Indian J Hematol Blood Transfus (Oct-Dec 2021) 37(4):699–701
https://doi.org/10.1007/s12288-021-01443-8

CORRESPONDENCE

SARS-CoV2 Infection in Hematopoietic Stem Cell Transplant recipients: A Case Series from a Tertiary Cancer Centre in India

Akhil Rajendra[1,6] · Anant Gokarn[1,6] · Sumeet Mirgh[1,6] · Rahul Ravind[1,6] · Anuj Singh[1,6] · Vasu Babu Goli[1,6] · Sachin Punatar[1,6] · Akanksha Chichra[1,6] · Prashant Tembhare[2,6] · Nikhil Patkar[2,6] · Vivek Bhat[3,6] · Preeti Chavan[4] · Bhakti Trivedi[5,6] · Amit Joshi[1,6] · Navin Khattry[1,6]

Received: 29 January 2021 / Accepted: 1 May 2021 / Published online: 13 May 2021

Dear Editor,

Severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2) virus associated COVID-19 (coronavirus disease) pandemic, has led to more than 2.5 million deaths worldwide. Hematopoietic stem cell transplant (HCT) recipients may be at a greater risk of morbidity and mortality due to their immunosupressed state [1]. Here, we report 6 cases of SARS-CoV-2 infection in HCT recipients.

Between May and September 2020, six HCT recipients were diagnosed with SARS-CoV-2 infection at our centre, based on reverse transcriptase polymerase chain reaction (RTPCR) on nasopharyngeal swab. Baseline characteristics of all the six patients are shown in Table 1. Severity of COVID-19 disease was graded as per WHO ordinal scale [2]. We used triplet antiviral combination with Lopinavir/Ritonavir (LPV/r), Ribavirin (RBV) and Interferon β1b (IFN β1b) in the initial period of pandemic and then remdesivir (once available in India) for moderate-severe COVID-19 or for mild COVID-19 with ongoing immunosuppressants. Tocilizumab was used for severe COVID-19, as per physician discretion. Nasopharyngeal swab was repeated every 2 weeks till negativity and antibodies to SARS-CoV-2 were tested after 2 weeks of initial RTPCR positivity and then 2 weekly.

We found that 5 of these 6 patients required prolonged time to clear the viral infection, with median time to RTPCR negativity of 31 days (Table 1). Three patients (patient A, C and D) developed neutralising IgG antibodies (IgG) to SARS-CoV-2 at 83 days, 22 days and 31 days post infection respectively. However, Patient C who developed antibodies at day 22, continued to remain persistently RTPCR positive for SARS-CoV-2 (Table 1). At a median follow-up of 40 days, all patients in our cohort are alive.

With emerging evidence, treatment options in COVID-19 are becoming clearer. However, there is no standard of care for immunocompromised patients, especially post HCT recipients.

In a phase II randomized trial, triplet combination consisting of oral LPV/r (400 mg/100 mg) and RBV 400 mg twice daily (14 days) along with IFN β1b was compared with LPV/r alone. Along with significantly improved clinical response, the triplet combination resulted in early nasopharyngeal negativity [3]. Amongst the 6 patients in our series, 3 received triplet antivirals, and showed rapid defervesence with clinical improvement. However, in contrast to Hung et al. [3], the time to negative nasopharyngeal swab was longer in our patients who received this combination. Production of excessive cytokines results in severe inflammatory responses in the lung resulting in severe COVID-19 manifestations and use of Tocilizumab, has been found to abrogate this inflammation [4]. In patient A, Tocilizumab was used twice in view of impending respiratory failure on third day and fifth day of infection resulting in rapid clinical benefit and radiological response.

