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JOURNAL EDITORIAL BOARD'S REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 88842

Title: Role of anti-tumor necrotic factor therapy in Crohn's perianal fistula closure rate after stem cell transplantation

Journal Editor-in-Chief/Associate Editor/Editorial Board Member: Shengwen Calvin Li

Country/Territory: United States

Editorial Director: Jia-Ping Yan

Date accepted review: 2024-01-23 19:36

Review time: 10 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	[ ] Accept
[Y] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] High priority for publication
[ ] Grade C: Good	[Y] Grade C: A great deal of language polishing	[ ] Rejection
[ ] Grade D: Fair		[ ] Minor revision
[ ] Grade E: Poor	[ ] Grade D: Rejected	[Y] Major revision

JOURNAL EDITORIAL BOARD COMMENTS TO AUTHORS

Comment: The topic is of great importance as the manuscript exploits the co-treatment of hASC with infliximab (Remicade®, Janssen Biotech, Inc., Horsham, PA, United States) and adalimumab (Humira®, AbbVie, Inc., North Chicago, IL, United States). However, the current version lacks the necessary clarity for acceptance, as evidenced by the specific comments provided below. EIC Specific comments: 1) The title did not capture the content. A more concrete title should be conveyed. 2) The abstract did not reflect the schemes. 3) Page 6: Autologous adipose tissue-derived mesenchymal stem cells (hASC) (Cupistem®, Antrogen, South Korea) were used in this study. How did they standardize "Autologous hASC procedures and quality controls of the MSCs? What were their MSC dosing schemes? How did they assess the efficacy for each patient? 4) Page 6: anti-TNF agents used in this study were infliximab (Remicade®, Janssen Biotech, Inc., Horsham, PA, United States) and adalimumab (Humira®, AbbVie, Inc., North Chicago, IL, United States). The agents should be clearly

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labeled in both Fig 1 and 2. 5) A treatment timeline should be provided, including Autologous adipose tissue-derived mesenchymal stem cells, infliximab, and adalimumab. For example, page 5 says, "However, few studies have focused on the long-term outcomes of stem cell transplantation and the risk factors affecting them." How did they call it "long-term?" What was the outcome? For clarity, thus, a timeline schematic diagram of diagnostic and treatment courses should be provided, including the duration of the time of treatment and outcomes. Separated timelines should be drawn for those patients corresponding to Table 1 and all the other figures for specific mentions in the text. 6) All the Figures (1-2): Figure titles must carry self-explanatory information. An ideal figure title should give complete information to the reader even without reading the text. The figure should have a governing title followed by the descriptive interpretation of panel contents. All the figure legend descriptions were not written in keeping this point in mind in the current manuscript version. For example, all the abbreviations should be spelled out so that the readers not in the field do not need to search around. Precisely, "Figure 1 Closure rate with and without anti-tumor necrosis factor agents. TNF: Tumor necrosis factor." This figure legend did not give a complete picture of the data without searching for corresponding text. 7) Another example was that the authors needed to elaborate on concrete descriptions of "advantages and disadvantages" and specific examples of "various samples and provide biomolecular information," which should be illustrated within the Figure and the table, as the current version manifested too simple (common sense without reading this manuscript) to convey any expert literature review. 8) Neither the abstract nor the conclusion gave a clear picture of what the cohort was designed about (e.g., not precise inclusivity and exclusivity), confusing the reader with how to reference their treatment schemes and outcome measurements. 9) Peer-reviewer 1 asked: "1. Introduction: "Stem cell transplantation is a promising therapeutic option..."You should provide a clear statement on how your study's approach or findings differ from or build upon existing research, as currently, your introduction lacks specific differentiation from previous studies." On page 5, they did not fully address this requirement: Neither did they specifically narrate any single treatment outcomes, nor did they specifically differentiate from previous studies. 10) Page 5: "2. Efficacy of Combined Treatment: "Furthermore, the combination of medication and surgery was more effective than either alone, with 52% and 43% complete healing rates, respectively [15]." Peer-reviewed 1 specifically requested, "To clarify the efficacy rates of combined treatments compared to individual treatments, please reference specific studies." The authors did not clarify it. 11) Page 7: "The stromal vascular fraction isolated from the fat tissue was cultured in Dulbecco's modified Eagle's medium (DMEM) with 10% fetal bovine serum and 1 ng/mL human basic fibroblast growth factor to obtain the required number of ASCs for injection." How did they remove residue trace animal products from clinically-used hASCs? How did you manage the immunity rejections if they did not clear it? How did they know if in vitro culture procedures introduce detrimental factors? How did the cultured ASCs deviate from the original biomarker profiles? It is well known that fetal bovine serum cultured modifies stem cell genome profiles. How did they ensure that change? How did they elaborate on the severity of inflammation in the fistula caused by the animal products (page

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12)? Note: "Examining the influence of various experimental and culture-related factors on hASC immunoregulatory functions in vitro is essential, including interaction mode (contact vs. contactless), and oxygen tension on hASCs; Conditioning methods before hASC interaction, culture medium type (xenogenic or xenofree)(Here, they used FBS), dimensionality (two-dimensional vs. three-dimensional with biomaterials), and passage number (Mahmoud, M., Abdel-Rasheed, M., Galal, E.R. et al. Factors Defining Human Adipose Stem/Stromal Cell Immunomodulation in Vitro. Stem Cell Rev and Rep 20, 175–205 (2024). https://doi.org/10.1007/s12015-023-10654-7). All these parameters affect the efficiency of MSCs due to the cultured subclonal evolution [https://doi.org/10.3389/fcell.2022.699144]. 12) Page 7: "suspended in DMEM, and packaged into single-use vials containing 3 × 107 cells/mL" – Why in DMEM (compositions complicate local physiology)? How much volume did they use clinically? How many ASC cells did they use for a patient? 13) Page 7: "Then, 3 × 107 autologous adipose tissue-derived mesenchymal stem cells/mL (Cupistem®, Antrogen, South Korea) were injected into the submucosa around the internal opening and fistula tract." Did they do any assays or histological assessments to ensure the viability and engraftment of ASCs? Where were their data sets? 14) Pages 9-10: "During the follow-up, closure rate after stem cell transplantation was 76.9%. The mean duration from stem cell transplantation to fistula closure was 6.94 ± 9.68 months. Moreover, the recurrence rate in patients experiencing fistula closure was 14.0%, with the mean period from fistula closure to recurrence being 16.57 ± 19.38 months. All recurrences were detected in 3 years. The patients who received anti-TNF treatment experienced fistula closure within two years. The closure rates at 1 year and 2 years for the patients who received anti-TNF-treatment were 63.0% and 66.7%, respectively." The above statement is confusing: from 76.9% only with ASCs, went down with combinations of anti-TNF treatment to 63.0% and 66.7%? Why? 15) "Anti-TNF therapy did not increase CPF closure rates..." The conclusion is brief and lacks a summary of the study's implications. Provide a concise summary of the main findings and their significance in the field." What was the molecular mechanism underlined the outcomes?