機械的換気を必要とする重症 SARS-CoV-2 肺炎患者に対する脂肪由来間葉系間葉系間質細胞の治療法。

概念実証試験

フェルミン・サンチェス・ギヨ 1

マリアノ・ガルシア＝アランツ 1

ミリアム・ロペス・パラ 1

パブロ・マネデロ

カルメン・マタ＝マルティネス

アルノルド・サントス　他

抄録

背景

機械的人工呼吸を必要とする COVID-19 の重症例における有効な治療法の特定は、アンメット・メディカル・ニーズを表している。我々の目的は、脂肪組織由来間葉系間葉系間葉系間質細胞（AT-MSC）の投与がこれらの患者に安全であり、有用である可能性があるかどうかを判断することであった。

方法

侵襲的機械換気下にある 13 人の COVID-19 成人患者で、以前に抗ウイルス剤および／または抗炎症剤（ステロイド剤、ロピナビル／リトナビル、ヒドロキシクロロキンおよび／またはトシリズマブなどを含む）による治療を受けたことのある患者を、同種 AT-MSC で治療した。10 人の患者に 2 回投与し、2 回目の投与は 1 回目の投与から中央値で 3 日後（四分位間範囲-IQR-1 日）に投与した。2 人の患者は 1 回の投与を受け、もう 1 人の患者は 3 回の投与を受けた。1 回の投与あたりの細胞数の中央値は 0.98×10^6（IQR 0.50×10^6）AT-MSC/体重 kg であった。細胞注入に関連する潜在的な副作用と臨床転帰を評価した。解析されたその他のパラメータには、イメージング、分析、炎症性パラメータの変化が含まれています。

- この記事の関連コンテンツを見る

調査結果

AT-MSC の初回投与は、機械的人工呼吸後、中央値 7 日（IQR 12 日）で行われた。細胞治療に関連した有害事象はなかった。初回投与後の経過観察期間の中央値は 16 日（IQR 9 日）で、9 人の患者（70%）に臨床的改善が認められた。7 人の患者は抜管して ICU から退院したが、4 人の患者は挿管したままであった（2 人は人工呼吸と放射線学的パラメータに改善が見られ、2 人は安定した状態であった）。2 名の患者が死亡した（1 名は MSC 治療とは無関係の大量の消化管出血によるもの）。AT-MSC による治療は、炎症性パラメータの低下（C 反応性蛋白質、IL-6、フェリチン、LDH、d-ダイマーの低下）とリンパ球の増加、特に臨床的に改善した患者でのリンパ球の増加をもたらした。

解釈

小規模な症例シリーズにおいて、機械換気下での重症 COVID-19 肺炎 13 例を対象に AT-MSC を静脈内投与したところ、有意な有害事象は誘発されず、その後ほとんどの被験者で臨床的・生物学的改善がみられた。

·   Fermín Sánchez-Guijo 1
·   Mariano García-Arranz 1
·   Miriam López-Parra 1
·   Pablo Monedero
·   Carmen Mata-Martínez
·   Arnoldo Santos

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.

• [View related content for this article](#)

Findings

First dose of AT-MSC was administered at a median of 7 days (IQR 12 days) after mechanical ventilation. No adverse events were related to cell therapy. With a median follow-up of 16 days (IQR 9 days) after the first dose, clinical improvement was observed in nine patients (70%). Seven patients were extubated and discharged from ICU while four patients remained intubated (two with an improvement in their ventilatory and radiological parameters and two in stable condition). Two patients died (one due to massive gastrointestinal bleeding unrelated to MSC therapy). Treatment with AT-MSC was followed by a decrease in inflammatory parameters (reduction in C-reactive protein, IL-6, ferritin, LDH and D-dimer) as well as an increase in lymphocytes, particularly in those patients with clinical improvement.

Interpretation

Treatment with intravenous administration of AT-MSC in 13 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.

Keywords

- COVID-19
- SARS-CoV-2
- Pneumonia
- Mechanical ventilation
- Mesenchymal stromal cells
- Cellular therapy
- Case series

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 60% [

2

,

3

,

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

,

6

,

7

,

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

,

16

,

17

]. This inflammatory reaction underlies 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

,

19

,

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, more than 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 accordance with any one of the following criteria were included in the study: 1) tachypnea (RR ≥ 30 times / min), 2) finger oxygen saturation ≤ 93% in resting state, 3) arterial oxygen partial pressure (PaO2) / fraction of inspired oxygen (FiO$_2$) ≤ 300 mmHg, 4) pulmonary imaging with evidence of progression > 50% in 24–48 h and a Sequential Organ Failure Assessment (SOFA) score [

26

] >3 points, World Health Organization (WHO) Ordinal Scale for Clinical Improvement [

27

] level 6 and no evidence of multiorgan failure. Additional inclusion criteria included age older than 18 years, a creatinine clearance above 30 ml per minute and serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) less than five times the upper limit of the normal range (40 units/liter). Patients with active neoplasms or with systemic immunosuppressive treatments prior to admission were excluded from this program. All patients were treated at four different Spanish academic hospitals that are members of the Spanish Cell Therapy Network (TerCel) [

25

] and had the experience and infrastructure to administer allogeneic MSC: Hospital Universitario de Salamanca, Fundación Jiménez Diaz, Hospital Universitario Gregorio Marañón and Clínica Universidad de Navarra. Treatment with AT-MSC was approved by The Spanish Medicines Agency

(AEMPS, https://www.aemps.gob.es/) as part of a compassionate use program after informed consent from the patients' relatives was obtained.

2.2 Cell treatment

AT-MSC were obtained by liposuction from voluntary donors performed by surgeons from the Plastic Surgery Departments of the participating hospitals. In all cases, donors were young (less than 50 years) with no comorbidities or concomitant treatments. The analytical and serological studies required by the legislation on cell and tissue donation in the European Union and in Spain were obtained in each case, as well as specific informed consent to use the cells for clinical application.

Cell production was carried out in the Good Manufacturing Practices (GMP) Facilities of the Hospital Universitario de Salamanca, Clínica Universidad de Navarra and Hospital Gregorio Marañón in accordance with the investigational Medicinal Product Dossier (IMPD) with reference code PEI-15–103, approved by the Spanish Medicines Agency (AEMPS). Briefly, 100 ml of lipoaspirate (corresponding to 50 g of fat tissue) were obtained from each donor. Samples 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 Therapy (ISCT) definition criteria with morphology, immunophenotypic profile, multi-lineage differentiation ability [

30

]. In addition, comparative 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 dexchlorpheniramine 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 individual 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 clinically 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

