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Short Communication

An Argentinian Proposal: Mesenchymal Stem Cells, Convalescent Plasma and Dexamethasone in Covid-19. Could be a Triple Strategy Effective for the Treatment of Severe Pneumonia Complications?

Matias Cristian Fernández Viña[1,2,3,4]*, Roberto Fernández Viña[1,3,4], Liliana Camozzi[1,3,4], Matías Iván Spitaleri[1,2,4] and Lorenzo Fernández Viña[4]

[1]*Facultad de Medicina y Cs. de la Salud, Universidad Abierta Interamericana, Rosario, Argentina*

[2]*Stem Cell Therapy Argentina, San Nicolás de los Arroyos, Argentina*

[3]*Fundación Don Roberto Fernández Viña, San Nicolás, Argentina*

[4]*Clínica San Nicolás S.A, San Nicolás, Argentina*

Abbreviations

MSC: Mesenchymal Stem Cell
AD-MSC: Adipose Derived Mesenchymal Stem Cells
UC-MSC: Umbilical Cord Mesenchymal Stem Cells

Background

SARS-CoV-2 infections are a worldwide pandemic, posing a severe risk to health [1]. Human coronavirus, SARS-CoV-2, is highly pathogenic with severe pneumonia associated with rapid virus replication. Arising in Wuhan China December 2019, the current COVID-19 epidemic has rapidly grown with person-to-person infection expanding to become a global health emergency now on pandemic scale [2]. Since there are no currently accepted therapies for corona virus disease 2019 worldwide search for treatment options are ongoing. Past experiences with viral infections are important in this respect, like in Argentina practiced by Dr. Julio Maiztegui [3]. Convalescent plasma therapy and mesenchymal stem cell therapy are two of potential options for Covid-19, mentioned, in case series and non-randomized studies from different countries [4]. On the other hand, Glucocorticoids like Dexamethasone, may modulate inflammation-mediated lung injury and thereby reduce progression to respiratory failure and death [5].

Methods

On this short paper communication, we propose the use of a triple strategy for Covid-19 in patients with severe pneumonia, showing safety in different separated publications reviewed Figure 1.

Proposed dose for the triple treatment strategy for severe Covid-19

Mesenchymal Stem Cells + Convalescent Plasma + Dexamethasone

Mesenchymal Stem Cells (MSC)	1M x KG (80 to 100 X 10 (6) MSC in 50 ml in 40 minutes
Convalescent Plasma	300 ML in 40 mins
Dexamethasone	6 MG per day during 10 days

Figure 1: Triple treatment strategy with MSC + Convalescent Plasma + Dexamethasone applied on a same day for severe Covid-19.

The triple strategy that has shown individually, safe and possible effectiveness in the treatment for Covid-19 pneumonia, could be a way of synergic treatment, following this review.

Mesenchymal stem cell therapy

Mesenchymal stem cell (MSC) therapy has been the subject of research in many different fields of medicine due to its immunomodulatory and reparative effects.

The alveolar injury by COVID-19 is characterized by the impairment of endothelial and type I alveolar cell (pneumocyte) barrier, which eventually results in an intense accumulation of proteinaceous fluid (alveolar edema) and mononuclear cell (lymphocytes) infiltrates in interalveolar septa. Extravasated and/or resident MSCs can trigger a series of direct and indirect repairing mechanisms. Clearance of the increased alveolar edema can be induced by the release of KGF by enhancing sodium-dependent alveolar fluid clearance through type II alveolar sodium channels. The MSC-released TSG6 decreases

***Corresponding author:** Matias Cristian Fernández Viña, Facultad de Medicina y Cs. de la Salud, Universidad Abierta Interamericana, Rosario, Argentina; Stem Cell Therapy Argentina, San Nicolás, Argentina; Fundación Don Roberto Fernández Viña, San Nicolás, Argentina; Clínica San Nicolás S.A, Argentina, E-mail: Matias.FernandezVina@UAI.edu.ar / matiasfernandezvina@hotmail.com

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neutrophil functions, which directly affects improvement of the vascular endothelial and alveolar epithelial barriers [6].

The resolution of inflammation can be further enhanced by the increased release of IL-10 and decreased release of TNF-α, which are mediated by LXA4 and PGE2. Increased epithelial repair in type II alveolar cells can be restored by the release of Ang1. MSCs can also facilitate the phagocytosis of bacteria by the intra-alveolar and interalveolar macrophages by releasing the antimicrobial peptide LL-37 or by the transfer of extracellular vesicles to macrophages from MSCs [6].

Additionally, MSCs can exert their actions through mitochondrial transfer to injured alveolar cells, thus increasing their ATP content, which would improve bioenergetics and increase alveolar epithelial function, improving surfactant release by type II alveolar cells. MSCs can degrade or inhibit ARDS-induced fibrotic tissue formation (collagen fiber accumulation) to modulate the extracellular matrix by releasing MMPs and TIMPs. In MSC-based therapies, infusion of auto/allogeneic MSCs is applied through two primary routes (intravenous and intratracheal/intrabronchial) [7].

The most important mechanism is that MSCs release many paracrine factors, such as micro-RNA, interacting with the immune response to exert immunoregulation and anti-inflammatory effects [8].

