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ORIGINAL ARTICLE

Dual combined antiviral treatment with remdesivir and nirmatrelvir/ritonavir in patients with impaired humoral immunity and persistent SARS-CoV-2 infection

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Abstract

Despite global vaccination efforts, immunocompromized patients remain at high risk for COVID-19-associated morbidity. In particular, patients with impaired humoral immunity have shown a high risk of persistent infection. We report a case series of adult patients with B cell malignancies and/or undergoing B cell targeting therapies with persisting SARS-CoV-2 infection and treated with a combination antiviral therapy of remdesivir and nirmatrelvir/ritonavir, in three Italian tertiary academic hospitals. A total of 14 patients with impaired adaptive humoral immunity and prolonged SARS-CoV-2 infection were treated with the dual antiviral therapy. The median age was 60 (IQR 56–68) years, and 11 were male. Twelve patients had B cell lymphoma, one patient had chronic lymphocytic leukemia and one patient had multiple sclerosis. Thirteen out of 14 patients had received prior B cell-targeting therapies, consisting of anti-CD20 monoclonal antibodies in 11 patients, and chimeric antigen receptor T therapy in 2 patients. The median time between diagnosis and therapy start was 42.0 (IQR 35–46) days. Seven patients had mild, 6 moderate and one severe disease. Nine patients had signs of interstitial pneumonitis on chest computed tomography scans before treatment. The median duration of nirmatrelvir/ritonavir and remdesivir combination therapy was 10 days. All patients showed resolution of COVID-19-related symptoms after a median of 6 (IQR 4–11) days and viral clearance after 9 (IQR 5–11) days. Combination therapy with remdesivir and nirmatrelvir/ritonavir is a promising treatment option for persistent COVID-19 in immunocompromized patients with humoral immunity impairment, worthy of prospective comparative trials.

KEYWORDS
B cell malignancies, B cell targeting therapies, COVID-19, persistent SARS-CoV-2 infection, viral infections in the hematological patient

1 | INTRODUCTION

From the early months of a deadly infection to the present days, the clinical commitment to the SARS-CoV-2 pandemic has significantly decreased due to the effectiveness of global vaccination and antiviral treatments. Nevertheless, immunocompromized patients with underlying conditions impairing their immune response to vaccines or natural infections are still at increased risk for COVID-19-associated morbidity and mortality.[1,2] States of relative immunologic vulnerability affect the severity of COVID-19, making it crucial to find targeted approaches to manage different levels of clinical complexity. In particular, patients with impaired adaptive humoral immunity have a high risk of prolonged viral shedding, viral rebound, and/or persistent infection.[3–7] This group, which includes patients with B cell malignancies or undergoing B cell targeting therapies such as anti-CD20 and chimeric antigen receptor T (CAR-T) cell therapy, faces additional complications related to the high risk of delay in life-saving treatments.[8,9]

Current COVID-19 treatment guidelines recommend the use of a single agent as early treatment for all out-patients with risk factors for progression to severe disease, including the generic term of immunocompromized condition. In case of progression to lower respiratory tract infection (LRTI), remdesivir remains the only recommended antiviral within 10 days from symptoms onset. After this time point, patients with SARS-CoV-2 infection are no longer considered eligible for antiviral treatments, regardless of their symptoms, radiological evidence of pneumonia, or immune status. Moreover, specific therapeutic indications for the management of immunocompromized patients with SARS-CoV-2 infection are lacking; even the prescription of long-acting monoclonal antibodies (MoAB) as pre-exposure prophylaxis for individuals with a demonstrated inadequate immune response to vaccination has been counteracted by the loss of activity against omicron subvariants.[10–12]

Therefore, in clinical practice, the predicted lack of evidence has resulted in the use of various off-label treatment approaches, including prolonged or reiterated single agent-based or combination-based therapies.[13–22]

In this scenario we introduced in our clinical practice the combination of two antiviral drugs, remdesivir and nirmatrelvir/ritonavir, in a selected subgroup of patients with severe impairment of adaptive humoral immunity and persistent SARS-CoV-2 infection. Patients urgently needing to resume the treatment of their original comorbidity were favored. Our decision was primarily motivated by the potential synergistic effect of two antiviral drugs with different biological targets[23,24] and by the minimal residual activity of MoAB related to the increasing prevalence of omicron subvariant BA.5 and BQ.1.1.[11,12]

