International Journal of Sciences: Basic and Applied Research (IJSBAR)

ISSN 2307-4531
(Print & Online)

http://gssrr.org/index.php?journal=JournalOfBasicAndApplied

The Monoclonal Antibody Cocktail in SARS-CoV 2: A Bonanza for Patients with Chronic Lymphocytic Leukemia?

Brunda MS[a*], Arushi Mohan[b], Anant Patil[c], Hashif P[d], Prakash Doraiswamy[e], Samriddha Thapa[f]

[a,b,d,e]*Aster CMI hospital, 43/2, New Airport Road, NH.7, Sahakara Nagar, Bengaluru, Karnataka 560092*

[c]*Padmashree Dr. D.Y. Patil University Sector 15, Plot no 50, CBD Belapur Navi Mumbai (District Mumbai) Maharashtra, India - 400614*

[f]*Patan Academy of health sciences, Lagankhel, Lalitpur,Nepal.*

[a]*Email:brundamysore@gmail.com,* [b]*Email:arushimohan@gmail.com,* [c]*Email: anantd1patil@gmail.com,*

[d]*Email: hashifp786@gmail.com,* [e]*Email: Prakash.doraiswamy@asterhospital.com,*

[f]*Email:samshines@msn.com*

Abstract

Monoclonal antibody cocktail is currently one of the most promising approaches being studied in the management of severe acute respiratory syndrome coronavirus 2 (SARS CoV-2). We present a case of an elderly patient with coronavirus disease (COVID-19) and Chronic lymphocytic leukaemia (CLL) who had recurrent episodes of desaturation and admission in intensive care unit (ICU) despite receiving the treatment for moderate to severe COVID-19. After careful selection, weighing the benefits and risks, the patient was started on the combination of the two monoclonal antibodies, casirivimab and imdevimab. The results suggest that this could be a game changer in COVID-19 with a focused approach of management of COVID-19 positive patients especially in the vulnerable population.

Keywords: medicine; pulmonology.

---

* Corresponding author.

1. Introduction

The rate of spread of the novice condition, with vicissitudes in presentation, surges and pathogenesis, the severe acute respiratory syndrome coronavirus (SARS CoV-2), a potentially lethal airborne virus has the potential to not only cause a mishap by its presence, but also trigger an oversensitive immune system [1]. Treating patients with cancer with coronavirus disease (COVID-19) infection could stir up a hornet's nest for clinicians, probably due to the immunosuppressed state, particularly in haematological cancers. A study involving 218 patients reported a case fatality rate of 37%in haematological cancers compared to 25% for solid malignancies, possibly due to a maladaptive immune response [2]. Being a relatively new formulation, casirivimab and imdevimab was approved for Emergency Use Authorisation (EUA) by the Food and drug administration (FDA).

It is available in vials to be administered either intravenously which is preferred as a single dose (under supervision) or subcutaneously requiring 4 doses. The antibody cocktail is utilized in the treatment of mild to moderate COVID-19 infection in patients that are above 12 years of age and weighing at least 40Kg with a positive viral test for SARS CoV -2.

However, immunocompromised patients and those that were not able to mount an effective antibody response can receive a targeted individualised therapy with the cocktail. It is also very suitable in patients with co-morbid conditions although sufficient data on their safety profile is yet to be investigated [3,4]. We present a case of an elderly patient who has severe COVID-19 infection and coexisting chronic lymphocytic leukaemia treated with a cocktail of monoclonal antibodies.

1.1. Case Report

A 68-year-old male diagnosed with chronic lymphocytic leukemia who completed 6 cycles of chemotherapy with a combination of bendamustine (an alkylating chemotherapeutic agent that works by breaking the links between DNA strands thus leading to cell death) and rituximab (monoclonal antibody against CD 20).

