Dear Reviewer 1 (05220432)

Thank you for your comments that you performed to our submitted manuscript to World Journal of Stem Cells.

We have performed the revisions to our manuscript, and a new version of it is provided. All performed changes are represented as highlight text in the manuscript.

Below you will find our responses to your comments.

Comments about review

"Mesenchymal Stromal Cells as potential immunomodulatory players in severe acute respiratory distress syndrome induced by SARS-CoV-2 infection"

It is good review however needs further work to advance the field appropriately.

This review links the possibility of using Mesenchymal Stromal Cells for coronavirus.

Could be improved further by focusing the association of MSC and coronavirus. The author claims that MSCs should be used as potential therapeutic agents in patients suffering from COVID-19.

1) **Could you please elaborate which stage of COVID-19, and what are your recommendation for high titer of virus.**

Author response

Until now there is no specific time point for the MSCs administration in COVID-19 patients. In some clinical trials, the administration of MSCs is performed at 0, 2, 6, 10, 14 weeks. Whereas in the study of Leng et al (Transplantation of ACE2-Mesenchymal Stem Cells Improves the Outcome of Patients with COVID-19 Pneumonia), the MSCs were administrated in severe and critically severe conditioned COVID-19 patients. The specific time point where MSCs should be administrated is of paramount importance in order to act in a beneficial way for the patient condition. Indeed, in severe and critically severe conditioned patients, where clinical manifestations are existed (e.g. severe clinical manifestations include fever, respiratory distress -RR $\geq$ 30/ min, low oxygen saturation - $\leq$ 93% at rest state, low arterial partial pressure of oxygen (PaO2)/ fraction of inspiration O2 - FiO2 $\leq$ 300 mn Hg, while respiratory failure- connection of patients to ECMO, shock and organ failure). Alongside with the above manifestations, the virus load should be higher in those patients, leading to increased replication cycle and increased alveolar endothelium damage. The exact pathogenetic mechanism has been explained in detail in the section titled Immune System and COVID-19 (pages 6-8), leading to tremendous cytokine production and severe manifestations. Despite the high cytokine levels, MSCs seems to exert their immunoregulatory role and suppress the induced cytokine storm, as shown in the study of Leng et al. Moreover, MSCs in order to exert their immunoreulatory properties, initially must be activated by IFN-γ or TNF-α, as has been shown by others. At the disease initiation, the SARS-CoV-2 is not characterized by high virus load (now is starting to replicate), in this way has not induced severe damage to alveolar epithelium. So no high content of inflammatory cytokines are produced. On the other

hand, upon high virus load, the alveolar epithelium has been severe damaged, initiating specific immune responses towards cytokines production from damaged cells. This in turn could lead to overactivation of imuune system, resulting to the "cytokine storm" effect. The increased levels of proinflammatory cytokines (especially, IL-6, IFN-γ, IL-1, TNF- α) efficiently activates the MSCs, and thus cell-cell contact or via the production of soluble factors can efficiently regulate the overactivated immune system and downregulate the "cytokine storm".

Also, there is a number of clinical trials where MSCs are administrated at disease onset, in order to evaluate if they have any prophylactic potential against SARS-CoV-2. More research is required in this field in order to have safe conclusions regarding the immunoregulatory potential of MSCs.

The following sentences were added to the manuscript.

MSCs and COVID-19 pages 20-21:

"Another important issue, that should be mentioned is the time point of MSCs administration to COVID-19 patients. The exact time point for MSCs administration, varies among the studies. In a number of clinical trials, the MSCs are infused at specific time points (0, 2, 6, 10, 14 weeks) after the disease oncet. In other studies, MSCs are infused in severe conditioned COVID-19 patients as a co-therapy alongside with their primary therapeutic protocol. Severe COVID-19 condition is established through the determination of specific clinical manifestations. Specifically, severe clinical manifestations include fever, respiratory distress (RR ≥ 30/ min), low oxygen saturation (≤ 93% at rest state), low arterial partial pressure of oxygen (PaO2)/ fraction of inspiration O2 (FiO2) ≤ 300 mn Hg, while respiratory failure (connection of patients to ECMO), shock and organ failure are compromising the critically severe manifestations. The cytokine levels of IL-2, IL-6, IL-7, GSCF, IP10, MCP1, MIP1A, and TNF-α are also determined and mostly found to be elevated when patients are suffering from the severe manifestations and crtically severe manifestations. MSCs can exert their immunoregulatory properties upon activation by inflammatory cytokines including IL-1, IL-6, IFN-γ and TNF-α. At disease oncet, patients are not characterized by increased alveolar epithelium damage, due to the low virus replication. On the other hand, and when high virus load is existed, this in turn leads to severe alveolar epithelium damage, occurring the production of inflammatory cytokines and the initiation of "cytokine storm". MSCs can now be activated (by inflammatory cytokines), which can lead immunoregulation of overactivated immune system. Besides, these facts, MSCs could also have prophylactic effect and this could be the primary reason for their use at disease oncet. Taking into consideration the above data, the specific time point for the administration of MSCs should be established, leading to patients' condition improvement."

Concluding Remarks pages 27:

"The exact time point of MSCs administration should be established in order to have the best outcome to patients' condition. In literature, it has been shown the beneficial effect of MSCs in suppressing the overactivated immune system of severe and critically severe patients, while at the same time MSCs may also poses a prophylactic effect upon used at disease oncet.."

2) **How many MSC should be needed.**

Author Response

The amount of MSCs that should be administrated according to the current protocols are 1 x 10^6 / kg weight. However, higher MSCs doses have been applied in several clinical trials. Specifically, in the study of Matthay et al 10 x 10^6 MSCs / kg were intravenously infused in patients with ARDS, and the overall treatment was well tolerated and safe. Recently, there is a number of clinical trials focused in COVID-19, that are suggesting the infusion of 100 x 10^6 MSCs / dose at disease onset, and at specific time points. Also, we must have in mind that after MSCs infusion, over 60% are cleared, and only a small percentage of MSCs are engrafted (for a short time period), activated and exerted the key immunoregulatory properties. From previous studies, it has been shown that the allogeneically infused MSCs are safe and well tolerate by the recipient. Indeed, in a phase I clinical trial performed by Iacobaeus et al in patients with multiple sclerosis, it was shown that the infused MSCs were not permanently engrafted and finally were cleared from circulation through the secondary lymphoid organs. No clot formation or capillary vessel thrombosis in the lungs were reported. To conclude the intravenously infusion of 1 x 10^6 – 10 x 10^6 / kg weight or 100 x 10^6 / dose will be feasible, without causing any issue to the recipient.

The above data are well documented in the main manuscript in the following section

MSCs and COVID-19 page 20 “The MSCs were administrated in a number of 1 x 106 cells/kg with an infusion rate of 40 drops/ minute.”

MSCs and COVID-19 Page 22 “The safe and tolerability of allogeneically infused MSCs have been reported in the past. There was evidence that intravenously infused MSCs could be accumulated in capillary vessels of lungs, thus raising the possibility of pulmonary embolism performance. In a phase I clinical trial performed by Iacobaeus et al reported that no long-term engraftment of MSCs has been performed in patients with MS [110]. MSCs were further cleared from the circulation through the secondary lymphoid organs[110]. In another phase I clinical trial performed for the treatment of ARDS, allogeneic BM-MSCs were well tolerated by the patients and no infusion or treatment related adverse events were reported[111]. Moreover, in the study of Matthay et al. reported that intravenous injection of MSCs in a number of 10 x 106 cells/ kg was safe in patients with moderate ARDS[112]. In both studies, after MSCs infusion the levels of IL-6, IL-8 and the in-hospital mortality of patients were critically decreased, promoting even more the therapeutic potential of MSCs.”

3) **Is there any advantage of using one source of MSC over the other such as using bone marrow MSC over umbilical cord MSC**

Author response

Typically, MSCs from different sources are characterized by a few differences regarding their functional role, regenerative and immunoregulatory properties. BM-MSCs are the most common source for MSCs isolation that can be used in various therapeutic approaches, mostly in autologous way. BM-MSCs represent 0.01-0.001% of the total nucleated cells in the BM. Additionally, adipose tissue is a rich source of

MSCs, and the AT-MSCs are currently be used in various regenerative medicine applications. Both sources require invasive procedures to isolate the MSCs. On the other hand, WJ-MSCs can be isolated in non-invasive procedure from the discarded umbilical cord after the gestation. There are numerous clinical trials, where the WJ-MSCs are applied. WJ-MSCs fulfill the minimum criteria of ISCT, and under specific conditions may have improved differentiation / regenerative and immunoregulatory properties. In addition WJ-MSCs are originated from the umbilical cord which is an extraembryonic fetal tissue. In this way, WJ-MSCs are characterized by longer telomeres with fewer DNA mutations and epigenetic modification compared to other sources. There are reports indicate the advanced osteogenic and chondrogenic potential of WJ-MSCs. Regarding the immunoregulatory role, besides the immunomodulation mechanisms that used from MSCs, WJ-MSCs, express the HLA-G. The immunomodulatory role of HLA-G was initially described during pregnancy, where trophoblast express this molecule in order to prevent the rejection of the semi allogeneic embryo. HLA-G has significant key immunoregulatory properties and can efficient suppresses the macrophages, NK, DCs, T and B cells. WJ-MSCs upon stimulation can express the HLA class II molecules, but are not expressing co-stimulatory molecules, and cannot be recognized by the immune cells, thus can be used in an allogeneic setting. Taking into account the above data, WJ-MSCs may have better therapeutic potential both in regeneration and immunomodulation than other sources.

In general, MSCs from all described sources have significant immunoregulatory properties. BM and AT-MSCs have the potential that can be used either in autologous or allogeneic way. On the other hand, WJ-MSCs can be used mostly allogeneicaly, and may characterized by better immunoregulatory and regenerative properties than MSCs from other sources. In the case of COVID-19, MSCs from all sources are now been investigated as possible therapeutical agents. The induced “cytokine storm” can be suppressed by the immunoregulatory properties of MSCs, improving in this way the overall condition of COVID-19 patients.

The above characteristics of MSCs are described in the manuscript in the following sections:

Origin and Properties of MSCs pages 9- 11, Immunomodulatory properties of MSCs pages 11 – 19, MSCs and COVID-19 pages 19 – 24.

4) **would be great if i Include that what are current treat options for COVID-19 as mentioned in "Novel Coronavirus (COVID-19) Treatment Options" and then explain why MSC should be comparable to that list or superior than the current treatments.**

Author Response

This a great comment by the reviewer. Current treatment options have been added in the manuscript as Table 1 (page 44 Table 1. Most common used therapeutically compounds used for the treatment of COVID-19.) Furthermore, the publication of Mujib Ullah – Novel Coronavirus (COVID-19) Treatment Options was cited in the current manuscript. MSCs are known for their immunoregulatory properties which can

be exerted either with cell-cell contact or via the secretion of soluble factors. The administration of MSCs in COVID-19 patients and the outcomes that may resulted cannot be comparable or superior compared to those arising from the use of pharmaceutical agents. Each treatment has pros and cons upon application. For example, MSCs do not cause antiviral effects but are significant immunomodulatory players suppressing in this way the overactivated immune responses and the induced "cytokine storm". On the other hand, antiviral drugs may have significant effects in inhibition of virus replication but once the "cytokine storm" is initiated, a more advanced therapy is needed. In this way, my suggestion is the combined use of antiviral treatment with MSCs in order to have the best outcomes and more patients to be saved. MSCs are only superior to pharmaceutical agents, regarding the adverse reactions occurrence. Indeed, a great number of clinical trials have been performed investigating, the safety, tolerability and efficacy of MSCs. No severe adverse reactions have been observed after the MSCs administration in patients with different diseases. The above information is described in detail in the revised version of the manuscript.