,

32

,
[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 inotropic drugs, enteral or parenteral nutrition, antibiotics and/or diuretics, 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 immediately 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, coagulation (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), and 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, ferritin or IL-6 every 5–10 days after the first 5–7 days, and when clinically 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 compassionate-use program, we registered and quantified prospectively the incidence 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 extubation, 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, Washington) 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, California) was used to create the graphic that compose Fig. 2. Median and interquartile ranges (IQRs) were calculated for quantitative variables.
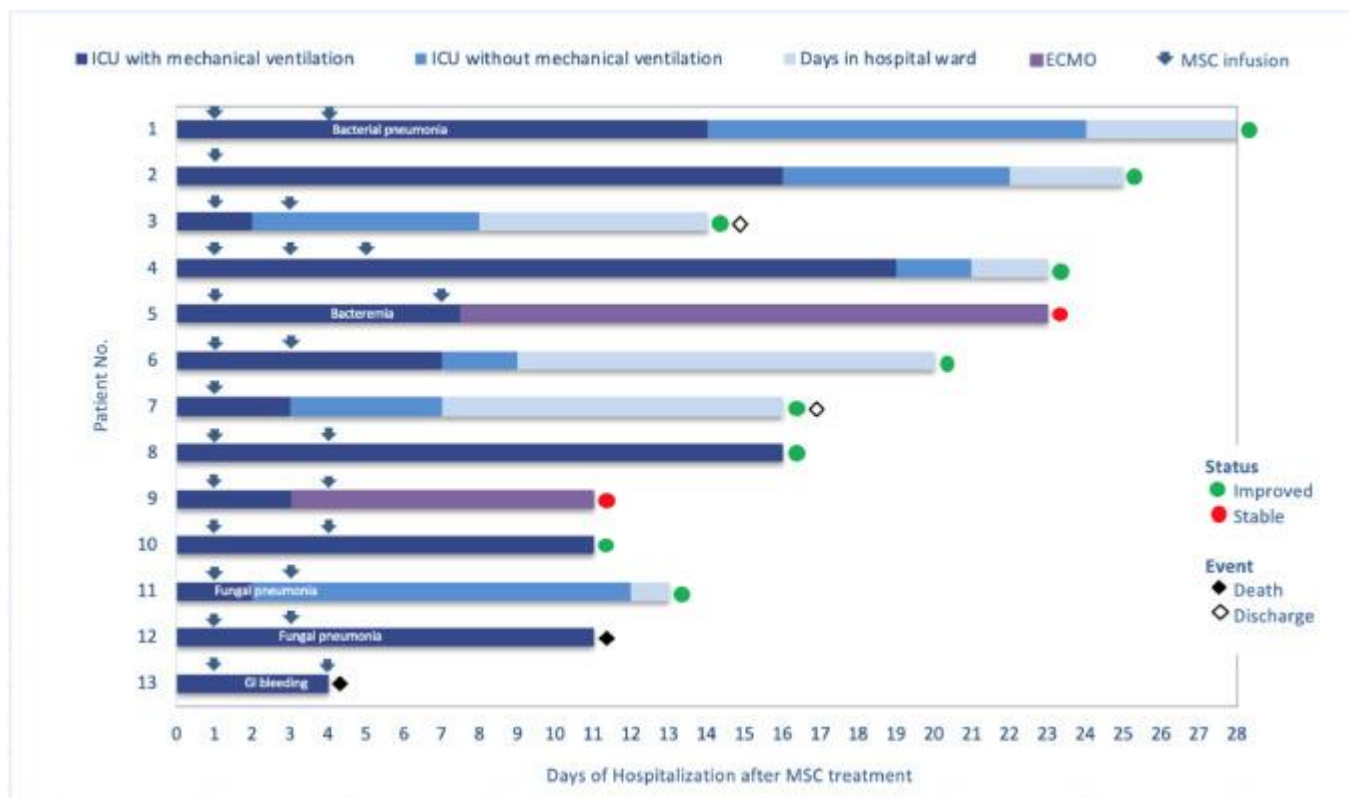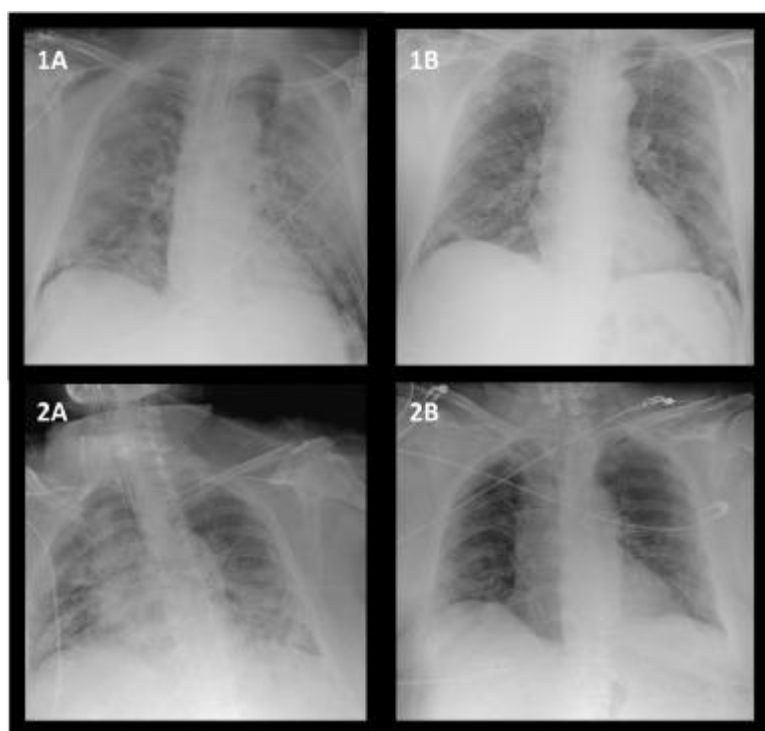
Fig. 1 Patient disposition and outcome.

Show full caption

- View Large Image
- Download Hi-res image
- Download (PPT)

Fig. 2 Chest X-ray changes of two representative patients improving after AT-MSC administration.

Show full caption

- View Large Image
- Download Hi-res image

2.5 Role of funding

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.

Table 1 Patient baseline characteristics and treatments.

Patients	1	2	3	4	5	6	7	8	9	10	11	12	13
Age (years)	55	64	68	55	47	62	63	62	50	59	55	71	73
Gender	M	M	F	M	M	M	M	M	M	M	M	M	M
Ethnicity	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian
BMI	24.49	30.86	35.16	25.83	26.12	25.83	25.06	27.55	25.95	25.95	28.29	26.73	24.49
Days from diagnosis (P	8	22	3	14	14	8	9	5	19	24	19	18	4

	Patients												
	1	2	3	4	5	6	7	8	9	10	11	12	13
CR SARS-CoV positive)													
Comorbidities	HBV	None	Diabetes Hypertension	COPD Hyperthyroidism	None	Hypertension Behçet syndrome	Hypertension	None	None	Hypothyroidism	Hypertension	Hypertension COPD	Hypertension
Smoking	No	No	No	Ex-sm	No	Ex-sm	Ex-sm	No	No	No	Ex-sm	Ex-sm	No

	Patients												
	1	2	3	4	5	6	7	8	9	10	11	12	13
				oker		oker	oker				oker	oker	
Laboratory													
IL-6	10000	238	87.2	7.8	82.3	92.8	209	NT	NT	NT	1954.4	2066.6	13.7
CRP	2.221	1.90	3.67	10.80	0.50	0.70	13.10	9.10	26.80	34.00	3.71	0.60	3.60
Ferritin	10622	31944	401	35592	10995	36603	24400	NT	21155	1602	14011	531	5428
D-dimer	25,00000	18655	9700	299800	18211	75000	63352	64400	34456	852	16900	17500	17666

	Patients												
	1	2	3	4	5	6	7	8	9	10	11	12	13
Fibrinogen	213	176	699	788	287	90	630	640	896	793	426	226	622
Hb	14.6	11	9.9	12.8	11.4	12.8	14.9	13.7	9.2	9.4	8.9	10.2	14.7
Platelets	215	210	429	221	134	131	297	449	224	158	170	138	349
Lymphocytes	1.98	0.5	1.16	0.46	0.50	0.46	0.30	0.40	0.40	0.40	0.70	0.71	0.30
LDH	519	308	543	774	299	1453	530	677	239	187	305	316	777
SOFA score before	6	5	2	3	7	3	2	2	4	2	4	11	2

Patients													
	1	2	3	4	5	6	7	8	9	10	11	12	13
AT–MSC infusion													
Previous therapy for COVID													
Tocilizumab (doses)	2×4000 mg	1×4000 mg	1×6000 mg	No	1×4000 mg	1×4000 mg	2×6000 mg	1×6000 mg	1×6000 mg	No	1×6000 mg	1×6000 mg 1×4000 mg	1×4000 mg

	Patients												
	1	2	3	4	5	6	7	8	9	10	11	12	13
Anakinra	No	No	No	No	No	1 × 100 mg	No	No	No	1 × 100 mg	No	No	No
Siltuximab	No	No	No	No	No	1 × 800 mg	No	No	NO	No	No	No	No
Hydroxychloroquine	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Lopinavir/Ritonavir	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes

	Patients												
	1	2	3	4	5	6	7	8	9	10	11	12	13
Steroids	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
AT–MSC, No. doses	2	1	2	3	2	2	1	2	2	2	2	2	2
Days in ICU with mechanical ventilation after AT–MSC	14	16	2	19	23	7	3	16	11	11	2	11	4

	Patients												
	1	2	3	4	5	6	7	8	9	10	11	12	13
infusion													
Days in ICU without mechanical ventilation after AT–MSC infusion	10	6	6	2	0	2	4	0	0	0	10	0	0

M: male; F: female; BMI: Body Mass Index (kg/m^2); 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: ng/mcL; Fibrinogen (mg/dL), Hb: hemoglobin (g/dL); Platelets: (x10^3/mcL); Lymphocytes (x10^3/mcL); LDH: lactate dehydrogenase (U/L). AT-MSC: Adipose-tissue derived mesenchymal stromal cell; ICU: Intensive Care Unit; NT: non tested.

- Open table in a new tab

3.2 Safety

No adverse events were associated with the infusion of AT-MSC including fever orworsening of respiratory or hemodynamic 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.

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).

3.3 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 (described before) and another one from secondary fungal pneumonia by *Saccharomyces spp*. One patient developed a concurrent respiratory pneumonia due to a methicillin-resistant *Staphylococcus aureus* and one patient developed a fungal infection by *Candida spp*. However, they subsequently improved after appropriate antibacterial and antifungal therapy according to the respective antibiogram and antifungigram and were then extubated. Radiological improvement in sequential X-rays was confirmed after AT-MSC administration (in the quantitative scale previously described [

34

]) in 40% of evaluable patients (Fig. 2). For radiological evaluation we considered 10 evaluable patients, excluding the patient who died early 24 h after cell administration and the two patients with concomitant fungal infection at the time of cell infusion.

When we examined the time from intubation to administration of AT-MSC, we observed that patient successfully extubated had received the cells earlier than patients that were not extubated (median 5 days, IQR: 11 days versus 10 days, IQR: 15 days).

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 five of them (86%), 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.
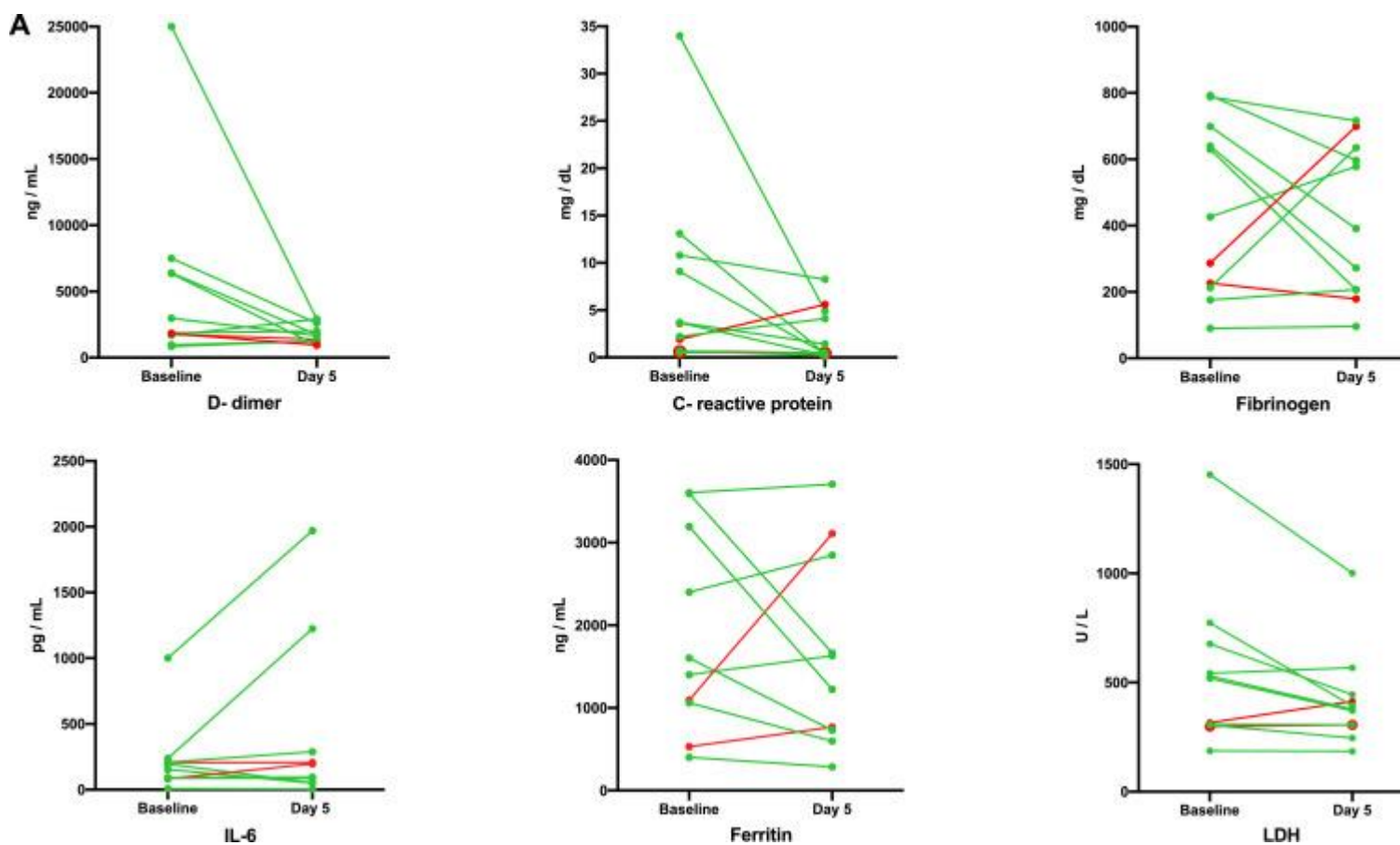
Fig. 3(A) Changes in acute phase reactants and coagulation parameters after AT-MSC therapy.
Show full caption

