Mesenchymal stem cells Therapy in Patients with COVID-19 Pneumonia

Date: 04 May 2020-30 July 2020

Attached is a copy of trial by Ayca Sultan Sahin titled 'Mesenchymal stem cells Therapy in Patients with COVID-19 Pneumonia' which is being submitted.
This trial is original, it is not being considered for publication elsewhere. Our trial is original because the application of MCSs in COVID-19 pneumonia patients are not common.
Correspondence regarding this trial is Ayca Sultan Sahin, at the address indicated in the forms.
Looking forward to hearing from you soon. Many thanks in advance for your consideration and cooperation.

Purpose of our study:
Due to the cytokine storm that develops as a result of COVID-19 infection, some patients are hospitalized to intensive care unit for pneumonia, ARDS and multiple organ failure. Mortality is higher in treatment-resistant cases.

1) Providing immune modulation by Stem Cell Transplantation and reducing the damage caused by cytokine storm to tissues and organs,
2) Correcting immunosuppression and fight against COVID-19 virus by editing B and T cells,
3) It is to accelerate healing in organ damage by increasing growth factors through mesenchymal stem cells.

Primary outcome: Weaning of patients, from mechanical ventilation
Secondery outcome: Improvement of clinical symptoms, reduction of cytokine storm
Clinical outcome assessment
The patients were observed after MSC infusion, and clinical symptoms, laboratory tests, and radiological results were recorded and confirmed by experienced physicians. The primary clinical outcomes included the incidence of progression from severe to critical illness and the time to a clinical improvement of two points on a seven-category ordinal scale that has been used widely in clinical symptom assessment or discharge from the hospital. The secondary clinical outcomes included patient status at days 7 and 14 assessed with a seven-category ordinal scale, hospital stay, changes in oxygenation index, hematological inflammatory factors, and imaging.

Methods

Study design and participants

This study was a single-center open-label, randomized trial conducted at an Education and Training Hospital, Istanbul from May to July, 2020, and it was performed according to the Declaration of Helsinki and approved by the Ethics Committee and health ministry (No.KAEK/2020.05.20). Written informed consent was obtained from all patients or their representatives when data were collected prospectively.

Age, gender, mortality status, APACHE II score, number of days in bed, procalcitonin and CRP values, leukocyte values, concomitant diseases, CD4, CD8, IL-2, IL-6, TNF-alpha-beta levels will be recorded. These tests are studied in the conditions of our hospital.

Clinical results, changes in inflammatory and immune function levels, and side effects will be evaluated. The patient's lung function and symptoms will be recorded in the days after MSC transplantation. After treatment, lymphocyte, C-reactive protein, TNF-a level, IL-6 levels will be recorded.

Patients were divided into 3 groups: (Figure 1)

1.group: Intubated without comorbidity (n:7)

2.group: Intubated with comorbidity (n:7)

3.group: No intubated (n:7)

Dosage of MSCs:

1. 1 million cell/kg iv----------day 0
2. 1 million cell/kg iv ----------day 2
3. 1 million cell/kg iv ----------day 4

Inclusion criteria included the following:

• aged 18-80 male or female

• laboratory approve of RT-PCR with 2019-nCoV infection

• pneumonia assessed by chest radiography or computed tomography

• In accordance with any of the following:

1) Respiratory rate ≥ 30 times / min

2) oxygen saturation ≤ 93%

3) PaO2/FiO2) ≤ 300MMHG

4) pulmonary imaging of focus within 24-48 hours > 50% progression

• patients who remain unresponsive to medications administered according to Ministry of health guidelines

• Patients who receiving invasive or non-invasive mechanical ventilation therapy in intensive care

Exclusion criteria included the following:

- Pregnancy
- Any kind of cancer, severe liver disease
- Failure to provide informed consent or comply with test requirements
- Known allergy or hypersensitivity to MSCs

Statistical Analyses

CD values

Stem cell therapy received patients who were divided into 3 groups have the following descriptive characteristics in terms of CD values (Table 1: mean±standard deviation) according to dosage of MSCs. Four different time periods were handled as "Time 0" (before MSCs infusion,) and as "Time 1", "Time 2" and "Time 3" (after 1st infusion, after 2nd infusion, after 3th infusion, respectively). Linear mixed effects model was used whether both the groups and time affected blood values differently. Given 21 stem cell therapy received patients, the linear mixed-effects model can be described as follows:

$$\boldsymbol{y}_i = \boldsymbol{X}_i\beta_i + \boldsymbol{Z}_i\eta_i + \boldsymbol{\varepsilon}_i$$

where $\boldsymbol{y}_i$ is the vector of blood values for patient $\boldsymbol{i}$ and $\boldsymbol{X}_i$ is the design matrix. β is a vector of fixed effects (group and time) that are common to all patients and η is a vector of random effects (subject-specific). The model is a linear combination of fixed and random effects where random effects are assumed to have normal distribution $\boldsymbol{\beta}_i \sim \boldsymbol{N}(\boldsymbol{0}, \boldsymbol{\sigma}^2)$. The residual vector $\boldsymbol{\varepsilon}_i \sim \boldsymbol{N}(\boldsymbol{0}, \boldsymbol{\sigma}^2)$. Models were estimated with nlme package in R-Studio

Clinical Behavior

Clinical behaviours of stem cell therapy received patients were divided into 3 groups and the blood values were recorded for different six time periods such as "Time 0" (before MSCs infusion) "Time 1" (after 1st infusion), "Time 2" (after 2nd infusion), "Time 3" (after 3th infusion), "Time 4" (extubation time) and "Time 5" (discharge time). Table 2 shows the descriptive characteristics (mean±standard deviation) of blood values according to dosage of MSCs. Linear mixed effects model was used whether both the groups and time affected blood values differently.

Figure 1. Flow diagram of the study