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Efficacy and Tolerability of high dose SARS-COV-2 Antibody Cocktail (Casirivimab-Imdivimab) in post covid-19 infection with Hodgkin's lymphoma: A case report

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Abstract
A case report of 59 years old gentleman admitted post covid-19 infection with Hodgkin's lymphoma, we have given high dose SARS-COV-2 Antibody Cocktail Casirivimab–Imdivimab (REGN-COV-2). These investigational monoclonal antibodies approved in November 2020 by the Food and Drug Administration for emergency use in mild and moderate COVID-19. These two noncompeting human IgG1 monoclonal antibody target the receptor-binding domain of the spike protein of SARS-CoV-2, prevent its entry into human cells, and reduce viral load. The purpose of the case report is to review that low incidence of serious adverse events that occurred or worsened during the observation period and of infusion-related or hypersensitivity reactions was observed and observed all the important renal and hepatic lab parameter before and after administration of SARS-COV 2 antibody cocktail there is no dramatic abnormality seen in the patient on safety and tolerability in COVID-19 treatment using Casirivimab and Imdevimab for the immune compromised Hodgkin's lymphoma patient. In the clinical trial, REGN-COV-2 decreased viral load, particularly in patients with a non-initiated immune response (serum antibody-negative) and with high viral load at baseline. Casirivimab and imdevimab seem to be effective and safe antiviral therapy for hospitalized patients with COVID-19.

Keywords: SARS-COV-2, Hodgkin's lymphoma, Klebsiella Pneumoniae, Chemotherapy

1. Introduction
The SARS COV-2 Antibody cocktail is a combination of two antibodies **(**Casirivimab-Imdivimab) that bind to two different sites on the receptor binding domain of the SARS-COV-2 spike protein. We aimed to evaluate the safety and efficacy of high dose of SARS-COV-2 antibody cocktail in patients admitted with covid-19 infection with Hodgkin's lymphoma.

2. Case report
This 59-year-old gentleman admitted with a history of Hodgkin's Lymphoma III-B since 2016 (received Chemotherapy with ABVD Regimen-6 cycles and Radiotherapy in 2017), PET CT repeated in 2017 showed Radiation Pneumonitis, without remission till 2020, found to have Non-Hodgkin's Lymphoma in October, 2020 (received an R-COP regimen). History of patient had Covid 19 Pneumonia got treated elsewhere in April, 2021 with Remdesivir and Steroids. History of patient had persisting fever for 1 month since May, 2021 associated with the history of Dyspnoea for 1 week, and Weight loss around 15 Kgs in past 2 weeks, admitted elsewhere from 22/06/2021 to 24/06/2021 and came here for further treatment. On arrival, the patient was febrile and hypoxic and needed 6L Oxygen via Face mask to maintain SpO2-96%. History of Bronchoscopy done as outpatient and BAL culture and sensitivity revealed the growth of Klebsiella Pneumoniae. ID Physician opinion sought and the patient was treated with appropriate antibiotics. PET CT scans repeated on 26/06/2021 showed bilateral patchy areas of ground glass opacities with interstitial thickening in both lungs sign of infective etiology. His oxygen requirement worsened, and hence he got shifted to Critical care unit. He was intubated in view of worsening Hypoxemia and tested Covid 19 RTPCR Positive and antibody negative there were doubt regarding the presence of active Covid. He was treated with antivirals for the benefit of doubt remdesivir intravenous 100mg once daily was continued 10 days. As antibody negative, he may benefit from monoclonal antibody therapy. So, SARS-COV-2 antibody cocktail Casirivimab –Imdivimab (4000mg /4000mg) in 500ml 0.9 % sodium chloride over 6 hr (83ml/hr) was given after infusion all the liver and kidney function seem to be normal, which indicates it safe for hepatic and renal impairment patient. We observed 48 hours the liver enzymes, creatinine and urea. Since

