Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Research Note

Pre-exposure prophylaxis with tixagevimab and cilgavimab (Evusheld) for COVID-19 among 1112 severely immunocompromised patients

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ABSTRACT

Objective: Immunocompromised patients have an increased risk of a severe form of COVID-19. The clinical efficacy of the tixagevimab/cilgavimab monoclonal antibody combination as pre-exposure prophylaxis against BA.1 and BA.2 SARS-CoV-2 Omicron sublineages is unknown. We aimed to describe the incidence and outcomes of COVID-19 among immunocompromised patients receiving tixagevimab/cilgavimab as preexposure prophylaxis during the Omicron wave in France.
Methods: This was an observational multicentre cohort study of immunocompromised patients receiving tixagevimab/cilgavimab as preexposure prophylaxis between December 28, 2021 and March 31, 2022. Patients received tixagevimab/cilgavimab 150/150 mg intramuscularly if they had impaired vaccine response and a high risk of severe form of COVID-19.
Results: Tixagevimab/cilgavimab was administered to 1112 immunocompromised patients. After a median (range) follow-up of 63 (49–73) days, COVID-19 was confirmed in 49/1112 (4.4%) ≥5 days after treatment. During the study period, mean weekly incidence rate was 1669 in 100 000 inhabitants in Ile-

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de-France and 530 in 100 000 among patients who received tixagevimab/cilgavimab prophylaxis. Among infected patients, 43/49 (88%) had a mild-to-moderate form and 6/49 (12%) had a moderate-to-severe form of COVID-19. Patients with moderate-to-severe illnesses were less likely to have received early therapies than patients with mild forms (53.5% vs. 16.7% respectively) and 2/49 (4%) patients died from COVID-19.

Discussion: Our study reported a low rate of infections and severe illnesses among immunocompromised patients treated with tixagevimab/cilgavimab. A global preventive strategy including vaccines, pre-exposure prophylaxis with monoclonal antibodies, and early therapies might be effective to prevent severe forms of COVID-19 among severely immunocompromised patients. **Yann Nguyen, Clin Microbiol Infect 2022;28:1654.e1–1654.e4**

Introduction

Immunocompromised patients have an increased risk of severe form of COVID-19 pneumonia [1] and are more likely to have impaired vaccine response.

Monoclonal antibodies against SARS-CoV-2 have been approved as preexposure prophylaxis of COVID-19 for patients at risk of severe disease with impaired vaccine response. Patients first received casirivimab/imdevimab [2], until the fast spread of SARS-CoV-2 Omicron, given their lack of neutralizing activity on this new variant [3,4].

More recently, tixagevimab/cilgavimab (Evusheld), a monoclonal antibody combination, was authorized for high-risk patients with impaired vaccine response [5], after results of the Phase III Double-blind, Placebo-controlled Study of AZD7442 for Pre-exposure Prophylaxis of COVID-19 in Adult (PROVENT) trial, during which unvaccinated treated patients exhibited a decreased risk of symptomatic infection [6]. However, this trial occurred in early 2021 and included only <4% immunocompromised patients. Because of the fast spreading of the BA.1 and BA.2 SARS-CoV-2 Omicron sublineages, with varying degrees of neutralizing activity of the monoclonal antibodies [3,7], and extremely scarce real-life data [8], the clinical efficacy of tixagevimab/cilgavimab needs to be further revisited [9].

Thus, our objective was to describe the incidence and the outcomes of COVID-19 among immunocompromised patients receiving tixagevimab/cilgavimab as preexposure prophylaxis during the Omicron wave in France.

Patients and methods

Study population

This was an observational multicentre cohort study of immunocompromised patients receiving tixagevimab/cilgavimab as preexposure prophylaxis in nine departments on three University Hospitals located in Ile-de-France (Nephrology, Haematology, Internal Medicine, Pulmonology, Rheumatology, and Cardiac Surgery) between December 28, 2021 and March 31, 2022. The patients' management was homogeneous, as common guidelines were provided by the working group (list of members in the *Supplementary appendix*).

Patients had impaired response, defined by anti-Spike IgG antibodies <264 binding antibody units per ml [10], after at least three doses of vaccine. Their medical condition included solid organ transplant recipients; autologous stem cell transplantation; haematologic malignancies; immunosuppressants including rituximab, obinutuzumab, mycophenolate mofetil, azathioprine, and/or cyclophosphamide; or primary immune deficiency.

Patients with confirmed SARS-CoV-2 infection <5 days after tixagevimab/cilgavimab administration were excluded from the analyses, as they could have been infected before treatment. The study was approved by the local institutional review board (IRB 000111928).

Data collection

The demographic and clinical data were collected using an anonymized form. COVID-19 were defined by a positive SARS-CoV-2 real-time reverse transcriptase-polymerase chain reaction and/or rapid antigen test on nasal swabs. All patients were asked to report a diagnosis of COVID-19 infection to their physician as soon as the diagnosis was made (by phone and/or e-mail).

