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Human umbilical cord derived mesenchymal stem cells induce tissue repair and regeneration in collagen-induced arthritis in rats

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Review timeline:

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1st Editorial decision
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Ref.: Ms. No. JCTRes-D-20-00080
Human umbilical cord-derived mesenchymal stem cells induce tissue repair and regeneration in collagen-induced arthritis in rats
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Dear Professor Arora,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.
We would like you to focus on the comments of reviewer 2 in particular in terms of novelty. Please ensure that you give an account of what the work contributes to the field in the Introduction section and discuss your results in the Discussion section in light of what is already known. Update the references as requested by reviewer 2.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript.Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Oct 15, 2020.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: in-vitro should be in italics

"successfully as cell-based therapeutic option" should be changed to "successfully as a cell-based therapeutic option"

In the keywords "rheumatoid" has a bold "r"

some "the" articles are missing in the Introduction

For UC-MSC differentiation, the induction media are missing as are the staining protocols

For Histological analysis, after how many weeks were the animals sacrificed?

For X-ray analysis please include the week in "At the end of experiment, before sacrificing" since in the Results section it says "After two- and six-weeks post treatment"

For Gene expression profiling, the cycling conditions should be included

"Human umbilical cord driven MSCs" to "Human umbilical cord derived MSCs"

FACS, PHA, RA and MFI should be described in full upon first mention

On Page 17 there is a missing space in "6weeks"

"et al" should be in italics

The phrase "relatively least manipulated population" needs rewording

In the Conclusion there is no need to reintoduce UC-MSCs in full

Reviewer #2: The manuscript lacks the novelty parameter as many studies have already reported the UC-MSCs therapeutic application for several degenerative diseases including arthritis. Please find some of the recent work DOI below.
DOI: 10.3390/cells9061343
DOI:10.4252/wjsc.v4.i10.101
DOI: 10.1111/1756-185X.13834

DOI: https://doi.org/10.1016/j.jot.2020.03.007
DOI: https://doi.org/10.1038/s41598-019-50435-2

However, few more comments can be find below:

- References found quite outdated and few recent references of 2019 and 2020, when tracked seems the old one only.

- Within the text, Page- 19, Line 12-15, Reference was not found for the highlighted reported study.

- Relevance of Animal induced model and why such doses were used found missing and not supported by any literature part.

- Control group was not mentioned within the materials and methods. However, few data have shown control results and somewhere, it was found missing like Fig 6.g.

- As per the MSCs characterization standard by International Society for Stem Cell Research, the UC-MSCs should present the HLA Class II flow results, which is missing in the manuscript.

- Magnification of Images should be maintained like Figure 5: Day 15, Untreated and MSC treated CIA rats.

- Bar legends style should be maintained in Figure: 6.

- Induction protocol for adipogenic, osteogenic and chondrogenic lineages is missing.

- Why 1:10 Co-culture ratio selected. Any literature or previous data to justify the selected ratio?

- Is Histological examination scoring approved one?

- Re-framing of text required on Page 10- Line 4.

Authors' response

Comments and Response as per the suggestions made for the manuscript titled "Human Umbilical Cord derived Mesenchymal Stem Cells induce tissue repair and regeneration in collagen-induced arthritis in rats"

Pointwise comments and response to the suggestions of Reviewer 1:

Comment 1: in-vitro should be in italics
Response 1: All throughout the document the suggested change has been made
Comment 2: successfully as cell-based therapeutic option" should be changed to "successfully as a cell-based therapeutic option"
Response 2: Suggested change has been made
Comment 3: In the keywords "rheumatoid" has a bold "r"
Response 3: Suggested change has been made
Comment 4: some "the" articles are missing in the Introduction

Response 4: The manuscript has been updated
Comment 5: For UC-MSC differentiation, the induction media are missing as are the staining protocols
Response 5: For induction of differentiation into different lineages, the induction media from Himedia, India was used. The same has been mentioned in the text along with the staining method in brief.
Comment 6: For Histological analysis, after how many weeks were the animals sacrificed?
Response 6: After 2 weeks and 6 weeks post stem cell treatment the animals were sacrificed and there Tibiotarsal joints were collected and processed for histological analysis
Comment 7: For X-ray analysis please include the week in "At the end of experiment, before sacrificing" since in the Results section it says "After two- and six-weeks post treatment"
Response 7: Suggested change incorporated in the manuscript
Comment 8: For Gene expression profiling, the cycling conditions should be included
Response 8: In the material and methods section, the cycling conditions have been included
Comment 9: "Human umbilical cord driven MSCs" to "Human umbilical cord derived MSCs"
Response 9: Change done in the manuscript
Comment 10: FACS, PHA, RA and MFI should be described in full upon first mention
Response 10: All the four terms have been described in the manuscript
Comment 11: On Page 17 there is a missing space in "6weeks"
Response 11: Suggested change done
Comment 12: "et al" should be in italics
Response 12: Throughout the manuscript et al has been made italics
Comment 13: The phrase "relatively least manipulated population" needs rewording
Response 13: Necessary change incorporated
Comment 14: In the Conclusion there is no need to re-introduce UC-MSCs in full
Response 14: Necessary change incorporated

