International Journal of Infectious Diseases 144 (2024) 107042

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Short Communication

Risk of SARS-CoV-2 infection in patients with hematologic diseases receiving tixagevimab/cilgavimab as pre-exposure prophylaxis in most recent Omicron sublineages era

Alessandra Vergori[1,*], Alessandro Cozzi Lepri[2], Marta Chiuchiarelli[3], Valentina Mazzotta[1], Elisabetta Metafuni[3], Giulia Matusali[4], Valentina Siciliano[3], Jessica Paulicelli[1], Eleonora Alma[5], Agostina Siniscalchi[6], Simona Sica[3], Elisabetta Abruzzese[7], Massimo Fantoni[3], Andrea Antinori[1], Antonella Cingolani[3]

[1] *Viral Immunodeficiency Unit, Clinical and Research Infectious Diseases Department, National Institute for Infectious Diseases Spallanzani, IRCCS, Rome, Italy*
[2] *Centre for Clinical Research, Epidemiology, Modelling and Evaluation (CREME), Institute for Global Health, UCL, London, UK*
[3] *UOC Malattie Infettive, Fondazione Policlinico A. Gemelli, IRCCS*
[4] *Laboratory of Virology, National Institute for Infectious Diseases Spallanzani, IRCCS, Rome, Italy*
[5] *UOC Ematologia, Fondazione Policlinico A. Gemelli, IRCCS*
[6] *UOSD Ematologia ASL Roma 1, San Filippo Neri Hospital, Rome, Italy*
[7] *UOC Ematologia, Sant'Eugenio Hospital, Rome, Italy*

ARTICLE INFO

Article history:
Received 13 February 2024
Revised 19 March 2024
Accepted 3 April 2024

Keywords:
SARS-CoV-2
COVID-19
Hematologic disease
Pre-exposure prophylaxis
Tixagevimab/cilgavimab

ABSTRACT

Objectives: Whether pre-exposure prophylaxis (PrEP) with tixagevimab/cilgavimab 150 mg/150 mg (T/C) in individuals with hematologic disease (HD) may lead to a reduced risk of SARS-CoV-2 breakthrough infection (BTI)/hospitalization, or death in the Omicron era remains to be established.
Methods: An observational study included participants with HD who received PrEP. BTIs were defined as SARS-CoV-2 positivity by reverse transcription-polymerase chain reaction. The incidence of BTIs (95% CI) and of BTIs/hospitalization/death was calculated using the Kaplan-Meier method and as the number of BTIs per 100 person-years of follow-up according to the circulating variant of concern (VoC). A Poisson regression model was used to evaluate the association between the rate of incidence and circulating VoCs after controlling for demographics and clinical factors.
Results: We included 550 HD patients: 71% initiated T/C PrEP when BA.5 was the most prevalent, followed by XBB/EG, BA.2, and BA.1 (19%, 7%, and 3%, respectively). Overall, the 1-year incidence estimate of BTIs/hospitalization/death was 24% (18.7-29.4%). A greater risk of incident infections was observed when BA.5 and XBB/EG sub-lineages circulated (aRR 5.05 [2.17, 11.77]; $P < .001$ and 3.82 [1.50, 9.7]; $P = 0.005$, compared to BA.1, respectively).
Conclusions: The 1-year incidence of SARS-CoV-2 BTIs/hospitalization/death was 24% which is in line with what was observed in other similar studies. The risk appeared to be higher when more recent Omicron sub-lineages were circulating suggesting a reduction of *in vitro* neutralization.

Introduction

Although the overall mortality during the SARS-CoV-2 Omicron variants of concern (VoC) wave might be lower than that seen with other previous variants of concern (VoCs), immunocompromised individuals remain at increased risk of hospitalization and prolonged duration of the infection compared to the general population [1]. Moreover, persons with immunosuppression may experience reduced vaccine immune response with impaired seroconversion and effectiveness [2]. To address the need to protect these individuals from breakthrough infections (BTIs) and possibly from long-lasting SARS-CoV-2 infections, in December 2021

* Corresponding author:
E-mail address: alessandra.vergori@inmi.it (A. Vergori).

https://doi.org/10.1016/j.ijid.2024.107042

Table 1
General characteristics of the study population according to circulating variant of concern.

