Research Paper

Adipose-derived mesenchymal stromal cells for the treatment of patients with severe SARS-CoV-2 pneumonia requiring mechanical ventilation. A proof of concept study


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ABSTRACT

Background: Identification of effective treatments in severe cases of COVID-19 requiring mechanical ventilation represents an unmet medical need. Our aim was to determine whether the administration of adipose-tissue derived mesenchymal stromal cells (AT-MSC) is safe and potentially useful in these patients.

Methods: Thirteen COVID-19 adult patients under invasive mechanical ventilation who had received previous antiviral and/or anti-inflammatory treatments (including steroids, lopinavir/ritonavir, hydroxychloroquine and/or tocilizumab, among others) were treated with allogeneic AT-MSC. Ten patients received two doses, with the second dose administered a median of 3 days (interquartile range-IQR-1 day) after the first one. Two patients received a single dose and another patient received 3 doses. Median number of cells per dose was 0.98 ± 10^6 (IQR 0.50 ± 10^6) AT-MSC/kg of recipient’s body weight. Potential adverse effects related to cell infusion and clinical outcome were assessed. Additional parameters analyzed included changes in imaging, analytical and inflammatory parameters.

* These authors contributed equally to the manuscript.

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1. Introduction

The current SARS-CoV-2 pandemic has stretched the capacity of the health systems in many of the affected countries to the limit, conditioned by the need for intensive care in many of these patients [1]. Patients admitted to the Intensive Care Unit (ICU) requiring mechanical ventilation show significant mortality that ranges between 30 and 80% [2–4]. Factors that have been associated with a worse prognosis in patients with severe SARS-CoV-2 pneumonia include age over 65 years, the existence of comorbidities as diabetes, male gender, and elevated levels of C-reactive protein or lactate dehydrogenase (LDH), among others [5–8]. Even, in those patients with a favorable outcome, an additional problem that contributes to the ICU saturation, is the long average stay under invasive mechanical ventilation [9]. Therefore, any adjuvant treatment that contributes to accelerate the recovery will represent a major step forward.

One of the most striking facts of the physiopathology of pneumonia in COVID-19 disease [10] is the development of a massive inflammatory phase [11,12], with elevation of numerous acute phase reactants and cytokines (e.g. ferritin, C-reactive protein, fibrinogen, LDH or IL-6), leading to acute respiratory distress syndrome (ARDS) and macrophage activation syndrome (MAS)-like disease [13,14]. In addition, the presence of a progressive endothelial thrombo-inflammatory syndrome (with elevated d-dimer) not described in other viral infections adds differential features and aggravates the disease’s prognosis [15–17]. This inflammatory reaction underlines the rationale for the development of clinical trials evaluating the role of drugs with anti-inflammatory activity, such as tocilizumab, anakinra, siltuximab, and others [18–20].

Among the potential therapeutic options to reduce this clinical and biological picture of massive inflammation the use of mesenchymal stromal cells (MSCs) is generating increasing interest. Nevertheless, to date, information published on critically ill patients undergoing mechanical ventilation treated with MSC is reduced to a single reported case [21]. However, over 17 clinical trials are registered in ClinicalTrials.gov to evaluate the role of mesenchymal cells from different sources [22]. MSC have been approved for the treatment of Crohn’s disease or graft-versus-host disease after hematopoietic transplantation [23] based in their anti-inflammatory and immunomodulatory effects thus suggesting that adipose tissue-derived MSCs (AT-MSCs) could be an attractive therapeutic option for the treatment of severe SARS-CoV-2 pneumonia [24]. In the current report we describe the outcome of a group of 13 patients with severe SARS-CoV-2 pneumonia requiring mechanical ventilation, who had not responded to previous antiviral and anti-inflammatory treatments (including in some cases tocilizumab, steroids, anakinra and/or siltuximab), and who were treated with AT-MSCs on a compassionate-use basis. These results represent the preliminary experience of four academic centers of the Spanish National Cell Therapy Network (TerCel) [25] and establishes the basis for the current phase 2 randomized controlled clinical trial (BALMYS-19 “BATTLE against CO using Mesenchymal Stromal cells; EudraCT: 2020-001266-11; clinicaltrials.gov identifier NCT04348461) already in progress.