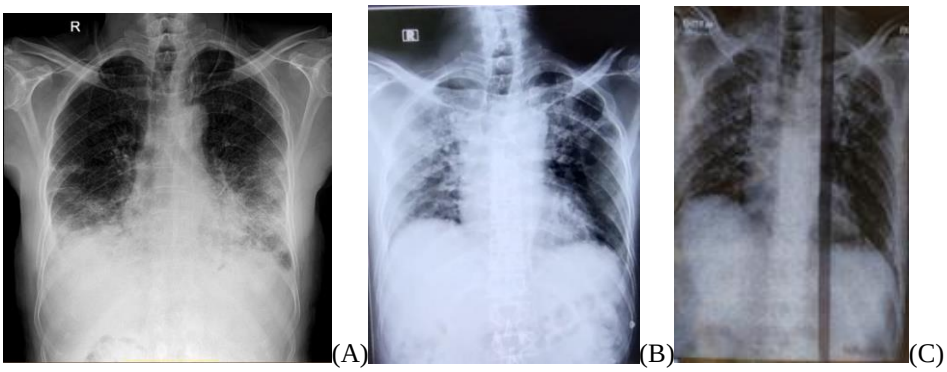
The last dose was given about 4 weeks ago. The patient presented with primary complaints of headache and tiredness for 10 days and cough with expectoration for 7 days. He was found to be positive for COVID-19 by reverse transcriptase polymerase chain reaction (RT-PCR) on admission.The laboratory investigations during hospitalisation were found to have values as follows (Table 1).

The patient required about 1-2 liters of oxygen to maintain the oxygen saturation in the range of 93%-95%. On the third day of admission, he developed a dull pain in upper abdomen, which on ultrasound examination revealed no significant abnormalities. He also underwent an echocardiography which showed an ejection fraction of 60% and mild left ventricular hypertrophy. He was diagnosed with a moderate to severe SARS-CoV -2 infection and was started on ceftriaxone, remdesivir (5-day therapy), steroid and low molecular weight heparin. He was hospitalized for 10 days and after being clinically stable without significant laboratory abnormalities, was discharged on intermittent oxygen (first admission) The patient presented again (second admission) after 3 days with recurrent spikes of fever and persistent cough since his previous discharge. This time, chest X ray showed inhomogeneous opacities bilaterally in the lower zones (Figure 1).

Table 1: Laboratory investigations.

	C-reactive protein(mg/L)	**Ferritin** (mg/mL)	**D-Dimer** (ng/mL)	**LDH** (U/L)	**PCT** (ng/ml)
On admission	101.91		790.07		0.07
Day Five	63.29	1651	1497.79	397	
Day Six (ICU)	17.15	>2000		536	
Day Seven					0.05
Day Eight	3.71	>2000			
Day Ten (WARD)	1.63	>2000	2737		
Day Thirteen	0.51	2000	3062	729	<0.05
Day Fifteen (post cocktail)	1.91				<0.05
(ICU)					
One-month post cocktail administration			557.9	585	
A week after the previous entry		1485		291	

LDH: Lactate Dehydrogenase, PCT: Procalcitonin , ICU: Intensive care unit.



(A) (B) (C)

Figure 1(A-C):

A: Chest X ray showing a resolution of the initial homogenous opacities

B: Chest X ray a week post monoclonal antibody administration.

C: Chest X ray a month post monoclonal antibody administration.

High resolution computed tomography (HRCT) of chest had score of 22/25 (Figure 2). His laboratory parameters were monitored and he was treated with ceftriaxone, steroids and low molecular weight heparin. After about a week, interleukin -6 level measures about 32.8 and he was started on colistin. He initially required about 3-4 liters of oxygen via a nasal prong to maintain a saturation between 92-94%. However, after about a week after the second admission, he started deteriorating and required about 15 liters of oxygen via a non-rebreather mask (NRBM). His saturation was between 90-92% and respiratory rate of 35 per minute. He was shifted to intensive care unit (ICU).

