	22 (25%)	4 (22%)	
Liver	14 (13%)	10 (11%)	4 (22%)	
Lungs	8 (7.5%)	3 (3.4%)	5 (28%)	
Other(s)	0 (0%)	0 (0%)	0 (0%)	
HIV infection	2 (1.9%)	2 (2.2%)	0 (0%)	>0.999
Long term steroid				0.024
No	53 (49%)	48 (54%)	5 (26%)	
< 20mg/die	49 (45%)	38 (43%)	11 (58%)	
>= 20mg/die	6 (5.6%)	3 (3.4%)	3 (16%)	
Biological immunosuppressor				0.019
Anti TNF-alfa	1 (6.7%)	1 (7.7%)	0 (0%)	
Anti IL6	1 (6.7%)	1 (7.7%)	0 (0%)	
Anti IL1	0 (0%)	0 (0%)	0 (0%)	
Anti IL17a	0 (0%)	0 (0%)	0 (0%)	
Anti CD20	3 (20%)	3 (23%)	0 (0%)	
TK inhibitors	2 (13%)	0 (0%)	2 (100%)	
Anti CD52	0 (0%)	0 (0%)	0 (0%)	
Other(s)	8 (53%)	8 (62%)	0 (0%)	
Chemotherapy	7 (6.5%)	5 (5.6%)	2 (11%)	0.604
Anti-rejection therapy	51 (47%)	38 (43%)	13 (68%)	0.041

Table 2. COVID-19 related clinical outcomes.

COVID-19 outcomes	Overall, N = 108	mAbs, N = 89	TIX/CIL, N = 19	p-value
Hospital admission within 14 days from infusion	8 (7.4%)	7 (7.9%)	1 (5.3%)	>0.999
of which related to COVID-19	5 (4.6%)	4 (4.5%)	1 (5.3%)	>0.999
Emergency department admission within 14 days from infusion	4 (3.7%)	3 (3.4%)	1 (5.3%)	0.544
ICU admission within 14 days from infusion	0 (0%)	0 (0%)	0 (0%)	
Death within 14 days from infusion	2 (1.9%)	1 (1.1%)	1 (5.3%)	0.322
of which related to COVID-19	2 (1.9%)	1 (1%)	1 (5.3%)	0.322

ICU: intensive care unit.

Overall, no significant difference was observed. In the TIX/CIL cohort, one patient (1/19, 5.3%), who was admitted to the emergency room within the first 14 days from treatment and was hospitalised due to COVID-19 progression, died. Regarding the time to nasal swab negativity, no significant difference (p=0.088) emerged between the two groups, with 36/89 (40.4%) and 5/19 (26.3%)

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of patients being negative at 14 days since treatment administration in the mAbs and TIX/CIL group, respectively (Figure 1).

Supplementary Table S1 describes signs and symptoms displayed by enrolled patients at the time of treatment evaluation, the only difference is a lower frequency of fever among the TIX/CIL patients. Supplementary Table S2 provides details about the different mAbs administered and the vaccine doses received by the enrolled patients. Overall, the mAbs most frequently administered was sotrovimab whereas patients in the TIX/CIL group received more vaccine doses compared to those in the mAb cohort.

Discussion

In our study, early treatment of SARS-CoV-2 infection with TIX/CIL shows favourable outcomes in a small group of immunocompromised patients, reporting no significant difference when compared to subjects with comparable health condition treated with other mAbs. Likewise, the time to the negativity of nasal swabs was not different among the different treatments. Our findings have been obtained in Italy in the period August-October 2022, after the approval of TIX/CIL as early COVID-19 treatment by the Agenzia Italiana del Farmaco [7]. In this timeframe the SARS-COV-2 variant of concerns (VOCs) predominant in the Italian territory were Omicron BA.4 and BA.5 [8], thus our data can be applied to a setting where these VOCs, or others with susceptibility to TIX/CIL combination, are those most frequently responsible of infection.

Clinically significant protection against progression to severe COVID-19 or death has been demonstrated for TIX/CIL early treatment in large phase 3, registration studies [4,5]. Evidence are accumulating showing the efficacy of TIX/CIL primary prophylaxis among immunocompromised patients [9–11], but there are no current studies which have assessed specifically the impact of TIX/CIL early treatment among this group of patients. Overall, in the ACTIV-3/TICO and TACKLE studies, immunocompromised patients were 57 (8%) and 22 (5%), respectively [4,5]. Our study is therefore the first one providing preliminary evidence for this vulnerable group of people, employing as comparators others mAbs and not placebo, thus reflecting more accurately the real-life experience. Unfortunately, recently published *in vitro* data has suggested how emerging Omicron sub-lineages are resistant to most (i.e., BA.4.6, BA.2.75.2, and BJ.1) or all (BQ.1.1) mAbs used in routine practices, including TIX/CIL [11]. As infections due to VOCs BQ.1/1.1 are skyrocketing in Western countries, including Italy, our data might soon become less relevant because of the rapidly evolving epidemiology [8].

Our study has some inherent limitations related to its retrospective design. Particularly, TIX/CIL treatment has been compared with a historic group of patients treated with other mAbs, with different SARS-Cov-2 VOCs representing the dominant strain at the time and with a population who received fewer vaccine dose and experienced fewer past SARS-CoV-2 infections. Nonetheless, considering the similarity of the patients included in the two study groups, and the impossibility for ethical reasons to compare TIX/CIL with mAbs with known inefficacy against Omicron VOC, we believe that our results are still of interest. Another theoretical limit is the follow-up time for clinical outcomes restricted to 14 days since treatment administration, which may have reduced the detection of long-term outcomes due to COVID-19.

Overall, TIX/CIL early treatment has demonstrated favourable outcomes among immunocompromised patients, supporting its employment in this population which usually does not have access to other treatments because of drug-drug interactions (i.e., nirmatrelvir/ritonavir and tacrolimus in SOT) or comorbidities (i.e., nirmatrelvir/ritonavir or molnupiravir among patients with estimated glomerular filtration rate <30 mL/min). TIX/CIL should be offered as early treatment until the evolution of circulating VOCs will not lead to its futility.

Evidence on the effectiveness of TIX/CIL treatment in clinical practice is limited, specifically among fragile subjects, who have been poorly represented from major randomized controlled trials but are those who may benefit the most from these approaches. There is, therefore, an urgent need to shed light on the safety, efficacy, and long-term outcomes of early treatment with TIX/CIL among this peculiar population, especially in the context of SARS-CoV-2 VOCs BQ.1/1.1 diffusion.

Authors contributions: AL, SV, AG, and AB conceived the study. GV, SB, EP, CA, NI, BM, CG, MT, AT, MF, AGV, LCM, FD, GC, RC, MC and AM enrolled the patients and collected clinical data. AL and SV performed the statistical analysis. AL, GV and SV wrote the first draft of the manuscript. All the other authors reviewed the final version of the manuscript.

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Conflicts of Interests: AL Gilead Sciences Inc. and Insmed Italia. AB Quiagen, Pfizer, Nordic Pharma, ViiV, SOBI, and Gilead Sciences. FD Kedrion, Gilead Sciences, Biotest, and Novartis. AM Gilead Sciences, Menarini, and Nordic Pharma. SB Infectopharma. MC Takeda and Kedrion. All the other authors have nothing to declare.

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