2. Methods

2.1. Patients

Patients with SARS-CoV-2 infection confirmed by reverse-transcriptase-polymerase-chain-reaction assay and COVID-associated pneumonia diagnosed by either chest X-ray or computed tomography and requiring mechanical ventilation in the ICU and in
Cells were cryopreserved in bags containing from 50 to 75
volumes were digested with collagenase and further expanded in the
Medicines Agency (AEMPS). Briefly, 100 ml of lipoaspirate (corre-
sponding to 50 g of fat tissue) were obtained from each donor. Sam-
ples were digested with collagenase and further expanded in the
GMP facilities in standard conditions, as previously reported [28,29].
Cells were cryopreserved in bags containing from 50 to 75 × 10^6
MSC. In all cases, less than 20 population doublings and less than 2
passages were performed before administration. Characterization of
the final product included the International Society for Cellular Ther-
apy (ISCT) definition criteria with morphology, immunophenotypic
profile, multi-lineage differentiation ability[30]. In addition, compar-
ative genomic hybridization arrays to ensure genomic stability and a
potency test evaluating the inhibition of the proliferation of activated
T-lymphocytes were performed.

Cell were cryopreserved and stored until use. Cell viability was
tested only before cryopreservation. Cryopreserved cells were
administered immediately after thawing in a medium containing AB
serum and 10% dimethyl sulfoxide without washing at the Hospital
Universitario de Salamanca and Clinica Universidad de Navarra, while
the remaining centers used "refreshed" cells that were seeded back
onto plastic surface for a period of less than 72 h and then trypsinized
and resuspended in a solution of Ringer's lactate with 1% albumin
before administration, that in all cases were infused in less than 24 h
from harvesting. In the first case, steroids and dexamethasone were
administered prior to cell infusion. In every case, administration
was performed intravenously by personnel experienced in the use of
AT-MSCs using a standard 200-micron transfusion filter at a target
dose of 1 × 10^6 AT-MSCs/kg of recipient's body weight. Treated
subjects received cells from five different donors, although each indi-
vidual patient received cells from the same cell product batch. In this
compassionate use program, patients received a first dose of AT-
MSCs (day 1) and were scheduled for a second dose if deemed clini-
cally appropriate by the treating physician, between 48 and 96 h
later. This was based on previous literature, clinical course and on the
putative mechanism of action[31–33]. Eventually, a third dose was
allowed to be administered. Supportive therapy included, in addition
to mechanical ventilation and sedation, the use of vasopressor or ino-
tropic drugs, enteral or parenteral nutrition, antibiotics and/or diure-
tics, among other standard procedures, and was provided at the
discretion of the clinicians until discharge from ICU or death.

2.3. Study assessments

In each patient, toxicity and potential adverse events related to
cell administration were recorded. All intubated patients in the ICU
were continuously monitored with electrocardiography, continuous
invasive blood pressure, pulse oximetry and capnography to immedi-
ately detect any potential adverse reaction during the infusion of cells
and afterwards. Ventilatory, radiological and analytical parameters
including complete blood counts (CBC) and basic biochemistry, coag-
ulation (including fibrinogen and d-dimer) and acute phase reactants
(C-reactive protein, ferritin, LDH and/or IL-6) were obtained before
the first dose of AT-MSCs (routinely in the morning of the same day),
daily for 5 days and at regular intervals thereafter depending on
clinical or institutional criteria. Specifically, most centers performed
CBC, biochemistry and coagulation daily in ICU, and chest-X rays, fer-
ritin or IL-6 every 5–10 days after the first 5–7 days, and when clini-
cally appropriate. Chest X-rays were evaluated by two independent
observers according to the score proposed by Wong et al. [34].
Although there were no pre-specified end points for this compassion-
ate-use program, we registered and quantified prospectively the inci-
dence of potential adverse events, as previously indicated, through
continuous monitoring while in ICU. In addition, we evaluated the
proportion of patients with clinical improvement, as defined by extu-
bation, discharge from ICU, radiographic improvement or at least
one-point decrease in the World Health Organization (WHO and R&D
Blueprint Group Ordinal Scale for Clinical Improvement) [27]. The
appearance of respiratory or other concomitant infections was also
collected, as well as any concomitant medications administered from
date of hospital admission. Main lymphocyte subpopulations in
peripheral blood (B cells, CD4+ T cells, CD8+ T cells, NK cells) were
quantified before and 10 days after AT-MSCs administration. The
length of time from admission to the start of mechanical ventilation,
the time between mechanical ventilation and the first AT-MSC
administration, and the time between the latter and extubation or
death were also analyzed.

2.4. Statistical analysis

All data were stored in and Excel file (Microsoft, Redmond, Wash-
ington) and then imported into the SPSS.v25 (IBM, Armonk, New
York) statistical package. Tables and Fig. 1 were performed with Excel
(Microsoft) and GraphPad.v8 (GraphPad software, San Diego, Califor-
nia) was used to create the graphic that compose Fig. 2. Median and
interquartile ranges (IQRs) were calculated for quantitative variables.

2.5. Role of funding

Funding source: none. Fermin Sanchez-Guijo had full access to all
the data in the study and had final responsibility for the decision to
submit for publication.
3. Results

3.1. Patient and baseline characteristics

Thirteen patients were treated with AT-MSC between April 3rd and April 22nd, 2020. In two cases, a single dose was administered, one patient received 3 doses and the remaining ten patients received 2 doses, the second administered at a median of 3 days (IQR 1 day) after the first one. More specifically, the two patients that received a single dose did improve significantly after administration of the AT-MSC and no need for additional doses was deemed necessary. On the other hand, in one patient, although improvement was observed after the first 2 doses, worsening of his condition and availability of an additional cell dose was considered as a reason for an additional administration of cells. Median number of AT-MSCs per dose was 0.98 (IQR 0.5) x 10^6 /kg. In 7 patients, cells were reseeded and refreshed for 72 h while in the remaining 6 patients AT-MSCs were directly thawed and immediately infused intravenously. Baseline and treatment characteristics of the patients are summarized in Table 1. Median age was 60 years (IQR 11 years). Twelve of the 13 patients were male. All patients were under invasive mechanical ventilation at baseline (before the first MSC administration). Median time from Hospital admission to mechanical ventilation was 4 days (IQR 3 days) and the median duration of invasive mechanical ventilation before the first dose of AT-MSC was 7 days (IQR 12 days). All patients received corticosteroids, prophylactic antibiotics (mainly ceftriaxone) and low-molecular weight heparin. Eleven of 13 patients (85%) had received hydroxychloroquine (7 in combination with azithromycin), and the same percentage had received tocilizumab. Anakinra was given in 2 patients (15%), one after tocilizumab, whereas siltuximab was additionally administered after tocilizumab and anakinra in one patient. Finally, lopinavir/ritonavir was also administered in 11 patients (85%). At the time of cell administration only steroids were administered concomitantly. Most patients received supportive treatment during their ICU stay. This included, in addition to mechanical ventilation and sedation, the use of vasopressor or inotropic drugs, enteral or parenteral nutrition, antibiotics and/or diuretics, among other standard procedures.

