

RESEARCH LETTER

Incidence of severe COVID-19 in patients with chronic lymphocytic leukaemia or indolent B-cell non-Hodgkin lymphoma who received vaccination and pre-exposure prophylaxis with tixagevimab and cilgavimab in Italy: An observational study by the GIMEMA working party on chronic lymphoproliferative disorders and by the Fondazione Italiana Linfomi

To the Editor,

In the early years of the COVID-19 pandemic, haematological patients with chronic lymphocytic leukaemia (CLL) and indolent B-cell non-Hodgkin lymphoma (iB-NHL) were shown to be at high risk of developing severe COVID-19, with an 18%–30% death rate¹ and a poor response to COVID-19 vaccination, especially in those treated with anti-CD20 monoclonal antibodies, Bruton tyrosine kinase inhibitors or the BCL2 inhibitor venetoclax.² Targeted interventions have been promoted to support vulnerable patients including repeated vaccinations and pre-emptive prophylaxis with monoclonal antibodies. Likewise, a timely diagnosis and a prompt anti-viral treatment were shown to have a critical role in preventing severe COVID-19 complications.³ Indeed, in haematological patients, this multimodal strategy has led to a significant reduction in critical infections and a decrease in mortality from 29% to 4%, although hospitalization, particularly in intensive care units, remained associated with higher mortality rates.^{4,5} Pre-exposure prophylaxis (PrEP) with tixagevimab/cilgavimab (T-C) at a dosage of 150/150 mg was shown to reduce the incidence of symptomatic COVID-19 in unvaccinated subjects at high risk of infection.⁶ The emergence of new resistant variants reduced the effectiveness of this prophylaxis particularly in the era of Omicron prevalence⁷ and led to the approval of a higher 300/300 mg dosage and later to the withdrawal of T-C from clinical use. In the Omicron period, several real-world studies investigated the effectiveness of T-C for prevention of COVID-19 symptomatic infection and complications in people with immuno-compromising conditions. Variable levels of effectiveness were observed depending on the numerosity and heterogeneity of the study populations, on the period of follow-up post-PrEP and on the dynamic of circulating SARS-CoV-2 variants.^{8–12} In this context of evolving viral landscape, analyses on homogenous subsets of patients

with immunocompromising conditions could be helpful and informative to identify patients who are at higher risk of developing severe COVID-19 complications and who could be proposed for targeted therapeutic approaches.

This is an observational real-world multicentre study aimed at describing the role of the COVID-19 prophylaxis with T-C in the vaccination era in patients with CLL or iB-NHL patients (follicular, marginal zone and lymphoplasmacytic lymphoma). Patients were diagnosed and treated at 32 centres (Table S1) belonging to the Gruppo Italiano Malattie EMatologiche dell'Adulto (GIMEMA) group and the Fondazione Italiana Linfomi (FIL) group. Adult (>18 years) patients who received the first dose of 150/150 mg T-C according to the Italian drug agency AIFA indication between March and October 2022 were followed for at least 6 months. The primary end-point of the study was the incidence of severe COVID-19, defined as COVID-19-related hospitalization or COVID-19-related death. All COVID-19 diagnoses were confirmed either by polymerase chain reaction or rapid antigen test kits. The study was approved by the Ethics Committee and was registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (Number NCT05803395) and informed consent was obtained from all patients.

Overall, 636 patients were enrolled, 630 were eligible at the time of the study entry and 573 patients eligible for the analyses (195 iB-NHL and 378 CLL cases) while 57 patients were excluded because of insufficient data on T-C administration. Main clinical and biological characteristics are summarized in Table S2. CLL patients were older than iB-NHL patients (74 vs. 69 years, $p < 0.001$). More CLL patients were on treatment at the time of T-C administration while more iB-NHL cases had received anti-CD20 treatment within 12 months from T-C PrEP. All but three patients received PrEP with T-C at the approved single 150/150 mg dose. In three cases, the 300/300 mg dose was administered. Within 6 months from PrEP, 20 patients

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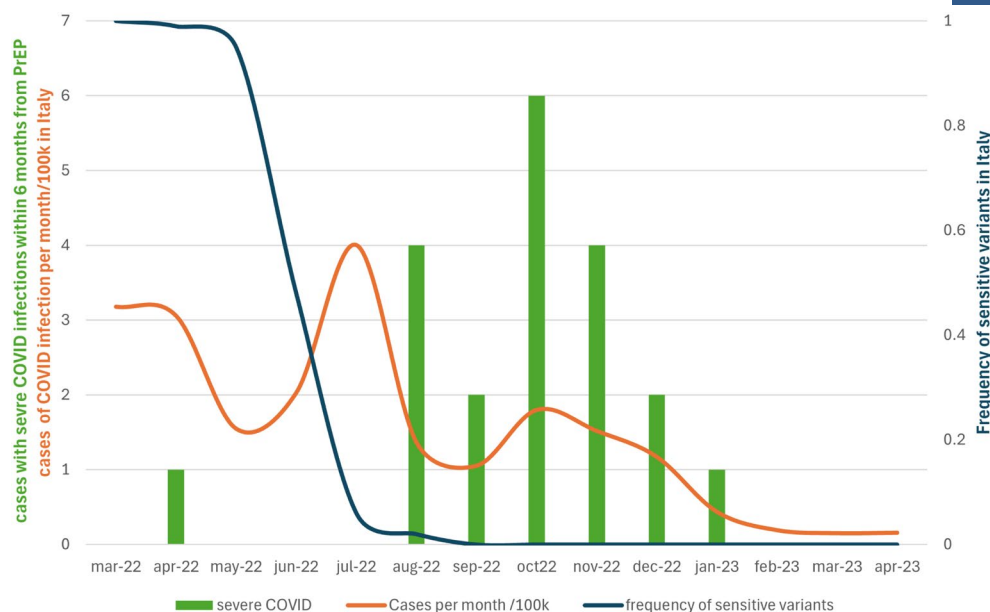


FIGURE 1 Severe COVID-19 within 6 months from PrEP (green bars) and cases of COVID-19 (orange line) (data from <https://www.epicentro.iss.it/coronavirus/sars-cov-2-sorveglianza-dati-archivio>) and frequency of sensitive SARS-CoV-2 variants (blue line) in Italy in the period from April 2022 to April 2023 (data from <https://covariants.org/per-country>).

(7 iB-NHL and 13 CLL) experienced severe COVID-19 with a rate of severe COVID-19 at 6 months of 3.5%. Median time between PrEP and severe infection was 3.7 months (range 0.4–5.8). Twelve patients (60%) with severe infection required oxygen therapy, 4 (20%, 4 CLL) had intensive care hospitalization and 4 (20%, 3 CLL and 1 iB-NHL) died because of COVID-19 (3 of them admitted in ICU). In comparison to all other patients, cases with severe COVID-19 were older (77 vs. 72 years, $p=0.015$), while no differences were observed concerning eastern cooperative oncology group performance status (ECOG-PS), comorbidities, stage of the disease, being or not on active treatment, previous anti-CD20 exposure and previous COVID-19 (Table S3). Of note, 19/20 cases of severe and 92/97 of symptomatic COVID-19 occurred in a period (June 2022–January 2023) when newer resistant SARS-CoV-2 variants were prevalent in Italy (Figure 1; Figure S1). COVID-19 mortality rate at 6 months was 4.1% among infected patients and 0.7% on the entire study population. Overall, 97 patients (17%) had symptomatic COVID-19 within 6 months from PrEP (Table S4). Median time from PrEP and infection was 2.9 months (range 0–6 months). In comparison to all other cases, patients with symptomatic COVID-19 were more frequently affected by CLL and with a lower incidence of previous COVID-19, while, compared to patients with mild symptomatic COVID-19, those with severe COVID-19 were older (77 vs. 72 years, $p=0.019$) and with a higher incidence of previous COVID-19 (32% vs. 12%, $p=0.038$, Table 1). More patients with severe COVID-19 received antiviral treatment than those with mild COVID-19 ($p=0.002$).

To the best of our knowledge, this is the largest study investigating the role of the COVID-19 prophylaxis with T-C in a homogeneous patient population with CLL and iB-NHL who received anti-COVID-19 vaccination but with a low

probability of responding to vaccination and a significant risk for severe COVID-19 complications.²

In the interpretation of these results, several aspects should be considered. First, this study demonstrated in this high-risk setting of patients, a low rate of severe COVID-19 complications with minimal side effects (Table S5), as observed in studies that included large but heterogeneous populations with various immunocompromising conditions.⁵

Second, our analysis covered an epidemiologic era when the Omicron subvariants, less sensitive or resistant to T-C, were becoming prevalent in Italy. We do not have virological and serological data for correlations, but recent analyses conducted during the Omicron period, suggested that T-C reduced COVID-19 hospitalizations among immunocompromised individuals particularly within 90 days from PrEP.¹¹ However, in patients with CLL, the 90-day mortality was still relevant (12.8%) particularly in subjects over 75 years and on treatment.¹² Although we do not have a group of patients who did not receive prophylaxis for comparison, there is some evidence from a case-control study performed in the same period that CLL patients receiving PrEP with T-C had lower rates of severe COVID-19 sequelae including hospitalization (38% vs. 53%¹⁰), but not enough to strongly support the efficacy of prophylaxis in the long-term follow-up.¹³

Third, of interest is the observation that, in this homogeneous subset of patients, age and a previous COVID-19 were associated with the occurrence of severe COVID-19. This finding could be related to a high vulnerability of this subset of patients because of advanced age and persistent low response to repeated vaccinations.¹⁴ A recent analysis of predictors of SARS-CoV-2 Omicron breakthrough infection after PrEP with T-C among patients with haematological

TABLE 1 Patients who received T-C and had COVID-19 within 6 months from PrEP: Mild versus severe infection.

	Mild <i>n</i> = 77 (79.4%)	Severe <i>n</i> = 20 (20.6%)	<i>p</i>
iB-NHL/CLL	17 (22%)/60 (78%)	7 (35%)/13 (65%)	Ns
Age median years (range)	72 (46–91)	77 (62–89)	0.019
Sex M/F	49 (64%)/28 (36%)	12 (60%)/8 (40%)	Ns
ECOG-PS 0–2/>2	69 (99%)/1 (1%)	18 (100%)/0 (0%)	Ns
Adv stage (Ann Arbor III–IV/Binet B–C) yes/no	42 (59%)/29 (41%)	11 (61%)/7 (39%)	Ns
Previously untreated yes/no	4 (5%)/73 (95%)	3 (15%)/17 (85%)	Ns
Anti-CD20 MoAb < 12 months ^a yes/no	22 (29%)/55 (71%)	6 (30%)/14 (70%)	Ns
Ongoing treatment yes/no	57 (74%)/20 (26%)	15 (75%)/5 (25%)	Ns
BTKi/venetoclax/others	30 (60%)/8 (16%)/12 (24%)	7 (58%)/3 (25%)/2 (17%)	Ns
Previous COVID-19 ^b yes/no	9 (12%)/66 (88%)	6 (32%)/13 (68%)	0.038
COVID-19 vaccination yes/no	68 (99%)/1 (1%)	19 (100%)/0 (0%)	Ns
Comorbidities ^c yes/no	56 (73%)/21 (27%)	16 (80%)/4 (20%)	Ns
Time from T-C to COVID-19 months (range)	2.7 (0.0–6.0)	3.7 (0.4–5.8)	Ns
Treatment with nirmatrelvir/ritonavir or remdesivir yes/no	5 (12.8%)/34 (87.2%)	6 (37.5%)/10 (63.5%)	0.002

^aIn the current or in a previous line of treatment.^bSymptomatic COVID-19 confirmed either by polymerase chain reaction or rapid antigen test kits.^cIncluding at least one among hypertension, obesity, diabetes, asthma, chronic cardiac or kidney or liver disease, smoking.

malignancy did not identify any predictive factor.⁹ PrEP with T-C was shown to prevent COVID-19 and severe COVID-19 in patients with haematological malignancies treated with anti-CD20 monoclonal antibodies during the early pandemic Omicron phase when resistant variants were less prevalent.

Additionally, it remains difficult to dissect the role of effective therapeutic measures in the clinical outcome. Anti-viral therapy was used in a minority of our patients, mainly due to delayed diagnosis of COVID-19 in patients not accessing the clinic at the onset of symptoms. Of note, in the SUPERNOVA trial that included immunocompromised patients who had received PrEP with the new anti-spike monoclonal antibody Sipavibart, a moderate protective effect in preventing symptomatic COVID-19 was reported, with rare cases of severe COVID-19 and hospital admissions.¹⁵ This finding could be explained by the efficacy of PrEP, by the widespread use of antivirals, by humoral or cell-mediated immunity elicited by either repeated infection or vaccination as well as by impact of less aggressive SarCov-2 variants.¹⁴ In our series, it is worth noting that only 20% of patients received antivirals, thus allowing us to speculate that the low death rate could be in part ascribed to the use of the T-C prophylaxis together with the improved management of such patients.

In conclusion, we showed that, in patients with CLL and iB-NHL who had received anti-COVID vaccination, a multimodal strategy that included PrEP with T-C resulted in a rather low incidence of symptomatic and severe COVID-19 and that older patients and those with previous COVID-19 represented the subset at higher risk for severe COVID-19 complications. Although these results may have not evident future implications, they could help to identify those patients at higher risk of COVID-19 sequelae to be proposed

for targeted prophylactic and therapeutic interventions. In a landscape of rapidly emerging resistant viral variants, strategies such as immune bridging may accelerate the evaluation of anti-spike monoclonal antibodies for the protection of immunocompromised patients.

KEYWORDS

B-cell non-Hodgkin lymphoma, chronic lymphocytic leukaemia, COVID-19, pre-exposure prophylaxis

AUTHOR CONTRIBUTIONS

GMR, LS, GG, PG, AJMF, SL and AC designed the research study, analysed the data and wrote the paper; SS, AP, and PF analysed the data and performed statistical analyses; GMR, RD, IS, AMF, FRM, FA, MM, LS, PS, AG, AM, SM, NM, CP, AT, AS, RR and CVV collected and analysed the data. All authors revised the manuscript for important intellectual content.

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CONFLICT OF INTEREST STATEMENT

GMR received honoraria for participation in congresses and advisory board from AbbVie, AstraZeneca, BeOne and Janssen. AP received honoraria as consultant for Amgen, GSK, Takeda, MSD, Janssen and for participation in the advisory board from Servier. AC received honoraria for

participation in congresses and advisory board from AbbVie, AstraZeneca, BeOne, Jannssen, Lilly and Merck Sharp&Dome. PG received honoraria from AbbVie, AstraZeneca, BeOne, BMS, Johnson & Johnson, Lilly/Loxo Oncology, MSD and Roche. PS received honoraria for participation in congresses and advisory board from Abbvie, AstraZeneca, BeONE, Jannssen and Lilly. AS received honoraria for participation in the advisory board from AbbVie, AstraZeneca, Johnson & Johnson, BeOne, and for consultancy from AbbVie, Johnson & Johnson, AstraZeneca and Lilly. AG received honoraria for participation in the advisory board from AbbVie and Johnson & Johnson and for consultancy from AstraZeneca and Johnson & Johnson. IS received honoraria for participation in the advisory board from AbbVie. CP received honoraria for participation in the advisory board from AbbVie, Johnson & Johnson, AstraZeneca and Lilly.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study was approved by the Institutional Review Board (n: 498/2023/Oss/AOUFE).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.