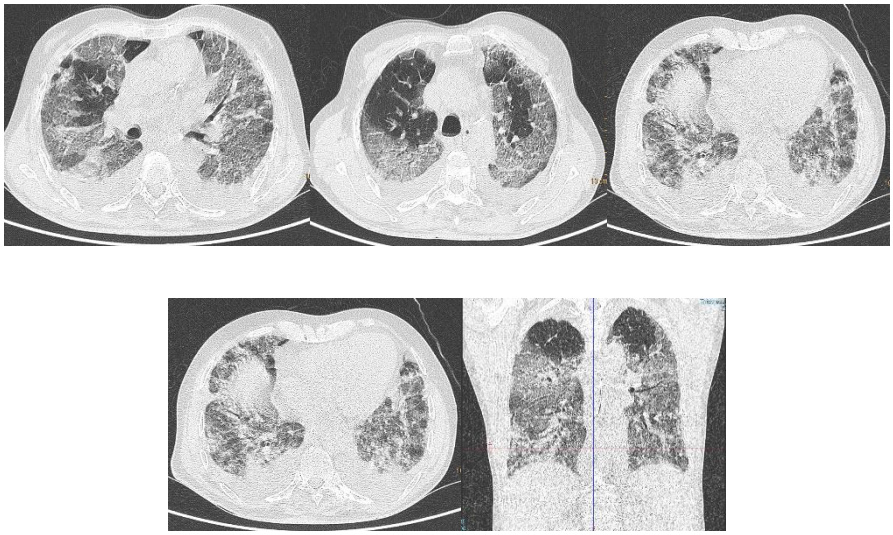


Figure 2: Chest computed tomography showing increased ground glass density and reticular interstitial thickening of bilateral lung parenchyma involving all lobes- consistent with typical findings of COVID-19 pneumonia.

In the ICU, he was continued on the NRBM with saturation of 92%-94% and then gradually tapered after improvement in the oxygen saturation. A nasogastric tube was placed as he was not able to meet his daily requirement of calories. After improvement of clinical and laboratory parameters with tocilizumab administration, he was shifted to the ward where initially he required about 5-6 liters of oxygen to maintain a saturation of about 95-97%. Again, an episode of desaturation required ICU admission. After consultation with the infectious disease specialist and informed consent from the patient and family, the antibody cocktail of casirivimab(600mg) and imdevimab(600mg) was administered. Multi-vitamins, piperacillin and tazobactam were the other medications administered. After stable status for 2 days, he desaturated again and was shifted to the ICU where he was on a NRBM which was tapered later. After a total of 15 days of stay with 3 visits to the ICU, he was admitted to another hospital, due to monetary constraints, where oxygen, antibiotics, anticoagulants and steroids were continued. He was started on antifungals as sputum culture and sensitivity analysis revealed candida species. On being stable during the course of stay in the ICU, he was shifted to the ward where he was weaned off oxygen and was started on antifibrotic medication (pirfenidone). He was discharged on 2 litres of oxygen. Total duration of stay was 22 days. Nebulisation with a short acting beta 2 agonist, inhaled corticosteroid (Budesonide) and a mucolytic (N acetyl cysteine) were given for supportive care. After receiving the monoclonal antibody combination therapy of Casirivimab and Imdevimab, the patient's requirement of oxygen had reduced and patient developed a positive antibody response. The patient is now symptomatically better with resolution of the chest X ray findings and normalization of the laboratory values.

1.2 Discussion

Chronic lymphocytic leukemia is a lymphoproliferative disorder characterized by an increased production of monoclonal mature B lymphocytes, that are morphologically mature however are immunologically dysfunctional. [5]. A metanalysis involving 32 studies demonstrated a significant increase in mortality (RR,

1.66; 95% CI, 1.33 to 2.07; P < .0001), increased incidence of ICU admissions (RR, 1.56; 95% CI, 1.31 to 1.87; P < .0001) in comparison with patients without cancer [6]. Thus, in our patient, with the unfortunate diagnosis of having cancer, enhanced the likelihood of developing a severe form of COVID 19. The use of a combination of remdesivir and steroids is recommended in case of moderate to severe disease requiring high flow oxygen within 10 days of symptom onset, the anti-inflammatory properties of the steroids have theoretically shown to reduce systemic inflammation and diminish the potentially fatal inflammatory response [7]. Our patient received this therapy and was discharged. However, patient was readmitted due to desaturation. In a trial with patients that required oxygen (saturation of <92%) and evidence of systemic inflammation (CRP> 75 mg/L), 621/2022 (31%) and 729 /2094(34.8%) in the tocilizumab and control group respectively died within 28 days of admission [7]. Thus, tocilizumab (a monoclonal antibody against interleukin -6) has been shown to have a survival advantage. However, the study included COVID patients without malignancy. Our patient was started on a remdesivir and steroid combination therapy, followed by the addition of tocilizumab in combination with steroids.

