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Case Report

Effectiveness of Convalescent Plasma Therapy in Critically Ill COVID-19 Patient: A Case Report

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Abstract

Background: COVID-19 is a pandemic with no specific therapeutic agents yet approved. Presenting our experience with the clinical efficacy of convalescent plasma (CP) therapy in a critically ill non-responsive COVID-19 patient.

Case Summary: A diabetic hypertensive 70-year-old patient presented to ER with dyspnea, SO_2 90% RA and low-grade fever along with COVID-19 positive swab by PCR, and bilateral fine basal crackles, chest CT shows ground glass opacities (GGOs) in the right upper Lobe, CRP 3 mg/dl and IL-6 18 pg/ml. After initial 3 days stay in ICU, condition improved on oral Favipiravir, Azithromycin and Oseltamivir, and IV Ceftriaxone and IM dexamethasone. One week after initial discharge from ICU, condition gradually deteriorated with no response to Tocilizumab administration then pulse therapy methyl prednisolone and Remdesivir. Patient readmitted to ICU and treatment with CP was started with 2 units derived from a recently recovered single donor with plasma SARS-CoV-2 anti-S1/S2 IgG antibodies of 20 AU/mL. After initial improvement patient was discharged from ICU, but then condition deteriorated again with dramatic rise of IL-6. After extra 2 doses of Convalescent Plasma but this time derived from another donor with higher neutralizing activity as inferred by a higher plasma anti-S1/S2 IgG antibodies level of 39 AU/mL, patient condition improved dramatically with SO_2 90-92% on RA sitting position. He was then finally discharged on home medication and domiciliary oxygen during effort and sleep.

Discussion: This case supports the role of CP with sufficient neutralizing capacity, as an effective treatment for critically ill COVID-19 patients.

Keywords: COVID-19; SARS-CoV-2; Convalescent Plasma (CP)

Case Presentation

A-70-year male patient presented to the emergency department on 25th October, 2020 with dyspnea and low grade fever along with COVID-19 positive swab (by PCR). He was diabetic and hypertensive with a history of ischemic heart disease, cardiac catheterization and stenting in 2016. His home medications were Candesartan 8 mg OD, Bisoprolol 2.5 mg OD, Empagliflozin 25 mg

OD, Asprin 100 mg OD, Simvastatin 10 mg OD, Clopidogrel 75 mg OD.

He was fully conscious and vital signs showed blood pressure of 130/70, heart rate of 75, respiratory rate of 18, and Oxygen saturation (SO_2) 90% on room air (RA) at rest. Clinical examination was unremarkable with normal heart sounds, no murmurs, no gallop, and soft, non-tender, non-distended abdomen. No lower limb edema. The only significant finding was bilateral fine basal crackles on chest examination.

Initial laboratory work up showed increased levels of, C-reactive protein (CRP) 3 mg/dl (reference interval: 0 – 0.5 mg/dl), Interleukin-6 18 pg/ml (reference interval up to 7 pg/ml), international normalized ratio (INR) 1.28 (reference interval 0.8 - 1.1) and alanine aminotransferase (ALT) 38 U/L (reference interval: 10 - 34 U/L), while other tests results were within normal levels for age and sex, white blood cell count 6.73 10^3/µL (reference interval: 4.0 - 11.0 10^3/µL), d-dimer 0.4 µg/mL/FFU (reference interval: 0-0.5 µg/ml/FFU) and ferritin 177 ng/mL (reference interval: 22-204 ng/mL), lactate dehydrogenase (LDH) 120 U/L (reference interval: 135 - 225 U/L), creatinine 0.7 mg/dL (reference interval 0.6-1.2), N terminal pro-Brain natriuretic peptide (NT-proBNP) 28 pg/mL (reference interval: 0 - 450 pg/mL).

The chest CT showed a small ill demarcated area of ground glass opacities (GGOs) in the right upper Lobe.

