Mediterranean Journal of Hematology and Infectious Diseases

Scientific Letter

Impact of Sars-CoV-2 Prophylaxis with Tixagevimab-Cilgavimab in High-Risk Patients with B-Cell Malignancies: A Single-Center Retrospective Study

Keywords: COVID-19; Tixagevimab-cilgavimab; B-Cell malignancies; Pre-exposure; Prophylaxis.

Published: November 01, 2023 **Received: July 07, 2023** **Accepted: October 16, 2023**

Citation: Assanto G.M., Totaro M., Poggiali R., Delli Paoli A., Annechini G., D'Elia G.M., Aji F., Petrucci L., Fazio F., Del Giudice I., Martelli M., Micozzi A., Gentile G. Impact of Sars-CoV-2 prophylaxis with tixagevimab-cilgavimab in high-risk patients with B-cell malignancies: a single-center retrospective study. Mediterr J Hematol Infect Dis 2023, 15(1): e2023061, DOI: http://dx.doi.org/10.4084/MJHID.2023.061

To the editor.

Severe Acute Respiratory Syndrome CoronaVirus-2 (SARS-CoV-2) infection can result in different clinical manifestations (COVID-19), from asymptomatic disease to life-threatening respiratory insufficiency.[1] Onco-hematologic patients are at higher risk of developing severe COVID-19.[2] In particular, patients affected by lymphoproliferative diseases, given the impaired cell-mediated and antibody-mediated immunity and treatment toxicity, more often develop a symptomatic and more serious COVID-19 disease.[2-3] Various prophylactic and therapeutic strategies are used against COVID-19, such as vaccines, antiviral drugs, and S-protein monoclonal antibodies (anti-S MoAbs). The efficacy of antiviral strategies often proved to be dependent on SARS-CoV-2 variants.[4-6] Pre-exposure prophylaxis with AZD442/Evusheld (tixagevimab-cilgavimab) may be a complementary strategy to decrease the incidence or severity of COVID-19 for patients with hematologic malignancies. Tixagevimab-cilgavimab is a combination of two monoclonal antibodies (T-C MoAb) that bind SARS-CoV-2 spike protein and inhibit the attachment to the surface of cells, preventing viral entry in the cell and COVID-19 development.[7,8] In the PROVENT trial, a phase 3 study, 5197 patients were randomized to receive T-C MoAB or placebo, reporting a favorable incidence of only 0.2% of symptomatic COVID-19 in the T-C MoAb arm, even if it included only 3.3% of cancer patients receiving T-C MoAb and was conducted before the Omicron era.[8] Based on these findings, T-C MoAB was approved by the Agenzia Italiana del Farmaco (AIFA) as pre-exposure prophylaxis for patients at high risk of severe COVID-19; therefore, it was regularly employed at our institution.[9] However, recent studies, mainly performed in vitro, suggested inferior efficacy against omicron variants.[10-12]

Our aim was to evaluate if this strategy's upcoming reported clinical benefit and safety to patients with hematologic malignancies were still in force in a real-life setting of high-risk hematologic patients during the omicron-predominant COVID-19 wave in Italy.

Methods. We retrospectively collected data of patients affected by B-cell malignancies who received T-C MoAb (300 mg: dose 150+150 mg, the authorized dose for pre-exposure prophylaxis in our country) as pre-exposure prophylaxis at the Institute of Hematology, Sapienza University of Rome, between February 2022 and February 2023. Outpatients were stratified according to disease-specific clinical risk (**Table 1**). High risk patients received T-C MoAb at different times (before chemoimmunotherapy started, before conditioning regimen, before maintenance therapy) according to the treatment phase at the time of T-C MoAb availability. This study respects the principles of the Declaration of Helsinki and was approved by the internal review board. Diagnosis of SARS-CoV-2 infection was performed with Reverse Transcription Polymerase Chain Reaction (RT-PCR) on nasal swabs. Antigenic tests, as well as RT-PCR, were employed to determine the end of infection. All patients received the standard of care in force at the time of infection. Infection course and COVID-19 severity were monitored according to radiologically documented pneumonia, hospitalization, and oxygen therapy requirement; major comorbidities were registered.[13] Statistical analysis was performed using IBM software SPSS statistics v.25. Descriptive statistics are presented for normally distributed variables. Differences between the groups were evaluated using univariate logistic regression to assess potential risk factors associated with death or severe COVID-19 infection. The $\chi 2$ test was used for categorical variables, and the Mann-Whitney U-test was used for continuous variables.

Table 1. Characteristics of hematologic patients who received SARS-CoV-2 prophylaxis with tixagevimab-cilgavimab.