Data concerning clinical symptoms and patients' management were collected. For early infections without need for oxygen, early specific treatments were collected (sotrovimab, nirmatrelvir/ritonavir, remdesivir, or intravenous tixagevimab/cilgavimab). The treatment choice was left to the physician's decision. The patients were classified as follows: mild (any various signs or symptoms of COVID-19 without need for oxygen) or moderate/severe (requiring oxygen therapy, noninvasive ventilation, or invasive mechanical ventilation).

Statistical analysis

The patients' characteristics were described with mean (SD) for quantitative variables and count (percent) for qualitative variables. Weekly COVID-19 incidence rates among patients treated with tixagevimab/cilgavimab were smoothed using a LOcally Estimated Scatterplot Smoothing (LOESS) (local polynomial) regression and plotted against incidence rates in the Ile-de-France general population using R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria). Data for Ile-de-France and for COVID variants data were obtained from Santé Publique France on March 31, 2022 (https://geodes.santepubliquefrance.fr).

Results

Study population

During the study period, 1112 patients received tixagevimab/cilgavimab as pre-exposure prophylaxis (Supplementary Figure). There were several causes of immunosuppression: kidney ($n = 511$; 46%), heart (83; 7.5%), lung ($n = 36$; 3.2%), or liver ($n = 1$; 0.1%) transplant recipients; haematologic malignancies ($n = 306$; 37.5%), rituximab for autoimmune diseases ($n = 125$; 11.3%), other immunosuppressive treatments (27; 2.4%), and primary immune

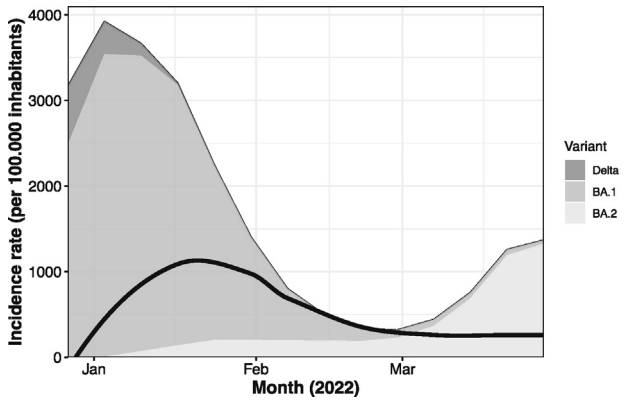

Fig. 1. Comparative incidence rate of COVID-19 in the general population and the tixagevimab/cilgavimab-treated population. Black curve, COVID-19 incidence rate among patients treated with tixagevimab/cilgavimab, smoothed using a LOESS local weighted regression model. Shaded areas, COVID-19 incidence rates in Ile-de-France according to the COVID-19 variant. All incidence data are shown as weekly incidence per 100 000 inhabitants. Data for Ile-de-France and variant data were obtained from Santé Publique France on March 31, 2022 (https://geodes.santepubliquefrance.fr).

deficiency (n = 23; 2.1%). The median (IQR) follow-up was 63 (49–73) days after treatment (63 362 patient-days).

COVID-19 and outcomes

As of March 31, 2022, 56 patients had confirmed SARS-CoV-2 infection: 7 were diagnosed before 5 days after tixagevimab/cilgavimab and were excluded (see Methods), and 49/1112 (4.4%) had confirmed infection ≥5 days after treatment, after a median (IQR) of 21 (13–36) days. Variant determination was available for 29/49 (59%) patients and identified Omicron in all cases.

During the study period, the mean weekly incidence rate was 1669 in 100 000 inhabitants in Ile-de-France and 530 in 100 000 among our study population. The incidence rates among our study population and Ile-de-France population, depending on the predominant SARS-CoV-2 variant are shown in Fig. 1.

Among infected patients, 43/49 (88%) had a mild form and were treated as outpatients, whereas 6/49 (12%) patients had a moderate-to-severe form (Table 1). Compared with patients with mild illness, the patients with moderate-to-severe illnesses were older (mean (standard deviation) 55.7 (20.2) vs. 78.0 (12.9) years, respectively) and less likely to have received an early therapy (1/6 (16.7%) vs. 23/53 (53.5%), respectively). Among them, 4/6 (66.6%) were kidney transplant recipients (KTR), and 2/6 (33.3%; 4% of infected patients) died (one 74-year-old KTR, and one 85-year-old patient with chronic lymphocytic leukaemia treated with obinutuzumab); none of them had received early therapy.

Discussion

In this large multicentre cohort of immunocompromised patients receiving pre-exposure prophylaxis with tixagevimab/cilgavimab during the Omicron wave in France, <5% had subsequent confirmed COVID-19 with a median follow-up of 2 months. Although proper comparisons between our study population and Ile-de-France population are possibly biased, the incidence rates were lower among patients treated with tixagevimab/cilgavimab, especially when BA.2 sublineage was predominant.