Three publications, two from China, one case report and one case series, and one from Spain, have reported positive results of intravenous administration of Umbilical Cord-MSC (UC-MSC) or Adipose Derived-MSC (AD-MSC) in severely ill COVID-19 patients [9,10]. It has been reported that, clinical, radiological, and laboratory improvement has been observed within days of therapy in these patients [8-10]. Up to date, there are more than 50 trialsregistered on going with MSC for Covid-19 (10) (56 clinical trials were registered in clinicaltrials.gov under COVID and "*mesenchymal"* terms as of the writing date of this review).

Treatment with intravenous administration of AD-MSC or UC-MSC in severe COVID-19 pneumonia under mechanical ventilation in a small case series did not induce significant adverse events and was followed by clinical and biological improvement in most subjects [8-10]. It is considered that infection of mesenchymal stem cells with SARS-CoV-10 is not an expected condition since they lack ACE2 receptors [11-13]. 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. The remarkable new data using MSC demonstrate successful harnessing of natural endogenous pathways with powerful protective properties [2]. The dose recommended in the BALMYS-19-"BAttLe against COvid using MesenchYmal Stromal cells" was 1.000.000 MSC X kg [10].

Dexamethasone

In patients hospitalized with Covid-19, the preliminary results of the controlled, open-label Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial of dexamethasone showed that the use of it resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support [5].

The benefit was also clear in patients who were being treated more than 7 days after symptom onset, when inflammatory lung damage is likely to have been more common [5].

The protocol combines the methods that were used in large, simple trials of treatments for acute myocardial infarction in the 1980s with the opportunities provided by digital health care in the 2020s [14-16].

The RECOVERY trial provides evidence that treatment with dexamethasone at a dose of 6 mg once daily for up to 10 days reduces 28-day mortality in patients with Covid-19 who are receiving respiratory support [5].

Dexamethasone is on the list of essential medicines of the World Health Organization and is readily available worldwide at low cost. Guidelines issued by the U.K. chief medical officers and by the National Institutes of Health in the United States have already been updated to recommend the use of glucocorticoids in patients hospitalized with Covid-19 [17,18].

Slower clearance of viral RNA has been observed in patients with SARS, MERS, and influenza who were treated with systemic glucocorticoids, but the clinical significance of these findings is unknown. Unlike with SARS, in which viral replication peaks in the second week of illness, viral shedding in SARS-CoV-2 appears to be higher early in the illness and de- clines thereafter [18].

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 [20]. In Argentina it was used for the treatment of the Argentine hemorrhagic fever with very good results to reduce mortality [3] a few years ago by Dr. Julio Maiztegui.

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. It is considered to be most effective during the initial week, and it may be considered to be ineffective after 14th day [21-23].

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 [20].

Evidence shows that convalescent plasma from patients who have recovered from viral infections can be used as a treatment without the occurrence of severe adverse events. Therefore, it might be worthwhile to test the safety and efficacy of convalescent plasma transfusion in SARS-CoV-2-infected patients [22].

The doses of Convalescent Plasma used as described by the different studies are varied. A Chinese pilot study showed a minimal use of a single dose of 200 mL convalescent plasma with neutralizing antibody titers >1:640. Another study by Bin Zhang et al., reported a maximum of 2400 mL of convalescent plasma administered to a 73 years old male patient [23].

The dose we recommend of Convalescent Plasma is 300 mL/ unique dose.

The Argentinian Protocol. Triple Treatment Strategy as Immunomodulatory and Antiviral Effect for Covid-19

Although it has been observed from one case that intravenous infusion of plasma and mesenchymal stem cells have a synergistic therapeutic effect on patients with severe COVID-19 pneumonia [8], in theory, the mechanisms of action of convalescent plasma and mesenchymal stem cells have complementary characteristics. We believe that a triple treatment strategy, including dexamethasone, might benefit patients with COVID-19 pneumonia without better options to stop the cytokine storm.

Eligibility for MSC + Convalescent Plasma + Dexamethasone as a Triple Treatment Strategy on a Same Day

Inclusion criteria

1. Patient 18 years old or older.
2. Hospitalized with highly severe COVID-19 respiratory symptoms and confirmation of infectionpositive using the RT-PCR test COVID-19 SARS-CoV-2 (real-time PCR).
3. Patient duly informed, to the extent of their conditions, who is a voluntary signer of a comprehensive Informed Consent Form. In case of not being able to do so, the authorizing signature of the legal representative, the support, the spouse, the cohabitant, the relative or the close friend will be obtained.
4. Severely compromised patient, presenting any of these symptoms and / or parameters:

- Dyspnea
- Respiratory rate ≥ 30 / min
- Blood oxygen saturation ≤ 93%
- Ratio between partial pressure of arterial oxygen and fraction of inspired oxygen <300
- Lung infiltrates> 50% within 24 to 48 hours

Or that it is in a terminal state and for whom the doctor considers that it has a high-riskmortality

- Respiratory failure
- Septic shock
- Multiple organ failure or dysfunction

Exclusion criteria

1. Contraindication to transfusion: history of anaphylaxis to blood products.
2. In relation to other comorbidities: according to the criteria of the treating physician.

Conclusion

Based on evidence reported in systematic reviews, meta-analysis and clinical trials including systemic applied MSC, Convalescent Plasma and Dexamethasone, this triple theoretical therapy strategy appears to be safe in different conditions and situations and could prove a useful way for COVID 19 patients given their immunomodulatory and anti-inflammatory properties. This theoretical treatment stimulates our group to design a Phase 1 protocol for the treatment of severe pneumonia for Covid-19 in Argentina.

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Declarations

MFV, LC, MIS, RFV, have nothing to declare related to this manuscript.

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