Patient Characteristics		Patients who did not develop SARS-CoV-2 infection		Patients who developed SARS-CoV-2 infection		Whole Cohort		
		N (88)	%	N (18)	%	N (106)	%	p
Sex	Male	53	60.2%	7	38.9%	60	56.6%	0.09
	Female	35	39.8%	11	61.1%	46	43.4%	
Age	>65years	37	42%	10	55.6%	47	44.3%	0.29
	<=65years	51	58%	8	44.4%	59	55.7 %	
Diagnosis	B-Cell NHL	53	60.2%	16	88.8%	69	65.1%	0.09
	HL	10	11.4%	0	0.0%	10	9.4%	
	MM	22	25%	1	5.6%	23	21.7%	
	CLL/SLL	3	3.4%	1	5.6%	4	3.8%	
Comorbidities	None	42	47.7%	4	22.2%	46	43.4%	0.046
	At least 1	46	52.3%	14	77.8%	60	56.6%	
ECOG PS	0-1	80	95.9%	18	100%	98	97%	0.43
	2	3	4.2%	0	0.0%	3	3%	
Disease Stage	Early	20	23.5%	4	22.2%	24	23.3%	0.9
	Advanced	65	76.5%	14	77.8%	79	76.7%	
Risk stratification according to disease	Low	7	9.2%	0	0.0%	7	7.4%	0.36
	Intermediate	19	25.0%	6	33.3%	25	26.6%	
	High	50	65.8%	12	66.7%	62	66%	
Active Hematologic Disease	No	53	60.2%	9	50.0%	62	58.5%	0.4
	Yes	35	39.7%	9	50.0%	44	41.5%	
Number of prior lines of therapy	0	61	72.6%	11	61.1%	72	70.6%	0.87
	1	13	15.5%	4	22.2%	17	16.7%	
	2	3	3.6%	1	5.6%	4	3.9%	
	≥3	7	8.4%	2	11.1%	9	8.9%	
Ongoing Treatment at time of infection	No	40	45.5%	7	39%	47	44.4%	0.71
	Yes	48	54.5%	11	61%	59	55.6%	
Last Treatment regimen or planned at infusion	Chemotherapy	5	5.7%	3	16.6%	8	7.5%	/
	Immuno-Chemotherapy	39	44.3%	10	55.5%	49	46.2%	
	Immune-modulators	6	6.8%	4	22.2%	10	9.4%	
	Immuno-Chemotherapy + ASCT	20	22.7%	1	5.6%	21	19.8%	
	CAR-T cells	5	5.7%	0	0.0%	5	4.7%	
	Others	13	14.7%	0	0.0%	13	12.2%	
Anti-CD38 MoAbs	No	70	83.3%	17	94.4%	87	85.3%	0.22
	Yes	14	16.7%	1	5.6%	15	14.7%	
Anti-CD20 MoAbs	No	29	34.5%	3	16.7%	32	31.4%	0.13
	Yes	55	65.5%	15	83.3%	70	68.6%	
Bendamustine Exposed	No	69	78.4%	13	72.2%	82	77.4%	0.67
	Yes	19	21.6%	5	27.8%	24	22.6%	
Number of vaccine doses received	0	3	3.4%	0	0.0%	3	2.9%	0.53
	2	10	11.4%	2	11.1%	12	11.3%	
	≥3	75	85.2%	16	88.9%	91	85.9%	
Previous COVID19	No	56	63.6%	14	87.8%	70	66%	0.13
	Yes	32	36.4%	4	22.2%	36	34%	

Chi-square test, and Mann-Whitney U test were employed to assess significant differences in distribution. Not all data were available for every patient.

Results. A total of 106 patients received T-C MoAb prophylaxis. Median age at infusion was 64 years (range 30-83), the majority of patients were affected by non-Hodgkin lymphoma (NHL) (65%, 69/106, 44% aggressive NHL, 21% indolent NHLs), followed by multiple myeloma (MM) (21.7%), Hodgkin lymphoma (HL) (9.4%), chronic lymphocytic leukemia (CLL) (2.8%) and hairy cell leukemia (1.5%) (**Table 1**). Nine-point four percent received T-C MoAb before, 39.6% within 6 months, and 50.9% within 1 year of hematologic treatment (**Table 1**). Twelve-point-three percent (13/106) received maintenance treatment with anti-CD20 monoclonal antibodies. One-hundred and three patients (103/106 = 97.1%) received at least 2 doses of BNT162b2 messenger RNA vaccine before infusion of T-C MoAb, 34% (36/106) had a previously documented SARS-CoV-2 infection (**Table 1**). No serious adverse events were related to T-C MoAb administration. Median follow-up was 124 days (25-380).