3.2. Safety

No adverse events were associated with the infusion of AT-MSC including fever or worsening of respiratory or hemodynamic...
<table>
<thead>
<tr>
<th>Patients</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>BMI</th>
<th>Days from diagnosis (PCR SARS-CoV positive)</th>
<th>Comorbidities</th>
<th>Smoking</th>
<th>Laboratory</th>
<th>Previous therapy</th>
<th>AT-MSC, No. doses</th>
<th>Days in ICU with mechanical ventilation after AT-MSC infusion</th>
<th>Days in ICU without mechanical ventilation after AT-MSC infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55</td>
<td>M</td>
<td>Caucasian</td>
<td>24.49</td>
<td>8</td>
<td>HBV None</td>
<td>No</td>
<td>IL-6</td>
<td>Tocilizumab (doses)</td>
<td>No</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
<td>M</td>
<td>Caucasian</td>
<td>30.86</td>
<td>22</td>
<td>Hypertension None</td>
<td>No</td>
<td>CRP</td>
<td>Anakinra No</td>
<td>No</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>68</td>
<td>F</td>
<td>Caucasian</td>
<td>35.16</td>
<td>3</td>
<td>COPD None</td>
<td>No</td>
<td>Ferritin</td>
<td>Siltuximab No</td>
<td>No</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>55</td>
<td>M</td>
<td>Caucasian</td>
<td>25.83</td>
<td>14</td>
<td>Hyperthyroidism No</td>
<td>No</td>
<td>D-dimer</td>
<td>Hydroxychloroquine Yes</td>
<td>No</td>
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<td>0</td>
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<tr>
<td>5</td>
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<td>M</td>
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<td>25.83</td>
<td>14</td>
<td>Sindrome None</td>
<td>No</td>
<td>Fibrinogen</td>
<td>Lopinavir/Ritonavir Yes</td>
<td>No</td>
<td>0</td>
<td>0</td>
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<tr>
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<td>M</td>
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<td>26.12</td>
<td>9</td>
<td>Hypertension None</td>
<td>No</td>
<td>Hb</td>
<td>Steroids Yes</td>
<td>No</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>63</td>
<td>M</td>
<td>Caucasian</td>
<td>25.83</td>
<td>9</td>
<td>Hypertension None</td>
<td>No</td>
<td>Platelets</td>
<td>AT-MSC No</td>
<td>No</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>62</td>
<td>M</td>
<td>Caucasian</td>
<td>25.06</td>
<td>5</td>
<td>Hypertension None</td>
<td>No</td>
<td>LDH</td>
<td>AT-MSC No</td>
<td>No</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>50</td>
<td>M</td>
<td>Caucasian</td>
<td>27.55</td>
<td>19</td>
<td>Hypertension None</td>
<td>No</td>
<td>SOFA score before AT-MSC infusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>59</td>
<td>M</td>
<td>Caucasian</td>
<td>25.95</td>
<td>24</td>
<td>Hypertension None</td>
<td>No</td>
<td>AT-MSC, No. doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>55</td>
<td>M</td>
<td>Caucasian</td>
<td>25.95</td>
<td>19</td>
<td>Hypertension None</td>
<td>No</td>
<td>Days in ICU with mechanical ventilation after AT-MSC infusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>71</td>
<td>M</td>
<td>Caucasian</td>
<td>28.29</td>
<td>18</td>
<td>Hypertension None</td>
<td>No</td>
<td>Days in ICU without mechanical ventilation after AT-MSC infusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>73</td>
<td>M</td>
<td>Caucasian</td>
<td>26.73</td>
<td>4</td>
<td>Hypertension None</td>
<td>No</td>
<td>M: male; F: female; BMI: Body Mass Index (kg/m²); HBV: Hepatitis B virus; COPD: Chronic Obstructive Pulmonary Disease; IL-6: Interleukin-6 (pg/mL); CRP: C-reactive protein (mg/dL); Ferritin (mg/dL); D-dimer; mg/mL; Fibrinogen (mg/dL); Hb: hemoglobin (g/dL); Platelets: (x10^3)/mL; Lymphocytes (x10^3)/mL; LDH: lactate dehydrogenase (U/L); AT-MSC: Adipose-tissue derived mesenchymal stromal cell; ICU: Intensive Care Unit; NT: non tested.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
parameters. One patient developed severe hypotension and tachycardia 24 h after cell administration despite treatment with steroids and dexchlorpheniramine. Subsequently, a severe decrease in hemoglobin was observed. A CT scan and upper gastrointestinal endoscopy were performed showing massive digestive bleeding due to a gastric ulcer, whose location coincided with the position of the nasogastric tube. Despite intensive supportive therapy, the patient died. In light of this information, this early complication was deemed not to be related to cell administration.

3.3. Clinical and radiological improvement

After a median follow-up of 16 days (IQR 9 days) after the first dose of AT-MSCs, 9 patients (70%) had improved clinically and 7 (53%) were extubated (Fig. 1) with a median time from the first MSC dose to extubation of 7 days (IQR 14 days). In two patients, extracorporeal mechanical oxygenation (ECMO) was required but both remain stable at the time of writing this report, 11 and 23 days after the first cell dose. Two patients died, one from massive gastrointestinal bleeding due to a gastric ulcer, whose location coincided with the position of the nasogastric tube. Despite intensive supportive therapy, the patient died. In light of this information, this early complication was deemed not to be related to cell administration.

No significant changes in physiological parameters measured by continuous monitoring were observed immediately after AT-MSC infusion, nor in the biological parameters (including coagulation, hepatic, cardiac or renal function) performed daily after cell administration (Supplementary Table 1).

