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, Alessandro Cozzi Lepri, Marta Chiuchiarelli, Valentina Mazzotta, Elisabetta Metafuni, Giulia Matusali, Valentina Siciliano, Jessica Paulicelli, Eleonora Alma, Agostina Siniscalchi, Simona Sica, Elisabetta Abruzzese, Massimo Fantoni, Andrea Antinori, Antonella Cingolani

PII: S1201-9712(24)00113-9
DOI: https://doi.org/10.1016/j.ijid.2024.107042
Reference: IJID 107042

To appear in: International Journal of Infectious Diseases

Received date: 13 February 2024
Revised date: 19 March 2024
Accepted date: 3 April 2024

Please cite this article as: Alessandra Vergori, Alessandro Cozzi Lepri, Marta Chiuchiarelli, Valentina Mazzotta, Elisabetta Metafuni, Giulia Matusali, Valentina Siciliano, Jessica Paulicelli, Eleonora Alma, Agostina Siniscalchi, Simona Sica, Elisabetta Abruzzese, Massimo Fantoni, Andrea Antinori, Antonella Cingolani, Risk of SARS-CoV-2 infection in patients with hematologic diseases receiving tixagevimab/cilgavimab as pre-exposure prophylaxis in most recent Omicron sublineages era, International Journal of Infectious Diseases (2024), doi: https://doi.org/10.1016/j.ijid.2024.107042

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2024 Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)
Highlights

- The 1-year incidence estimate of BTIs/hospitalization/death was 24%
- A greater risk of incident BTIs was observed with BA.5 and XBB/EG
- The search for a new prophylaxis is urgently needed
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 Vergori¹, Alessandro Cozzi Lepri², Marta Chiuchiarelli³, Valentina Mazzotta¹, Elisabetta Metafuni⁴, Giulia Matusali⁵, Valentina Siciliano³, Jessica Paulicelli¹, Eleonora Alma⁶, Agostina Siniscalchi⁷, Simona Sica⁴, Elisabetta Abruzzese⁸, Massimo Fantoni³, Andrea Antinori¹, Antonella Cingolani³

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 UOC Malattie Infettive, Fondazione Policlinico A. Gemelli, IRCCS
5 Laboratory of Virology, National Institute for Infectious Diseases Spallanzani, IRCCS, Rome, Italy
6 UOC Ematologia, Fondazione Policlinico A. Gemelli, IRCCS
7 UOSD Ematologia ASL Roma 1, San Filippo Neri Hospital, Rome, Italy
8 UOC Ematologia, Sant'Eugenio Hospital, Rome, Italy

Short Title: SARS-CoV-2 infection in PrEP

Corresponding author:
Alessandra Vergori, no conflicts

Viral Immunodeficiency Unit
Clinical and Research Infectious Diseases Department
National Institute for Infectious Diseases L.Spallanzani, IRCCS
Via Portuense, 292
00149 Rome, Italy
e-mail: alessandra.vergori@inmi.it

Co-authors:

**Alessandro Cozzi Lepri, no conflicts**
Centre for Clinical Research, Epidemiology, Modelling and Evaluation (CREME) Institute for Global Health, UCL, London, UK; a.cozzi-lepri@ucl.ac.uk

**Marta Chiuchiarelli, no conflicts**
UOC Malattie Infettive, Fondazione Policlinico A. Gemelli, IRCCS, Rome, Italy, martachiu95@gmail.com

**Valentina Mazzotta, no conflicts**
Clinical and Research Infectious Diseases Department National Institute for Infectious Diseases L. Spallanzani, IRCCS, Rome, Italy; valentina.mazzotta@inmi.it

**Elisabetta Metafuni, no conflicts**
UOC Ematologia e trapianto di cellule staminali emopoietiche, Fondazione Policlinico A. Gemelli, IRCCS, Rome, Italy; elisabetta.metafuni@policlinicogemelli.it

**Giulia Matusali, no conflicts**
Laboratory of Virology, National Institute for Infectious Diseases Spallanzani, IRCCS, Rome, Italy; giulia.matusali@inmi.it

**Valentina Siciliano, no conflicts**

UOC Malattie Infettive, Fondazione Policlinico A. Gemelli, IRCCS, Rome, Italy; valentina.siciliano@policlinicogemelli.it

