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Antiviral and Monoclonal Antibody Combination Therapy in Haematological Patients in the Omicron Era

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To the editor.

Immunocompromised (IC) patients are at higher risk for persistent and/or severe SARS-CoV-2 infection caused by different viral variants, with a high case-fatality ratio.[1,2] The first persistent SARS-CoV-2 infection (5 months) was reported in 2020 in an IC patient with a long persistence of SARS-CoV-2,[3] immediately followed by further reports.[2,4] Indeed, the impairment of the immune system changes the natural history of COVID-19. However, no consensus exists on clinical management of IC COVID-19 patients.[5] Several reports emphasize the clinical relevance of a combination therapy between small-molecule antivirals (AV) and anti-spike monoclonal antibodies (MoAbs) both in early and prolonged COVID-19 clinical management.[6,7] In 2022, tixagevimab/cilgavimab (T/C) MoAb fixed combination was introduced as early therapy for outpatient with COVID-19.[8] We describe here a single-center case series of 22 IC COVID-19 in patients with hematological disorders (HD) treated with a combined therapy based on tixagevimab/cilgavimab (T/C) plus small-molecule antivirals (AV), between April 1, 2022, and November 30, 2022.

The viral genomic evolution was assessed by sequencing the whole SARS-CoV-2 genome in a subgroup of patients (pts). Pts were consecutively admitted for COVID-19 to the Lazzaro Spallanzani National Institute for Infectious Diseases, Rome, Italy (INMI). Demographic characteristics, medical history, clinical presentation, treatment, adverse drug reactions, and clinical outcome (survival/death) during follow-up were collected from patient clinical records. Real-time reverse transcription polymerase chain reaction (RT-PCR) on nasopharyngeal swab (NPS) samples was performed according to the laboratory workflow using Alinity m SARS-CoV-2 Assay (Abbott, Chicago, Illinois, United States) targeting RdRp and N genes. When possible, molecular characterization of the SARS-CoV-2 virus was performed using whole genome sequencing (WGS) at diagnosis and during follow-up.[9] Whole Genome sequencing (WGS) was carried out on an Ion Torrent Gene Studio S5 platform using Ion AmpliSeq SARS-CoV-2 in-sight research assay following the manufacturer's instructions (ThermoFisher Scientific, Waltham, MA, USA). The whole genome reconstruction was performed using ESCA software.[10] All the mutations were identified with respect to the reference suggested by NCBI Wuhan-Hu-1 (NC_045512.2). A phylogenetic tree was built using 16 Italian SARS-CoV-2 sequences that were selected among those available on the GISAID platform with a collection date closer to that of the INMI patients and clustered using cd-hit with 99% identity.[11] The transition model (TIM+I+F+G) was identified as the best-fitting nucleotide substitution model, and a phylogenetic tree was constructed with 5,000 bootstrap replications using the IQ-Tree program.[12]

Table 1 shows the characteristics of the study population. All patients were fully vaccinated against COVID-19 with at least 3 doses, 11 (50%) of them males, with a median age of 78 years old (IQR 69-83) (**Table 1**).

Twenty patients were under active chemotherapy. They were admitted with a median of 11 days (IQR 1-33) after the first NPS positive for SARS-CoV-2. The study population had a median total lymphocyte count of 910/µl (IQR 520-1547), and 15 out of 22 (68%) had hypogammaglobulinemia. All patients had pneumonia, but only 14 of them required respiratory support. Seven patients had severe COVID-19 (WHO COVID-19 ordinary scale 5), and 15 patients had moderate/mild COVID-19 (6 patients with a score of 4 and 9 patients with a score of 3). Steroid therapy (oral or intravenous 6 mg dexamethasone daily) was started in 14 patients with