3.4. Laboratory response and immune monitoring

For laboratory evaluation, the patient who died prematurely and the patient who was on ECMO before day +5 (after the first AT-MSC dose) was excluded from the analysis. An additional patient was not evaluable for ferritin and IL-6 as these analyses were not performed on the fifth day after cell infusion. When we analyzed the nine patients that improved clinically (according to Fig. 1), a decrease in inflammatory parameters associated with AT-MSC therapy was observed at day 5 after infusion (Fig. 3A) with a decrease in C-reactive protein in 8 patients (88%), LDH in 9 (100%), and D-dimer and ferritin in 5 of 8 evaluable patients (63%), since one responding patient did not have the results of both parameters at day +5 after the first AT-MSC dose. In six patients in which lymphocyte counts were measured by flow cytometry, an increase in the levels of total lymphocytes was observed in 5 of them (83%), as well as an increase in B- (67%) and CD4+ and CD8+ (100%) T lymphocytes (Fig. 3B). Lymphocyte subset analysis was available in six patients that improved after MSC therapy, but no information on non-responding as well as in 3 responding patients was available.
4. Discussion

The severity of the COVID-19 pandemic and the lack of effective proven therapies represents a formidable challenge and have stimulated multiple research groups on an urgent search for potentially useful therapeutic options [18–20]. Multiple clinical trials are currently underway with a wide range of drugs (in the https://clinicaltrials.gov website accessed on May 1st are registered up to 600 clinical trials, almost half of which are already under recruitment). Furthermore, due to the therapeutic urgency many treatments are being used off-label through compassionate use programs [35]. Here, we report the first series of COVID-19 patients requiring mechanical ventilation treated with AT-MSC, generating preliminary evidence of the absence of significant adverse events along with improvement in most of these patients. These results warrant conducting a multicenter randomized controlled trial already underway.

The outcome of COVID-19 patients admitted to the ICU is poor. In a recent series of 1581 Italian patients with COVID-19 ARDS admitted to ICU (88% requiring mechanical ventilation), with a median follow up of 9 days, 26% have died and only 16% had been discharged [36]. In another series of patients with longer median follow-up (19 days), one third of them (31%) have been discharged from ICU and 23% have died [37]. In our series, with a median follow-up of 16 days, mortality rate was 15%, while seven patients (53%) had been extubated and discharged from ICU and two additional patients were improving.

One of the most relevant findings of our work is the lack of adverse events associated with cell administration in these extremely critical patients with respiratory insufficiency, massive inflammation and prothrombotic risk. Safety of MSC treatments administered intravenously has been well demonstrated in multiple clinical trials for different conditions (e.g. Crohn’s disease, graft-versus-host disease, etc.) as reported in two meta-analyses including almost 3000 patients [38,39]. Pre-clinical evidence of the potential for MSCs in viral lung infections is still scarce and, in some cases, controversial [22,40]. It is true that there are no preclinical studies in animal models of SARS-CoV-2 infection and that most preclinical evidence comes from influenza virus infection models, where the pathophysiology and systemic manifestations are different. Nevertheless, although results of these studies are not uniformly positive, no adverse events related to cell therapy in this setting has been reported [22,40]. Stromal cells have been employed at the clinical level in other instances of severe pulmonary disease induced by viral infection [41]. In this regard, menstrual-blood derived MSCs were administered in 17 Chinese patients H7N9-induced ARDS patients during the 2013–2014 outbreak, again with no associated toxicity and a better survival compared to a control group of 44 patients (82.4% versus 45.4%) [42]. However, cases of secondary concomitant or subsequent bacterial or fungal infection after cell administration merit further comment. Although in patients with COVID-19 under mechanical ventilation the risk of bacterial or fungal secondary infection has been described to be around 8% and its diagnosis is challenging [43–45], theoretically an anti-inflammatory or immunomodulatory treatment such as MSC can potentially increase this risk and should be monitored and strictly assessed and followed in subsequent clinical trials.