✉ Navin Khattry
nkhattry@gmail.com

1 Department of Medical Oncology, ACTREC, Tata Memorial Centre, Mumbai, India

2 Hematopathology Department, ACTREC, Tata Memorial Centre, Mumbai, India

3 Department of Microbiology, ACTREC, Tata Memorial Centre, Mumbai, India

4 Composite Laboratory, ACTREC, Tata Memorial Centre, Mumbai, India

5 Department of Anaesthesiology, Pain and Critical Care, Tata Memorial Centre, Mumbai, India

6 Homi Bhabha National Institute, Mumbai, India

Table 1 Clinical characteristics of patients with SARS-CoV-2 infections post BMT

	Patient A	*Patient B*	*Patient C*	*Patient D*	*Patient E*	*Patient F*
Baseline Diagnosis	JAK2 Neg Primary Myelofibrosis	Multiple myeloma, IgG Kappa	Philadelphia Positive ALL in CR 1	Primary progressive non-hodgkin lymphoma	AML FLT3-ITD+ NPM1+	Philadelphia Positive ALL with early CNS Relapse
Age	61	42	34	25	37	23
Gender	M	F	M	M	F	M
Time from transplant	78 months	36 months	5 months	9 months	9 months	57 months
Type of Transplant	Allogeneic matched sibling transplant	Autologous Stem Cell Transplant	Allogeneic matched sibling transplant	Autologous Stem Cell Transplant	Allogenic matched sibling transplant	Allogenic matched sibling transplant
Concomitant GVHD(Yes/No)	No	NA	Yes	NA	No	No
Presenting symptoms	Fever , Sore throat	Fever, Chills, Cough , Breathlessness, Sore throat, Ageusia	Fever, Cough, Sore throat	Fever, Headache, Myalgia	Fever, Sore throat, Rhinorrhea	Breathlessness, Chest pain
Duration of symptoms before COVID diagnosis	3 days	2 days	3 days	1 day	3 days	3 days
Severity of COVID infection (as per WHO ordinal scale)	Severe	Mild	Mild	Mild	Mild	Mild
Treatment given	Tocilizumab 4 mg/kg x 2 doses Lopinavir/ Ritonavir (400/100 mg) bd Ribavirin 400 mg BD x 21 days IFN beta1b 8 MU every alternate days x 2 doses	Lopinavir/Ritonavir(400/100 mg) bd X 10 days Ribavirin 400 mg BD x 10 days IFN beta 1b 8 MU every alternate days x 3 doses	Lopinavir/Ritonavir (400/100 mg) bd X 10 days Ribavirin 400 mg BD x 10 days IFN beta 8 MU every alternate days x 3 doses	Only supportive treatment	Only supportive care	Injection Remedesvir (200 mg IV on day 1 followed by 100 mg iv day 2 to day 5)
Requirement of High Flow Oxygen	Yes (High flow nasal cannula)	No	No	No	No	No
Anticoagulation given	Yes Prophylactic	Yes (Prophylactic)	Yes (Prophylactic)	No	No	Yes
Total duration of admission (days)	36	10	15	10	10	5
Any triggering or worsening of GVHD	No	NA	Yes upper Gut GVHD	NA	No	No
Baseline Absolute lymphocyte count (x 10^9/L)	1.32	0.81	1.11	1.2	1.07	3.57
Nadir ALC (X10^9/L)	0.42	0.81	0.43	NA	0.83	3.34
Baseline IL-6 (pg/ml)	21	8.97	11.58	5	11.7	1.2
Baseline Covid swab RT PCR Cycling Threshold (CT)values	E gene – 28.61 RdRP gene – 32.06	E gene- 25 RdRp gene - 27	E gene – 16.9 RdRp gene – 19.7	E gene – 9.6 RdRp gene– 11.3	E gene – 31.5 RdRp – 32.5	E gene – 28.4 N gene – 28.9
Time to Covid swab negativity	31 days	22 days	Not yet negative (2 months since diagnosis)	53 days	15 days	19 days
Covid Specific Antibody Formation (IgG) – YES/NO	Yes	No	Yes	Yes	No	No
Time to Antibody formation	83 days	Negative (40 days post COVID infection)	22 days	31 days	Negative (21 days post COVID infection)	Negative
Final Outcome	Alive COVID RT-PCR negative COVID Antibody positive	Alive COVID RT-PCR negative COVID Antibody negative	Alive COVID RT-PCR positive COVID Antibody positive	Alive COVID RT-PCR negative COVID Antibody positive	Alive COVID RT-PCR negative COVID Antibody negative	Alive COVID RT-PCR negative COVID Antibody negative

Legends: JAK2: Janus kinase 2, IgG: Immunoglobin G, ALL: Acute Lymphoblastic Leukemia, NLPHL: Nodular Lymphocyte Predominant Hodgkin Lymphoma, AML: Acute Myeloid Leukemia
FLT3-ITD: FMS Like Tyrosine kinase 3 Internal Tandem Duplication, NPM1: Nucleophosmin 1, GVHD: Graft Versus Host Disease, WHO: World Health Organisation, RT-PCR: Reverse Transcriptase Polymerase Chain Reaction, E gene: Envelope small membrane protein, RdRp gene: RNA dependent RNA polymerase, N gene: Nucleoprotein gene.