Introduction pages 4-5

"Until now, several treatments have been tested, including prophylactic hydroxychloroquine and colchine administration in combination with antiviral agents, monoclonal antibodies against SARS-CoV-2 or transfusion of convalescent plasma[16-19]. The majority of the above treatments have Food and Drug Administration (FDA) approval for their application to other diseases, while their use in COVID-19 patients is still under investigation. Remdesivir, an experimental drug to treat Ebola, has been tested in clinical trials for its efficacy in SARS-CoV-2 infection, while globally a great effort has been performed for the production of satisfactory vaccines against the current virus[19-24]. Recently, remdesivir, has been approved by the FDA for application in COVID-19 patients. Knowing that COVID-19 can cause significant modifications to the patient's immune system, alternative strategies should also be tested. In this way, the MSCs, a mesodermal cellular population, originated mostly from bone marrow (BM), Wharton's Jelly tissue (WJ-tissue) and adipose tissue (AT), could be potentially applied in COVID-19 patients[25-28]. MSCs are known for their immunoregulatory/immunosuppressive properties, exerted in several ways[25]. MSCs are currently applied in severe autoimmune disorders such as multiple sclerosis (MS), amyotrophic lateral sclerosis

(ALS), Crohn's disease, diabetes mellitus, etc, thus reducing disease manifestations[29]. In this way, MSCs can be applied mostly as cotherapy in combination with the above pharmaceutical agents to reverse the severe manifestations induced by SARS-CoV-2 infections."

Immune System and COVID-19 pages 8-9

"Moreover, from previous experience, it is known that most neutralizing antibodies are against the S, and E proteins[11, 51]. However, the manufacturing of COVID-19 specific drugs and vaccines is still an ongoing process. Alternative strategies should also be tested for the suppression of the hyperacute immune response, which can lead to increased patient survival. To date, a great number of pharmaceutical agents, including antiviral agents, monocolonal antibodies against inflammatory cytokines, and convalescent plasma are under investigation for their efficacy in COVID-19 treatment (Table 1). Most of these agents have specific targets (e.g. S protein of SARS-CoV-2, IL-6R and IL-6), and as pharmaceuticals agents, adverse reactions are accompanied their use. Moderate adverse effects may be presented in patients following these medications, including fever, headache, nausea, skin rash, diarhea and impairment of liver function. Except from the use of pharmaceutical agents, it has been suggested, that MSCs can effectively suppress the patient's overactivated immune system, through their immunoregulatory properties. MSCs have been used extensively in a wide number of registered clinical trials, supporting their tolerability, safety and efficacy[52]. No severe adverse reactions have been observed after the MSCs infusion to patients. In this way, MSCs could be employed as an alternative treatment strategy or as cotherapy for severely conditioned COVID-19 patients."

5) **Relate why COVID-19 is important issue as mentioned in "The Pandemic of Novel Coronavirus Disease 2019 (COVID-19): Need for an Immediate Action"**

COVID-19 is an important issue indeed. In December 2019, was SARS-CoV-2 initially was reported in Wuhan of China, and since then more 4.748.000 new cases and 315.800 deaths have been reported worldwide. No specific antiviral drugs are currently exists and the a great number of experimental treatments are under investigation. The scientific community is focused on the production of vaccines specific to SARS-CoV-2 proteins like S protein. Also, the use of human antibodies from recovered COVID-19 patients, have also been tested. Additionally, antiviral drugs such as those to treat HIV infection, are accompanied by severe adverse reactions and their use must be strongly considered before their administration. SARS-CoV-2 and the related COVID-19, can