Nirmatrelvir, a novel inhibitor of the SARS-CoV-2 main protease, has been authorized by the United States Food and Drug Administration (FDA) in combination with ritonavir, a strong CYP3A inhibitor, for emergency use since December 2021 for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19.[25]

Remdesivir was the first antiviral granted emergency use authorization by the FDA in May 2020, and subsequently approved in October 2020, for the treatment of hospitalized patients with COVID-19.[26]

While nirmatrelvir/ritonavir exerts its antiviral efficacy by inhibiting a necessary protease in the viral replication procedure,[27] remdesivir acts as a nucleoside analog and inhibits the RNA-dependent RNA polymerase (RdRp) of coronaviruses, including SARS-CoV-2.[28] Both drugs have demonstrated activity against Omicron subvariants.[29]

In this case series, we report the experience of three Italian tertiary academic hospitals that have adopted the same therapeutic approach in this subgroup of patients.

2 | MATERIAL AND METHODS

2.1 | Study population and study period

We described a series of 14 patients managed from November 2022 to February 2023 at three Italian tertiary university hospitals (9 patients from Sant'Orsola-Malpighi Research Institute of Bologna, 3 patients from Lazzaro Spallanzani Research Institute of Rome and 2 patients from Humanitas Hospital Research Institute of Milan). All included patients were adults affected by B cell malignancies and/or undergoing B cell targeting therapies with persisting SARS-CoV-2 infection (see definition below) despite several and varying previous antiviral treatments. These patients were treated with a combination antiviral therapy based on remdesivir (200 mg first day, then 100 mg daily) and nirmatrelvir/ritonavir (300/100 mg bid, or 150/100 mg in case of mild kidney impairment with estimated glomerular filtration rate (eGFR) <60 mL/min). Among them, priority was given to those who had more severe symptoms, evidence of pneumonia, and required chemotherapy treatment, provided they had given informed consent for the off-label treatment.

2.2 | Definitions and data collection

Persisting Sars-CoV-2 infection was defined by a positive real time polymerase chain reaction (RT-PCR) Sars-CoV-2 test, including nasopharyngeal swab (NPS) or lower respiratory tract sample, with radiological and/or clinical signs of infection after at least 21 days from the first Sars-CoV-2 positive test.[6,7]

Data regarding demographic characteristics (age and sex), hematologic comorbidity or other conditions requiring B-cell targeted therapies, type of treatment for the undergoing disease, clinical signs and symptoms, and any type of previous anti SAR-Cov-2 treatment, were collected. The severity of SARS-CoV-2 related disease was defined according to the Word Health Organization (WHO) classification of COVID disease severity.[30]

A Sars-CoV-2 RT-PCR test was evaluated at the enrollment before the starting of combination therapy on a NPS. A lower respiratory tract sample was performed for those patients with persisting symptoms and NPS negative test.

A lung computed tomography scan (CTS) was carried out for all patients before starting combination therapy and, when initially altered, after the end of treatment. The clinical conditions of enrolled patients were monitored during the treatment course, with daily vital parameters evaluation (body temperature, blood pressure, respiratory rate, peripheral oxygen saturation and need of oxygen supply).[25] The follow up was maintained up to 30 days after the end of treatment.

2.3 | Microbiology

The SARS-Cov-2 diagnosis and the monitoring of virological status were made by RT-PCR, performed according to the laboratory workflow using different platforms (Allplex™ SARS-CoV-2 Assay, Allplex™ SARS-CoV-2/FluA/FluB/RSV Assay, DiaSorin Molecular Simplexa™ COVID-19, Xpert® Xpress SARS-CoV-2, STANDARD™ M10 Flu/RSV/SARS-CoV-2). We did also collect the number of threshold cycles (CT) when available.

SARS-COV-2 serology was performed at time of dual antiviral start, either by an enzyme-linked immunosorbent assay (ELISA) detecting anti-SARS-CoV-2 IgG, IgM, and IgA (ENZY-WELL SARS-CoV-2 ELISA on SkyLab platform; DIESSE), or by two chemiluminescence microparticle assays (CMIA) detecting anti-nucleoprotein (anti-N) IgG and anti-Spike/RBD IgG (ARCHITECT SARS-CoV-2 IgG, and ARCHITECT SARS-CoV-2 IgG II Quantitative, on ARCHITECT® i2000sr; Abbott Laboratories, Wiesbaden, Germany, respectively), or by two electro-chemiluminescence immunoassay (ECLIA) detecting anti-nucleoprotein (anti-N) IgG and anti-Spike/RBD IgG (Elecsys® Anti-SARS-CoV-2 and Elecsys® Anti-SARS-CoV-2 S, Roche, Basle, Switzerland respectively).