respiratory failure. At the admission, NPS for SARS-CoV-2 was positive with a median cycle threshold (Ct) of 20 (IQR 16-24). All patients were treated with a first combination regimen of MoAbs (T/C in 17 cases, sotrovimab in 3 cases, and casirivimab/imdevimab in 2 cases) plus a 5-day course of intravenous remdesivir (200 mg on day one followed by 100 mg on day 2-5). Eleven out of 22 (50%) patients with an NPS<35 Ct required a second course of antivirals (remdesivir in 2 cases and oral nirmatrelvir/ritonavir in 9 cases, 300mg/100 mg twice daily for 5 days) associated with T/C in the five subjects initially treated with different MoAbs. Two patients who, after 2 courses of antivirals and T/C, still had an NPS<35 Ct received at least 2 doses of COVID-19 convalescent plasma (CCP) with > 1:160 SARS-CoV-2 neutralizing antibody titer. Four patients died (all with positive NPS PCR at the last available time point, i.e., at days 103, 115, 43, and 41, respectively, since the first positive NPS) (see Table 2). In particular:

- Patient #3 died of gastrointestinal severe graft-versus-host diseases (GvHD) at month 2 after hematopoietic stem cell transplantation for acute myeloid leukemia.
- Patient #9 died of recurrent *Clostridioides difficile* infection during a relapse of NHL.
- Patient #19 died from a relapse of NHL.
- Patient #22 died of respiratory failure and pneumonia sustained by *Aspergillus* spp. and *Stenotrophomonas maltophilia*.

In the remaining 18 patients, the SARS-COV-2 NPS PCR was negative at a median of 59 (IQR 47-93) days since the first evidence of SARS-CoV-2 infection (**Table 2**) and 47 days (IQR 28-51) after starting the treatment. The median duration of hospital stay was 32 days (IQR 24-41).

Spike-gene sequencing was possible in 18 out of 22 patients and identified a BA.2* VoC in 9, a BA.4/5* VoC in 7, a BA.1.1* in 1, and a BQ.1.1* VoC in 1.

The whole SARS-CoV-2 genome was sequenced in 4 out of 22 BA.2 patients (Patient#1, #3, #4, and #7). A deeper analysis was conducted on the Spike glycoprotein. No recurrent amino acid mutations in the 21 sequenced patients were found. In baseline sequences, no mutations that were not lineage-related were found in patients #3 and #4 (**Table 3**), while V445A mutation in patient #1 and E340Q, R683W, and G798S mutations in patient #7 were found. Patients #1 and #4 exhibited 3 and 1 additional Spike mutations at the available second timepoint (T1), compared to the baseline sequences. In particular, T1 patient #1 sequence showed a deletion in position S: A243-L244. Finally, the phylogenetic tree showed that whole genome sequences collected at baseline clustered with a significative bootstrap with sequences collected after days 22 and 80 for patients #1 and #4, respectively, while the baseline sequence of patient #3 was interspersed between other BA.2 sequences currently circulating in Italy (**Figure 1**).

In the context of SARS-CoV-2 infection, IC patients face heightened vulnerability. Although they have been underrepresented in previous randomized clinical trials, they are likely overrepresented among currently hospitalized patients with severe and/or persistent symptoms associated with SARS-CoV-2 infection.[5,13] Nevertheless, there is no evidence-based approach for managing these patients. Several recent studies support the use of MoAb and AV combination therapy in IC inpatients and outpatients or, for inpatients, prolonged antiviral therapy.[7,14-18] At admission, the cohort had a median of 11 days since the first SARS-CoV-2 positive NPS, with a median Ct value of 20, suggesting a persistently high viral replication. Notably, Ct-values, a measure of viral burden, between 17 and 32 represent an amount of virus that is likely to be replicative competent.[19] Seventy-one percent of patients had a BA.2* VoC that retains *in-vitro* susceptibility to cilgavimab; T/C has reduced efficacy against BA.5* VoC, although it was unclear at that time of use. All patients were considered at high risk of clinical progression and underwent a full course of remdesevir and MoAb combined therapy with an off-label 600 mg tixagevimab/cilgavimab prescription with no reported adverse event. Half of them achieved viral clearance after the first course of treatment, whereas the remaining 11 patients necessitated a second AV and MoAb combined course.

