Journal of Microbiology, Immunology and Infection 57 (2024) 189—194

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

Short Communication

Combination treatment of persistent COVID-19 in immunocompromised patients with remdesivir, nirmaltrevir/ritonavir and tixegavimab/cilgavimab

Tal Brosh-Nissimov [a,b,*], Nir Ma'aravi [a], Daniel Leshin-Carmel [a], Yonatan Edel [a,b], Sharon Ben Barouch [a,b], Yafit Segman [a,b], Amos Cahan [a], Erez Barenboim [a]

[a] *Samson Assuta Ashdod University Hospital, Ashdod, Israel*
[b] *Faculty of Health Sciences, Ben Gurion University in the Negev, Beer Sheba, Israel*

Received 26 June 2023; received in revised form 1 September 2023; accepted 17 September 2023
Available online 27 September 2023

KEYWORDS
COVID-19;
-Immunocompromised;
Tixegavimab/cilgavimab;
Remdesivir;
Nirmatrelvir

Abstract We present a retrospective study on the treatment outcomes of severely immunocompromised patients with persistent COVID-19. The study analyzed data from 14 patients who received a combination of tixegavimab/cilgavimab and antiviral medications. Response was evaluated based on symptom improvement, PCR cycle-threshold values, and C-reactive protein levels. Eleven patients achieved complete clinical and virological resolution, while three showed partial responses. The study suggests a potential association between non-response and tixegavimab/cilgavimab neutralization. The findings underscore the need for tailored treatment approaches and further research on optimal strategies for managing persistent COVID-19, as well as the development of antivirals and variant-specific monoclonal antibodies.

* Corresponding author. Head of the Infectious Diseases Unit, Samson Assuta Ashdod University Hospital, Harefua st. 7, Ashdod 7747629, Israel.
E-mail address: talbros@assuta.co.il (T. Brosh-Nissimov).

https://doi.org/10.1016/j.jmii.2023.09.004

Introduction

The COVID-19 pandemic has been mitigated to some extent through vaccines, natural immunity, and antiviral drugs. However, immunocompromised individuals, such as those with hematological malignancies, B-cell depleting therapy (BCDT) recipients, and transplant patients, may experience persistent COVID-19 (pCOVID), characterized by prolonged symptomatic infection and lack of serologic responses.[1] The optimal treatment for pCOVID remains uncertain. This retrospective study analyzes the outcomes of immunocompromised patients with pCOVID who were treated with a combination of monoclonal antibodies, antivirals, and corticosteroids at Samson Assuta Ashdod University Hospital in response to the increasing number of cases during the Omicron variant wave in Israel.

Methods

Starting in March 2022, highly-immunocompromised COVID-19 patients were treated with tixegavimab/cilgavimab, combination antivirals, and corticosteroids. Data was collected retrospectively, including PCR cycle-threshold (Ct) values and anti-S antibody levels. Treatment response was evaluated based on symptom improvement, C-reactive protein (CRP) levels, and Ct values. The infecting SARS-CoV-2 variant was categorized as definite when identified with sequencing, or probable according to the most common (>50% frequency) circulating variant in Israel at the onset symptoms.

Results

Patients' baseline characteristics (see Table 1)

The median age was 74 years (interquartile range, IQR, 69,79). Two patients were kidney transplant recipients. Eleven patients had a B-cell lymphoproliferative disease: Seven patients had non-Hodgkin B-cell lymphoma, and 4 with chronic lymphocytic leukemia (CLL). All the lymphoma patients received BCDT, a median of 165 days (IQR 46,704) before disease onset. Three CLL patients were treated with ibrutinib. One patient had rheumatoid arthritis, treated with BCDT. Comorbidities associated with COVID-19 included hypertension (8 patients), diabetes mellitus (6), chronic renal failure (4), ischemic heart disease (3), congestive heart failure (3), chronic lung disease (3), obesity (2), and chronic liver disease in 1 patient. Nine patients had received four vaccine doses against COVID-19, a median of 146 (IQR 119,244) days before disease onset, which was considered adequate according to Israeli recommendations. Five patients were not adequately vaccinated: one received three doses 262 days before disease onset, two received two doses more than a year before disease onset, and two were unvaccinated. Three patients had received tixegavimab/cilgavimab prophylaxis 86, 104 and 114 days before disease onset, all with a 150/150 mg dose.