2.4 | Statistical analysis

To describe our population, we presented continuous variables as median and interquartile range (IQR) and categorical variables as number and percentage.

3 | RESULTS

A total of 14 patients with impaired adaptive humoral immunity and persistent SARS-CoV-2 infection were treated with a dual antiviral therapy consisting of remdesivir and nirmatrelvir/ritonavir. The median age was 60.0 (IQR 56.25–68.5) years and 11 patients (78.6%) were male. Twelve patients had B cell lymphoma, one patient had chronic lymphocytic leukemia and one patient had multiple sclerosis treated with ocrelizumab. Thirteen patients (92.9%) had received prior B cell-targeting therapies, 11 with anti-CD20 monoclonal antibodies and two patients with CAR-T cell therapy. The underlying pathologies and chemotherapy treatments are listed in Table 1.

At the time of acute SARS-CoV-2 infection, 66.7% (8 out of 12 available) of patients had hypogammaglobulinemia, a median neutrophil count of 3440/mmc (IQR 2505–3865), and a median lymphocyte count of 800 (IQR 525–1595). All patients had completed a full vaccination course with anti-SARS-CoV-2 mRNA vaccines, 7 with three doses, 6 with 4 doses and one with 5 doses. Four patients had received long-acting MoAB (tixagevimab/cilgavimab), two as pre-exposure prophylaxis and two after acute infection. Early treatment was administered in 8 patients (57%), 6 were treated with nirmatrelvir/ritonavir, one with molnupiravir and one with sotrovimab. An anti-spike IgG serology test was conducted in 10 patients before starting combination therapy, with a median time of 39.5 days (IQR 30.5–56.5) days from the diagnosis of infection. Serology test resulted positive in 7 cases (70%), including three who had previously received tixagevimab/cilgavimab, two before and one after SARS-CoV-2 diagnosis.

The median time between diagnosis of SARS-CoV-2 infection and initiation of combination therapy was 42.0 days (IQR 35.0–45.7). The median number of PCR CT performed just before starting the treatment was 27.8 (IQR 25.9–30.3). Twelve patients had a positive NPS test, while two patients had a positive lower respiratory tract sample with a negative NPS test. Both these two patients (number 1 and number 8 in Table 1) had persisting cough and CTS signs of pneumoniae after 5 and 4 months respectively from the first positive NPS swab.

Among the treated patients, 7 had mild disease, 6 had moderate disease, of whom 5 required low-flow oxygen support, and one had severe disease requiring high-flow nasal cannula oxygen support. Nine patients had signs of interstitial pneumonitis on chest CTS before treatment, and 5 of them underwent follow-up CTS after treatment showing a marked improvement in pneumonia (Figure 1).

The median duration of nirmatrelvir/ritonavir and remdesivir combination therapy was 10 days (IQR 10.0–10.0). Ten patients received a 10-day treatment cycle, while three (patient number 4, 6 and 8) had longer courses of 13, 22, and 12 days, respectively, due to persistence of PCR test positivity. One patient (number 13) discontinued treatment after 5 days because viral clearance was confirmed after 3 days of treatment. Overall, the treatment was well-tolerated and no major adverse events were recorded. No discontinuations of treatment were reported. All patients showed resolution of COVID-19-related symptoms after a median of 6 days (IQR 4.2–10.7) and oxygen support was discontinued at the same time. Viral clearance, as confirmed by a PCR test, was achieved in all patients and the median time to a negative PCR test was 9 days (IQR 5.2–10.7). PCR tests performed every 5 ∓ 1 day showed a steady progressive increase in CT values (Figure 2). Among the 4 patients

TABLE 1 Overall patients' characteristics.