Additionally, two patients only partially responder (NPS<35 Ct) after two full combined antiviral regimens, received CCP, a major therapeutic option as a source of exogenous specific antibodies against SARS-CoV-2 Spike glycoprotein: one patient died, and one recovered. We considered the 35 Ct cut-off value during therapy as a surrogate marker of successful viral response. Lower Ct values are commonly related to active viral replication and potential contagiousness.[19,20]

All COVID-19 survival patients had a negative SARS-CoV-2 NPS PCR after combined therapy, with a median time of 52 days since the first positive NPS and of 38 days since hospitalization. The observed case fatality rate in our cohort was 18%, which falls within the previously reported range of 13.8% to 39%.[21] The four deceased patients tested positive for NPS PCR at the time of death: in three patients, the death was due to recurrence of the underlying HD, and in one case, to complication of stem cell transplant.

The literature poorly describes IC patients treated by T/C, and this MoAb has provided new therapeutic opportunities apart from the already two registered indications.[8] Lahouati describes the treatment of a cohort of 223 IC patients, although patients with HD represented 25%, and among them, 12% were treated with T/C, corresponding to 7 pts.[22]

Table 1. Clinical features of study population

PT	SEX	AGE	ONGOINGIMMUNOSUPPRESSIVE THERAPY	LAST IMMUNOSUPPRESSOR ADMINISTRATION (DATE)	UNDERLYING DISEASE	FIRST NPS POSITIVE	SYMPTOMS ONSET	HOSPITAL ADMISSION	TIME TO HOSPITALIZATION FROM FIRST NPS
1	M	84	None	>2 years	KS	11/04/22	04/04/22	10/05/22	29
2	M	80	CHT	Ongoing	AML	25/06/22	28/06/22	28/06/22	3
3	M	48	Venetoclax	Ongoing	AML,GVHD	18/04/22	18/04/22	19/04/22	1
4	M	70	1-obinutuzumab ,	Ongoing	NHL, DM	06/04/22	02/04/22	14/05/22	38
5	F	88	Rituximab	Ongoing	CLL, CRF	15/06/22	15/06/22	05/07/22	20
6	F	78	R-COMP	Ongoing	NHL	14/04/22	14/04/22	14/07/22	91
7	F	64	CHOEP	Ongoing	NHL, HA	02/05/22	02/05/22	15/07/22	74
8	F	80	Rituximab	Ongoing	NHL, SS	19/08/22	18/08/22	20/08/22	1
9	F	70	Rituximab	Ongoing	NHL	05/05/22	05/05/22	05/08/22	90
10	M	81	Rituximab	Ongoing	DLBCL	23/03/22	14/03/22	24/03/22	1
11	F	56	R-CHOP	Ongoing	NHL	08/05/22	08/05/22	09/05/22	0
12	M	83	Daratumumab	None	MM	29/06/22	26/06/22	29/06/22	0
13	M	74	Rituximab, Bendamustine	Ongoing	NHL	18/09/22	18/09/22	29/09/22	11
14	F	71	Obinotuzumab	Ongoing	NHL	30/09/22	24/09/22	01/10/22	1
15	F	82	Ibrutinib	Ongoing	CLL	14/10/22	05/10/22	17/10/22	3
16	F	84	Lenalidomide, Steroid	Ongoing	MM, NHL	18/10/22	18/10/22	21/10/22	3
17	M	75	Bendamustina, Rituximab	Ongoing	LPL	15/10/22	15/10/22	26/10/22	11
18	M	69	Rituximab	Ongoing	NHL	15/07/22	14/10/22	14/11/22	122
19	M	67	CHT	Ongoing	NHL, DM	03/10/22	13/10/22	14/10/22	11
20	F	87	None	None	CLL	25/10/22	30/10/22	09/11/22	15
21	M	64	Obinotuzumab+COMP	Ongoing	NHL	25/08/22	25/08/22	22/11/22	90
22	F	85	Acalabrutinib	Ongoing	CLL	20/07/22	16/07/22	02/08/22	13