Characteristics at T/C prophylaxis initiation	VoC					
	BA.1	BA.2	BA.5	XBB/EG	*P*-value[a]	Total
	N = 18	N = 37	N = 390	N = 105		N = 550
Age, years						
Median (IQR)	68 (61, 71)	65 (51, 71)	65 (55, 74)	63 (51, 72)	0.266	64 (55, 73)
Gender, n(%)						
Female	12 (66.7)	19 (51.4)	166 (42.5)	62 (59.0)	0.006	259 (47.0)
Hematologic disease type, n(%)					0.002	
Hodgkin Lymphoma	0 (0.0)	2 (5.7)	33 (8.9)	4 (4.1)		39 (7.5)
Non-Hodgkin Lymphoma	10 (58.8)	25 (71.4)	228 (61.3)	70 (72.2)		333 (63.9)
Multiple Myeloma	2 (11.8)	2 (5.7)	63 (16.9)	2 (2.1)		69 (13.2)
Chronic Leukemia	5 (29.4)	6 (17.1)	48 (12.9)	21 (21.6)		80 (15.4)
Other comorbidities, n(%)					0.069	
Yes	9 (50.0)	22 (59.5)	222 (56.8)	74 (70.5)		327 (59.3)
Year of starting T/C prophylaxis						
Median (IQR)	2022 (2022, 2022)	2022 (2022, 2022)	2022 (2022, 2022)	2023 (2023, 2023)	<.001	2022 (2022, 2023)
No. of vax doses, n(%)					<.001	
3-4	16 (88.9)	32 (86.5)	347 (88.7)	83 (79.0)		478 (86.8)
Anti-CD20 treatment, n(%)					0.077	
Yes	5 (27.8)	15 (40.5)	196 (50.1)	73 (69.5)		289 (52.5)
CAR-T treatment, n(%)					<.001	
Yes	0 (0.0)	4 (10.8)	14 (3.6)	0 (0.0)		18 (3.3)
Stem cell transplants, n(%)					0.012	
Yes	0 (0.0)	11 (29.7)	33 (8.4)	2 (1.9)		46 (8.3)

[a] Chi-square or Kruskal-Wallis test as appropriate.
Abbreviations: VoC, variant of concern; T/C, tixagevimab/cilgavimab.

the combination tixagevimab/cilgavimab (T/C) (EvusheldTM, AstraZeneca) received the emergency use authorization (EUA) from the United States Food and Drug Administration (FDA) as pre-exposure prophylaxis (PrEP) at the dosage of 150/150 mg in moderate to severely immunocompromised individuals (aged 12 years or older and weighing >40 kg) who could not be vaccinated against COVID-19 or who may have had an inadequate response to SARS-CoV-2 vaccination. Subsequently, the same drug combination was approved in Europe and Italy, in March 2022, at the dosage of 150/150 mg given intramuscularly (IM). As of March 2024, this is the official mainstay for Europe, the Middle East, Africa and the Italian drug regulatory agency to protect those with hematologic disease (HD) and other fragile populations, although in practice is no longer used in the clinics because of *in vitro* data showing poor neutralizing activity against newly circulating Omicron subvariants [3–6].

Based on its *in vitro* reduced effectiveness against Omicron, initially, the FDA revised the recommendation for PrEP by supporting the double dose of T/C (300/300 mg) in February 2022, and in January 2023 the use of T/C was paused for PrEP with the withdrawal of the EUA [7]. However, the European Medicines Agency did not take the same action as the use of T/C was paused for treatment but not for PrEP and did not recommend the use of double dosage. Several studies evaluated the real-world efficacy of T/C prophylaxis but predominantly in the early Omicron era characterized by BA.1 and BA.2 variants circulation. The clinical efficacy of T/C as PrEP in patients with HD against the newest Omicron sub-variants of SARS-CoV-2 was rarely investigated and long-term incidence data are sparse.

Methods

Study population and design

This is an observational study (Studio Osservazionale sui CorrelaTi immunOlogici di Protezione nella profilaSsi pre-esposizione di COVID-19 con Tixagevimab/Cilgavimab-OCTOPUS study) including adult immunocompromised subjects who received 150/150 mg of T/C given IM as PrEP between March 2022 and August 2023.

The study includes clinical and immunological outcomes of PrEP with T/C in immunocompromised patients' non-responder or weakly responder to SARS-CoV-2 natural infection and/or vaccination, conducted at two infectious diseases centers in Italy (project details are reported in Supplementary Material). In this analysis, only participants with HD have been included, and demographic and clinical data have been used.