Patient	Sex	Age	Disease	Last chemiotherapic scheme	Anti-RBD antibodies level	Early antiviral treatment	Days of Sars-CoV-2 positivity at the start of antiviral therapy	Number of CT	Covid severity	Radiological signs of pneumonia	Need of oxygen supply	Total days of dual antiviral therapy
1	Male	46	Centrofollicular B cell NHL	Obinotuzumab + zanobrutinib	1777[a]	Nirmatrelvir/r[c]	144	NA	Mild	Yes	No	10
2	Male	58	Centrofollicular B cell NHL	Mosunetuzumab	21,8[a]	Nirmatrelvir/r	33	30,23	Moderate	Yes	Yes	10
3	Female	57	Centrofollicular B cell NHL	Obinotuzumab	NA	Nirmatrelvir/r	45	26,87	Mild	No	No	10
4	Male	54	Indolent NHL	Rituximab + bendamustine	0,4[a]	Nirmatrelvir/r	43	27,5	Mild	Yes	No	13
5	Male	63	Centrofollicular B cell NHL	Obinotuzumab + CHOP	0,4[a]	Molnupiravir[c]	42	NA	Moderate	Yes	Yes	10
6	Male	35	DLBCL	Rituximab + BFM + DHAP	NA	Nirmatrelvir/r	35	30,67	Mild	No	No	22
7	Male	84	Mantellar NHL	Rituximab + bendamustine	NA	No	48	32,24	Moderate	Yes	No	
8	Male	69	DLBCL	Obinotuzumab + glofitamab + polatuzumab	>2500[a]	Sotrovimab[d]	116	23	Severe	Yes	Yes	10
9	Male	59	DLBCL	CAR-T	>2500[a]	Nirmatrelvir/r	46	28	Mild	Yes	Yes	12
10	Male	56	MS	Ocrelizumab	0[b]	No	21	28,16	Moderate	Yes	No	10
11	Female	89	DLBCL	Rituximab + CHOP	1106[b]	No	42	32,99	Mild	No	Yes	10
12	Female	71	CLL	None	141[b]	No	30	22,75	Moderate	No	Yes	10
13	Male	67	DLBCL	Rituximab	NA	No	37	27	Moderate	Yes	No	5
14	Male	61	DLBCL	CAR-T	NA	No	35	22	Moderate	NA	No	10

Abbreviations: BFM, Berlin-Frankfurt-Munich; CAR-T, chimeric antigen receptor T cell therapies; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; CLL, chronic lymphocytic leukemia; DHAP, dexamethasone, high-dose Ara-C - cytarabine, platinol; DLBCL, diffuse large B-cell lymphoma; MS, multiple sclerosis; NHL, non Hodgkin Lymphoma; Nirmatrelvir/r, Nirmatrelvir/ritonavir.

[a]Sars-CoV-2 serology performed by quantitative Elecsys® Anti Sars-CoV-2 S and results expressed in BAU/mL.

[b]Sars-CoV-2 serology performed by ARCHITECT Sars-CoV-2 IgG II Quantitative (on ARCHITECT® i2000sr) and results expressed in AU/mL.

[c]Nirmatrelvir/ritonavir and molnupiravir early treatment are considered a 5 days complete treatment.

[d]Sotrovimab early treatment is considered a single dose of sotrovimab.

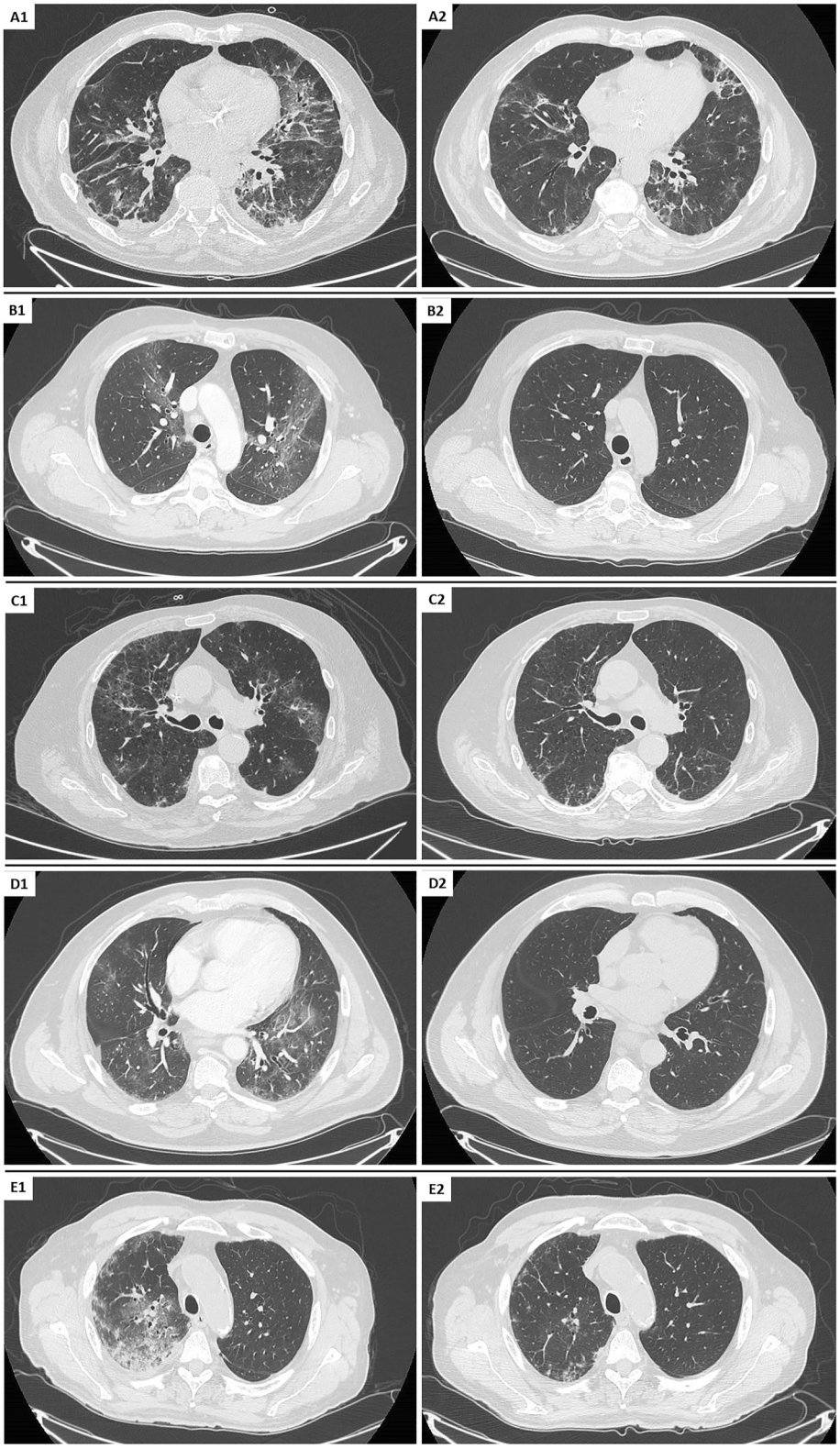

FIGURE 1 Lung computed tomography scan (CTS) features before and after dual antivirals treatment with remdesivir + nirmatrelvir/ritonavir of the five patients who underwent radiological follow-up. (A) (1–2) correspond to patient 8, (B) (1–2) correspond to patient 4, (C) (1–2) correspond to patient 5, (D) (1–2) correspond to patient 2, (E) (1–2) correspond to patient 7.

who received long-acting MoAB (tixagevimab/cilgavimab), one had mild disease, two had moderate disease, and one had severe disease. The clinical outcomes after combo treatment were comparable to the other patients, with symptom resolution occurring after a median of 6.5 days (IQR 2.7–11.5) and viral clearance achieved after a median of 10 days (IQR 9.0–12.7).