On presentation, among patients who had not received tixegavimab/cilgavimab prophylaxis, anti-S antibody was negative in eight patients and borderline in two. The infecting SARS-Cov-2 variant was definite in three patients, and probable in the rest, with one, four, eight and one cases with BA.1, BA.2, BA.5, and BQ.1/BQ.1.1, respectively.

Clinical presentation

The median time from disease onset to presentation was 20 days (IQR 15,39). All patients sought care due to significant symptoms, including cough (11 patients), fatigue (11), fever (10), dyspnea (5), weight loss (4) and diarrhea (4). Nine patients were hypoxemic. In many cases of prolonged symptoms, patients had been treated elsewhere for respiratory tract infections with recurrent courses of antimicrobials. Most patients had lymphopenia on presentation, with a median count of 500/ml (IQR 300,700). CRP was elevated in all cases, with a median value of 107 (IQR 67,130) mg/L. Twelve patients had abnormal findings in chest x-ray or CT scan, mainly diffuse or patchy bilateral interstitial infiltrates. All patients had a positive PCR result for SARS-CoV-2, with a median Ct value on presentation of 27 (IQR 24,32). Ten and five patients had Ct values below 30 and 25, respectively.

Treatment

All patients received intramuscular tixegavimab/cilgavimab. All patients received a five-day course of remdesivir. Eleven patients received concomitant nirmatrelvir/ritonavir for five days. Two transplanted patients (#4,6) had a major drug—drug interaction precluding ritonavir administration. One was administered concomitant molnupiravir, and the other received single-agent treatment with remdesivir. One lymphoma patient refused nirmatrelvir/ritonavir treatment. Twelve patients received concomitant dexamethasone 6 mg daily for 5—10 days.

Response to treatment (see Fig. 1)

Median follow-up was 45 (IQR 12,89) days. All 14 patients had a subjective symptomatic improvement at the end of treatment. Eleven patients had a complete response, with PCR tests taken between day 4—16 from treatment onset that were negative in seven cases, and with a Ct value > 30 in four additional cases. CRP levels gradually decreased in all eleven complete responders. Three patients were readmitted due to clinical relapse with either fever or dyspnea occurring soon after discharge. Of these three partial responders, one has died and two responded to repeated and prolonged antiviral treatments with eventual complete remission.

Discussion

In this analysis of fourteen patients with or at-risk for pCOVID, combination treatment including two antiviral medications and monoclonal antibodies, led to complete clinical and virological resolution in eleven patients, and partial responses in three.

SARS-CoV-2 clearance heavily relies on an effective adaptive B-cell response.[2] Immunocompromised patients,

Table 1 Clinical characteristics, treatments, and responses of persistent COVID-19 in immunocompromised patients.