Abbreviations: AML acute myeloid leukemia; CHOEP cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone; CHT unknown chemotherapy; CLL chronic lymphocytic leukemia; CRF chronic renal failure; DLBCL Diffuse large B cell lymphoma; DM diabetes mellitus; GVHD graft-versus-host disease; HA hemolytic anemia ;KS Kaposi sarcoma; NHL Non- Hodgkin Lymphoma;; R-COMP Rituximab, Prednisone, Cyclophosphamide, Vincristine, Myocet®

Table 2. Virological, therapeutic features and clinical outcome of study population.

PTS	VOC	PNEUMONIA	VENTILATORY SUPPORT	STEROIDS	FIRST AV CYCLE	SECOND AV CYCLE	FIRST MoAbs	SECOND MoAbs	HYPERIMMUNE PLASMA (doses)	TIME TO PCR NEGATIVIZATION	LENGTH OF STAY	CLINICAL OUTCOME
1	BA.2	yes		None	RDV	NMT/R	C/I - MoAb	T/C-MoAb		78	32	Recovery
2	BA.2	yes		Yes	RDV		T/C-MoAb			38	37	Recovery
3	BA.2	yes		Yes	RDV	RDV	C/I- MoAb	T/C-MoAb	3		47	Death
4	BA.2	yes	VM	Yes	RDV	NMT/R	T/C-MoAb			98	53	Recovery
5	BA.2	yes	VM	Yes	RDV		T/C-MoAb			47	17	Recovery
6	BA.2	yes		Yes	RDV	NMT/R	T/C-MoAb			102	13	Recovery
7	BA.2	yes	C-PAP	Yes	RDV	RDV	SOT- MoAb	T/C-MoAb	2	114	27	Recovery
8	BA.4/5	yes	VM	Yes	RDV	NMT/R	T/C-MoAb			52	17	Recovery
9	BA.4/5	yes	NIV	Yes	RDV		SOT- MoAb	T/C-MoAb			25	Death
10	BA.1.1	yes	VM	Yes	RDV		T/C-MoAb			60	44	Recovery
11	BA.2	yes	VM		RDV		T/C-MoAb			101	101	Recovery
12	BA.4/5	yes	VM	Yes	RDV		T/C-MoAb			47	49	Recovery
13	BA.4/5	yes			RDV		T/C-MoAb			67	21	Recovery
14	BA.4/5	yes	C-PAP	Yes	RDV	NMT/R	T/C-MoAb			29	39	Recovery
15	BA.5	yes			RDV	NMT/R	T/C-MoAb			74	36	Recovery
16	BA.5	yes	C-PAP	Yes	RDV		T/C-MoAb			na	33	Recovery
17	BQ.1.1	yes	C-PAP	Yes	RDV	NMT/R	T/C-MoAb	SOT-MoAb		59	52	Recovery
18	na	yes			RDV	NMT/R	T/C-MoAb	/		136	15	Recovery
19	na	yes			RDV		T/C-MoAb	/			31	Death
20	na	yes			RDV		T/C-MoAb	/		51	30	Recovery
21	na	yes			RDV	NMT/R	T/C-MoAb	/		45	23	Recovery
22	BA.2	yes	C-PAP	Yes	RDV		SOT-MoAb	T/C-MoAb			30	Death

VoC Variant of concern, AV antivirals, RDV remdesevir, NMT/r nirmatrelvir/ritonavir, Molnupiravir, C/I casirivimab/imdevimab, T/C tixagevimab/cilgavimab, S sotrovimab, C-PAP countinuos positive airway pressure, NIV non invasive ventilation, MoAb monoclonal antibody, na not available