- View Large Image
- Download Hi-res image
- Download (PPT)
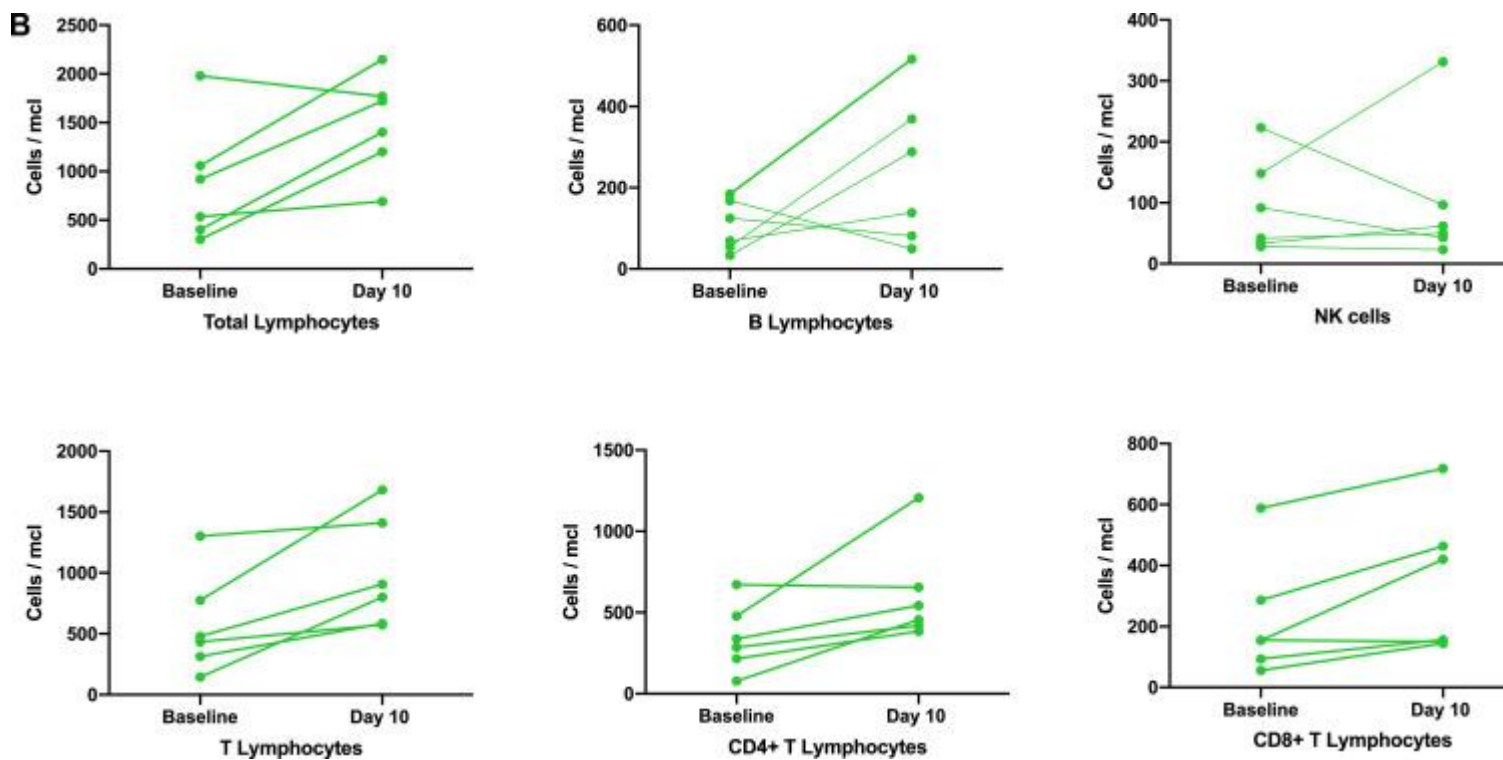
Fig. 3(A) Changes in acute phase reactants and coagulation parameters after AT-MSC therapy.

Show full caption

- View Large Image
- Download Hi-res image
- Download (PPT)

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

,

19

,

20

]. Multiple clinical trials are currently underway with a wide range of drugs (in the https://clinicaltrials.gov/hclinicaltrials.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](#)

,

[44](#)

,

[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 microenvironment [

[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 anakinra 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 anakinra 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 have 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 definite 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"-; EudraCT: 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

Acknowledgement

Appendix. Supplementary materials

- Download .pptx (.04 MB)

  Help with pptx files

- Download .pptx (.04 MB)

  Help with pptx files

References

1. [1].

    o   Guan W.
    o   Ni Z.
    o   Hu Y.
    o   Liang W.
    o   Ou C.
    o   He J.
    o   et al.

    Clinical Characteristics of coronavirus disease 2019 in China.
    N Eng J Med. 2020; **382**: 1708-1720
    [View in Article](#)

    o   [Scopus (2043)](#)
    o   [PubMed](#)
    o   [Crossref](#)
    o   [Google Scholar](#)

2. [2].

    o   Grasselli G.
    o   Zangrillo A.
    o   Zanella A.
    o   Antonelli M.
    o   Cabrini L.
    o   Castelli A.
    o   et al.

    Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy.
    JAMA. 2020; (April 6)https://doi.org/10.1001/jama.2020.5394
    [View in Article](#)

    o   [Scopus (204)](#)
    o   [Crossref](#)
    o   [Google Scholar](#)

3. [3].

    o   Yang X.

- o Yu Y.
- o Xu J.
- o Shu H.
- o Xia J.
- o Liu H.
- o et al.

Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study.
Lancet Respir Med. 2020; (February 24)https://doi.org/10.1016/S2213-2600(20)30079-5
View in Article

- o Scopus (710)
- o Summary
- o Full Text
- o Full Text PDF
- o Google Scholar

4. [4].

- o Bhatraju P.K.
- o Ghassemieh B.J.
- o Nichols M.
- o Kim R.
- o Jerome K.R.
- o Nalla A.K.
- o et al.

Covid-19 in critically Ill patients in the seattle region - case series.
N Engl J Med. 2020; (March 30)https://doi.org/10.1056/NEJMoa2004500
View in Article

- o Scopus (170)
- o PubMed
- o Crossref
- o Google Scholar

5. [5].

- o Wynants L.
- o van Calster B.
- o Bonten M.M.J.
- o Collins G.S.
- o Debray T.P.A.

- o de Vos M.
- o et al.

Prediction models for diagnosis and prognosis of covid-19 infection: systematic review and critical appraisal.
BMJ. 2020; **369**: m1328https://doi.org/10.1136/bmj.m1328
View in Article

- o Scopus (32)
- o PubMed
- o Crossref
- o Google Scholar

6. [6].

- o Ji D.
- o Zhang D.
- o Xu J.
- o Chen Z.
- o Yang T.
- o Zhao P.
- o et al.

Prediction for progression risk in patients with COVID-19 Pneumonia: the CALL Score.
Clin Infect Dis. 2020; **April 9**https://doi.org/10.1093/cid/ciaa414
View in Article

- o Scopus (9)
- o Crossref
- o Google Scholar

7. [7].

- o Du R.-.H.
- o Liang L.-.R.
- o Yang C.-.Q.
- o Wang W.
- o Cao T.-.Z.
- o Li M.
- o et al.

Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study.
Eur Res J. 2020; (April 8)https://doi.org/10.1183/13993003.00524-2020

[View in Article](#)

- [Scopus (31)](#)
- [Crossref](#)
- [Google Scholar](#)

8. [8].

- Abu-Raya B.

Predictors of refractory coronavirus disease (COVID-19) pneumonia.
Clin Infect Dis. 2020; (April 9)https://doi.org/10.1093/cid/ciaa409
[View in Article](#)

- [Scopus (0)](#)
- [Crossref](#)
- [Google Scholar](#)

9. [9].

- Phua J.
- Weng L.
- Ling L.
- Egi M.
- Lim C.-.M.
- Divatia J.V.
- et al.

Intensive care management of coronavirus disease 2019 (COVID-19): challenges and recommendations.
Lancet Respir Med. 2020; **8**: 506-517
[View in Article](#)

- [Scopus (64)](#)
- [PubMed](#)
- [Summary](#)
- [Full Text](#)
- [Full Text PDF](#)
- [Google Scholar](#)

10. [10].

- Tay M.Z.
- Poh C.M.

- o Rénia L.
- o MacAry P.A.
- o Ng L.F.P.

The trinity of COVID-19: immunity, inflammation and intervention.
Nat Rev Immunol. 2020; (April 28)https://doi.org/10.1038/s41577-020-0311-8
View in Article

- o Scopus (50)
- o PubMed
- o Crossref
- o Google Scholar

11. [11].

- o Moore B.J.B.
- o June C.H.

Cytokine release syndrome in severe COVID-19.
Science. 2020; **368**: 473-474
View in Article

- o Scopus (35)
- o PubMed
- o Crossref
- o Google Scholar

12. [12].