the patient was not able to mount an adequate immune response against Covid 19 Pneumonia. He was extubated to NIV, gradually weaned to Face mask and shifted to ward. He had new onset fever spikes and persistent Tachycardia. Urine culture and sensitivity sent revealed growth of Pseudomonas Aeruginosa and sensitive Antibiotics given. Cardiologist opinion sought, ECHO and ECG repeated, found to have Sinus Tachycardia. Patient had Right Scrotal swelling and pain, Urosurgeon Opinion sought, USG Scrotum done and found to have Bilateral Epididymitis and Right Hydrocoele. His fever spikes stopped and the Bilateral Orchidectomy plan was deferred. He had Type II Respiratory failure and his oxygen requirement worsened needing Mechanical Ventilation. ET Secretions sent for Covid 19 RTPCR where patient was proned and his oxygen requirement gradually improved. CBC repeated showed Anemia and 1 packed RBCs transfused. CT CHEST repeated showed Bilateral extensive fibrotic changes, Interstitial thickening and patchy opacities. He was proned for second time because of severe ARDS with the high oxygen requirement. ABG showed persistent Type II Respiratory failure. Diuretics were given as per nephrologist advise to maintain negative fluid balance. Hematologist opinion was obtained and his Immunoglobulin levels were found to be low and he was treated with IV Immunoglobulin. He improved symptomatically and he is switched from PSV mode to BiPAP. Chest Physiotherapy was continued and he was mobilized to the sofa. He slowly weaned off from BiPAP support and switched to T piece. He was slowly weaned off from VCV mode and switched back to BiPAP. But he became drowsy on 27/08/2021. His CO2 level was high and GCS was low. Repeat chest x ray showed no new changes. Neurologist opinion was obtained for low GCS and CT brain showed no infarct or hemorrhage. CSF analysis done was not significant. He improved clinically, he was gradually weaned off from BiPAP support to nasal prongs, tracheostomy capping was done and he had no hemodynamic instability and decannulation was done on 20/09/2021, followed by that he had no desaturation. He was shifted toward on 30/09/2021. Hematologist opinion was obtained to evaluate for lymphoma, patient discharged with oral rivaroxaban 10mg once daily for two weeks.

Condition at Discharge: SPO2-98% with 1 liter of O2/ Afebrile

3. Discussion

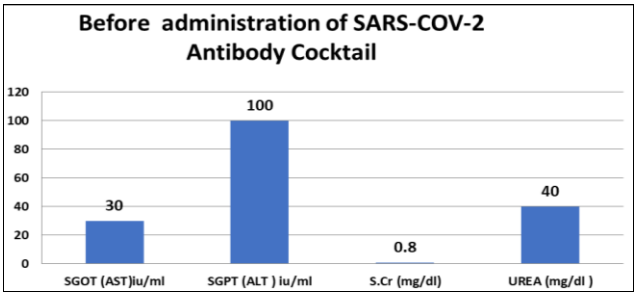
On 21st November 2020, imdevimab and casirivimab cocktail was authorized for emergency use by the United States Food and Drug Administration (FDA). These are investigational drugs not approved for any specific indication. The FDA allowed these drugs only to be administered together. Imdevimab (REGN10987), and casirivimab (REGN10933) is also known as REGN-COV2 or Regeneron. The combination drug has been shown to decrease viral load and decrease the risk of hospitalization and emergency visits. It has also been shown to prevent virus-induced pathological sequelae when administered prophylactically or therapeutically in rhesus monkeys and hamsters [1, 2]. SARS COV-2 Antibody cocktail is a combination of two antibody **(**Casirivimab-Imdivimab) that bind to two different sites on the receptor binding domain of the SARS-COV-2 spike protein. The SARS-CoV-2 genome encodes four major structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N), as well as nonstructural and accessory proteins. The spike protein is further divided into two subunits, S1 and S2, that mediate host cell attachment and invasion. Through its receptor-binding domain (RBD), S1 attaches to angiotensin-converting enzyme 2 (ACE2) on the host cell; this initiates a conformational change in S2 that results in virus-host cell membrane fusion and viral entry. Anti-SARS-CoV-2 monoclonal antibodies (mAbs) that target the spike protein have been shown to have a clinical benefit in treating SARS-CoV-2 infection [3, 15]

To test the hypothesis that exogenously provided antibodies would have the most benefit in patients whose own immune response had not yet been initiated, possible reason for this observation is that patients whose endogenous immune responses were active (serum antibody–positive) were already efficiently clearing the virus, as compared with patients whose immune response had not yet been initiated (serum antibody–negative). These findings are consistent with those in other studies that have shown an association between native antibodies against SARS-CoV-2 and viral loads [1, 6, 7]. Overall, our findings are consistent with the hypothesis that most infected persons successfully recover because of their endogenous immune response. [1] This understanding of the natural history of Covid-19 supported our prospective hypothesis that an exogenously provided antibody cocktail would have the most benefit in patients whose own immune response had not yet been initiated, since such patients would have higher baseline viral loads and a higher likelihood of seeking additional medical treatment.