#	Age and sex	Predisposing immunosuppression	Other predisposing comorbidities	Vaccination and T/C prophylaxis	Time from symptom onset to treatment (days)	Clinical presentation	Anti-S antibody titer[a]	Infecting variant, definite or (presumed)[b]	Response to primary treatment protocol	Follow up time, days
1	72M	Follicular lymphoma, Obinutuzumab treatment 190d before disease onset	DM	4 doses	62	Cough, fever, fatigue, weight loss, diarrhea. CXR — normal.	0	(BA.1)	Complete	102
2	74M	Follicular lymphoma, Obinutuzumab treatment given before and after disease onset	HTN	4 doses	52	Fatigue, weight loss. CXR — bilateral diffuse interstitial infiltrates.	0	(BA.1/BA.2)	Complete	39
3	80M	CLL, ibrutinib treatment	HTN, IHD, CHF, COPD, CRF	4 doses	17	Fever, hypoxemia, fatigue, weight loss, diarrhea. CXR — bilateral diffuse interstitial infiltrates.	20.8	(BA.2)	Complete	85
4	75M	Kidney transplantation, tacrolimus and low dose steroid treatment	DM, HTN, IHD, CHF, COPD, CRF, BMI>30	4 doses	21	Cough, dyspnea, hypoxemia, fever, fatigue, diarrhea. CXR — bilateral peripheral interstitial infiltrates.	19	(BA.2)	Complete	171
5	69M	Mantle cell lymphoma, autologous HSCT, ibrutinib treatment, rituximab treatment 704 days before onset	CRF	4 doses	20	Cough, dyspnea, hypoxemia, fever, fatigue. Chest CT scan — bilateral ground glass infiltrates.	0	(BA.5)	Complete	50
6	62F	Kidney transplantation, everolimus, mycophenolate mofetil and low dose steroid treatment	DM, HTN, CRF	None	11	Cough, fever, fatigue. CXR — bilateral peripheral interstitial infiltrates.	0	(BA.5)	Complete	16
7	85F	CLL, ibrutinib and low dose steroid treatment	DM, HTN, CHF	4 doses	35	Cough, dyspnea, fatigue. CXR — patchy infiltrates.	0	(BA.5)	Complete	21
8	75M	Follicular lymphoma, Obinutuzumab treatment 46 days before disease onset	DM, HTN, BI > 30	4 doses, T/C 300 mg 104 days before onset	22	Cough, hypoxemia, fever. CXR — normal.	300 (after T/C administration)	**BA.5**	Partial response, severe relapse after discharge, readmission with partial response to prolonged antiviral treatments	159
9	79F	CLL	Chronic liver disease	3 doses	14	Cough, hypoxemia, fever, fatigue. CXR — right lower lobe infiltrate.	0	(BA.5)	Complete	10
10	81M	CLL, ibrutinib treatment	HTN, IHD, CRF	4 doses	0	Fever. CXR — bilateral interstitial infiltrates, more prominent on the left.	0	**BA.5**	Partial response, severe relapse after discharge leading to critical COVID-19 and death	57

(*continued on next page*)

Table 1 (*continued*)

#	Age and sex	Predisposing immunosuppression	Other predisposing comorbidities	Vaccination and T/C prophylaxis	Time from symptom onset to treatment (days)	Clinical presentation	Anti-S antibody titer[a]	Infecting variant, definite or (presumed)[b]	Response to primary treatment protocol	Follow up time, days
11	76F	MALT lymphoma, history of rituximab treatment (10 years)	HTN	None	15	Cough, dyspnea, hypoxemia, fatigue, weight loss. CXR — bilateral peripheral interstitial infiltrates.	0	(BA.5)	Complete	5
12	68F	Follicular lymphoma, Obinutuzumab treatment 165 days before disease onset	DM	2 doses	77	Cough, dyspnea, hypoxemia. CXR — bilateral peripheral interstitial infiltrates.	ND	**BA.2**	Complete	6
13	58M	Marginal zone lymphoma, Obinutuzumab treatment 108 days before disease onset	None	2 doses, T/C 300 mg 114 days before disease onset	33	Cough, fever, weight loss, fatigue, diarrhea. CXR — normal.	307 (after T/C administration)	(BA.5)	Partial response with relapse after discharge, complete response to prolonged antiviral treatment	84
14	70 M	Rheumatoid arthritis, Rituximab treatment 153 days before disease onset	Interstitial lung disease	4 doses, T/C 300 mg 86 days before disease onset	20	Cough, fever, fatigue, hypoxemia. CXR — bilateral peripheral interstitial infiltrates.	414 (after T/C administration)	(BQ.1)	Complete	13

[a] Anti-S antibody levels were tested with the Liaison® (DiaSorin, Saluggia, Italy) SARS-CoV-2 Trimeric IgG assay (negative, $\leq$12u/ml, borderline 13-22u/ml, positive $>$22u/ml, and a linearity range of up to 800 u/ml).

[b] The infecting SARS-CoV-2 variant was either definite, proven with sequencing, or probable according to the most common ($>$50% frequency) circulating variant in Israel at the onset symptoms.[11]

Abbreviations: T/C, tixegavimab/cilgavimab; M, male; F, female; DM, diabetes mellitus; CXR, chest X-ray; HTN, hypertension; CLL, chronic lymphocytic leukemia; IHD, ischemic heart disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CRF; chronic renal failure; BMI, body mass index; HSCT, hematopoietic stem cell transplantation; CT, computerized tomography; MALT, mucosal-associated lymphoid tissue.