- o Shi Y.
- o Wang Y.
- o Shao C.
- o Huang J.
- o Gan J.
- o Huang X.
- o et al.

COVID-19 infection: the perspectives on immune responses.
Cell Death Diff. 2020; **27**: 1451-1454
View in Article

- o Scopus (89)
- o PubMed
- o Crossref

- Google Scholar

13. [13].

- Mehta P.
- McAuley D.F.
- Brown M.
- Sanchez E.
- Tattersall R.S.
- Manson J.J.

COVID-19: consider cytokine storm syndromes and immunosuppression.
Lancet. 2020; **395**: 1033-1034
[View in Article](#)

- [Scopus (571)](#)
- [PubMed](#)
- [Summary](#)
- [Full Text](#)
- [Full Text PDF](#)
- [Google Scholar](#)

14. [14].

- McGonagle D.
- Sharif K.
- O'Regan A.
- Bridgewood C.

Interleukin-6 use in COVID-19 pneumonia related macrophage activation syndrome.
Autoimmun Rev. 2020; (April 3): 2020https://doi.org/10.1016/j.autrev.2020.102537
[View in Article](#)

- [Scopus (75)](#)
- [Crossref](#)
- [Google Scholar](#)

15. [15].

- Ciceri F.
- Beretta L.
- Scandroglio A.M.
- Colombo S.
- Landoni G.

- o Ruggeri A.
- o et al.

Microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS): an atypical acute respiratory distress syndrome working hypothesis.
Crit Care Resusc. 2020; (April 15)
View in Article

- o Google Scholar

16. [16].

- o Zhang L.
- o Yan X.
- o Fan Q.
- o Liu H.
- o Liu X.
- o Liu Z.
- o et al.

D‐dimer levels on admission to predict in‐hospital mortality in patients with Covid‐19.
J Thromb Haemost. 2020; (April 19)https://doi.org/10.1111/jth.14859
View in Article

- o Scopus (21)
- o Crossref
- o Google Scholar

17. [17].

- o Connors J.M.
- o Levy J.H.

COVID-19 and its implications for thrombosis and anticoagulation.
Blood. 2020; (April 27)https://doi.org/10.1182/blood.2020006000
View in Article

- o Scopus (37)
- o Crossref
- o Google Scholar

18. [18].

- o McCreary E.K.

- o Pogue J.M.

  Coronavirus disease 2019 treatment: a review of early and emerging options.
  Open Forum Infect Dis. 2020; **7**: ofaa105https://doi.org/10.1093/ofid/ofaa105
  View in Article

- o Scopus (21)
- o PubMed
- o Crossref
- o Google Scholar

19. [19].

- o Li H.
- o Zhou Y.
- o Zhang M.
- o Wang H.
- o Zhao Q.
- o Liu J.

  Updated approaches against SARS-CoV-2.
  Antimicrob Agents Chemother. 2020; (March 23)https://doi.org/10.1128/aac.00483-20
  View in Article

- o Crossref
- o Google Scholar

20. [20].

- o Barlow A.
- o Landolf K.M.
- o Barlow B.
- o Yeung S.Y.A.
- o Heavner J.J.
- o Claassen C.W.
- o et al.

  Review of Emerging Pharmacotherapy for the Treatment of Coronavirus Disease 2019.
  Pharmacotherapy. 2020; (April 7)https://doi.org/10.1002/phar.2398
  View in Article

- o Scopus (10)
- o PubMed
- o Crossref

o   Google Scholar

21. [21].

o   Leng Z.
o   Zhu R.
o   Hou W.
o   Feng Y.
o   Yang Y.
o   Han Q.
o   et al.

Transplantation of ACE2- mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia.
Aging Dis. 2020; **11**: 216-228
View in Article

o   Scopus (55)
o   PubMed
o   Crossref
o   Google Scholar

22. [22].

o   Khoury M.
o   Cuenca J.
o   Cruz F.F.
o   Figueroa F.E.
o   Rocco P.R.M.
o   Weiss D.J.

Current status of cell-based therapies for respiratory virus infections: applicability to COVID-19.
European Respir J. 2020; (April 7)https://doi.org/10.1183/13993003.00858-2020
View in Article

o   Scopus (7)
o   PubMed
o   Crossref
o   Google Scholar

23. [23].

o   Galipeau J.

- o Sensébé L.
- o Sensebe L.

Mesenchymal Stromal cells: clinical challenges and therapeutic opportunities.
Cell Stem Cell. 2018; **22**: 824-833
View in Article

- o Scopus (242)
- o PubMed
- o Summary
- o Full Text
- o Full Text PDF
- o Google Scholar

24. [24].

- o gentile p.
- o sterodimas a.

Adipose-derived stromal stem cells (ASCs) as a new regenerative immediate therapy combating Coronavirus (COVID-19)-induced pneumonia.
Expert Opin Biol Ther. 2020; (April 29)https://doi.org/10.1080/14712598.2020.1761322
View in Article

- o Scopus (1)
- o Crossref
- o Google Scholar

25. [25].

- o Sánchez-Guijo F.
- o García-Olmo D.
- o Prósper F.
- o Martínez S.
- o Zapata A.
- o Fernández-Avilés F.
- o et al.

Spanish cell therapy network (TerCel): 15 years of successful collaborative translational research.
Cytotherapy. 2020; **22**: 1-5
View in Article

- o Scopus (0)

- o [PubMed](#)
- o [Summary](#)
- o [Full Text](#)
- o [Full Text PDF](#)
- o [Google Scholar](#)

26. [26].

- o Lambden S.
- o Laterre P.F.
- o Levy M.M.
- o Francois B.

The SOFA score - Development, utility and challenges of accurate assessment in clinical trials.
Crit Care. 2019; **23**https://doi.org/10.1186/s13054-019-2663-7
[View in Article](#)

- o [Scopus (3)](#)
- o [PubMed](#)
- o [Crossref](#)
- o [Google Scholar](#)

27. [27].

World Health Organization. World Health Organization and R&D Blueprint strategy for COVID-19 n.d. https://www.who.int/teams/blueprint/covid-19 (Accessed May 2, 2020).

[View in Article](#)

- o [Google Scholar](#)

28. [28].

- o Araña M.
- o Mazo M.
- o Aranda P.
- o Pelacho B.
- o Prosper F.

Adipose tissue-derived mesenchymal stem cells: isolation, expansion, and characterization.
Methods Mol Biol. 2013; **1036**: 47-61
[View in Article](#)

- o [Scopus (37)](#)

- o PubMed
- o Crossref
- o Google Scholar

29. [29].

- o Garcia-Arranz M.
- o Garcia-Olmo D.
- o Herreros M.D.
- o Gracia-Solana J.
- o Guadalajara H.
- o de la Portilla F.
- o et al.

Autologous adipose-derived stem cells for the treatment of complex cryptoglandular perianal fistula: a randomized clinical trial with long-term follow-up.
Stem Cells Transl Med. 2020; **9**: 295-301
View in Article

- o Scopus (0)
- o PubMed
- o Crossref
- o Google Scholar

30. [30].

- o Dominici M.
- o Le B.K.
- o Mueller I.
- o Slaper-Cortenbach I.
- o Marini F.
- o Krause D.
- o et al.

Minimal criteria for defining multipotent mesenchymal stromal cells.
Int Soc Cell Ther Position Stat Cytother. 2006; **8**: 315-317
View in Article

- o Scopus (9172)
- o Google Scholar

31. [31].

- o Sanz-Baro R.

- García-Arranz M.
- Guadalajara H.
- de la Quintana P.
- Herreros M.D.
- García-Olmo D.

First-in-human case study: pregnancy in women with Crohn's perianal fistula treated with adipose-derived stem cells: a safety study.
Stem Cells Transl Med. 2015; **4**: 598-602
View in Article

- Scopus (22)
- PubMed
- Crossref
- Google Scholar

32. [32].

- Le Blanc K.
- Frassoni F.
- Ball L.
- Locatelli F.
- Roelofs H.
- Lewis I.
- et al.

Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study.
Lancet. 2008; **371**: 1579-1586
View in Article

- Scopus (1907)
- PubMed
- Summary
- Full Text
- Full Text PDF
- Google Scholar

33. [33].

- Sánchez-Guijo F.
- Caballero-Velázquez T.
- López-Villar O.
- Redondo A.

- o Parody R.
- o Martínez C.
- o et al.

Sequential third-party mesenchymal stromal cell therapy for refractory acute graft-versus-host disease.
Biol Blood Marrow Transpl. 2014; **20**: 1580-1585
View in Article

- o Scopus (59)
- o PubMed
- o Summary
- o Full Text
- o Full Text PDF
- o Google Scholar

34. [34].

- o Wong H.Y.F.
- o Lam H.Y.S.
- o Fong A.H.T.
- o Leung S.T.
- o Chin T.W.Y.
- o Lo C.S.Y.
- o et al.

Frequency and distribution of chest radiographic findings in COVID-19 positive patients.
Radiology. 2020; (March 27)201160https://doi.org/10.1148/radiol.2020201160
View in Article

- o Scopus (65)
- o Crossref
- o Google Scholar

35. [35].

- o Kalil A.C.

Treating COVID-19 - off-label drug use, compassionate use, and randomized clinical trials during pandemics.
JAMA. 2020; (March 24)https://doi.org/10.1001/jama.2020.4742
View in Article

- o Scopus (47)

- o [Crossref](#)
- o [Google Scholar](#)

36. [36].

- o Grasselli G.
- o Zangrillo A.
- o Zanella A.
- o Antonelli M.
- o Cabrini L.
- o Castelli A.
- o et al.

Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy.
JAMA. 2020;https://doi.org/10.1001/jama.2020.5394
[View in Article](#)

- o [Scopus (231)](#)
- o [Crossref](#)
- o [Google Scholar](#)

37. [37].

- o Zangrillo A.
- o Beretta L.
- o Scandroglio A.M.
- o Monti G.
- o Fominskiy E.
- o Colombo S.
- o et al.

Characteristics, treatment, outcomes and cause of death of invasively ventilated patients with COVID-19 ARDS in Milan, Italy.
Crit Care Resusc. 2020; (April 23)
[View in Article](#)

- o [Google Scholar](#)

38. [38].

- o Lalu M.M.
- o McIntyre L.
- o Pugliese C.

- o Fergusson D.
- o Winston B.W.
- o Marshall J.C.
- o et al.

Safety of cell therapy with mesenchymal stromal cells (SafeCell): a systematic review and meta-analysis of clinical trials.
PLoS ONE. 2012; **7**: e47559
View in Article

- o Scopus (538)
- o PubMed
- o Crossref
- o Google Scholar

39. [39].

- o Thompson M.
- o Mei S.H.J.
- o Wolfe D.
- o Champagne J.
- o Fergusson D.
- o Stewart D.J.
- o et al.

Cell therapy with intravascular administration of mesenchymal stromal cells continues to appear safe: an updated systematic review and meta-analysis.
EClinicalMedicine. 2020; **19**199249
View in Article

- o Scopus (2)
- o Summary
- o Full Text
- o Full Text PDF
- o Google Scholar

40. [40].

- o Yen B.L.
- o Yen M.
- o Wang L.
- o Liu K.
- o Sytwu H.

Current status of mesenchymal stem cell therapy for immune/inflammatory lung disorders: gleaning insights for possible use in COVID‑19.

Stem Cells Transl Med. 2020; (June 11)https://doi.org/10.1002/sctm.20-0186

View in Article

- Scopus (0)
- Crossref
- Google Scholar

41. [41].

- Du J.
- Li H.
- Lian J.
- Zhu X.
- Qiao L.
- Lin J.

Stem cell therapy: a potential approach for treatment of influenza virus and coronavirus-induced acute lung injury.

Stem Cell Res Ther. 2020; **11**: 192

View in Article

- Scopus (0)
- PubMed
- Crossref
- Google Scholar

42. [42].

- Chen J.
- Hu C.
- Chen L.
- Tang L.
- Zhu Y.
- Xu X.
- et al.

Clinical study of mesenchymal stem cell treatment for acute respiratory distress syndrome induced by epidemic influenza A (H7N9) infection: a hint for COVID-19 treatment.

Engineering (Beijing). 2020; (February 28)https://doi.org/10.1016/j.eng.2020.02.006

View in Article

- Scopus (15)

o   Crossref
o   Google Scholar

43. [43].

o   Rawson T.M.
o   Moore L.S.
o   Zhu N.
o   Ranganathan N.
o   Skolimowska K.
o   Gilchrist M.
o   et al.

Bacterial and fungal co-infection in individuals with coronavirus: a rapid review to support COVID-19 antimicrobial prescribing.
Clin Infect Dis. 2020; (May 2)https://doi.org/10.1093/cid/ciaa530
View in Article

o   Crossref
o   Google Scholar

44. [44].

o   François B.
o   Laterre P.-.F.
o   Luyt C.-.E.
o   Chastre J.

The challenge of ventilator-associated pneumonia diagnosis in COVID-19 patients.
Crit Care. 2020; **24**: 289
View in Article

o   Scopus (0)
o   PubMed
o   Crossref
o   Google Scholar

45. [45].

o   Rawson T.M.
o   Ming D.
o   Ahmad R.
o   Moore L.S.P.
o   Holmes A.H.

Antimicrobial use, drug-resistant infections and COVID-19.
Nat Rev Microbiol. 2020; (June 2)https://doi.org/10.1038/s41579-020-0395-y
View in Article

- Scopus (0)
- PubMed
- Crossref
- Google Scholar

46. [46].

- Maes B.
- Bosteels C.
- de Leeuw E.
- Declercq J.
- van Damme K.
- Delporte A.
- et al.

Treatment of severely ill COVID-19 patients with anti-interleukin drugs (COV-AID): a structured summary of a study protocol for a randomised controlled trial.
Trials. 2020; **21**: 468
View in Article

- Scopus (0)
- PubMed
- Crossref
- Google Scholar

47. [47].

- Golchin A.
- Seyedjafari E.
- Ardeshirylajimi A.

Mesenchymal Stem Cell Therapy for COVID-19: present or Future.
Stem Cell Rev Rep. 2020; (April 13)https://doi.org/10.1007/s12015-020-09973-w
View in Article

- Scopus (10)
- PubMed
- Crossref
- Google Scholar

48. [48].

- o Atluri S.
- o Manchikanti L.
- o Hirsch J.A.

Expanded umbilical cord mesenchymal stem cells (UC-MSCs) as a therapeutic strategy in managing critically Ill COVID-19 patients: the case for compassionate use.
Pain Phys. 2020; **23**: E71-E83
View in Article

- o PubMed
- o Google Scholar

49. [49].

- o Cardenes N.
- o Aranda-Valderrama P.
- o Carney J.P.
- o Sellares Torres J.
- o Alvarez D.
- o Kocydirim E.
- o et al.

Cell therapy for ARDS: efficacy of endobronchial versus intravenous administration and biodistribution of MAPCs in a large animal model.
BMJ Open Respir Res. 2019; **6**https://doi.org/10.1136/bmjresp-2018-000308
View in Article

- o Scopus (3)
- o PubMed
- o Crossref
- o Google Scholar

50. [50].