Of 106 patients, 18 developed COVID-19 (17%) after a median of 85 days (range 35-222) from T-C MoAb infusion. Among them, 83.3% (15/18) developed symptoms and fever, 44.4% (8/18) required hospitalization and 16.7% (3/18) required oxygen support. Antiviral treatment was administered in 44.4% (8/18) of patients: 3 received remdesivir, 1 sotrovimab, 2 nilmatrelvir-ritonavir and 2 molnupinavir. Three out of 18 patients had previous COVID-19, one was hospitalized and died. The median time of SARS-CoV-2 infection (since positive nasal swab) was 17 days (range 6-52).

The baseline characteristics of patients receiving T-C MoAb were heterogeneous. Comparing patients who developed breakthrough SARS-CoV-2 infection (n=18) to patients who did not (n=88), we observed a significantly higher frequency of at least 1 comorbidity among the former (77.8% vs 52.3%, p=0.047) (**Table 1**). Anti-spike antibodies were tested before MoAb in 9 of 18 infected patients; 6 (66%) had a negative and 3 (33%) a positive titer. SARS-CoV-2 breakthrough infection was not significantly related to any of the following risk factors: active hematologic disease (20.9% vs. 14.9% infection rate, p=0.41); age above 65 years (21.3% vs 14.5%, p=0.37); hematologic treatment regimen including anti-CD20 MoAbs (21.4% vs. 9.4%, p=0.13), anti-CD38 MoAbs (6.7% vs. 19.5%, p=0.22) and bendamustine (20.8% vs. 17.1%, p=0.67). Age above 65 years was related to hospitalization (75% vs 25%, p=0.047).

Overall, the death rate was 6.8% (6/88) in patients without breakthrough infection (due to hematologic disease progression in all cases) and 22.2% (4/18) in the group with breakthrough infection (p=0.04); among the latter, 3 cases of COVID19 related death (16.7%, 3/18) and 1 due to hematologic disease progression were observed. Patients who experienced COVID-related death had positive nasal swabs after 34, 156, and 172 days after T-C MoAb administration, respectively; they received 1 nirmatrelvir-ritonavir, 1 remdesevir, and molnupinavir, respectively; two patients developed severe COVID-19 with subsequent admission to intensive care unit, 1 patient died from secondary bacterial infection. Two of the 3 COVID-related deaths occurred after 5 months of T-C MoAb infusion. Two COVID-related deaths had negative SARS-CoV-2 anti-spike titer and age above 65 years. For patients developing breakthrough COVID-19, hospitalization (3/4, p=0.02) and oxygen therapy requirement (3/4, p=0.006) were the only significant death-related risk factors.

Discussion. We present a real-life retrospective monocentric cohort of patients affected by high-risk lymphoproliferative diseases who received the COVID-19 vaccine and prophylaxis with T-C MoAb. We report a rate of breakthrough infection of 17%, hospitalization of 7.5%, and COVID-related mortality of 2.8%. Our findings agree with those of the TACKLE randomized trial that proved a significant reduction of 51% of severe infection or death among immunocompromised outpatients who received T-C MoAb versus placebo and developed SARS-CoV-2 breakthrough infection.[15]

Real-life data are upcoming on the impact of pre-exposure prophylaxis in several hematological malignancies (e.g., hematopoietic stem cell transplantation, CAR-T cell patients, CLL), given the multiple factors involved in the clinical behavior of SARS-CoV-2, as shown in **table 2**.[10,12,14] A large recent Israelian retrospective experience highlighted a significant reduction in infection rate (3.5%) and mortality (0%) among immunocompromised patients receiving T-C MoAb versus no administration (**Table 2**).[11] Our study's breakthrough infection rate agreed with the data reported by Davis et al. Patients with hematologic malignancies receiving T-C MoAbs (150/150 mg or 300/300 mg) experienced a confirmed COVID-19 breakthrough infection in 11% of cases (**Table 2**).[16] This cohort received B-cell-depleting therapy like our group, with 60.8% of patients receiving either rituximab, obinutuzumab, or blinatumomab;[16] no deaths were reported, and the hospitalization rate was 15%. In the EPICOVIDEHA registry, a matched-control cases analysis was performed, showing a 90% breakthrough infection rate, higher than in our study, with a comparable death rate, but with the limit of a small cohort (n=47) (**Table 2**).[12]

In the present experience, no risk factors associated with severe COVID-19 or hospitalization, or death were identified, in contrast with our previous experience, which focused on the treatment of COVID-19 with MoAbs other than T-C, where the presence of comorbidity was associated with the risk of developing COVID-19 infection, and hospitalization and oxygen

Table 2. Summary of studies reporting use of tixagevimab-cilgavimab in patients with hematological malignancies.