The patient was admitted to ICU and medical treatment consisted of Favipiravir 1800 mg orally every 12 hours for 1 day, then 800 mg orally every 12 hours for 13 days, Oseltamivir 75 mg orally every 12 hours for 7 days, Ceftriaxone 1g IV every 12 hours for 7 days, Azithromycin 500 mg orally OD for 5 days, PPI 40 mg IV OD for 7 days, Clexane 60 mg sub-cutaneous BID for 30 days and dexamethasone 8 mg intramuscular OD for 7 days. On the 28th October, he improved both subjectively and objectively with an SO_2 of 95% on RA after walking. Consequently, he was transferred from ICU to isolation regular ward.

On the 29th of October, he had a spiked fever of 39 C° and SO_2 of 94% at rest on RA and 90% on RA after walking. There was a sharp rise in IL6 (50 pg/ml) while ferritin and CRP were gradually raised. The chest X-ray revealed bilateral peripheral soft shadows. That's why Tocilizumab were administered as two doses (400 mg) IV infusion each within 12hr, but there was no improvement. Clinically, the dyspnea worsened, SO_2 declined with progressive increase in O_2 requirements, and the inflammatory markers (CRP, ferritin, and IL6) were increasing sharply. After a third dose of Tocilizumab, CRP and ferritin declined but IL6 was still rising. CT chest showed a significant deterioration from that on admission with bilateral GGOs. Over the subsequent days, he developed progressive increase of oxygen requirements with CT chest of CO-RADS 6 score. Ceftriaxone and azithromycin were replaced by Iperacillin/Tazobactam. In addition, pulse therapy methyl prednisolone 500 mg IV OD for 3 days was added. All the inflammatory markers including IL6 declined, but still there were bilateral crackles with no response to low dose diuretics. Therefore, Remdesivir was prescribed and Favipiravir was discontinued. There was a high suspicious of pnemothorax, but this was ruled out radiologically (Figure 1).

Figure 1: CT showing bilateral GGOs and a CO-RADS 6 score.

A dramatic increase of oxygen requirements occurred from 3 to 12 liter/min (LPM) and the patient was readmitted to the ICU and placed on face mask instead of nasal cannula. Remdesivir was discontinued after the 2nd dose (3rd vial). Two days later, the patient developed bradycardia and diarrhea. Clostridium difficle was excluded. The patient had SO_2 96% on non-rebreather mask (NRM) with 15 LPM.

Echocardiography revealed mild diastolic dysfunction. NT-proBNP was slowly rising, with normal procalcitonin (reference interval up to 0.5 ng/ml). In addition, there was mild leucocytosis and slight elevation of INR and ALT. The medication plan was then adjusted to add Solumedrol 40 mg OD and to discontinue dexamethasone and Bisoprolol.

The first dose of COVID Convalescent Plasma 2 units (200 ml q 12 hours) was initiated on the 7th of November and the second unit was administered the following day. He was subjectively better after the second unit of plasma and the oxygen requirement decreased till 7 LPM and SO_2 was 90% at rest and 88% on walking. Another COVID swab for PCR was still positive. He was discharged from ICU to regular isolation ward. Unfortunately, the oxygen requirements increased once more O_2 flow was increased to 12LPM, with a dramatic rise of IL6 (highest value throughout the episode) and increased ferritin.

Then when the improvement was minimal the decision was made to give extra 2 doses of COVID Convalescent Plasma but from another donor who was very ill before and with higher neutralizing activity. The 2nd dose given and in 17 hours patient's oxygen requirement decreased to 6 LPM on regular nasal canula SO_2 96%. After the 3rd dose patient was on 2 LPM Oxygen SO_2 sitting 93%, walking 6 minutes it goes down to 84%. The follow up CT chest revealed dramatic improvement (Figure 2). Patient stayed 3 days and his SO_2 sitting was 97% on 1 LPM and 6 minutes walking on 3 LPM SO_2 was 90%.

Figure 2: Follow up Chest CT after the last dose of Convalescent Plasma showing dramatic improvement.

The patient was then discharged with SO_2 90-92% on RA in the sitting position. He was discharged on domiciliary oxygen during effort and sleep. Discharge medications were Methyl prednisolone 30 mg OD for one week then decreased gradually, Xarelto 20 mg OD and pirfenidone 801 mg tablet TID for one month.