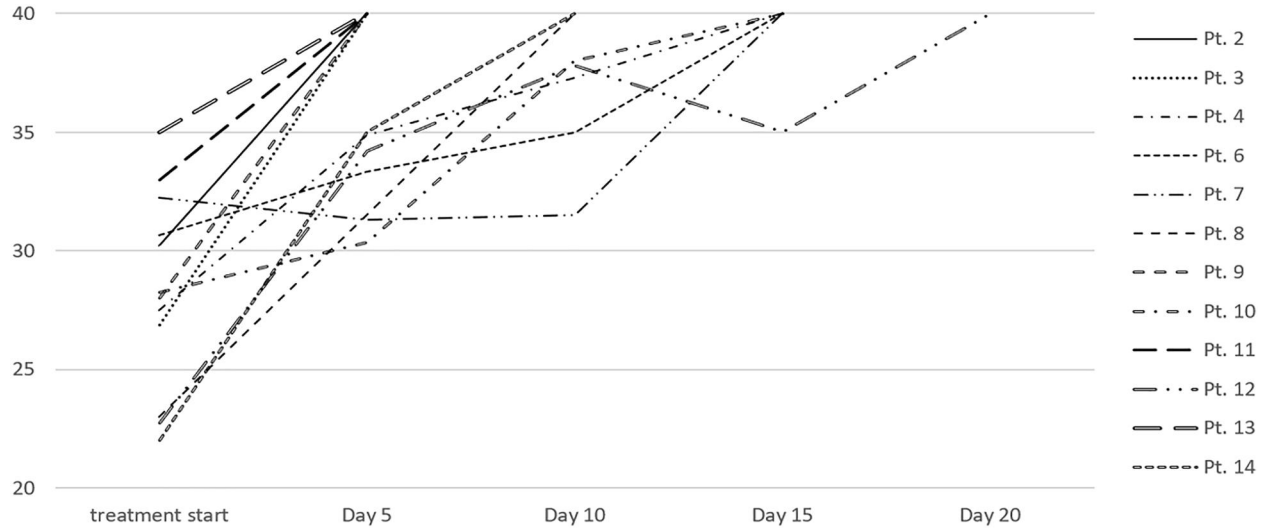

FIGURE 2 Trend of cycle threshold (CT) values from the start of combination antiviral treatment to the first negative polymerase chain reaction test. Patients 1 and 5 were excluded from this analysis, as they had a negative nasopharyngeal swab test but a positive lower respiratory tract sample.

The median follow-up after viral clearance was 26 days (IQR 17.2–57.0) and no early rebound was observed.

4 | DISCUSSION

Our preliminary clinical experience with a combination antiviral therapy of nirmatrelvir/ritonavir and remdesivir suggests that it could be useful in the management of patients with B-cell malignancy or undergoing anti-lymphocyte therapy who present with clinical and/or laboratory findings of persisting SARS-CoV-2 infection for more than 21 days. Indeed, we observed a resolution of symptoms and viral clearance in all patients after a median treatment duration of 10 days. Additionally, no patient experienced rebound after a median follow-up of 26 days.

Prior to this study, few case reports and small case series have described the management of patients with persisting infection with a wide range of therapeutic approaches. Prolonged courses of remdesivir[13] or nirmatrelvir/ritonavir,[14] dual antiviral therapy with remdesivir and nirmatrelvir/ritonavir,[15–17] and combination therapy with antiviral and monoclonal antibodies[18–22] have been described as treatment options. These studies have shown encouraging results, and they have provided valuable information for clinicians considering the lack of recommendations for these patients. However, the level of evidence remains low due to the limited number of cases in each study and the high variability among patients, timing, and different therapeutic schedules.

Our preliminary data are insufficient to establish the superiority of this therapeutic approach over others. However, we believe that there are several factors that support the use of this antiviral combination. Using a combination of two antivirals with different targets can potentially create a synergistic effect[23,24] and preventing the emergence of resistance. This is particularly important given that resistance to remdesivir has already been reported in immunocompromized patients after prolonged monotherapy.[31] Regarding nirmatrelvir/ritonavir, molecular resistance has been observed only in *in vitro* studies but it may theoretically occur *in vivo*[32] Although literature data suggest a potential clinical synergism between antivirals and MoAB, this combination was not considered due to the high prevalence of BQ.1.1 and BQ.5 variants in Italy, which accounted for 34.2% and 66.1%, respectively, during the study period.[33]

The fact that although enrolled patients had a significant defect of humoral immunity, the serological tests conducted before treatment were positive in 7 out of 10 cases, deserves a comment. Two main factors likely contribute to these positive results. Firstly, the serological tests were performed temporally close to an acute infection, where the absence of any correlation between disease severity and antibody response is well demonstrated. Furthermore, three patients had previously received tixagevimab/cilgavimab treatment in the previous 6 months, which could also potentially impact the serological outcomes. However, the lack of available data on previous serologies and antibody functionality limits our ability to determine the significance of these findings from an immunological and infection protection standpoint.

The main limitations of our study are the small sample size and the absence of controls. Moreover, the duration of the combination treatment was entirely arbitrary and not based on any clinical or virological evidence.

In conclusion, our study suggests that combination therapy with remdesivir and nirmatrelvir/ritonavir is a promising treatment option for persistent COVID-19 in immunocompromized patients with B-cell line hematological malignancies and/or anti-CD20 therapies. Further investigation with larger comparative interventional studies are needed to identify the optimal therapeutic approach for this patient population.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest regarding the subject of this manuscript and no external funding was received for this study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The study was conducted in accordance with the Declaration of Helsinki and ethics committee (CE-AVEC) approval n° 598/2021/Oss/AOUBo.

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PEER REVIEW

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