induce a wide modulation of immune responses involving macrophages, NK cells, DCs, T and B cells, which lead to the immune system overactivation and to the development of "cytokine storm". In addition, the ACE2 and TMPRSS2, the receptors used by SARS-CoV-2 for entrance to the cells, are expressed besides the alveolar epithelial cells, to other cellular populations including endothelial cells of liver, kidney and pancreas. In severe condition patients, the virus can infect all these cellular populations, in different locations of the human body and in combination with the "cytokine storm" can cause multiorgan failure and finally the patients' death. The most striking event of SARS-CoV-2 is the acute respiratory distress syndrome, and the patients finally are hospitalized in ICU and mostly need ECMO connection. Ground glass opacity of infected lungs in combination with tissue fibrosis have been currently observed in patients affected by SARS-CoV-2. Clinical doctors can use a wide variety of treatment protocols in order to improve the patients' overall condition. More research is needed to be performed towards the aim. An additional alternative therapeutic strategy may be the administration of MSCs to COVID-19 patients. Indeed, MSCs have unique immunoregulatory properties through the secretion of soluble factors (e.g. PGE2, IDO, NO) or through cell-cell contact (Fas-FasL, TRAIL). MSCs can efficiently modulate the specific immune responses of macrophages, DCs, NKs, T and B cells, through adaption of different phenotype and inhibition of maturation and cell proliferation. The tolerability, safety and efficacy of MSCs have been tested or are under investigation in various diseases (including autoimmune disorders and COVID-19). No severe adverse reactions are accompanied their use. Taking into consideration the above data, my suggestion is the use of MSCs as a cotherapy with current antiviral treatments, in order to improve patients' condition.

To conclude, SARS-CoV-2 is an important issue, which needs specific strategies in order to be eliminated. The information that are included in the publication of Mujib Ullah entitled "The pandemic of Novel Coronavirus Disease 2019 (COVID-19): Need for an Immediate Action are of paramount importance and this publication will be cited in the revised form of the manuscript.

In my opinion, the reasons why SARS-CoV-2 is an important issue is reflected to the whole submitted manuscript. In the submitted review, a great effort was performed to gather all the appropriate data that are needed, focused on SARS-CoV-2 infection, epidemiology and what will be the suggested for treatment options.

The following sections include information regarding the importance of SARS-CoV-2 regarding disease epidemiology, invasion mechanism and the use of MSCs as an alternative therapeutic strategy.

Invasion Mechanism of SARS-CoV-2 pages 5-6

Immune System and COVID-19 pages 6- 9

MSCs and COVID-19 pages 19-24

Concluding Remarks pages 25-27

"On the other hand, no specific treatment is currently be used, while most of them could be accompanied by significant adverse reactions, limiting their application to patients."

6. **The value of this paper is that MSCs can be applied in COVID-19 as co-therapy as MSC usually migrate to lungs.**

Author Response

Indeed MSCs may have significant beneficial impacts both in immunoregulation of the overactivated immune system and in lung tissue regeneration due to tissue fibrosis occurred from SARS-CoV-2 infection. MSCs can migrate through the periphery to specific locations in response to chemokine stimuli in order to exert their properties (Figure 1).

The whole manuscript was checked again thoroughly for grammatical or syntax errors and revised appropriately.

This manuscript means for me a lot, and it would be great if you satisfied from our responses towards to your comments. We have revised appropriately the whole manuscript, and we are in position to perform any further changes if in your opinion are required.

Dear Reviewer 2 (02559247)

We have performed the corrections to my submitted manuscript based on your following comments. All performed changes are represented as highlight text in the manuscript.

The article is interesting but is not suitable in the present form.