Discussion

Coronavirus disease 2019 (COVID-19) emerged in Wuhan, China [1] in December 2019 and it was declared as a pandemic by World Health Organization (WHO) in March 2020. In absence of specific anti-SARS-CoV2 therapy, the available treatment was directed to optimize respiratory care, manage thrombotic and inflammatory complications with anticoagulants and corticosteroids, and test existing antiviral therapies (eg, hydroxychloroquine, lopinavir/ritonavir and remdesivir).

Convalescent plasma (CP) was proved as an efficient and safe modality in the treatment of previous outbreaks of severe Acute Respiratory Syndrome (SARS) [2], Middle East Respiratory Syndrome (MERS), and the 2009 H1N1 pandemic [3,4].

A meta-analysis conducted on SARS coronavirus and severe influenza showed a significant reduction in mortality rates after CP therapy, compared with placebo or no treatment [5]. Since COVID-19 resembles SARS, and MERS, hence CP therapy was introduced as a promising treatment option for deteriorating COVID-19 cases [6].

In USA, CP was used in more than 40,000 COVID-19 patients pointing to strong safety data [7].

Several studies questioned the efficacy of CP therapy. The largest systematic review was conducted by Klassen., *et al*. They included a total of 38 studies including 5 RCTs, 13 matched-control studies and 20 case reports for a sum of 10,436 CODIV-19 cases. They reported a 51% reduction in mortality rate in patients transfused with CP compared to those receiving standard treatment regimens [8].

The timing of initiation of CP therapy was tackled in a number of studies. Mayo Clinic coordinated a large observational study. They reported decreased 7-day and 30-day mortality with CP therapy. The 7-day mortality effect was most pronounced when CP therapy was administered within 3 days of COVID-19 diagnosis as compared with delayed administration [9].

In our hospital, convalescent plasma donors are required to abide by eligibility requirements for the collection of plasma by plasma pheresis on the day of donation, including age 18<65 years, weight >50 kg, COVID-19 previous infection documented by positive SARS-CoV-2 PCR test from nasopharyngeal swab at the time of illness with complete resolution of symptoms at least 14 days prior to donation with two negative SARS-CoV-2 PCR tests from nasopharyngeal swabs collected 24 hours apart, finally passing through all other routine screening tests for blood donors including CBC, blood grouping (ABO, Rh phenotype) and screening for HIV1,2, HCV, HBV, parvovirus and syphilis. Convalescent plasma was collected by plasma apheresis method using Trima Automated Blood Collection System-Terumo BCT. The neutralizing capacity of the SARS-CoV-2 spike-binding antibodies in donors' CP were inferred from the quantitative determination of the plasma level of anti-S1 and anti-S2 specific IgG (S1/S2 IgG) antibodies to SARS-CoV-2 using the LIAISON XL® chemiluminescence immunoassay technology (DiaSorin S.p.A., Saluggia, Italy). The LIAISON SARS-CoV-2 S1/S2 IgG chemiluminescent assay detects IgG antibodies directed against a recombinant S protein (S1/S2) with an analytic measurement range from 3.8 AU/ml to 400 AU/ml. The cut-off for samples to be considered negative was < 12 AU/ml and borderline positive from 12-15 AU/ml and > 15 AU/ml was considered positive.

In our case, after the decline of our patient's SO_2 to (88-90%) and the rise in his O_2 requirements to 12 LPM, the first dose of CP

therapy was initiated using 2 units of CP from a donor with S1/S2 IgG level of 20 AU/ml,. The patient improved after the second unit of CP; SO_2 reached 90% at rest and O_2 flow of 7 LPM.