Results and discussion

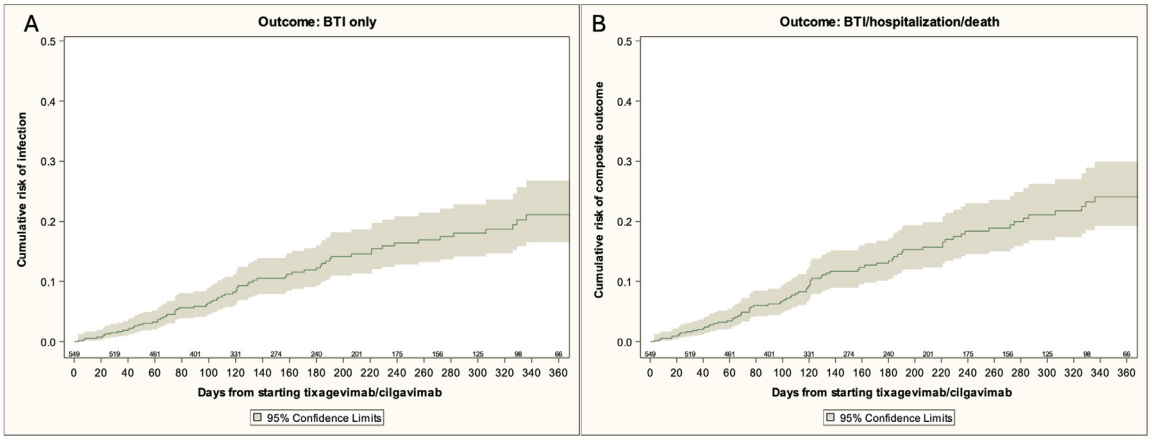
We included 550 participants with HD, their general characteristics according to the circulating VoC at the time of starting PrEP with T/C are reported in Table 1.

Briefly, the median age of the individuals included was 64 years (IQR 55-73), 47% were female, 59% had non-hematologic comorbidities and 87% of the participants received at least three vaccine doses before starting PrEP.

None of the patients reported adverse events secondary to T/C.

After a median follow-up post-PrEP of 149 (IQR:85-285) days, 69 BTIs were observed (12.5%), while severe COVID-19 occurred in six (7.7%) participants and four (5.1%) deaths due to COVID-19 and one (1.3%) non-COVID death were observed. Overall, the 1-year incidence estimate of BTIs was 21% (95% CI 16.0-26.2%), with a cumulative risk that appeared to increase linearly with a longer time since PrEP (Figure 1a). Similar results were obtained with the composite endpoint (BTIs/hospitalization/death with a total of 78 events) (Figure 1b).

The emergence of the Omicron sub-variants hindered T/C efficacy as PrEP, as several *in vitro* studies showed decreased potency against them [6]. Mixed results were reported regarding monoclonal antibodies neutralizing activity against Omicron lineages [5]. However, the true clinical efficacy of T/C in terms of risk of both BTIs and hospitalization and death related to COVID-19 in patients with severe immunosuppression observed during the circulation of the newer SARS-CoV-2 variants has yet to be well defined. In our analysis, which enrolled patients with HD, T/C led to 12% of BTIs with a 1-year incidence estimate of BTIs/hospitalization/death of 24% (18.7-29.4%) which is in line with what was expected especially considering that BA.5 and XBB/EG sub-lineages have started



1-year Estimate	95% CI Lower Limit	95% CI Upper limit	1-year Estimate	95% CI Lower Limit	95% CI Upper limit
21%	16.0%	26.2%	24%	18.7%	29.4%

Figure 1. Incidence estimates of breakthrough infections (a) and of breakthrough infections/hospitalization/death (b) by Kaplan-Meier curves.

to circulate throughout the study. Our estimate of the rate of BTI occurrence is higher than previously reported in immunocompromised subjects, prevalently with hematologic diseases in the Omicron era [8–10]. However, importantly our estimated risk of severe disease required hospitalization and death related to COVID-19 after T/C PrEp was low.

Nevertheless, it is worth noting that BTI incidence rates reported in the literature are very heterogeneous, making the results difficult to compare across studies. First, study populations are not strictly homogeneous in terms of immunodepression conditions, often mixing solid organ transplant patients and patients with different hematologic diseases. Second, follow-up time in the different studies tended to be limited, rarely exceeding 90 days of observation. Finally, most of the studies were conducted in epidemiologic eras in which early Omicron subvariants, namely BA.1 and BA.2, prevailed, and lower rates of BTIs and severe COVID-19 during these Omicron waves were, in general, reported [8–10].