- o Thachil J.
- o Tang N.
- o Gando S.
- o Falanga A.
- o Cattaneo M.
- o Levi M.
- o et al.

ISTH interim guidance on recognition and management of coagulopathy in COVID-19.
J Thromb Haemost. 2020; (March 25)https://doi.org/10.1111/jth.14810
View in Article

- o Scopus (74)
- o Crossref
- o Google Scholar

51. [51].

- o Oja S.
- o Kaartinen T.
- o Ahti M.
- o Korhonen M.
- o Laitinen A.
- o Nystedt J.

The utilization of freezing steps in mesenchymal stromal cell (MSC) manufacturing: potential impact on quality and cell functionality attributes.
Front Immunol. 2019; **10**https://doi.org/10.3389/fimmu.2019.01627
View in Article

- o Scopus (2)
- o PubMed
- o Crossref
- o Google Scholar

52. [52].

- o Moll G.
- o Geißler S.
- o Catar R.
- o Ignatowicz L.
- o Hoogduijn M.J.
- o Strunk D.
- o et al.

Cryopreserved or fresh mesenchymal stromal cells: only a matter of taste or key to unleash the full clinical potential of MSC therapy?.
Adv Exp Med Biol. 2016; **951**: 77-98
View in Article

- o Scopus (32)
- o PubMed

- o Crossref
- o Google Scholar

53. [53].

- o Oldenburg C.E.
- o Doan T.

Rigorous randomized controlled trial implementation in the era of novel coronavirus disease (COVID-19).
Am J Trop Med Hyg. 2020; (April 15)
https://doi.org/10.4269/ajtmh.20-0262
View in Article

- o Scopus (0)
- o Crossref
- o Google Scholar

Article Info

Publication History

Identification

Copyright
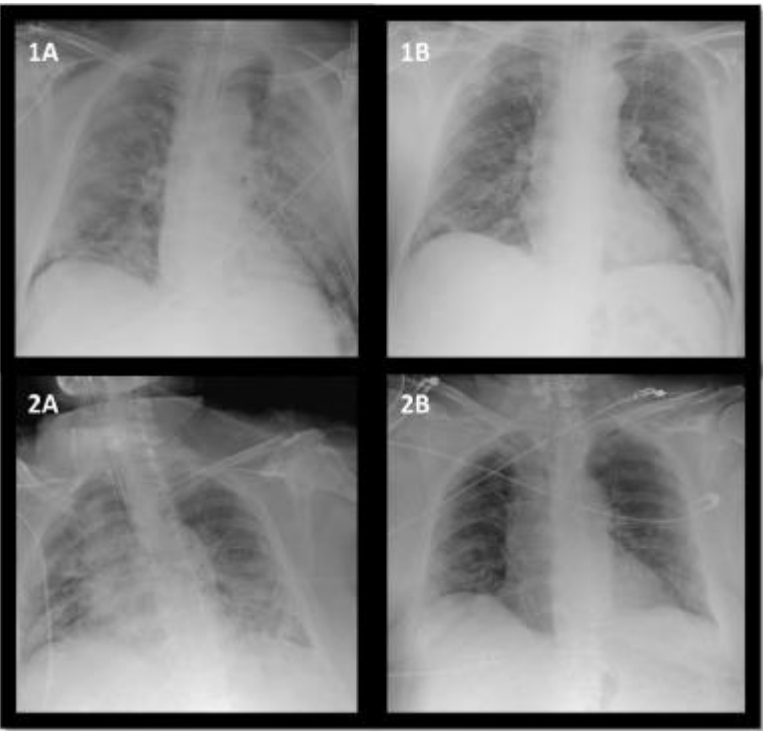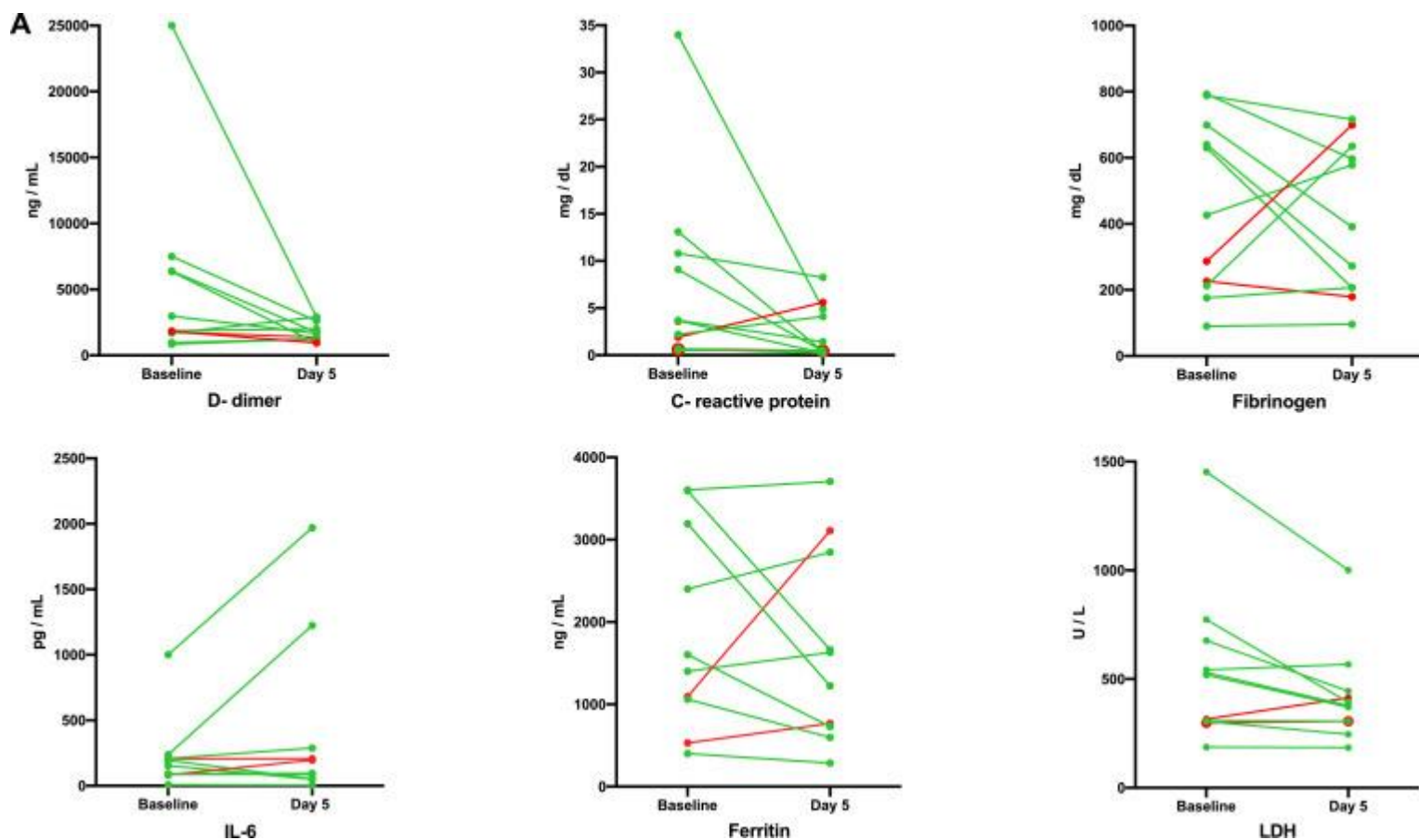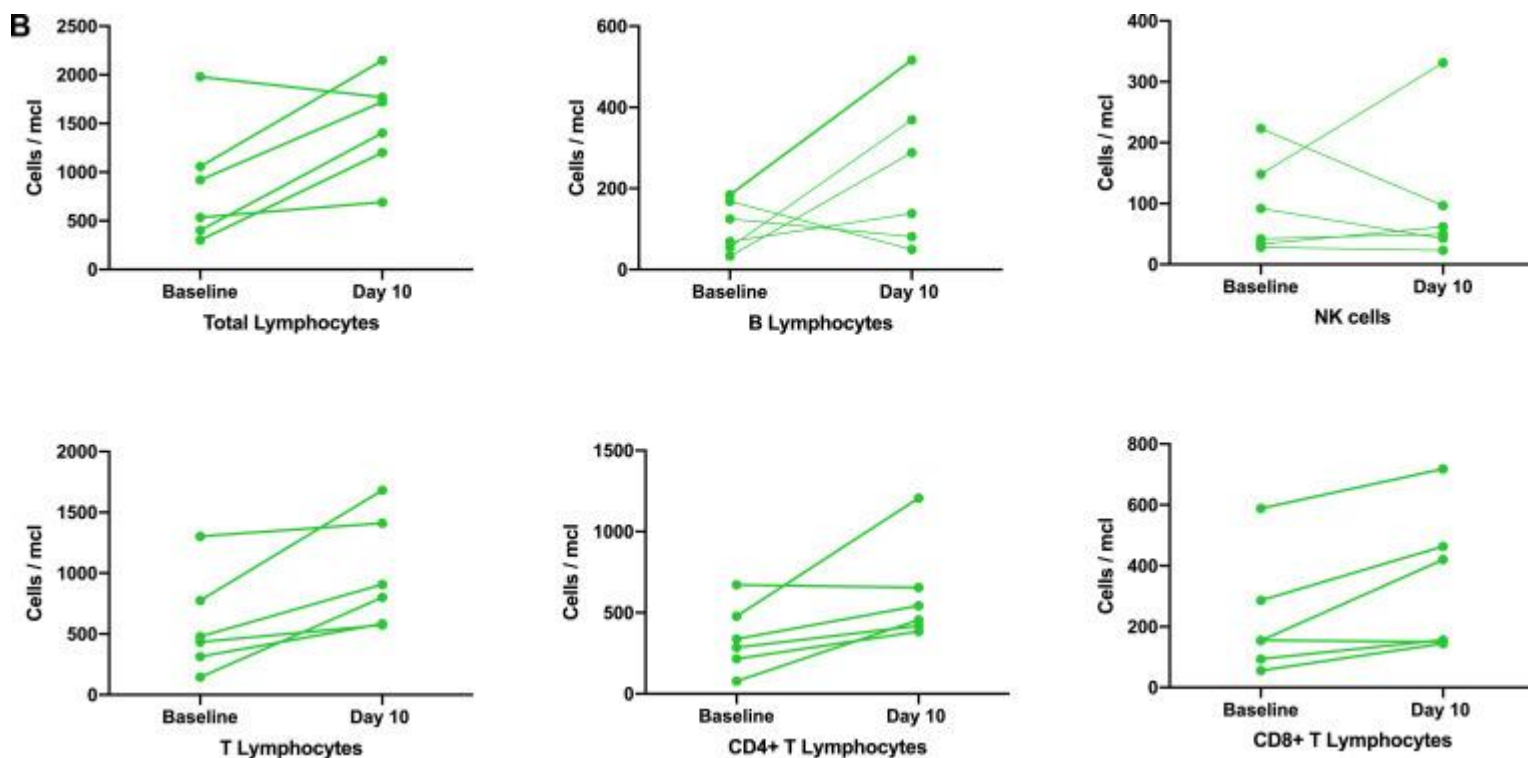
User License