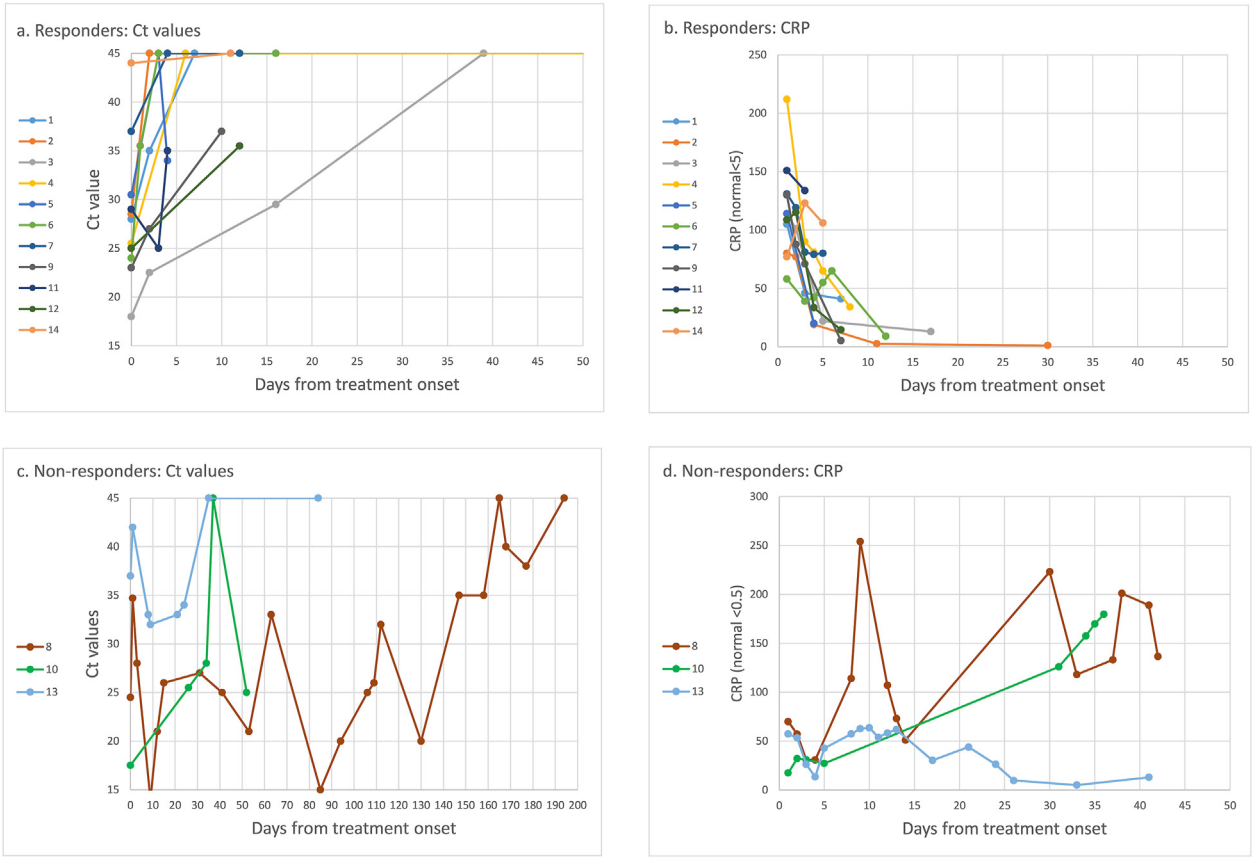

Figure 1. Response to treatment, manifested as SARS-CoV-2 polymerase chain reaction (PCR) cycle threshold (Ct) values and C-reactive protein (CRP, mg/L) levels beginning at treatment onset for eleven patients with complete response and three patients with partial response. (a,b) Ct values and CRP levels of eleven complete responders. (c,d) Ct values and CRP levels of three partial responders. Higher Ct values signify a lower SARS-CoV-2 viral load. Ct value of 45 signifies a negative SARS-CoV-2 PCR. CRP normal range 0—5 mg/L.