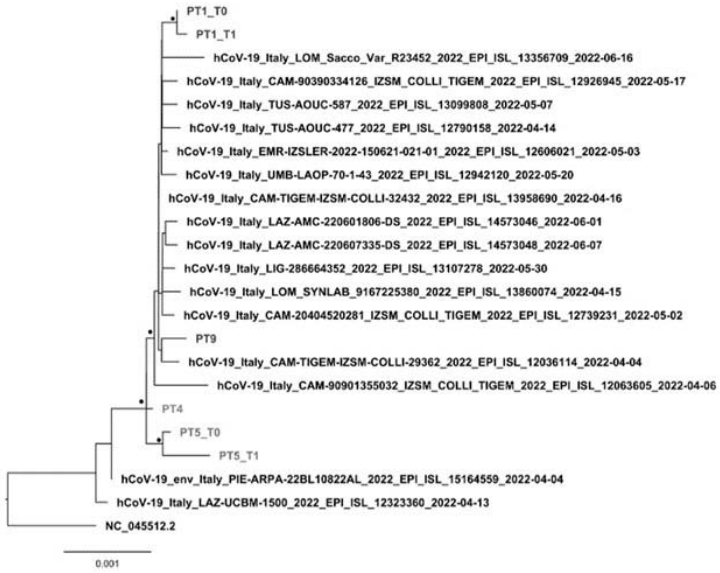
Table 3. Spike mutations of sequenced samples.

Reference amino acid position	PT1 T0 (REFaa;Pos;MUTaa)	PT1_T1 (REFaa;Pos;MUTaa)	PT3 (REFaa;Pos;MUTaa)	PT4_T0 (REFaa;Pos;MUTaa)	PT4_T1 (REFaa;Pos;MUTaa)	PT7 (REFaa;Pos;MUTaa)	BA.2 shared Mutations 21L (Omicron)
S: C15		C15R					
S: T19	x	x	x	x	x	x	T19I
S: L24	x	x	x	x	x	x	L24-
S: P25	x	x	x	x	x	x	P25-
S: P26	x	x	x	x	x	x	P26-
S: A27	x	x	x	x	x	x	A27S
S: G142	x	NA	x	x	x	x	G142D
S: N143		V143M					
S: N188		N188T					
S: V213	x	x	x	x	x	x	V213G
S: A243		A243-					
S: L244		L244-					
S: G339	x	x	x	NA		x	G339D
S: E340						E340Q	
S: S371	x	x	x	x	x	x	S371F
S: S373	x	x	x	x	x	x	S373P
S: S375	x	x	x	x	x	x	S375F
S: T376	x	x	x	x	x	x	T376A
S: D405	x	x	x	x	x	x	D405N
S: R408	x	x	x	x	x	x	R408S
S: K417	x	x	x	x	x	x	K417N
S: N440	x	x	x	x	x	x	N440K
S: K444					K444N		
S: V445	V445A	V445A					
S: S477	x	x	x	x	x	x	S477N
S: T478	x	x	x	x	x	x	T478K
S: E484	x		x	x	x	x	E484A
S: Q493	x	x	x	x	x	x	Q493R
S: Q498	NA	NA			x	NA	Q498R

S: N501	NA	NA	NA	NA	NA	NA	N501Y
S: Y505	NA	NA	NA	NA	NA	NA	Y505H
S: D614	x	x	x	x	x	x	D614G
S: H655	x	x	x	x	x	x	H655Y
S: N679	x	x	x	x	x	x	N679K
S: P681	x	x	x	x	x	x	P681H
S: R683						R683W	
S: N764	x	NA	x	x	x	x	N764K
S: D796	NA	x	x	x	x	x	D796Y
S: G798						G798S	
S: Q954	x	x	x	x	x	x	Q954H
S: N969	x	x	x	x	x	x	N969K

S: Spike protein; X: presence of characteristic mutations of BA.2 lineage according to CoVariants (https://covariants.org/shared-mutations); NA: position without a sufficient coverage to be identified

Figure 1: Phylogenetic analysis on whole genome sequences.