ScienceDirect

Figures
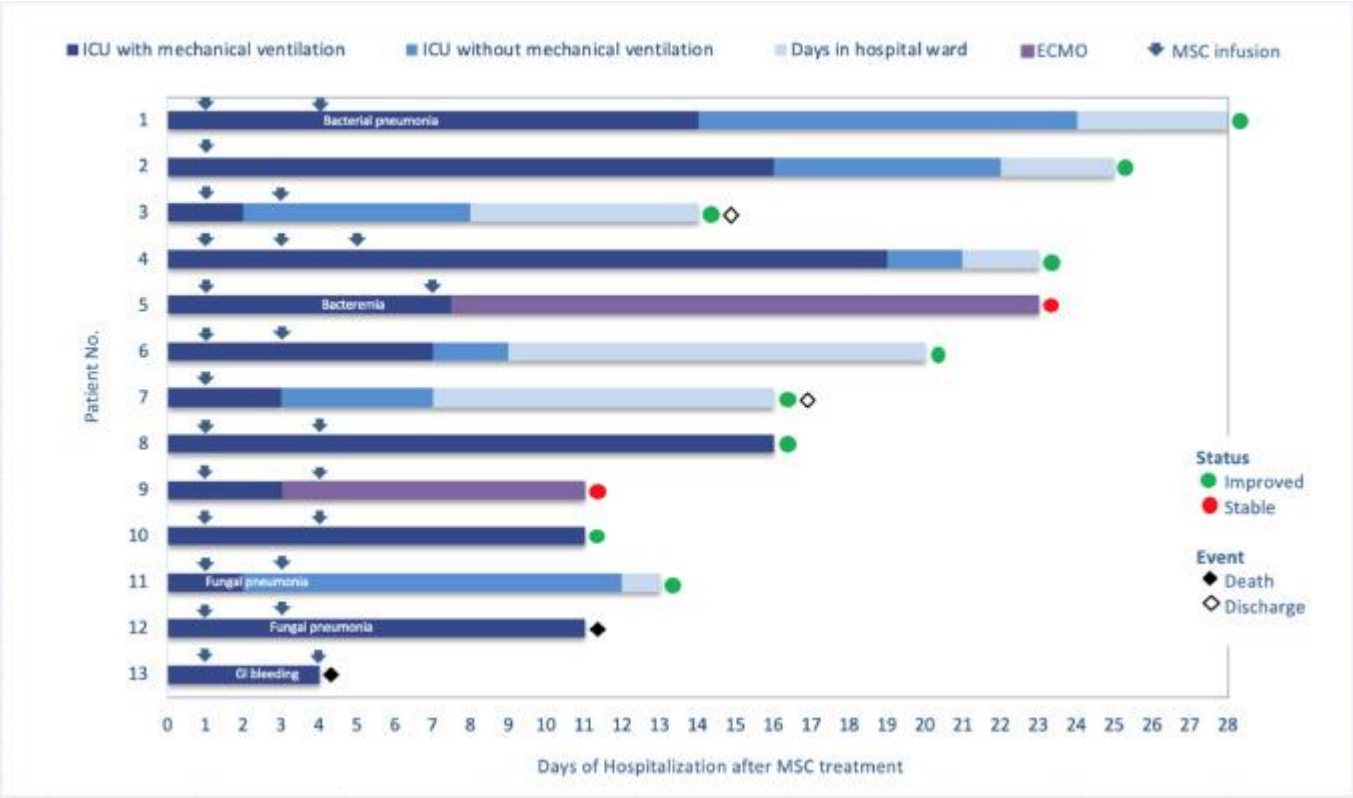
Fig. 1 Patient disposition and outcome.

Fig. 2 Chest X-ray changes of two representative patients improving after AT-MSC administration.

Fig. 3(A) Changes in acute phase reactants and coagulation parameters after AT-MSC therapy.

Fig. 3(A) Changes in acute phase reactants and coagulation parameters after AT-MSC therapy.

Tables

- **Table 1**Patient baseline characteristics and treatments.

Related Hub

COVID-19 Resource Centre

Access the latest 2019 novel coronavirus disease (COVID-19) content from across *The Lancet* journals as it is published.