The association between AT-MSC and a decrease in inflammatory parameters also support the hypothesis that cell administration may contribute to generate an inflammatory and immunomodulatory micro-environment [24]. This fact is of particular relevance, since almost all the patients included in our series had received steroids as well as tocilizumab (some also with anakinira and/or siltuximab), without clinical response. Unlike monoclonal antibodies that act only by blocking the effect of a single interleukin (e.g. tocilizumab for IL-6 or anakinira for IL-1) [46], AT-MSCs could act in the inflammatory microenvironment of endothelial and alveolar damage by interacting with various targets, releasing anti-inflammatory and anti-apoptotic molecules in a paracrine fashion, and modulating the action of the hyper-activated immune system, including macrophages, neutrophils and other cell types, and improving endothelial function [24,47,48].

Patients with COVID-19 pneumonia have been described to suffer from a pro-coagulant status and high levels of D-dimer has been associated to poor prognosis [16,17,37]. Remarkably, we observed a reduction of D-dimer 5 days after the first AT-MSC dose in most patients, and none of the patients developed a thromboembolic event, although mesenchymal cells preferentially home to the pulmonary circulation after endovenous administration [49]. Because of these pro-coagulant status patients with COVID-19 are routinely treated with low-molecular weight heparin [50]. It is possible that receiving prophylactic anticoagulant therapy may have contributed to decrease the potential prothrombotic risk that might have been induced by MSCs, but due to the sample size this should be further
evaluated in subsequent studies before making a definitive recommendation for concomitant administration of low weight heparin in patients with COVID-19 receiving AT-MSC.

Finally, although the sample size does not allow definitive conclusions, our results suggest that treatment with AT-MSC early after mechanical intubation might improve the outcome. This is also a potentially useful fact to take into account for the design of randomized clinical trials such as our BALMYS-19 trial. In addition, we have not found differences in patients treated with thawed versus fresh cells due to the limited number of patients included. This issue, that has been widely debated in the MSC field [51,52], should be also clarified in future trials.

Additional limitations of our study, besides the sample size, are related to the type of study (non-randomized case series) and to the variability inherent in the previous treatments, the different time of cell administration and the non-uniformity in the number of doses. The favorable response in many patients cannot be exclusively attributed to the effect of the cells, since other concomitant treatments were administered a few days before the cell administration and in a varied pattern. This proof-of-concept study, which constitutes the first case series of intubated COVID-19 patients treated with AT-MSC, has been used to design a randomized phase II clinical trial with a control arm that will provide better knowledge of the real scope of the potential of this therapeutic approach in this clinical setting.

In summary, our preliminary results, indicate that MSC derived from adipose tissue can be safely administered in critically ill patients with COVID-19 pneumonia and that administration of AT-MSC was followed by clinical improvement and changes in inflammatory and immune populations, which suggest a potential biological effect of the cells. These results have served as an initial proof of concept (especially taking into account the health emergency we are experiencing) for the design of a randomized, controlled phase 2 clinical trial of treatment with AT-MSCs in patients with COVID-19 requiring mechanical ventilation (BALMYS-19-“Battle against CO using Mesenchymal Stromal cells”-; EuadrCT: 2020-001266-11; clinicaltrials.gov identifier NCT04348461). Our trial, as other potential randomized trials with a control arm consisting of standard treatment, will contribute to understanding the real potential of this cell-based therapeutic strategy [35,53].

Declaration of Competing Interest

Dr. Sanchez-Guijo reports grants and personal fees from Novartis, personal fees from BMS, Pfizer, Incyte, Gilead, Roche and Amgen, outside the submitted work; Dr. Lopez-Parrà reports personal fees from Gilead, Novartis, BMS and Janssen, outside the submitted work. Dr. JL del Pozo reports grants from Novartis and personal fees from Novartis, Pfizer, Gilead and Roche, outside the submitted work; Dr. Moraleda reports personal fees and other from Gilead, grants and personal fees from Jazz Pharma, and personal fees from Novartis and from Sandoz, outside the submitted work. Dr. García-Olmo has received personal fees from Takeda, outside the submitted work; Dr. Prosper reports personal fees from Oryzon Genomics, and from Janssen, outside the submitted work; Dr. García-Arranz and Dr. García-Arranz have applied for two patents related with this study entitled “Identification and isolation of multipotent cells from nonosteochondral mesenchymal tissue” (WO 2006/057649) and “Use of adipose tissue-derived stromal stem cells in treating fistula” (WO 2006/136244), and both are shareholders of Biosurgery, an educational company providing services to Takeda. All other authors declare no conflict of interest.

Acknowledgement

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi: 10.1016/j.eclinm.2020.100454.

References