•The black point indicate bootstrap >80.

In our cohort, all patients were fully vaccinated against SARS-CoV-2. Indeed, COVID-19 vaccination among IC persons has been found to be highly protective against COVID–19–associated hospitalization, leading to fewer hospitalized patients and deaths.[23] All surviving patients were able to resume treatment for their underlying disease a few weeks after SARS-CoV-2 viral clearance. Although the molecular analysis was performed only in four patients, it showed that affected viruses did not contain any recurrent mutation present in all samples. This suggests that in the 4 sequenced patients, there was no specific mutation pattern that could be associated with the reported long shedding or clinical severity. Although the analysis of a second-time point was possible in only two patients, the follow-up mutation profile of patients #1 and #4 was consistent with the observations of Leung.[2] Patient #4 had a lower number of new mutations than patient #1, considering that the interval period between the two sampling was 80 and 22 days, respectively (**Table 3**). The V445A variant of SARS-CoV-2 Spike was found in patient #1 at both time points. This mutation is located within the ACE2 receptor-binding domain (RBD; aa 438-506) and causes full resistance to imdevimab and bebtelovimab[24] and partial resistance to but did not induce immune evasion to casirivimab.[25] In the second sampling of patient #4, the additional S: K444N mutations within the RBD were reported, which reduces neutralization by bebtelovimab[26] and imdevimab. A S: E340Q baseline mutation was reported in patient #9, which causes resistance to sotrovimab.[27]

Our case series showed that in IC patients, the use of AV combined with passive immunotherapy (MoAbs or CCP) is safe and can be effective. Indeed, AV blocks viral replication, while MoAbs or CCP directed to the Spike protein can neutralize the ability of the virus to bind and fuse with the target host cell, reduce cytokine storm intensity in COVID-19 patients, and alleviate symptoms.[28] Finally, combined antiviral therapy can reduce or completely limit the emergence of drug-resistant mutations during prolonged sequential antiviral monotherapy and is superior to monotherapy in terms of viral clearance.[6,7,14,15,29]

The study acknowledges limitations inherent to its retrospective, single-center design and restricted sample size. Additionally, the small cohort hinders the ability to analyze the impact of specific variables like hematological disorder types or disease severity. Furthermore, whole genome sequencing data, offering a more comprehensive analysis of viral strains, was only available for a subset of patients.

Despite being a small case series, this study offers valuable insights into a critical gap: the underrepresentation of immunocompromised patients with HD in COVID-19 clinical trials. The findings suggest a potential link between active HD and higher mortality in IC COVID patients, even with mild symptoms. This underscores the importance of treating all IC COVID patients with HD and the need for further research on standardized combination therapies for this population.

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Institutional Review Board Statement. Since the retrospective nature of our data, ethical approval was not required.

Informed Consent Statement. Informed consent was obtained from all subjects involved in the study.

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Serena Vita[1], Emanuela Giombini[1], Patrizia De Marco[1], Martina Rueca[1], Cesare Ernesto Maria Gruber[1], Alessia Beccacece[1], Laura Scorzolini[1], Valentina Mazzotta[1], Carmen Pinnetti[1], Priscilla Caputi[1], Daniele Focosi[2], Enrico Girardi[1], Andrea Antinori[1], Fabrizio Maggi[1], Alessandra D'Abramo[1#] and Emanuele Nicastri[1] and Spallanzani COVID-19 case investigation team*.

[1] National Institute for Infectious Diseases "Lazzaro Spallanzani" IRCCS- Rome Italy.
[2] North-Western Tuscany Blood Bank, Pisa University Hospital, Pisa, Italy.

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Correspondence to: Alessandra D'Abramo. National Institute for Infectious Diseases "Lazzaro Spallanzani" IRCCS via Portuense 292, 00149 Rome Italy. E-mail: alessandra.dabramo@inmi.it

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