

Convalescent Plasma and Mesenchymal Stem Cell Therapy

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ABSTRACT

Since there are no currently accepted therapies for corona virus disease 2019 (COVID-2019), worldwide search for treatment options are ongoing. Convalescent plasma therapy and mesenchymal stem cell therapy are considered as two of potential options. Convalescent plasma therapy may be recommended early during the course of severe or rapidly progressive illness, despite paucity of evidence. However, mesenchymal stem cell therapy for COVID-19 should only be considered in the context of a trial.

Keywords: SARS Virus, Treatment, Respiratory Failure, Cytokines

Introduction

SARS-CoV-2 infections are a worldwide pandemic, posing a severe risk to health. Since there are no currently accepted therapies for corona virus disease 2019 (COVID-2019), worldwide search for treatment options are ongoing. Past experiences with viral infections are important in this respect. Convalescent plasma therapy and mesenchymal stem cell therapy are two of potential options mentioned in case series and non-randomized studies from different countries (1,2).

Convalescent plasma

One of the potential treatment options that is being evaluated extensively is convalescent plasma therapy, which provides passive immunization. With convalescent plasma therapy, viral neutralization and consequently decreased target organ injury is aimed. The rationale behind this treatment is basic knowledge and experience from the recent studies on MERS, SARS and H1N1 infections and several other infections at the beginning of twentieth century. Favorable results from these studies are the basis for its use during severe SARS-CoV-2 infections. As a matter of fact, a study on 10 SARS-CoV-2 PCR (+) patients, during the period January -February 2020, has reported decreased oxygen needs and CRP levels within 3 days of treatment and

improvement of radiological findings and viremia on the 7th day (3). In a case series of 5 patients with respiratory failure (1 patient on ECMO, 4 on mechanical ventilation) treated with convalescent plasma therapy, 3 patients have been reported to be discharged free of respiratory support (4)

Patients who want to donate for convalescent plasma must have recovered from COVID-19 symptoms, their SARS-CoV-2 PCR tests should have become negative, and they must have adequate antibody response to SARS-CoV-2. Plasma from these patients is separated by apheresis and then processed to prepare convalescent plasma. This plasma should be devoid of other pathogens, and neutralizing antibody titers should be determined. Convalescent plasma may be used for prophylaxis or for treatment of patients. Since it is not a currently accepted treatment protocol, patient course and outcomes should be registered and data be evaluated periodically.

Despite poor evidence, convalescent plasma therapy may be indicated in severe or rapidly progressive disease. It is considered to be most effective during the initial week, and it may be considered to be ineffective after 14th day. Criteria mentioned below may be used to determine severe illness:

- Thorax computed tomography findings compatible with COVID-19;
- Respiratory rate > 30/minute;
- PaO₂/FiO₂ < 300 mm Hg;
- Oxygen saturation <93% under oxygen support;
- Need for invasive mechanical ventilation;
- Increase in SOFA score (indicating multi-organ failure);
- Need for vasopressors (presence of shock);
- Presence of other parameters indicating poor prognosis: lymphopenia, elevated ferritin and CRP levels, increased d-dimer levels;
- Presence of another disease that may adversely affect the outcome.

Prior to administration presence of IgA deficiency or known allergy to contents (i.e. citrate) of the product should be ruled out. Presence of IgA deficiency may result in severe anaphylactic reaction.

A recent Cochrane review of present studies (mostly case series) has reported that severe adverse effects seemed to be rare: one case of moderate fever and one case of an anaphylactic reaction were the two mentioned adverse effects in these studies. Antibody-dependent enhancement (ADE) of infection has been a concern with convalescent plasma therapy during the course of some viral infections (i.e. MERS) (5). ADE may facilitate virus activity resulting in disease flare-up. Another potential risk is that, it may cause suppression of a patient's innate immunity so that the patient may not develop effective antibodies against the virus, rendering him prone to reinfections. These patients will need to be vaccinated, later on when a vaccine is developed. In this respect, patients need to be carefully assessed for indications and for their responses to therapy. As well, it must be kept in mind that other known complications of transfusion may also be observed with convalescent plasma therapy. Patients should be observed for signs of transfusion related acute lung injury (TRALI), and transfusion associated circulatory overload (TACO) which may further compromise respiratory condition.

National application guidelines 'COVID-19 İMMÜN (KONVALESAN) PLAZMA TEDARİK VE KLİNİK KULLANIM REHBERİ' may be referred to at the related website of Ministry of Health: 'T.C. SAĞLIK BAKANLIĞI SAĞLIK HİZMETLERİ GENEL MÜDÜRLÜĞÜ Kan ve Kan Ürünleri Dairesi Başkanlığı'. (6)

Mesenchymal Stem Cell Therapy

Mesenchymal stem cell therapy has been the subject of research in many different fields of medicine due to its immunomodulatory and reparative effects. Two publications from China, one case report and one case series, have reported positive results of intravenous administration of mesenchymal stem cells in severely ill COVID-19 patients (7). It has been reported that, clinical and laboratory improvement has been observed within days of therapy in these patients.

It is considered that infection of mesenchymal stem cells with SARS-CoV-10 is not an expected condition since they lack ACE2 receptors (8,9). As well, ongoing cytokine production stimulate these cells to produce anti-inflammatory and trophic mediators, which help to confine the cytokine storm and the resulting lung injury. These immunomodulating actions are thought to be beneficial in the course of COVID-19.

The most important handicap of this treatment is that, it is still at an experimental stage, and there are no randomized controlled studies. It requires an infrastructure in place for cell therapy. There are also ethical considerations. When mesenchymal cell therapy is considered, informed consent should be obtained, data should be recorded and treatment outcomes should be evaluated scientifically.

Conclusion

In the light of current studies, early during the course of severe or rapidly progressive illness, convalescent plasma therapy may be recommended, despite paucity of evidence. On the other hand, mesenchymal stem cell therapy for COVID-19 should only be considered in the context of a trial.

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