Table 1
Characteristics of the 49 patients with confirmed COVID-19 infection at least 5 days after tixagevimab/cilgavimab preexposure prophylaxis

	Overall (n = 49)	Mild COVID-19 (n = 43)	Moderate-to-severe COVID-19 (n = 6)
Age, y	58.9 (20.7)	55.7 (20.2)	78.0 (12.9)
Underlying cause of immunosuppression			
Heart transplant	4 (8.2)	4 (9.3)	0 (0.0)
Lung transplant	3 (6.1)	3 (7.0)	0 (0.0)
Kidney transplant	17 (34.7)	13 (30.2)	4 (66.7)
Haematologic malignancies	12 (24.5)	11 (25.6)	1 (16.7)
Treatment with rituximab	10 (20.4)	9 (20.9)	1 (16.7)
Treatment with azathioprine	1 (2.0)	1 (2.3)	0 (0.0)
Primary immune deficiency	2 (4.1)	2 (4.7)	0 (0.0)
Days between treatment and infection	26 (17)	27 (18)	20 (11)
Previous treatment with REGEN-CoV2	27 (56.2)	23 (54.8)	4 (66.7)
Clinical symptoms			
None	3 (6.1)	3 (7.0)	0 (0.0)
ENT involvement	28 (57.1)	26 (60.5)	2 (33.3)
Diarrhoea, vomiting	9 (18.4)	5 (11.6)	4 (66.7)
Cough	23 (46.9)	18 (41.9)	5 (83.3)
Dyspnoea	7 (14.3)	3 (7.0)	4 (66.7)
Fever	17 (34.7)	14 (32.6)	3 (50.0)
Muscle pain	9 (18.4)	9 (20.9)	0 (0.0)
Early therapy	24 (49.0)	23 (53.5)	1 (16.7)
Sotrovimab	11 (22.4)	10 (23.3)	1 (16.7)
Nirmatrelvir/ritonavir	4 (8.2)	4 (9.3)	0 (0.0)
Remdesivir	4 (8.2)	4 (9.3)	0 (0.0)
Evusheld	5 (10.2)	5 (11.6)	0 (0.0)
Other treatment			
Dexamethasone	4 (8.2)	0 (0.0)	4 (75.0)
Tocilizumab	3 (6.1)	0 (0.0)	3 (50.0)
Convalescent plasma	1 (2.0)	0 (0.0)	1 (16.7)
Hospitalization	10 (20.4)	4 (9.3)	6 (100.0)
Oxygen therapy	6 (12.2)	0 (0.0)	6 (100.0)
Noninvasive ventilation	2 (4.1)	0 (0.0)	2 (33.3)
Death	2 (4.1)	0 (0.0)	2 (33.3)

Data are presented as mean (SD) or count (percent).
ENT, ear nose throat; N, number.

Importantly, only 12% of infected patients (mostly KTR) had a moderate-to-severe disease, and 4% died. Of interest, almost no patients who also received early therapies presented with a moderate-to-severe form. Thus, the global preventive strategy with vaccines, pre-exposure prophylaxis, combined with early therapies once COVID-19 infection is diagnosed, appeared to be efficient. Although the Omicron variants have been associated with less severe diseases than the Delta variant, mortality among immunocompromised patients (at least KTR) remains high without adequate pre-exposure prophylaxis treatment and early treatment [11].

Our study presented some limitations. First, the study was noncomparative, as pre-exposure prophylaxis was proposed to all identified eligible patients. The incidence rates could not be directly compared with the general population, regarding risk-taking behaviour, age, and vaccination. In addition, our rate of COVID-19 might have been underestimated, as we might have missed some cases (undiagnosed or not reported infections). However, it is unlikely that moderate-to-severe forms were missed, as we had access to their electronic medical record if they had been hospitalized. Furthermore, it is likely that the COVID-19 diagnosis rate was higher in our immunocompromised patients, strongly advised to perform a COVID-19 test in case of even mild symptoms. Most patients were diagnosed with rapid antigen test or with real-time reverse transcriptase-polymerase chain reaction performed in out-of-hospital laboratories, which did not provide variant data. Thus, we only had partial identification on Omicron sublineages. However, during the study period, BA.1 was predominant in January while BA.2 became dominant from the beginning of March 2022. This is of importance as BA.2 is more sensitive to cilgavimab than BA.1 *in vitro* [3]. Finally, follow-up duration was limited.

Our study had several strengths, including a large number of patients with various causes of immunosuppression, and a standardized management.

In conclusion, our study suggested the efficacy of tixagevimab/cilgavimab for immunocompromised patients who should benefit from a global preventive strategy (e.g vaccines, pre-exposure prophylaxis, and early therapies). Further data are required to determine whether this prophylaxis will remain efficient with time and if the now recommended increased dose of tixagevimab/cilgavimab 300/300 mg could improve its efficacy against all Omicron sublineages and future emerging variants.

Transparency declaration

No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article. None of the authors declared any competing interest in link with the present study. Data are available upon reasonable request.

Author contributions

All authors contributed to the manuscript. YN, AF, and LM were responsible for conception and design. YN, AF, Netilmicin, Clindamycin, Minocycline, PD, EL, Netilmicin, MT, EF were responsible for data collection. YN and AF were responsible for analysis. All authors were responsible for the interpretation of data. YN wrote the first version of the manuscript. All authors critically revised and approved the final version of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2022.07.015.

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