**Jessica Paulicelli, no conflicts**

Clinical and Research Infectious Diseases Department National Institute for Infectious Diseases L. Spallanzani, IRCCS, Rome, Italy; Jessica.paulicelli@inmi.it

**Eleonora Alma, no conflicts**

UOC Ematologia, Fondazione Policlinico A. Gemelli, IRCCS, Rome, Italy; eleonora.alma@policlinicogemelli.it

**Agostina Siniscalchi, no conflicts**

UOSD Ematologia ASL Roma 1, San Filippo Neri Hospital, Rome, Italy; agostina.siniscalchi@aslroma1.it

**Simona Sica, no conflicts**

UOC Ematologia e trapianto di cellule staminali emopoietiche, Fondazione Policlinico A. Gemelli, IRCCS Rome, Italy; simona.sica@policlinicogemelli.it
Abstract

Introduction

Whether pre-exposure prophylaxis (PrEP) with tixagevimab/cilgavimab 150mg/150 mg (T/C) in individuals with hematological diseases (HD) may lead to a reduced risk of Breakthrough SARS CoV2 infection/hospitalization or death in the Omicron era remains to be established.

Methods
Observational study including participants with HD who received PrEP. Breakthrough infections were defined as a SARS-CoV-2 positivity by RT-PCR. The incidence of breakthrough infections (95%CI) and of breakthrough infections/hospitalization/death was calculated using the Kaplan-Meier method and as the number of breakthrough infections per 100-PYFU according to the circulating variant (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 breakthrough infections/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, 9.72); p=0.005, compared to BA.1, respectively].

**Conclusions**

The one-year incidence of SARS-CoV-2 breakthrough infections/hospitalization/death was 24% which is in line with what 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.

**Key words:** SARS-CoV-2; COVID19; Hematological disease; pre-exposure prophylaxis; tixagevimab/cilgavimab.

**Introduction**

Although the overall mortality during SARS-CoV-2 Omicron variants of concern (VoC) wave might be lower than that seen with other previous VoCs immunocompromised individuals remain at increased the 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 an impaired seroconversion and effectiveness [2]. To address the need to protect these individuals from breakthrough infections and possibly from long-lasting SARS-CoV-2 infections, in December 2021 the combination tixagevimab/cilgavimab (EvusheldTM, AstraZeneca; T/C) 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. As of March 2024, this is the official mainstay for EMEA and the Italian drug regulatory agency to protect those with hematological diseases as well as 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 on January 2023 the use of T/C was paused for pre-exposure prophylaxis with the withdrawal of the emergency use authorization [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 pre-exposure prophylaxis 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 hematological diseases (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 (OCTOPUS study) including adult immunocompromised subjects who received 150/150 mg of T/C given intramuscularly (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 hematological diseases (HD) have been included, and demographic and clinical of data have been used.

Results & Discussion

We included 550 participants with hematological diseases, 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 hematological comorbidities and 87% of the participants received at least 3 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 breakthrough infections were observed (12.5%), while a severe COVID-19 occurred in 6 (7.7%) participants and 4 (5.1%) deaths due to COVID-19 and one (1.3%) non-COVID death were observed. Overall, the 1-year incidence estimate of breakthrough infections was 21% [95% Confidence Interval (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 (breakthrough infections/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 breakthrough infections 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 breakthrough infections with a 1-year incidence estimate of breakthrough infections/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 to circulate throughout the study. Our estimate of the rate of breakthrough infections 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 breakthrough infections 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 condition, 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 epidemiological eras in which early Omicron subvariants, namely BA.1 and BA.2 prevailed and lower rates of breakthrough infections 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 breakthrough infections 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 breakthrough infections/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 hematological patients at high risk of severe COVID-19 which were followed-up at the same timepoints under a common protocol according to clinical practice. The cohort was also homogenous in the sense that everybody had a diagnosis of hematological cancer, and all satisfied the 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 prior infection and previous receipts of a SARS CoV2 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 as well as 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 breakthrough infections. Third, the actual VoCs that caused breakthrough infections was 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 breakthrough infections 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 incidence of breakthrough infections was seen with 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 breakthrough infections was higher with more recently circulating VoCs. We speculate that this may be due to a reduction in neutralizing activity developed by our patients as well as 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 newly SARS COV2 circulating strains and its complications in this patient population.