1. **In particular the authors introduced briefly the potential role of adipose-derived stem cells (ASCs) in COVID-19 patients - correctly- but refer this to reference 24 -uncorrrect- because the only articles published on this potential role of ASCs are the following: Adipose-derived stromal stem cells (ASCs) as a new regenerative immediate therapy combating coronavirus (COVID-19)-induced pneumonia. Gentile P, Sterodimas A. Expert Opin Biol Ther. 2020 Apr 29:1-6 and Adipose Stem Cells (ASCs) and Stromal Vascular Fraction (SVF) as a Potential Therapy in Combating (COVID-19)-Disease Pietro Gentile, Aris Sterodimas Aging and disease. 2020, 11 (3): 465-469. DOI: 10.14336/AD.2020.0422 and Rationale for the clinical use of adipose-derived mesenchymal stem cells for COVID-19 patients. Rogers CJ, Harman RJ, Bunnell BA, Schreiber MA, Xiang C, Wang FS, Santidrian AF, Minev BR. J Transl Med. 2020 May 18;18(1):203. doi: 10.1186/s12967-020-02380-2**

Author Response

The reference 24 was used to indicate in general the broad applications of MSCs. As reviewer indicated the following references were added to the manuscript

26 Gentile P, 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, 10.1080/14712598.2020.1761322: 1-6 [PMID: 32329380 PMCID: PMC7196919 DOI: 10.1080/14712598.2020.1761322]

27 Gentile P, Sterodimas A. Adipose stem cells (ascs) and stromal vascular fraction (svf) as a potential therapy in combating (covid-19)-disease. Aging and disease 2020; 11: [PMID: DOI: 10.14336/ad.2020.0422]

28 Rogers CJ, Harman RJ, Bunnell BA, Schreiber MA, Xiang C, Wang FS, Santidrian AF, Minev BR. Rationale for the clinical use of adipose-derived mesenchymal stem cells for covid-19 patients. J Transl Med 2020; 18: 203 [PMID: 32423449 PMCID: PMC7232924 DOI: 10.1186/s12967-020-02380-2]

In addition, to indicate better the potential applications of AD-MSCs in COVID-19, rather just as short introduction to them, he following sentence was entered in the manuscript.

MSCs and COVID-19 pages 23.

"The last years, AD-MSCs have gained significant interest by the scientific society for their regenerative and immunoregulatory properties. Recently, Gentile et al. reported that AD-MSCs exert key immunosuppressive properties via the secretion of TGF-β1, HGF and IFN-γ and remarkably regenerative properties through the secretion of VEGF and PDGF[26, 27]. Indeed, besides their immunosuppressive properties, AD-MSCs can secrete pro-angiogenic factors such as VEGF and PDGF, which can stimulate the endothelial cells, promoting in this way the vascularization and the regeneration of damaged lung tissue[26-28]. Moreover, a phase I clinical trial, where autologous or allogenic AD-MSCs were used, was conducted since April 2020 in COVID-19 patients, determining the safety and tolerability of these cells[26]"

2. **Additionally the PRISMA flow, in agreement with guidelines of the journal was not reported.**

Author response

Prisma flow diagrams are not required in review articles according to the journal's guidelines. However, following reviewer's comments, a PRISMA flow diagram which describes the methodological framework of the current study was added as Supplementary figure 1. The following sentences were added to the main manuscript.

Introduction page 5

For the purposes of the current review article, we searched initially over 300 published articles focused on COVID-19 pathogenesis and MSCs biology. During the eligibility process 166 studies were excluded and the remained 134 articles were finally included to this review. PRISMA flow diagram describes the methodological framework that was followed in the current article (Supplementary Figure 1).

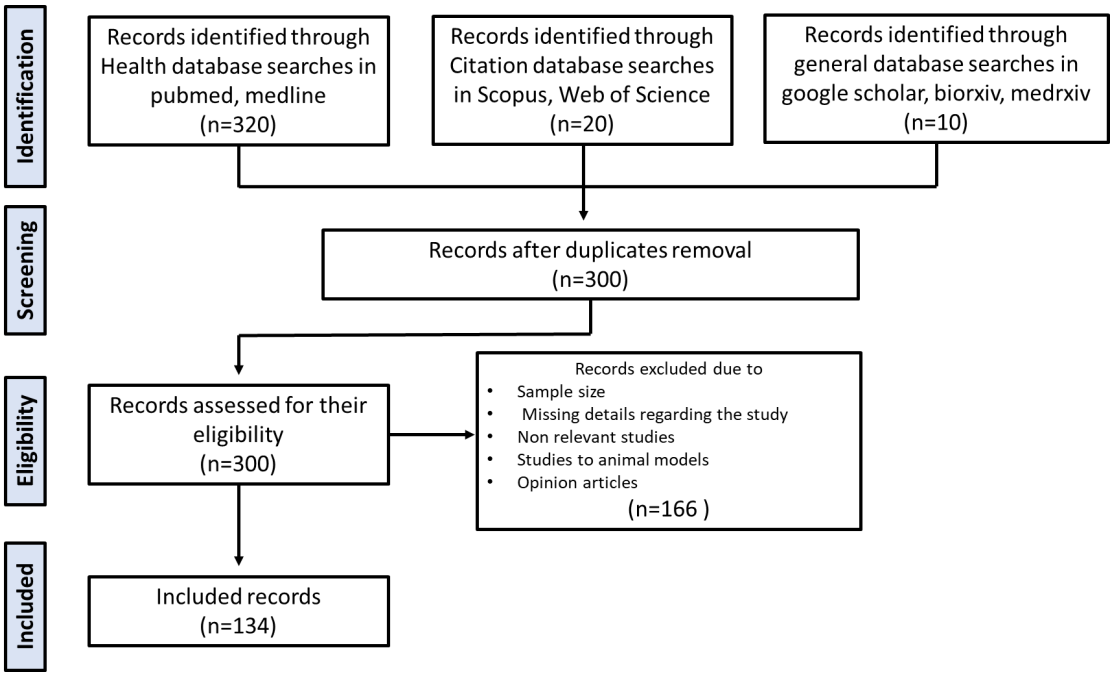

Figure S1. PRISMA flow diagram for the current review article

3. **The article should report in the discussion section the potential role of adipose stem cells in COVID-19 patients, discussing also the in vivo and in vitro result of ASCs, previously obtained as safe and effective therapy, as the most important MSCs as following: doi: 10.1002/term.2139. doi: 10.1002/stem.2498 doi: 10.3390/ijms20143446 doi: 10.1093/asj/sjz292 doi: 10.3390/jcm8040504 doi: 10.3390/cells8030282 doi: 10.3390/ijms20215471 doi: 10.3390/jcm8060855 doi: 10.2217/rme-2017-0076 doi: 10.1097/01.scs.0000436746.21031.ba doi: 10.1155/2013/434191**

Author response

We agree totally with the reviewer's comments regarding the potential use of AD-MSCs in COVID-19 and also that may represent the best option of MSCs.

The following sentences were added to the discussion, according to the reviewer's comments.

Concluding remarks page 26-27

"On the other hand, AD-MSCs which are extensively used in a great series of personalized regenerative medicine applications, including breast reconstruction with fat graft, androgenic alopecia,etc., are exhibited similar properties as the MSCs from other sources[127-133]. Recently, the application of AD-MSCs as immunoregulatory agents in COVID-19 patients, is gaining day by day more attention by the scientific society, worldwide[26, 27]. AD-MSCs can be efficiently isolated in

great quantities from stromal vascular fraction (SVF) or subcutaneous AT, expanded under clinical grade GMP conditions and applied through intravenously infusion to critically-ill COVID-19 patients[26, 27]. AD-MSCs exert equal immunoregulatory properties as MSCs from BM and WJ tissue, through secretion of soluble factors or cell – cell contact interactions, as has been described previously[26, 27]. Furthermore, AD-MSCs can efficiently be differentiated towards "chondrogenic" and "osteogenic" lineages and can produce significant amounts of proangiogenic factors, indicating their significant regenerative potential[26, 27, 127]. These regenerative properties of AD-MSCs may be proven of great importance in restoration of lung alveolar epithelium and reversion of ground-glass opacity in critically-il COVID-19 patients. Taking into account the above data, AD-MSCs may also represent a safe and effective therapeutic strategy for COVID-19 ptients, and may be the best option as cellular population, when a great number of MSCs are required for immediate use."