particularly those undergoing anti-CD20 therapy, have demonstrated an increased risk of pCOVID.[3] These patients often exhibit prolonged fever, cough, dyspnea, radiological signs of pneumonitis, and positive SARS-CoV-2 PCR tests, while failing to develop a serological response. Belkin et al. proposed criteria to define pCOVID, suggesting a symptom duration of 7—14 days and PCR positivity for over 21 days.[1]

Contemporary treatment approaches for COVID-19 encompass antivirals, monoclonal antibodies, and immunomodulators, all of which have shown benefits in high-quality clinical trials. However, severely immunocompromised patients were excluded from most. Due to limited evidence, clinical guidelines such of the National Institute of Health (NIH), do not recommend a distinct approach to the treatment of immunocompromised patients.[4] Nevertheless, COVID-19 in immunocompromised patients often follows a different course, necessitating a potentially different treatment strategy. Considering the impaired ability to mount an adaptive serological response and the prolonged SARS-CoV-2 replication in these patients, administering antivirals and antibody treatments beyond the initial disease stages and extending their duration may be theoretically justified. To maximize treatment success while minimizing the risk of antiviral resistance, as reported in pCOVID patients receiving remdesivir,[5] our approach involved combining two antiviral medications whenever possible. Additionally, we utilized tixegavimab/cilgavimab, a monoclonal antibody preparation known for its neutralizing activity against previously circulating Omicron variants.

Evidence regarding successful treatment of pCOVID remains limited to case-series and cohort studies. The earliest successful reports were for convalescent plasma therapy (CPT).[6] In a study evaluating the outcomes of various treatments in 31 cases of pCOVID, primarily following BCDT, a combination of remdesivir and either CPT or casirivimab/imdevimab showed better chances of symptomatic improvement and viral clearance than remdesivir only.[7] In several reports, monoclonal antibodies were curative after exceptionally prolonged infection, unresponsive to repeated treatments with remdesivir and steroids.[8] A similar approach to ours, including tixegavimab/cilgavimab, remdesivir and a second antiviral agent, was employed in another case series with similar response rate of 82% at end of follow-up.[9]

However, three of our patients did not achieve complete and sustained response despite the 5-day combination treatment. These non-responders were all infected with the BA.5 variant, while only 6/11 responders were infected with BA.5 or BQ.1 variants, which are not as efficiently neutralized by tixegavimab/cilgavimab as previous Omicron variants.[10] This difference was not statistically significant

(χ^2 test, $p = 0.26$). One non-responder (#13) declined nirmatrelvir/ritonavir during the primary treatment course and was treated only with remdesivir and tixegavimab/cilgavimab. Patient #10, upon re-admission, developed progressive pneumonitis and subsequently deteriorated and died after receiving steroids and baricitinib. The two other non-responders (#8,13) also failed to respond to this approach and experienced significant opportunistic infections. However, they achieved sustained full recovery with a prolonged combination antiviral treatment. These cases suggest that immunomodulatory treatment of severe COVID-19 in severely immunocompromised patients may carry more risks than benefits and that prolonged antiviral treatments could be useful for sustained responses or even a cure.

There are several limitations to this study. Patients were not treated using a standardized protocol, and as a single-arm study, a control group comparison could not be conducted. As most patients received a combination of various treatments, it remains unclear whether the responses were due to a specific treatment or their combination. An optimal assessment of treatment response in pCOVID has not been defined, and therefore we employed a combined assessment including symptom resolution, CRP levels and PCR results. We had sequencing results for only three patients, while the variants of the other patients were presumed according to national epidemiology, hence might be inaccurate. The follow-up period was short for some patients, but had they relapsed, it is likely they would have sought care at our hospital, being the only hospital in the area.