Pointwise comments and response to the suggestions of Reviewer 2:

Comment 1: The Manuscript lacks novelty parameter
Response 1: Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease. Infiltration of the immune cells in the synovium and its interaction with the resident synovial fibroblasts ultimately results in the cartilage and bone erosion. Despite the advancement in the treatment regime, few patients do not respond to conventional and biological DMARDs, numerous side effects are associated with their long-term use and RA patients with clinical remission display progressive joint erosion as evident from radiological examination. Although the inflammation can be suppressed with the use of drugs like NSAIDS and biologicals like anti-TNF α, yet the joint damage and erosion cannot be effectively repaired through pharmacotherapeutic interventions, thereby serving as a risk factor for progressive joint damage, secondary osteoarthritis, and joint dysfunction. While the results in our study have indicated that beside suppression of inflammation, the MSC treatment not only leads to inhibition of tissue damage and bone erosion, but also shows indications of reversal of osteoclastogenesis, which is a very encouraging result. The improvement in radiological and histopathological scorings in MSC-treated CIA rats strongly suggest that the MSC treatment can be an alternative therapeutic option in such patients. These are novel findings of our study.

Comment 2: References found quite outdated and few recent references of 2019 and 2020, when tracked seems the old one only.
Response 2: Updated references have been added into the manuscript

Comment 3: Within the text, Page- 19, Line 12-15, Reference was not found for the highlighted reported study.
Response 3: The references have been cross-checked please.

Comment 4: Relevance of Animal induced model and why such doses were used found missing and not supported by any literature part.
Response 4: Collagen Induced Arthritis (CIA) is the most commonly used animal model for studying possible pathogenic mechanism of Rheumatoid arthritis. There is a close resemblance between human RA and CIA in terms of affected tissue pathology, local production of inflammatory mediators such as chemokines, cytokines and autoantibodies. Pathological features which characterize both RA and CIA are synovitis with immune cell infiltration, thereby accompanying cartilage degradation and bone erosion. Animal studies showing long term impact of UC-MSC treatment with histopathological and radiological data is important to justify the future use of MSCs in clinical trials.
The induction of animal model was standardized in our laboratory and is well supported with many studies in the literature, which have been cited.
Comment 5: Control group was not mentioned within the materials and methods. However, few data have shown control results and somewhere, it was found missing like Fig 6.g.
Response 5: Modifications have been made in the material and method section. In some parameters like histological scoring and radiological scoring, the score 0 was given to the control rats and due to this reason they have not been plotted in the bar graphs. The same has been mentioned in the manuscript.
Comment 6: As per the MSCs characterization standard by International Society for Stem Cell Research, the UC-MSCs should present the HLA Class II flow results, which is missing in the manuscript.
Response 6: A representative histogram for HLA Class II has been added in the manuscript in Figure 1.
Comment 7: Magnification of Images should be maintained like Figure 5: Day 15, Untreated and MSC treated CIA rats.
Response 7: Clinical signs of untreated CIA and treated CIA were taken from Canon A90 1X macro mode. Suggested change has been done in the manuscript.
Comment 8: Bar legends style should be maintained in Figure: 6.
Response 8: Suggested change incorporated into the manuscript
Comment 9: Induction protocol for adipogenic, osteogenic and chondrogenic lineages is missing.
Response 9: For induction of differentiation into different lineages, media from Himedia, India was used. The same has been mentioned in the text along with the staining method in brief.

Comment 10: Why 1:10 Co-culture ratio selected. Any literature or previous data to justify the selected ratio?
Response 10: Various ratios were used in the standardization experiments, the response obtained at 1:10 ratio was better as compared to the other ratio's used. In addition, many published research studies used the same ratio for co-culture experiments between MSCs and lymphocytes. The reference of the same has been mentioned in the manuscript.
Comment 11: Is Histological examination scoring approved one?
Response 11: Scoring criteria has been taken from a previously published study, the reference has been mentioned in the manuscript.
Comment 12: Re-framing of text required on Page 10- Line 4.
Response 12: Suggested change incorporated into the manuscript

2nd Editorial decision
14-Oct-2020

Ref.: Ms. No. JCTRes-D-20-00080R1
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Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Comments from the editors and reviewers: