

Peer Review File

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Reviewer A

Thank you submitting your work to the AOJ. Congratulations on this rigorous narrative review that summarizes the evidence on MSCs therapy for OA.

The overall work is well performed. I have however 1 major comment and some minor comments that you should resolve.

Major comment:

Comment 1: I think the authors could better explain the (current) position of MSC therapy in clinical practice by reporting the effects of commonly used treatment options (physical therapy, corticosteroid, HA, PRP) and reporting the effect of MSC therapy in RCTs and meta-analyses. This will give clinicians more insight in the field of OA and the (possible) position of MSC therapy.

Reply 1: We have expanded the literature review covering the effects/outcomes of physical therapy, various injection therapies, and most common surgical procedure. With this addition, readers will see that conventional therapeutics are limited due to side effects and lack of symptom relief. This will help transition the article into the potential use of MSC. Additionally, a statement was made in the conclusion to highlight traditional therapy has its limitations.

Changes in the text: Line 59-106, Line 116-119, Line 410-412.

Minor comments:

Comment 2: Line 34. Typo: 'it' should be 'is'?

Reply 2: Typo was corrected to "is".

Changes in the text: Line 35.

Comment 3: Line 56-59: Could the authors explain the step-wise approach in treatment of OA more clearly in this section? In all cases, physical therapy can help to reduce symptoms and improve QoL in OA. In more advanced cases there are some injection therapies available as an add-on. Could the authors indicate the effect of common used injection therapies in effect sizes? (see Deyle et al. NEJM 2020, and Curr Rheumatol. Rep. 2017 - Platelet-Rich Plasma for the Management of Hip and Knee Osteoarthritis, Kim L. Bennell & David J. Hunter & Kade L. Paterson)

Reply 3: We have listed the step-wise approach at the beginning of each paragraph from mild (Line 57), disease progression (Line 68), to advanced or refractory cases (Line 108) with their supporting intervention. Additionally, we have emphasized that physical therapy is ongoing with injections therapies. We have further expanded the literature

review into the various injection therapies and their effects/outcomes.

Changes in the text: Line 57-106.

Comment 4: Line 66-71. In line with my previous suggestion. Could the authors indicate the effect of most performed surgical techniques on patient-reported outcome measures?

Reply 4: Here we referenced 2 articles highlighting the potential of persistent pain after arthroplasty.

Changes in the text: Line 116-119.

Comment 5: Line 89-91.

A. Please refer in the text to the table.

B. The search process is insufficiently described. Could the authors add some information about key words and/or searches performed. This makes the process for this review more clearly.

Reply 5: A method section was added following the recommend article for guidance suggested by the journal within the narrative review section of manuscript categories for author guidelines.

Changes in the text: Line 139-145.

Comment 6: Line 188-191. Safety issues are a major concern, however what data are available about risks of MSC therapy specifically for osteoarthritis (e.g. joints)? Please explain whether there is, with the current evidence, reason for concerns about safety in this field.

Reply 6: We did not change any information here in order to keep the flow of the article. As line 242-245 is a general introduction of mesenchymal stem cells characteristics, functions, and source. Whereas line 345-356 is specifically joint and clinical related.

Changes in the text: No changes in the text.

Comment 7: Line 274-284. From a clinical perspective this is too little information. Could the authors cite systematic reviews and report effect sizes of meta-analyses or RCTs in this paragraph? What is the effect of MSCs compared to current treatment options?

Reply 7: We have added results of a systemic review as well as added additional information reporting the benefits of both bone-marrow and adipose derived MSCs.

Changes in the text: Line 334-339.

Comment 8: Line 286-298. This is what I am looking for previously (comment 5). Please refer in line 188-191 to this part.

Reply 8: We did not change any information here in order to keep the flow of the article. As line 242-245 is a general introduction of mesenchymal stem cells characteristics, functions, and source. Whereas line 345-356 is specifically joint and clinical related.

Changes in the text: No changes in the text.

Comment 9: Line 300-302. This statement needs citations.

Reply 9: This statement is now cited.

Changes in the text: Line 358-360.

Comment 10: Line 303-305. What exactly do these % mean? Minimal improvement of pain? How many points on a Visual Analogue Scale?

Reply 10: Three test were performed including Lequesne index, Visual Analogue Scale (VAS), and Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index. The % indicated the improvement in pain over year starting from baseline. Instead of writing the results 65-78% improvement of pain (which include all 3 results), we have now written all three individual improvements as 65%, 69%, 78% improvement of pain from baseline, respectively.

Changes in the text: Line 360-364.

Comment 11: Line 337-341 (/ Conclusion paragraph). Please add no new information and citations in the conclusion. Could the authors replace this information to the main text? And make the conclusion more compact.

Reply 11: The initial conclusion was edited, moving the referenced information into making the last paragraph of the discussion and the non-reference statements were used and retyped into the new conclusion that's more compact.

Changes in the text: Line 395-407, Line 409-418.

Reviewer B

Comment 12: I suggest that in the last paragraph of the introduction a flowchart is inserted describing how many articles were included and excluded from the methods pre-selected by the authors during the search in the pubmed database.

Reply 12: A method section was added following the recommend article for guidance suggested by the journal within the narrative review section of manuscript categories for author guidelines.

Changes in the text: Line 139-145.

Comment 13: I also suggest the insertion of a table showing the number of works used in the publication according to cell origin (adipose tissue, bone marrow, among other cell niches, if used)

Reply 13: Unfortunately, we did not assess publications by cell origin due to the extreme variability on therapeutic outcomes.

Changes in the text: No changes in the text.