In summary, we show that severely immunocompromised patients with pCOVIDcan be effectively treated with a combination of antivirals and monoclonal antibodies, either through a short five-day treatment, or, for non-responders, with repeated and prolonged antiviral therapy. Non-response might have been associated with the BA.5 variant, which was not as well-neutralized by tixegavimab/cilgavimab. This report, along with others, calls for controlled studies to further assess the optimal treatment for pCOVID, and underscores the importance of ongoing development of new antivirals and variant-specific monoclonal antibodies.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval

The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the institutional review board (#AAA-22-113). Informed consent was waved due to the retrospective design.

Data availability

Unidentified data is available upon reasonable request to the corresponding author.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT (OpenAI) in order to Improve English language. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Declaration of competing interest

TBN received honoraria and consultation fees from AstraZeneca, MSD, GSK, Gilead, Medison.

References

1. Belkin A, Leibowitz A, Shargian L, Yahav D. The unique presentation of SARS-CoV-2 Infection in patients with B-cell depletion: definition of 'persistent inflammatory sero-negative COVID'. *Clin Microbiol Infect* 2023;**29**(1):1—3. https://doi.org/10.1016/j.cmi.2022.10.007.
2. DeWolf S, Laracy JC, Perales MA, Kamboj M, van den Brink MRM, Vardhana S. SARS-CoV-2 in immunocompromised individuals. *Immunity* 2022;**55**(10):1779—98. https://doi.org/10.1016/j.immuni.2022.09.006.
3. Lee CY, Shah MK, Hoyos D, Solovyov A, Douglas M, Taur Y, et al. Prolonged SARS-CoV-2 infection in patients with lymphoid malignancies. *Cancer Discov* 2022;**12**(1):62—73. https://doi.org/10.1158/2159-8290. CD-21-1033.
4. COVID-19 Treatment Guidelines Panel. Special considerations in people who are immunocompromised. In: *Coronavirus disease 2019 (COVID-19) treatment guidelines*. National Institutes of Health; 2022. Published, https://www.covid19treatmentguidelines.nih.gov/special-populations/immunocompromised/. [Accessed 25 November 2022].
5. Hogan JI, Duerr R, Dimartino D, Marier C, Hochman SE, Mehta S, et al. Remdesivir resistance in transplant recipients with persistent Coronavirus disease 2019 (COVID-19). *Clin Infect Dis* 2019;**2022**:1—4. https://doi.org/10.1093/cid/ciac769.
6. Hueso T, Pouderoux C, Péré H, Beaumont AL, Raillon LA, Ader F, et al. Convalescent plasma therapy for B-cell—depleted patients with protracted COVID-19. *Blood* 2020;**136**(20):2290—5. https://doi.org/10.1182/BLOOD.2020008423.
7. Brown LAK, Moran E, Goodman A, Baxendale H, Bermingham W, Buckland M, et al. Treatment of chronic or relapsing COVID-19 in immunodeficiency. *J Allergy Clin Immunol* 2022;**149**(2):557—561.e1. https://doi.org/10.1016/j.jaci.2021.10.031.
8. D'Abramo A, Vita S, Maffongelli G, Mariano A, Agrati C, Castilletti C, et al. Prolonged and severe SARS-CoV-2 infection in patients under B-cell-depleting drug successfully treated: a tailored approach. *Int J Infect Dis* 2021;**107**:247—50. https://doi.org/10.1016/j.ijid.2021.04.068.
9. Mikulska M, Speulcri C, Dentone C, Magne F, Balletto E, Baldi F. Triple combination therapy with two antivirals and monoclonal antibodies for persistent or relapsed SARS-cov-2 infection in immunocompromised apatients. *Clin Infect Dis* 2023. https://doi.org/10.1093/cid/ciad181. Published online.
10. Cao Y, Yisimayi A, Jian F, Song W, Xiao T, Wang L, et al. BA.2.12.1, BA.4 and BA.5 escape antibodies elicited by Omicron infection. *Nature* 2022;**608**(7923):593—602. https://doi.org/10.1038/s41586-022-04980-y.
11. NextStrain. *Genomic epidemiology of SARS-CoV-2 with global subsampling: Israel*. 2022. Published, https://nextstrain.org/ncov/gisaid/global?f_country=Israel. [Accessed 26 November 2022].