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


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

Conflict of interest

All authors report no conflicts of interest relevant to this article.
Funding: none

References


Figure 1. Incidence estimates of breakthrough infections (A) and of breakthrough infections/hospitalization/death (B) by Kaplan Meier curves.
Table 1. General characteristics of the study population according to circulating variant of concern (VoC)

<table>
<thead>
<tr>
<th>Characteristics at T/C prophylaxis initiation</th>
<th>VoC</th>
<th>BA.1</th>
<th>BA.2</th>
<th>BA.5</th>
<th>XBB/EG</th>
<th>P-value*</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years Median (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BA.1</td>
<td></td>
<td>68</td>
<td>65</td>
<td>65</td>
<td>63</td>
<td>0.266</td>
<td>64</td>
</tr>
<tr>
<td>BA.2</td>
<td></td>
<td>65</td>
<td>51</td>
<td>55</td>
<td>6 (51, 72)</td>
<td>0.006</td>
<td>64</td>
</tr>
<tr>
<td>BA.5</td>
<td></td>
<td>65</td>
<td>55</td>
<td>74</td>
<td>62 (59.0)</td>
<td>0.002</td>
<td>64</td>
</tr>
<tr>
<td>XBB/EG</td>
<td></td>
<td>65</td>
<td>68</td>
<td>74</td>
<td>4 (4.1)</td>
<td>0.069</td>
<td>64</td>
</tr>
<tr>
<td>Gender, n(%)</td>
<td></td>
<td>12</td>
<td>19</td>
<td>166</td>
<td>259 (47.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>(66.7)</td>
<td>(51.4)</td>
<td>(42.5)</td>
<td>(59.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematological disease type, n(%)</td>
<td></td>
<td>0</td>
<td>2</td>
<td>10</td>
<td>10</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Hodgkin Lymphoma</td>
<td></td>
<td>(0.0)</td>
<td>(5.7)</td>
<td>(8.9)</td>
<td>(41)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non Hodgkin Lymphoma</td>
<td></td>
<td>10</td>
<td>25</td>
<td>228</td>
<td>333 (63.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td></td>
<td>2</td>
<td>5</td>
<td>63</td>
<td>69 (13.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic Leukemia</td>
<td></td>
<td>5</td>
<td>6</td>
<td>48</td>
<td>80 (15.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other comorbidities, n(%)</td>
<td></td>
<td>9</td>
<td>22</td>
<td>222</td>
<td>327 (59.3)</td>
<td>0.069</td>
<td></td>
</tr>
<tr>
<td>Year of starting T/C prophylaxis Median (IQR)</td>
<td></td>
<td>2022</td>
<td>2022</td>
<td>2022</td>
<td>2022</td>
<td>&lt;.001</td>
<td>2022 (2022, 2023)</td>
</tr>
<tr>
<td>No. of vax doses, n(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-4</td>
<td></td>
<td>16</td>
<td>32</td>
<td>347</td>
<td>478 (86.8)</td>
<td></td>
<td>161</td>
</tr>
<tr>
<td>Anti-CD20 treatment, n(%)</td>
<td></td>
<td>5</td>
<td>15</td>
<td>196</td>
<td>289 (52.5)</td>
<td>0.077</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>(27.8)</td>
<td>(40.5)</td>
<td>(50.1)</td>
<td>(95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAR-T treatment, n(%)</td>
<td></td>
<td>0</td>
<td>4</td>
<td>14</td>
<td>18 (3.3)</td>
<td>0.012</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>(0.0)</td>
<td>(10.8)</td>
<td>(3.6)</td>
<td>(0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stem cell transplants, n(%)</td>
<td></td>
<td>0</td>
<td>11</td>
<td>33</td>
<td>46 (8.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>(0.0)</td>
<td>(29.7)</td>
<td>(8.4)</td>
<td>(1.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Chi-square or Kruskal-Wallis test as appropriate.

Abbreviations: VoC, variant of concern; T/C, tixagevimab/cilgavimab.

Declaration of Competing Interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The author is an Editorial Board Member/Editor-in-Chief/Associate Editor/Guest Editor for [Journal name] and was not involved in the editorial review or the decision to publish this article.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: