Letters

RESEARCH LETTER

Efficacy of Tixagevimab-Cilgavimab as Immunoprophylaxis in Patients With Hematologic Cancer

Patients affected by hematologic malignant tumors (HMTs) remain at high risk of COVID-19 because of lower response to anti-SARS-CoV-2 vaccination.[1] Tixagevimab and cilgavimab are fully human SARS-CoV-2-neutralizing monoclonal antibodies (mAbs) derived from B cells of patients that recovered from SARS-CoV-2. The combination of these mAbs (AZD7442) has been demonstrated to be a safe and efficient option for COVID-19 immunoprophylaxis in adults who are at higher risk of an inadequate vaccine response.[2]

Supplemental content

Only a few series to date have evaluated the efficacy of tixagevimab-cilgavimab as primary prophylaxis in patients with various HMTs, with conflicting results.[3-5] This cohort study aimed to compare the incidence and severity of COVID-19 among adult patients affected by HMTs who prophylactically received tixagevimab-cilgavimab and those who did not.

Table. Clinical Characteristics of Patients and Breakthrough COVID-19 Infections Among the Cohort Exposed to Tixagevimab-Cilgavimab and the Control Group

Characteristic	Patients, No. (%)		*P* value
	Tixagevimab-cilgavimab (n = 130)	Control (n = 74)	
Sex			
Female	63 (48)	34 (46)	.73
Male	67 (52)	40 (54)	NA
Age, median (range), y	68.5 (28-86)	64.5 (22-84)	.01
Category of hematologic malignant tumor			
Lymphoproliferative disorders and multiple myeloma	100 (77)	60 (81)	.49
Myeloproliferative neoplasms	25 (19)	9 (12)	.19
Acute leukemia	5 (4)	5 (7)	.50
Active treatment	124 (95)	68 (92)	.36
Last therapy			
BTK & JAK2 inhibitors	47 (36)	18 (24)	.09
Chemotherapy and/or ASCT	7 (5)	5 (7)	.76
Immunotherapy[b]	64 (49)	46 (62)	.08
Other novel agents	12 (9)	5 (7)	.54
Type of last COVID-19 vaccine			
BNT162b2	92 (71)	51 (69)	.78
mRNA-1273	38 (29)	23 (31)	NA
Status of anti-SARS-CoV-2 vaccination			
No. of doses received, median (range)	4 (2-5)	3.5 (2-5)	<.001
≥3 Vaccine doses received	124 (95)	65 (88)	.05
COVID-19 infection			
No. of events	28	28	NA
Follow-up (person-days)	20 225	9992	NA
Incidence rate [× 10 000] (95% CI)	13.8 (9.2-20.0)	28.0 (18.6-40.5)	.01
AHR[a]	0.47 (0.27-0.81)	1 [Reference]	.01
Severe or critical COVID-19			
No. of events	3	4	NA
Follow-up (person-days)	20 225	9992	NA
Incidence rate [× 10 000] (95% CI)	1.4 (0.3-4.3)	4.0 (1.1-10.3)	.18
AHR[a]	0.18 (0.03-0.99)	1 [Reference]	.05
Need of hospitalization due to COVID-19			
No. of events	3	5	NA
Follow-up (person-days)	22 554	12 631	NA
Incidence rate [× 10 000] (95% CI)	1.3 (0.3-3.9)	4.0 (1.3-9.2)	.12
AHR[a]	0.19 (0.04-0.91)	1 [Reference]	.04
Time from tixagevimab-cilgavimab to COVID-19, median (range), d	95.5 (3-170)	NA	NA
Duration of COVID-19, median (range), d	7.5 (2-48)	10 (2-129)	.54
Duration of hospitalization, median (range), d	9	8 (4-106)	NA

Abbreviations: AHR, adjusted hazard ratio; ASCT, autologous stem cell transplantation; NA, not applicable.

[a] Adjusted for age class, sex, category of hematologic malignant tumor, last therapy, active treatment, type and status of anti–SARS-CoV-2 vaccination, at least 3 doses of vaccine received.

[b] Immunotherapy refers to therapy based on mAbs such as anti-CD20, anti-CD38, anti-CD138, anti-CD30, anti-CD33, anti-CD52 or bispecific antibodies. Other novel agents refers to therapy containing proteasome inhibitors, immunomodulatory drugs, azacitidine, LSD1 inhibitors, SMAD2/3 inhibitors, anti-PD1, PI3K inhibitors.

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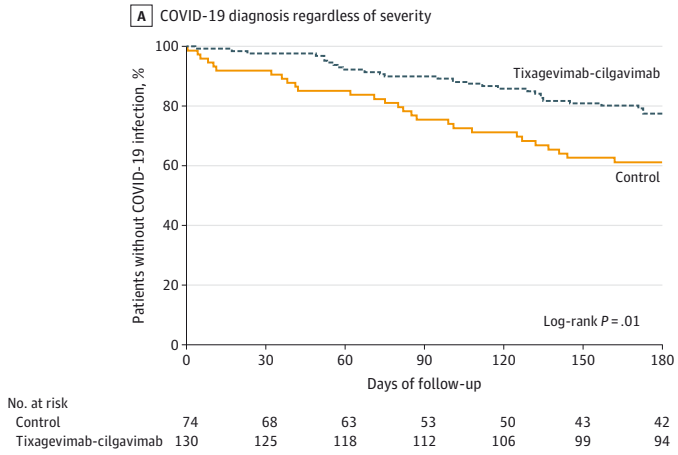
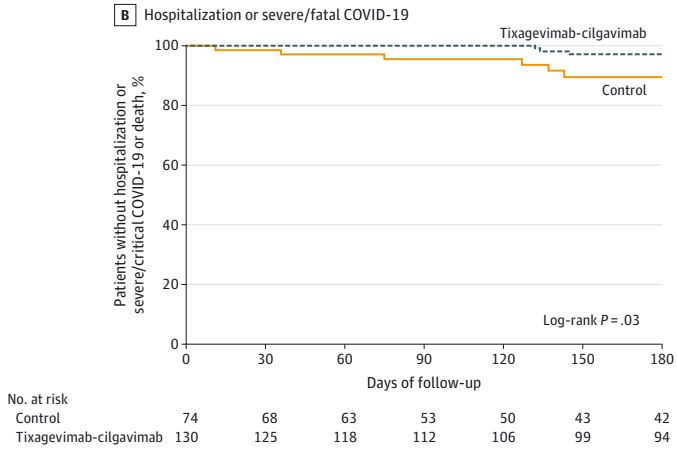
Figure. Event-Free Survival Curve





Rate of patients without SARS-CoV-2 infections along time between tixagevimab-cilgavimab cohort vs control group.

Methods | Consecutive patients eligible for tixagevimab-cilgavimab administration were enrolled between June 1 and September 1, 2022. Each patient was monitored for 6 months. Data regarding age, sex, HMTs, last hematologic therapy, status of anti-SARS-CoV-2 vaccination, and tixagevimab-cilgavimab administration were collected. At data cutoff, breakthrough SARS-CoV-2 infections were registered through phone interviews. All patients signed an informed consent. The study was approved by the Institutional Review Board of ASST dei Sette Laghi, Varese, Italy. This study followed the STROBE reporting guideline.

SAS version 9.4 was used for the statistical analysis. For all hypotheses tested, 2-tailed $P < .05$ was considered significant. Statistical methods are detailed in the eMethods of Supplement 1.

Results | In total, 204 patients were enrolled into the study: 130 (64%) received tixagevimab-cilgavimab at the European Union approved dose (150/150 mg), while 74 (36%) did not, due to refusal or logistical issues. No significant adverse events were reported. Clinical characteristics of the 2 cohorts are reported in the **Table**.

From June 2022 to March 2023, Omicron variants were prevalent in Italy. The BA.5 variant emerged as dominant over BA.2 in July 2022. The prevalence of BA.5 progressively decreased from 90% to 66% as the diffusion of recombinant Omicron variants raised from 2% in November 2022, to 21% in February 2023.[6] At data cutoff (March 1, 2023), the rate of breakthrough infections was 28 of 130 (21%) among patients exposed to tixagevimab-cilgavimab vs 28 of 74 (38%) in the control group ($P = .01$). The incidence of COVID-19 was 13.8 per 10 000 person-days in the tixagevimab-cilgavimab group vs 28.0 in the control arm (hazard ratio [HR], 0.47; 95% CI, 0.27-0.81; $P = .01$). Administration of tixagevimab-cilgavimab was associated with a significant reduction in the incidence of severe or critical COVID-19 (1.4 vs 4.0 per 10 000 person-days; HR, 0.18; 95% CI, 0.03-0.99; $P = .0495$). Need for hospitalization was also significantly lower in patients receiving

prophylactic tixagevimab-cilgavimab (1.3 vs 4.0 per 10 000 person-days; HR, 0.19; 95% CI, 0.04-0.91; P = .04) (Table). These results were confirmed by Kaplan-Meier estimator (**Figure**).

We performed a sensitivity analysis on 52 patients selected within each group with propensity score matching, which confirmed the significant reduced risk of COVID-19 infection for the tixagevimab-cilgavimab group (HR, 0.44; 95% 0.20-0.97; P = .04).

Discussion | Study limitations include no randomized design, heterogeneity of HMT, and different vaccination status. The sensitivity analysis mitigated the absence of randomization and confirmed the comparability of the 2 groups. Active treatment is recognized as the main risk factor for impaired immunogenicity from vaccination in patients with HMTs.[1] Notably, differences in vaccination status did not seem to affect these results. Our findings suggest that prophylactic tixagevimab-cilgavimab may reduce the incidence and severity of COVID-19 and may be a complementary tool to vaccination boosters in patients with HMTs.

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Author Contributions: Dr Salvini and Dr Passamonti had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Grossi, Merli, Passamonti.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Salvini, Cacioppo, Merli, Pellegrini, Brociner, Passamonti.
Critical review of the manuscript for important intellectual content: Salvini, Grossi, Merli, Passamonti.
Statistical analysis: Pellegrini.
Administrative, technical, or material support: Cacioppo, Brociner.
Supervision: Salvini, Grossi, Merli, Passamonti.

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Data Sharing Statement: See Supplement 2.

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