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Original Research Paper

Stem cell therapy in COVID: is it safe?

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ABSTRACT:
Mesenchymal stem cells (MSC) have emerged as a promising therapy for various conditions including neurologic, cardiovascular, autoimmune and musculoskeletal diseases due to their immuno modulatory and regenerative effects. SARS-CoV- 2 severe infection has been associated with a cytokine storm leading to multiple clinical manifestations including Acute Respiratory Distress Syndrome (ARDS) and sepsis. Due to a global lack of specific therapy for the virus and its complications, several strategies have been used to try to limit disease severity and hospital length of stay. Among these strategies, MSC have shown good results in phase I clinical trials, rising hope for physicians and patients around the world. Given this is a novel therapy, safety concerns about acute and long-term side effects limit their widespread use. Taking into account the everyday growing evidence of MSC therapy, a narrative review of its safety was conducted and discussion was made about current and possible future directions in MSC therapy and research.

Keywords: COVID 19, coronavirus, stem cells, regenerative medicine.

INTRODUCTION:

COVID-19 SUMMARY The emergence of SARS-CoV 2, COVID 19 etiologic agent, has become a worldwide challenge since pandemic declaratory (1). According to the World Health Organization, for June the 7th of 2020, 6'912.751 people had been diagnosed around the world, with 400.469 deaths and 216 countries affected (2). Recent estimates show that each infected person may infect other 2.2 people, with case duplication rates of approximately 7 days (3). SARS-CoV-2 belongs to *Corona viridae* family and Betacoronavirus genus. It is a single stranded positive sense RNA virus with a spiked envelop projecting in the viral surface (4) that mediate virus entry into the cell via the Angiotensin Converter Enzyme receptor 2 (ACE 2). Its main tropism is for type 2 pneumocytes and ciliated cells (5), but extrapulmonary manifestations such as diarrhea, lymphopenia and hepatic failure suggest tropism for non-pulmonary tissues with ECA 2 receptor expression(6).

The vast majority of cases are asymptomatic or have only mild presentations, but between16-17% of patients may progress to severe disease with pneumonia, ARDS or sepsis(7,8). Suggested mechanism involves a cytokine storm of factors such as interleukin (IL)-1, IL-6, IL-8 or Tumoral necrosis factorα (TNF- α)(9,10). In patients requiring Intensive Care Unit admission, elevations of IL-2, IL-7, granulocyte colony stimulating factor, interferon gamma induced protein 10, monocyte chemotactic protein (MCP) 1, MCP1α, TNFαand D dimer have been identified (11,12). Pediatric population tends to have milder symptoms. Ludvigsson(13), reported that almost 90% children had asymptomatic or non-severe illness, 5.2% had severe infection and only 0.6% had critical disease.

POTENTIAL TREATMENTS UNDER INVESTIGATION:

To date there is no specific treatment. Antimalarial medication emerged as a possible therapeutic strategy(4,14) but lack of efficacy and safety concerns have been recently reported(15–17). Remdesivir has shown promising results. Preliminary cohort reports have found that 68% of patients showed improvements in ventilatory parameters, including extubation in 17

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out of 30 patients(18). Another randomized clinical trial report preliminary faster recovery (11 vs. 15 days), with no impact neither mortality yet, but with a clear trend(19). Interferons (mainlyβ y γ) have been studied, but their use is limited by their adverse reactions profile(20). Recently, the Food and Drug Administration (FDA), approved convalescent plasma therapy in critically ill patients under clinical trials, given the lack of an effective treatment to date(21).

WHY MSC In this context, experimental therapies such as Mesenchymal Stem Cells (MSC) have been used in critically ill patients (22)due to their immuno modulatory activity, as it has been shown that they are capable of releasing a great variety for growth factors such as hepatocyte, epidermic, platelet and transforming growth factorβ. Under inflammatory stimuli, they are also capable of enhancing their intrinsically present immuno modulatory and anti-inflammatory effects, including indoleamine dioxygenase (IDO) activity, and synthesis of prostaglandin E2 (PGE2) and interleukin 10 (IL-10) among other factors (23,24) that may contribute to decrease inflammatory response and repair damaged tissue (25–27). For this reason, some authors have suggested its compassionate use in these patients (28).

CELL THERAPY EFFICACY IN ARDS IS STILL CONTROVERSIAL:

Despite promising results in several conditions, MSC therapy for ARDS has yet to show clinical efficacy. In a study including 9 ARDS patients treated with umbilical cord MSC, mortality rate was 33.3%, but no infusion related adverse events (AE) were identified. Cytokine profile improved in these patients (29). Zheng et al. and Matthay et al. had similar results with 12 and 60 patients treated with adipose derived and bone marrow MSC respectively, with improved inflammatory parameters, but no clinical correlation. No serious AE were reported in these studies (30,31).

MOTIVATION TO USE MSC Given their potential use, a safety review of the MSC therapy was made to provide evidence in different conditions, including SARS-CoV-2 sequelae.

METHODS:

MSC-based IV therapy: Safety analysis

A narrative literature review was made that included systemic (intravenous or intra arterial) administration and conditions to determine safety of MSC application in adult humans. Efficacy endpoints were excluded as they were beyond review objectives. Systematic reviews and meta-analysis were taken into account. These should include clinical trials in adults, both genderswith any condition and in which MSC therapy was the intervention, no matter the administration way. Primary and secondary outcomes must include adverse and severe adverse events reports. Language was limited to English and Spanish and only full texts were included.

Study selection:

At first, title exclusion was made. Abstracts and full text were then reviewed to check for inclusion criteria. Main Mesh search terms were:(Safety [Title/Abstract]) AND Mesenchymal Stem Cells [Title/Abstract] OR Adult Stem Cells. Filters: Meta Analysis; Systematic Reviews; Humans; Adult: 19+ years.

RESULTS:

50 citations were identified. After excluding for different topics or inclusion criteria, 20 papers were left, of which 9 complied with all criteria. Included meta-analysis are summarized in table 1.

Table 1. Systematic review and meta-analysis summary in safety of cellular therapy.

Author, country, publication date.	Condition.	n studies/ participants	Administration route/MSC source	Safety outcome	Conclusion
Lalu(32) , Canada, 2.012.	Stroke, Crohn's disease, myocardial infarction, graft versus host disease and healthy volunteers.	36studies/ 1.012participants	Intravenous or intra arterial application.	Studies showed relation between fever and MSC therapy (MD 16.82 CI 95% 5.33-23.10) but not in other Adverse events (AE) including acute infusional toxicity, infections, death, tumor-malignancy, cardiac, renal and gastric dysfunction.	There were no differences in adverse events between groups, results should provide some assurance to researchers that this therapy

					appears safe.
Kim (33), Korea, 2.015.	Cirrhosis	14 studies/ 448 participants	Autologous MSC, 8 peripheralapplication, 3 intrasplenic, 2 hepaticarteries y 1 portal vein.	No study reported severe AEs, nor statistically significant difference in adverse events reports among groups.	According to these results, MSC are considered safe for chronic cirrhosis.
El-Badawy(34), Egypt, 2.016	Type 1 and 2 Diabetes Mellitus.	22 studies/ 524 participants	6 studies used hematopoietic stem cells, 5 used bone marrow mononuclear stemcells, 5 used umbilical cord blood MSC, 2 used UCMSC, 2 used a combination of stem cells, 1 used BMMSC and 1 used placental MSC. 14 used IV adminsitration.	Only 21.72% of patients reported AEs, and no death occurred during follow ups.	Compared to whole organ or islet transplantation, MSC therapy appears to be safe and effective for type 1 and 2 diabetes mellitus patients.
Lalu (35), Canada, 2.018.	Acute myocardial infarction (AMI)and ischemic heart failure (IHF).	23 studies: 11 AMI: 470 participants, 12 IHF: 639participants	7 out 11 AMI studies used autologous MSC, 7, and 9 out of the 12 IHF studies also did. 18 studies used BM-MSC, 4 used umbilical cord	Acute (<24 hours) cardiac AEs were similar between groups(OR 3,20, CI 95% 0,70– 14,61). 3 MSC treated patients presented rhythm abnormalities, 2 AMI, 1 vessel obstruction during procedure and 1 pericardial effusion. Late onset AEs included fever, respiratory tract infections,	There was no association with acute EAs. Results support MSC therapy safety in AMI and IHF.

			MSC (UC-MSC) and 1 used AD-MSC. 12 studies used intracoronary administration, 3 intravenous and 4 intramyocardic. 2 used endocardic administration and other 2 used epicardic.	hematologic, cardiac, gastrointestinal, and neurologic AEs, with only neurologic ones presenting statistical significance compared to controls (OR 3,79, CI 95% 1,26–11,41). No details were provided. Late AEs related to therapy were infrequent.	
Lalu (36), Canada, 2.019.	Cerebro-Vascular disease.	10 studies/ 339 participants	IV in 7 studies, intracerebral in 2and intra-arterial in 1. 5 used autologous MSC, 4 allogenic, 1 not reported. 7 studies used BM-MSC, 2 used UC-MSC and 1 did not report source.	MSC treated patient had lower mortality risk compared to controls (Peto OR 0,43; CI 95%: 0,20-0,90). Only fever was associated with MSC therapy (OR 6,88; CI 95% 2,48–19,08). No differences were found in other AEs.	Authors conclude MSC therapy appears to be safe, without increasing AEs other than fever.
Xu(37), China, 2.019.	Spinal cord injury.	11 studies, 449 participants .	Intravenous and subarachnoid. Three studies used MSC and other three used chondrocytes. 5 used expanded cells and the other one was unexpanded.	Results showed MSC treated patients had more infusion toxicity than control (RR: 20,34; CI del 95%: 8,09-51,18, P <0,001). Main EAs were fever, headache, back pain, tringling, abdominal distension, that resolved without treatment.There were no severe AEs.	Treatment proved safe and effective to improve sensitivity and bladder function. Main AEs were mild and related to spinal tap. No severe AEs were observed,

					favoring safety.
Jayaraj(38), USA, 2.019.	Advanced heart failure.	6 studies, 569 participants.	Intravenous, intracoronary, intramyocardic, transendocardic. Main sources were BM-MSC and UC-MSCS. Some studies just specified "human".	There were no differences in mortality risk between groups(OR 0,97 CI 95% 0,52-1,78). The majority of studies did not report EAs during application. Authors highlight that heterogeneity could not be assessed due to low of studies.	Authors conclude MSC therapy appears safe as there was no difference in mortality and no severe Aes were reported.
Sang(39), China, 2.018.	Cirrhosis.	14 RCTs, 717 participants.	8 studies used IV route, 5 used hepatic artery y 1 did not specify.	4 studies did not describe AEs. The others reported just fever for MSC therapy, that subsided naturally in 24 hours.	MSC therapy appears to be safe as no deaths no serious Aes were reported in studies.
Thompson (40), Canada, 2.020.	Cardiac, neurologic, liver, respiratory, renal and hematologic diseases.	47studies, 2.696 participants.	Intravascular (arterial or venous). 31 used BMMSC, 16 used UCMSC, 4 used ADMSC, 2 used placenta derived MSC and 2 had unclear source.	Only fever was associated with therapy (RR 2.48 CI 95% 1.27-4.86). Infection, thrombotic/embolic events and malignancy were no different among groups. Death appeared to be inferior in MSC treated group (RR 0.78 CI 0.65-0.94).	With this updated review, the only associated EA is fever. No other serius Aes appear to be related.

DISCUSSION:

Increasing amount of evidence is emerging to back up MSC therapy safety in a wide variety of conditions, not finding serious AE related to systemic infusion. Concerning COVID 19, there is still a paucity of evidence but some case reports and preliminary data from clinical trials have emerged, showing experimental efficacy and safety in these population.

MSC evidence in COVID 19:

The first published paper was by Liang et al. with a case report of a 65yearold critically ill female patient with no previous response to standard treatment and multiorgan compromise. Patient received 3 intravenous infusions of $5x10^7$ cells and, and after the second dose, C reactive protein, lymphopenia, neutropenia and computed tomography showed improvements (41). Preliminary reports from a Chinese clinical trial (ChiCTR2000029990) showed that all 7 patients treated with MSC ($1x10^6$cells per kilogram of body weight) improved between 1 and 4 days after receiving therapy and 3 were discharged. Additionally, authors reported no ACE 2 receptor expression by MSC, suggesting that they are not-susceptible to SARS-CoV-2 infection. The same trial reported decrease in proinflammatory cytokines such as TNFα whereas anti inflammatory interleukin 10 increased (42). A Spanish proof of concept study reported results of 13 COVID 19 patients with mechanical ventilation and no response to previous treatment (including antivirals,

steroids, tocilizumab) showing no treatment related adverse events and clinical improvements in 70% of patients after the first dose (43). No author reported treatment related adverse events. Sample sizes are still small to accurately inform about MSC safety profile, but preliminary data is encouraging in both safety and efficacy in this population. As showed by Zhao et al., MSC therapy in pulmonary diseases also appears to be safe (44), thus encouraging its use as research product.

Systematic review and meta-analysis evidence discussion, Related to cell harvesting, studies show autologous source may produce pain and slightly increase infection risk. In this context, sources as placenta or umbilical cord may have advantages as they are usually discard tissues posing no risks for the patient(45). MSC may be applied locally or systemically, with different expected adverse reactions. When applied systemically, meta analysis shows no increased risk of severe AE, with just mild symptoms as fever arising from therapy and, in general, being the only statistically significant associated AE. Authors agree that therapy is in general safe. This conclusion is similar to that of Betemanet al. (46)in their MSC safety review. It is important to highlight that heterogeneity continues to be a main issue, and strategies such as longer follow up periods and AE standardized reports should be adopted. Some case reports have described worsening of visual impairment in advanced macular degeneration(47)and myocardial calcification injuries after MSC use (48).These infrequent reactions need to be assessed with larger samples that allow identification of uncommon manifestations.

Regarding late AEs and malignancy risk, most of the studies report follow ups of 3 years or less, without reporting tumor formation. Fehringeret al. published reports from a cohort with a follow up of de 12,5 years without finding increased risk of tumor formation after receiving MSC therapy(49). Nevertheless, as recommended Volare Vic et al. in their review,it is important to keep reporting long term follow up data to confirm these findings(50).

CONCLUSION:

Based on evidence reported in systematic reviews, meta-analysis and clinical trials including systemic or locally applied MSC, this therapy appears to be safe in different conditions and situations and could prove a useful strategy for COVID 19 patients given their immuno modulatory properties. While more data is necessary to accurately define safety in this condition, future clinical trials (56 clinical trials were registered in clinicaltrials.gov under COVID and "*mesenchymal"* terms as of the writing date of this review) will contribute valuable safety and efficacy information for these patients.

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