In a trial involving patients receiving monoclonal antibody cocktail (n=4839) and usual care group (n=4946), 98.6% and 98.8% completed the follow-up respectively. In this study, a total of 90% and less than 1% patients received cocktail therapy respectively. One seventh of the patients in the usual care group also received tocilizumab. In seronegative group, 28-day fatality rate (primary outcome) was observed in 24% and 30% patients respectively. Reduction in the use of mechanical ventilator was also significant in the combination therapy compared to usual care group (28% vs 32%; risk ratio 0.87; 95% CI; 0.77-0.98) with increased rate of discharge from the hospital [9]. Our patient was seronegative for COVID antibodies (IgM and IgG), even after 26 days into treatment initiation, possibly because of cancer related immunosuppression, justifying the use of neutralizing antibody in this case.

In a phase 3 trial, the use of the combination of casirivimab and imdevimab (600mg each) was associated with a relative risk reduction in the incidence of symptomatic infection by 81% (in the first week it was 72% and the following weeks it increased to 93%). Moreover, the relative risk reduction of high viral load infections and all infections was 86% and 66% respectively. The treatment also reduced the symptom duration by 2 weeks in those who became infected after receiving the cocktail as compared to placebo. In the antibody cocktail group, presence of antibodies was seen on the very first day which persisted for 4 weeks. These results suggest that this antibody cocktail can be started without a baseline serology. Our patient also did not have any significant adverse event as seen in the study [10]. In contrast to the trial [9], our patient had a longer duration of hospital stay. This possibly could be explained by the clinical presentation (mild to moderate) of the patients in the trial, unlike our patient who had moderate to severe disease.

Chronic lymphocytic leukemia has been shown to have increased risk of infections due to T cell exhaustion in early stages and B cell (defective antibody production) mediated mechanisms [11]. In our case, the other possible mechanism could be immunosuppression from the use of rituximab, a CD 20 inhibitor, which could hamper the formation of neutralizing antibodies in SARS-CoV-2. It has also been shown to have an inhibitory effect on a group of T cells (particularly CD4 and to a lesser extent CD 8 as well) that could offer an adequate immune response [12]. However, rituximab could also be a boon, because of it's potential to prevent the

cytokine storm mediated damage to the lungs which results in ARDS (acute respiratory distress syndrome), although not clearly known [13]. Bone marrow study in our patient revealed primarily atypical hypercellular cells which were mononuclear with a scant cytoplasm. Further, immunohistochemistry analysis revealed particularly, CD 19, CD 20, CD5, CD45, CD 22 cells an immunophenotyping was positive for CD5 and CD 10. Thus, demonstrating the involvement of both T and B cells in this patient's leukemia.

Given the above possible mechanisms of immunosuppression, the principle behind the use of monoclonal antibodies, as was demonstrated in animal models and in vitro studies on casirivimab and imdevimab is based on antibodies directed against specific viral proteins or on the surface of the infected cells, resulting in an antibody dependent phagocytosis of infected cells [14,15]. This combination therapy offers an advantage of reduced risk of resistance compared to monotherapy and has better efficacy because of its action at two distinct sites on the receptor [9].

This combination held its primacy against the strains (B.1.1.7(alfa), B.1.315 (beta), B.1.617.2(delta) B.1.429 (epsilon) and P.1 (gamma). However, we should be cautious of other evolving strains [9]. Future studies with the use of the antibody cocktail, could possibly be the light in the tunnel of SARS-CoV-2 infection.

A study has also demonstrated a reduced immunogenic response in patients with haematological cancers to the ongoing 2 dose vaccine, stressing the importance of monoclonal antibodies in the treatment of SARS CoV-2 in these groups of patients [16].

1.3 Conclusion

Cocktail (casirivimab + imdevimab) of monoclonal antibodies was beneficial in a COVID-19 patient with chronic lymphocytic leukaemia. We feel careful consideration of the cocktail could prove to be beneficial in reducing mortality in COVID-19 infection including in vulnerable populations such as those diagnosed with cancer.

Acknowledgements

The authors would like to extend their appreciation to the Department of Radiology at Aster CMI hospital for the images provided.