To our knowledge, ours is the study with the longest follow-up to date and PrEP administration mostly occurred when Omicron BA.5 was circulating. Our data confirms an association between the circulating VoC and the risk of incident BTIs which was higher when BA.5 and XBB/EG sub-lineages circulated (aRR 5.05 [2.17, 11.77]; $P < .001$ and 3.82 [1.50, 9.72]; $P = 0.005$), compared to BA.1, respectively (Supplementary Table 1, Panel A). Similar results were observed with the composite endpoint BTIs/hospitalization/death (Supplementary Table 2, Panel B).

Besides the length of follow-up, one of the major strengths of our analysis is the inclusion of a large cohort of hematologic patients at high risk of severe COVID-19 who were followed up at the same time points under a common protocol according to clinical practice. The cohort was also homogenous in the sense that everybody had a diagnosis of hematologic cancer, and all satisfied the Agenzia Italiana Del Farmaco (AIFA - the Italian drug regulatory agency) criteria for receiving prophylaxis. Our study also has some limitations. First, we controlled for age, gender, other comorbidities, type of disease, history of previous infection, and previous receipts of a SARS-CoV-2 booster dose in the Poisson regression model. Although we believe that this adjustment was sufficient to block all baseline confounding pathways, we cannot rule out that there might be time-varying confounders affected by current VoC and unmeasured confounding that we could not control for. For example, although none of the participants were in full remission or were off treatment for many months, the exact date of the last immunosuppressive treatment was not available in the database, and this could be a source of residual confounding. Second, because prophylaxis was still mandatory, we do not have a concurrent group of similar patients at our hospitals who did not receive prophylaxis to compare their 1-year incidence of BTIs. Third, the actual VoCs that caused BTIs were inferred based on regional circulation data. Finally, we have no available virological data on serological and neutralization activity or other immunological data to be correlated with the clinical outcome.

In conclusion, our analysis showed an incidence rate of BTIs which was as expected, if anything, possibly lower than what could predicted considering the calendar periods covered by the study. Also, a linear increase in the incidence of BTIs was seen with a longer time from the initiation of prophylaxis although, of note, a very low rate of severe disease requiring hospitalization was observed. We found evidence that the risk of BTIs was higher with more recently circulating VoCs. We speculate that this may be due to a reduction in neutralizing activity developed by our patients and the waning of such activity against more recent Omicron strains. Further studies are needed to investigate the effectiveness of alternative prophylactic interventions to prevent infection with new SARS-CoV-2 circulating strains and its complications in this patient population.

Declaration of competing interest

All authors report no conflicts of interest relevant to this article.

Funding

None.

Acknowledgments

We acknowledge all the participants, the nurse staff, the clinical support, and help with data collection provided by the OCTOPUS Study Group.

Octopus Study Group

Elisabetta Abruzzese, Samir Al Moghazi, Andrea Antinori, Roberta Battistini, Aurora Bettini, Licia Bordi, Paola Borrelli,

Emanuela Caraffa, Rita Casetti, Eleonora Cimini, Antonella Cingolani, Flavia Cristofanelli, Alessandra D'Abramo, Katleen De Gaetano, Federico De Zottis, Gianpiero D'Offizi, Massimo Fantoni, Massimo Francalancia, Eugenio Galli, Maria Grazia Garzia, Simona Gili, Enrico Girardi, Germana Grassi, Simone Lanini, Giovanni Luzi, Fabrizio Maggi, Davide Mariotti, Giulia Matusali, Valentina Mazzotta, Paola Mencarini, Silvia Meschi, Elisabetta Metafuni, Cosmina Mija, Eugenia Milozzi, Klizia Mizzoni, Emanuele Nicastri, Stefania Notari, Fabrizio Palmieri, Roberta Palazzi, Jessica Paulicelli, Luca Prosperini, Angela Rago, Silvia Rosati, Simona Sica, Agostina Siniscalchi, Federica Sorà, Fabrizio Taglietti, Eleonora Tartaglia, Alessandra Vergori, Serena Vita

Author contributions

Conception: AC, AA, ACL, and AV. Study design: AV, AA. Acquisition of data: AV, MC, JP, and VM. Statistical analysis: ACL. Data collection: JP, MC, VS, AS, and EA. Interpretation of the data: AV, AA, AC, ACL, EM, EA, SS, and MF. Drafted the article: AV and AC. Review of the article and critical revision for important intellectual content: all the authors. Final approval of the submitted version: all the authors.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2024.107042.

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