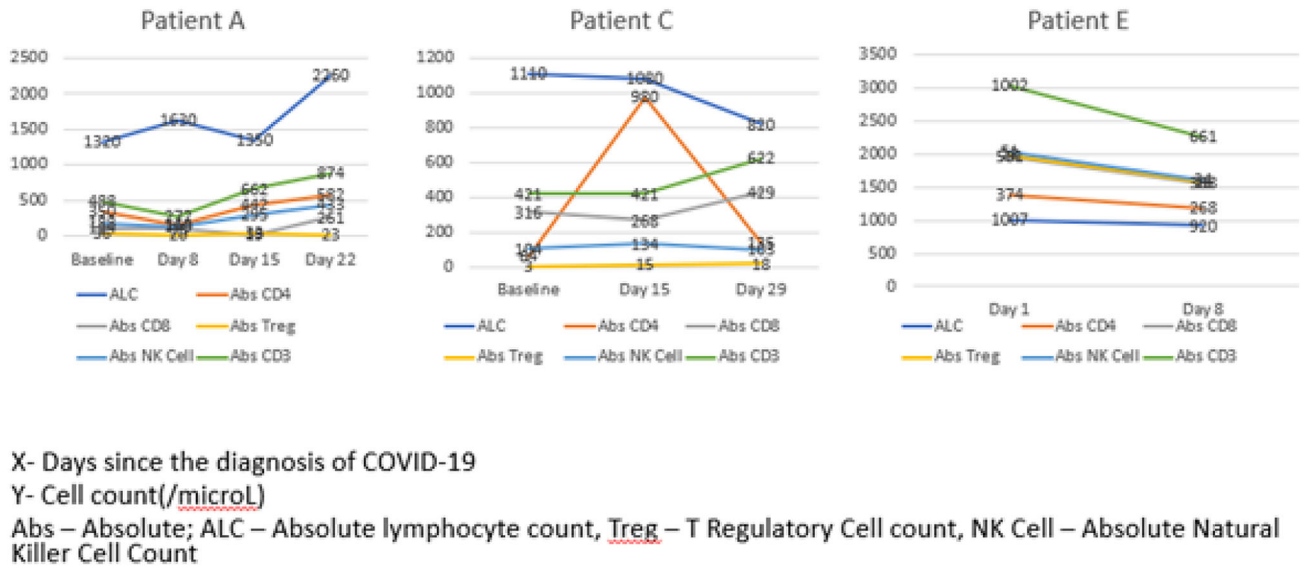

Fig. 1 Immune cell profile of Allogeneic stem cell transplant recipients post COVID infection

Thus, this case series highlights that use of antivirals (triplet antivirals and Remdesivir) and tocilizumab results in favorable outcome in post HCT patients with COVID-19 infection.

We recorded the immune kinetics of our allogeneic HCT patients during the course of illness (Fig. 1). In the early phases of infection, there was a decrease in the Absolute NK Cell, CD3, CD4 and CD8. By Day 8–15 there was a rise in these parameters. The graph pattern of patient E is in stark contrast to those of patients A and C. All the T-cell subsets and NK-cells appear to have stabilized, likely because this patient was diagnosed in late stages of the infection.

With the FDA authorizing the use of remdesivir, a more tolerated drug with better outcomes, for the treatment of moderate and severe COVID-19 infection, the place of triplet combination of LPV/r, RBV and IFN β1b in the therapeutic armamentarium is not clear, nevertheless, it still remains an alternative, if remdesivir is unavailable.

References

1. Saraceni F, et al Severe COVID-19 in a patient with chronic graft-versus-host disease after hematopoietic stem cell transplant successfully treated with ruxolitinib. Transpl Infect Dis n/a: e13401.
2. https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_180220 20.pdf. Last Accessed 10 Jan 2021.
3. Hung IF-N et al (2020) Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet 395:1695–1704
4. Toniati P, et al. (2020) Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: a single center study of 100 patients in Brescia, Italy. Autoimmun Rev **19**, 102568