But unfortunately, this improvement was not sustained and once again O_2 flow was increased to 12LPM with a sharp rise in IL-6. At this point, we re-evaluated our selection criteria and only CP with S1/S2 IgG levels of > 30 AU/ml were considered eligible for use in therapy. Thus, another CP donor was chosen with S1/S2 IgG levels of 39 AU/ml. Our patient received two more doses of CP from this new donor and after the last dose marvelous improvement occurred; O_2 saturation leaped to 93% and the patient was on 2LPM oxygen. This may offer substantial evidence, as noted by others, about the association between the efficacy of CP therapy with the neutralizing capacity of antibodies of recovered donors [10,11].

The FDA and EMA recommend the use of high levels of neutralizing antibodies of at least 1:80 to 1:160 and preferably higher titers [12]. Indeed, the direct laboratory assessment of neutralizing antibodies using virus neutralization assays, either using live native SARS-CoV-2 virus, engineered SARS-CoV-2 pseudotyped viruses, or replication-competent SARS-CoV-2 chimeric viruses, is cumbersome entailing level 3 biosafety lab to perform a timely labor-intensive technique with high technical expertise. The plaque-reduction neutralization test (PRNT) is the golden standard assay to measure the neutralizing capacity of serum antibodies. Several commercial assays were introduced to substitute PRNT such as pseudotype-based neutralization assays [13]. and virus neutralization test (sVNT) [14]. Many enzyme-linked immunoassays (ELISA) or chemiluminescent immunoassays (CLIA) that detect antibodies binding SARS-CoV-2 structural proteins, have been also marketed [15]. In January 2021 Valdivia., *et al*. [16] compared the level of correlation between the titers of neutralizing antibodies binding the SARS-CoV-2 spike (S) protein (directly evaluated by pseudotyped virus neutralization assay) and SARS-CoV-2-S-IgG levels measured across four commercial SARS-CoV-2 IgG immunoassays, the LIAISON SARS-CoV-2 S1/S2 IgG, the COVID-19 ELISA IgG assays, the MAGLUMI 2019-nCoV IgG, and the Euroimmun SARS-CoV-2 IgG ELISA. They reported that, the correlations were always positive and statistically significant for all tested platforms. Using ROC curve analysis they also compared the overall performance of all four platforms to discriminate samples with neutralizing antibodies titers of 1:160. They reported that the best combined sensitivity and specificity was achieved by the LIAISON SARS-CoV-2 S1/S2 IgG (which we used in the current study), and they reported that at a cutoff 90.6 AU/ml the LIAISON assay would discriminate such samples with a sensitivity 93.8 (81.5–100), sensitivity 67.6 (56.9–78.2) [16]. Our results suggest that good therapeutic effects may also be achieved at levels of SARS-CoV-2 S1/S2 IgG of at least 30 AU/ml or more.

Though not fully understood, the immune/inflammatory host response against SARS-CoV-2 infection has an essential role in the progression of COVID-19. Inflammatory markers, like C reactive protein (CRP), ferritin and procalcitonin (PCT) are usually increased in critically ill COVID-19 patients. Cytokines play an immunomodulatory function, and uncontrolled cytokine storm is responsible for high mortality and morbidity [17].

IL6 is highly implicated in the COVID-19 associated cytokine release storm (CRS). Liu., *et al*. reported a significant association between IL6 and COVID19 mortality, thus pointing to its predictive prognostic value [18] (Liu., *et al*. 2020). IL6 level was suggested to have a discriminative ability to distinguish COVID-19 severe cases indicated for ICU admission from milder cases which can be managed without ICU admission. Definitely, this postulation would affect the choice of IL6 blockade [19].

Tocilizumab (TCZ) is a monoclonal antibody (mAb) directed against the IL6 receptor. Several studies concluded that the combined administration of immune modulation agents and antiviral agents surpassed single therapy [19].

Conclusion

In our case, neither Tocilizumab nor Remdesivir relieved the severity of the clinical condition, hence the medication plan was shifted to CP therapy which caused significant clinical and laboratory improvement especially when using CP with higher SARS-CoV-2 S1/S2 IgG levels as a proxy for a sufficient neutralizing capacity. Convalescent plasma administration proved as an efficient therapeutic line in a critically ill COVID-19 patient.

Previous Presentations

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Conflicts of Interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

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