References

[1]. Coronavirus.Who.int.(2021).Internet.https://www.who.int/health-topics/coronavirus#tab=tab_1. Accessed: 19 October, 2021.

[2]. Mehta V, Goel S, Kabarriti R, Cole D, Goldfinger M, Acuna-Villaorduna A, Pradhan K, Thota R, Reissman S, Sparano JA, Gartrell BA. "Case fatality rate of cancer patients with COVID-19 in a New York hospital system". Cancer discovery. 2020 Jul 1;10(7):935-41

[3]. "FDA: fact sheet for health care providers emergency use authorization (eua) of regen-cov (casirivimab and imdevimab)". [Internet]. https://www.fda.gov/media/145611/download Accessed :16 October,

2021.

[4]. Science Brief: "COVID-19 Vaccines and Vaccination".Internet. https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html updated on September 15, 2021 Accessed: October 19,2021.

[5]. Mukkamalla SKR, Taneja A, Malipeddi D, et al. In: StatPearls .Internet. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470433/ .[Updated 2021 Oct 1].. Treasure Island (FL): StatPearls Publishing; 2021 Jan.

[6]. Giannakoulis VG, Papoutsi E, Siempos II. "Effect of cancer on clinical outcomes of patients with COVID-19: a meta-analysis of patient data". JCO global oncology. 2020 Jun;6:799-808.

[7]. "Therapeutic management of hospitalized adults with covid-19".Internet. https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/hospitalized-adults--therapeutic-management/. Revised :25 August, 2021.Accessed: 19 October,2021.

[8]. Horby PW, Pessoa-Amorim G, Peto L. for "the RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomised, controlled, open-label, platform trial". medRxiv. 2021:12-24.

[9]. Horby PW, Mafham M, Peto L, Campbell M, Pessoa-Amorim G, Spata E, Staplin N, Emberson JR, Prudon B, Hine P, Brown T. "Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial". medRxiv. 2021 Jan 1.

[10]. O'Brien, M. P., Al., E. the Covid-19 Phase 3 Prevention Trial Team*, Pharmaceuticals, A. A. F. R., Others, W. Z. and, Others, G. L. and, Others, G. C. and, D. M. Weinreich and Others, A. R. Falsey and Others, & T. T. Shimabukuro and Others "Subcutaneous regen-COV antibody combination to prevent covid-19": Nejm. New England Journal of Medicine. Retrieved October 7, 2021

[11]. Forconi F, Moss P. "Perturbation of the normal immune system in patients with CLL". Blood, The Journal of the American Society of Hematology. 2015 Jul 30;126(5):573-81.

[12]. Hardeman, P. et al., 1970. "Does rituximab cause depletion of T-cells in multiple sclerosis and Neuromyelitis Optica? (P2.158)": Semantic scholar. undefined. [Online]Available at: https://www.semanticscholar.org/paper/Does-Rituximab-Cause-Depletion-of-T-Cells-in-and-Hardeman-Mann/48f22881adfeaccb5a0d1ab8aa94055be5bce78a [Accessed March 31, 2022].

[13]. Ju B, Zhang Q, Ge J, Wang R, Sun J, Ge X, Yu J, Shan S, Zhou B, Song S, Tang X. "Human neutralizing antibodies elicited by SARS-CoV-2 infection". Nature. 2020 Aug;584(7819):115-9.

[14]. Hansen J, Baum A, Pascal KE, Russo V, Giordano S, Wloga E, Fulton BO, Yan Y, Koon K, Patel K, Chung KM. "Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail". Science. 2020 Aug 21;369(6506):1010-4.

[15]. Hansen J, Baum A, Pascal KE, Russo V, Giordano S, Wloga E, Fulton BO, Yan Y, Koon K, Patel K, Chung KM. "Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail". Science. 2020 Aug 21;369(6506):1010-4.

[16]. Herishanu Y, Avivi I, Aharon A, Shefer G, Levi S, Bronstein Y, Morales M, Ziv T, Shorer Arbel Y, Scarfo L, Joffe E. "Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. Blood". The Journal of the American Society of Hematology. 2021 Jun 10;137(23):3165-73.