Also, the following references were entered to the submitted manuscript.

References

127 Scioli MG, Bielli A, Gentile P, Cervelli V, Orlandi A. Combined treatment with platelet-rich plasma and insulin favours chondrogenic and osteogenic differentiation of human adipose-derived stem cells in three-dimensional collagen scaffolds. *J Tissue Eng Regen Med* 2017; **11**: 2398-2410 [PMID: 27074878 PMCID: 27074878 DOI: 10.1002/term.2139]

128 Gentile P, Scioli MG, Bielli A, Orlandi A, Cervelli V. Concise review: The use of adipose-derived stromal vascular fraction cells and platelet rich plasma in regenerative plastic surgery. *Stem Cells* 2017; **35**: 117-134 [PMID: 27641055 DOI: 10.1002/stem.2498]

129 Gentile P. Autologous cellular method using micrografts of human adipose tissue derived follicle stem cells in androgenic alopecia. *Int J Mol Sci* 2019; **20**: [PMID: 31337037 PMCID: PMC6678214 DOI: 10.3390/ijms20143446]

130 Gentile P, Kothari A, Casella D, Calabrese C. Fat graft enhanced with adipose-derived stem cells in aesthetic breast augmentation: Clinical, histological, and instrumental evaluation. *Aesthet Surg J* 2019, 10.1093/asj/sjz292: [PMID: 31637416 DOI: 10.1093/asj/sjz292]

131 Gentile P, Casella D, Palma E, Calabrese C. Engineered fat graft enhanced with adipose-derived stromal vascular fraction cells for regenerative medicine: Clinical, histological and instrumental evaluation in breast reconstruction. *J Clin Med* 2019; **8**: [PMID: 31013744 PMCID: PMC6518258 DOI: 10.3390/jcm8040504]

132 Gentile P, De Angelis B, Pasin M, Cervelli G, Curcio CB, Floris M, Di Pasquali C, Bocchini I, Balzani A, Nicoli F, Insalaco C, Tati E, Lucarini L, Palla L, Pascali M, De Logu P, Di Segni C, Bottini DJ, Cervelli V. Adipose-derived stromal vascular fraction cells and platelet-rich plasma: Basic and clinical evaluation for cell-based therapies in patients with scars on the face. *J Craniofac Surg* 2014; **25**: 267-272 [PMID: 24406591 DOI: 10.1097/01.scs.0000436746.21031.ba]

133 Cervelli V, Bocchini I, Di Pasquali C, De Angelis B, Cervelli G, Curcio CB, Orlandi A, Scioli MG, Tati E, Delogu P, Gentile P. P.R.L. Platelet rich lipotransfert: Our experience and current state of art in the combined use of fat and prp. *Biomed Res Int* 2013; **2013**: 434191 [PMID: 24191244 PMCID: PMC3804297 DOI: 10.1155/2013/434191]

With the above sentences, we assume that we have covered the reviewer's suggestion, regarding the potential use of AD-MSCs in COVID-19.

Furthermore, with this letter we declare that all reviewers comments have been answered appropriately in the submitted manuscript. All the performed changes are represented as highlighted (in yellow) text in the submitted manuscript. Also, the whole manuscript was checked for grammatical or syntax errors and revised.

This manuscript is of great importance for me and the rest of the authors to get published, and if you think that further corrections are needed, please inform us.

We are capable to perform all the required changes in order the manuscript to get published to your highly impact journal.

Yours sincerely,

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