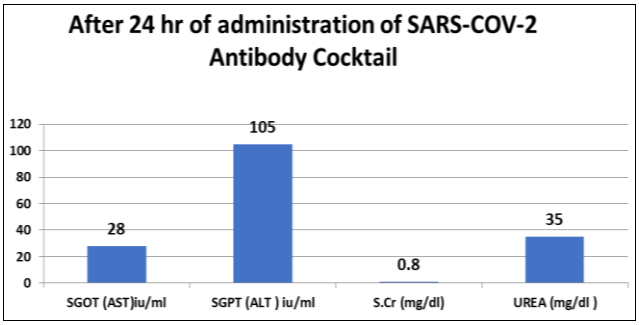
Our case report indicates that REGN-COV2 enhanced clearance of the virus, particularly in patients in whom an endogenous immune response had not yet been initiated (i.e., serum antibody–negative) or who had a high viral load at baseline.

The safety of REGN-COV2 was as expected for a fully human antibody against an exogenous target. A low incidence of serious adverse events that occurred or worsened during the observation period and of infusion-related or hypersensitivity reactions were observed, our patient infused high dose (4g/4g) with 500ml of 0.9% sodium chloride over 6 hr (83ml/hr) we observed post administration there was no infusion related reaction was observed. This longer half-life of REGN-COV2 suggests that treatment could result in long-term passive immunity for several months. The pharmacokinetic data were similar at each dose of REGN-COV2.

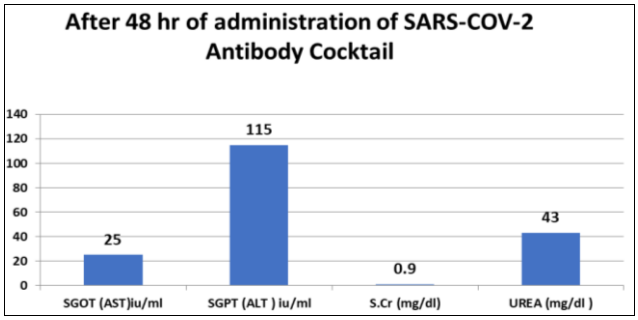
Hodgkin lymphoma (HL) is a lymphoid malignancy of B-cell origin, which is classified into either Nodular Lymphocyte Predominant Hodgkin lymphoma (NLPHL) or Classical Hodgkin Lymphoma (CHL) in accordance with 2008 WHO classification [4]. Our patient was already having a weakened immune system is a common complication of Hodgkin lymphoma and it can become more severe. If you have a weak immune system, you're more vulnerable to infections and there's an increased risk of developing serious complications from infections. It was a major challenge for our case report, but patient showed Radiation Pneumonitis, without remission till 2020, we adequately managed with intravenous antibiotics. Patient Neutrophils and lymphocyte value are abnormal 89% (high) & 4% (low) respectively, and also liver function biomarkers were low level before administration of SARS-COV-2 antibody cocktail.



Graph 1: Renal and hepatic lab parameter before administration of SARS-COV 2 antibody cocktail



Graph 2: Renal and hepatic lab parameter after 24hour administration of SARS-COV 2 antibody cocktail



Graph 3: Renal and hepatic lab parameter after 48hour administration of SARS-COV 2 antibody cocktail

4. Conclusion

The safety of REGN-COV2 was as expected for a fully human antibody against an exogenous target. A low incidence of serious adverse events that occurred or worsened during the observation period and of infusion-related or hypersensitivity reactions were observed. In our case report, we observed all the important renal and hepatic lab parameter before and after administration of SARS-COV 2 antibody cocktail there is no dramatic abnormality seen in the patient. High dose is safe and tolerable in post covid-19 infection with Hodgkin's lymphoma patient who is already immunocompromised. Casirivimab and Imdevimab seem to be promising effective and safe antiviral therapy for hospitalized patient with COVID -19 further observation concerning different groups of patient and clinical trials are extremely necessary to confirm the efficacy in a wider group of patient and potentially expand the indications for their use.

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7. Conflict of interest

The author(s) declared that they have no competing interest

8. Ethical approval

Not applicable

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