Ref.	Setting	Methodology (No. Of patients)	Period (Country)	Breakthrough rate %(N)	Hospitalization rate %(N)	Death rate %(N)
Ocon et al.[10]	Chronic Lymphoproliferative diseases T-C MoAb	Real-life prospective observational (206)	2022 (USA)	9.3% (19)	5% (1/19)	0% (0)
Kertes et al.[11]	Immunocompromised Patients	Real-world retrospective (825 T-C MoAb vs 4229 NA)	December 2021-April 2022 (Israel)	T-C MoAb: 3.5% (29/825) vs NA 7% (308/4299)	T-C MoAb: 3.4% (1/29) Vs NA 8.7% (27/308)	0% (0)
Marchesi et al.[12]	Lymphoproliferative diseases	Retrospective matched paired analysis (47)	2022 (Europe)	89.4% (42)	23.8% (10/42)	4.7% (2/42)
Davis et al.[16]	Patients with B-cell malignancies	Retrospective analysis of patients receiving T-C MoAb prophylaxis (252)	Jan-August 2022 (USA)	11% (27/252)	15% (4/27)	0% (0)
Laracy et al.[17]	High-risk hematologic malignancies	Retrospective analysis of patients receiving T-C MoAb prophylaxis (892)	Jan-July 2022 (USA)	10.9% (98/892)	8% (8/98)	1% (1/98)
Young-Xu et al.[19]	Immunocompromised Veterans	Retrospective matched analysis (1878-T-C MoAb vs 7014 NA)	Jan-Jun 2022 USA	T-C MoAb: 0.7% (13/1878) vs NA 0.97% (68/7014)	T-C MoAb: 0.5% (11/1878)[b] vs NA 1% (72/7014)[b]	T-C MoAb: 1.5% (29/1878) vs NA 2.45% (172/7014)[c]

T-C MoAb, receiving tixagevimab-cilgavimab; NA, not administered; N, number; [a]Incidence compared in the study was rate of death or severe COVID-19; [b]Hospitalized patients were counted separately from outpatients; [c]Mortality for any cause was considered in the analysis.

requirement were confirmed as prognostic factors for COVID-19 related death.[5] Similarly, as recently reported by Laracy et al. in a large cohort of patients (n=892) including different hematological malignancies, there were no risk factors that allowed to foresee the infectious outcome in this setting except for the augmented schedule of T-C MoAb (**Table 2**).[17]

The present study has several limitations given by the retrospective nature, the relatively small sample size, and the lack of data about SARS-CoV-2 genomic variants. However, it is possible to link the reported infections to the Omicron BA 1.1 and BA.4/5 variants, according to the time of infection and the epidemiological waves in Italy. The impact of genomic variants on in vivo T-C MoAb's efficacy is controversial: a sub-analysis of the PROVENT trial did not detect any variant predominance on the serum of patients developing SARS-CoV-2 breakthrough infection among patients receiving T-C MoAb, nor neutralizing test highlighted differences in SARS-CoV-2 Spike-based Lineages.[18] Regarding Omicron BA.1/2, a recent report from the US veteran registry showed a lower rate of severe COVID-19 in immunocompromised patients receiving T-C MoAb (n=1878) compared to untreated matched controls (n=7014) (Table II).[19] Moreover, the activity of T-C MoAb was demonstrated in neutralization test from serum samples (before T-C MoAbs and after 3 weeks) of 75 solid organ recipients on sublineages BA.4/5, although 6 out of 75 of these patients still developed breakthrough infection from BA.4/5.[20]

On the one hand, the in vitro studies have reported some levels of evasion of T-C-induced protection by different Omicron sub-variants, including those possibly responsible for infections in the present cohort. Thus, excluding a sub-optimal degree of protection in some of our cases is impossible. On the other hand, we add to the literature documenting the clinical benefit of this prophylaxis in high-risk hematologic malignancies. Randomized studies are ongoing, such as the ENDURE trial (https://classic.clinicaltrials.gov/ct2/show/NCT05375760), on immunocompromised patients to optimize the benefit of this strategy with an augmented dosage.

In conclusion, high-risk patients affected by lymphoproliferative B-cell malignancies are at risk for SARS-CoV-2 breakthrough infections despite using COVID-19 vaccination and pre-exposure prophylaxis with T-C MoAb. Nevertheless, the hospitalization rate and COVID-related deaths were low. Our study's results suggest maintaining a cautious daily practice and full pre-exposure prophylaxis, including vaccination and anti-spike monoclonal antibodies, that are mandatory to minimize the risk of developing a SARS-CoV-2 breakthrough infection.

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Competing interests: The authors declare no conflict of Interest.

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