



SEMMELWEIS UNIVERSITY

Department of Internal Medicine and Hematology

Budapest, August 8, 2022

Dear Lian-Sheng Ma, Company Editor-in-Chief,
Dear Professor Lu Cai, Professor Michael Horowitz, Professor Md. Shahidul Islam
and Professor Jian-Bo Xiao, Editor-in-Chiefs,
Dear Managing Editors,
Dear Reviewers,

On behalf of my fellow authors, first of all, I would like to thank you for your attention and opinion on our invited Minireview article entitled "New therapeutic approaches for type 1 diabetes: Do disease-modifying therapies have a future in routine clinical treatment?" We are grateful that you have found it to be interesting and suitable for publication in World Journal of Diabetes.

Our answers to the comments and suggestions raised in the reviews are given below.

Reviewer 1

The authors elucidated in detail the immunopathogenesis of T1DM and the staging classification system; Through a variety of targeted agents and treatment methods, this paper expounds the methods and choices of disease-modifying therapies; The characteristics of mesenchymal stem cells (MSCs) and its immunomodulatory function and clinical application in T1DM are introduced in detail. The topics are better, and the language is developed and clear. If the authors can modify some improper expressions or use in the paper, I believe the quality of the manuscript will increase a lot. I suggest the following modifications:

1) No matter how many efforts are made, the treatment and care of type 1 diabetes will definitely make great progress and improvement in the future. Therefore, the title of the article should be revised to actively yearn for, rather than be skeptical.

Thank you for your kind suggestion, the title had been changed to: **"New therapeutic approaches for type 1 diabetes: Disease-modifying therapies."**

2) The content of the Conclusion is just too scattered. It should be focused on summarizing the main content elaborated in the theme part, giving conclusions or putting forward their own opinions, such as what are the authors in favor of? Against what? What are the

suggestions and prospects for the future? The following content should do not appear in the conclusion, but in the corresponding part of the text. "The burden of living with the chronic disease is considerable for the patient, the family and the society." "In July 2021, the U.S. Food and Drug Administration considered the use of teplizumab in high-risk individuals but deemed further studies necessary before granting approval."

Conclusion had been revised. All sentences were moved to their corresponding part of the text, as suggested.

3) Keyword "mesenchymal stem cell" appears much more frequently than "mesenchymal stem cell transplantation", so "mesenchymal stem cell transplantation" should be replaced by "mesenchymal stem cell".

Thank you for the suggestion, it was changed accordingly.

4) Figure 2 comes from Ref. 12, which should be deleted (the text has been clearly stated) or modified, and at least the reference should be noted.

Thank you for your kind warning. Figure 2 was significantly changed and redrawn, and the citation was added.

5) In Immunopathogenesis of T1DM section: in "Furthermore, Th1 cells enhance antigen presenting, costimulatory and effector functions of macrophages and DCs (e.g., reactive oxygen species)", What does the term in parentheses mean to express or explain? It's not clear. Please clarify.

Text had been clarified.

6) The term "T1DM associated antibodies" should be expressed more accurately. It should be changed to "T1DM associated islet autoantibodies", and the autoantibodies that can be detected at present should be listed as far as possible.

The sentence has been changed as follows: *"It is characterized by the presence of immune markers, two or more of the T1DM-associated islet antibodies such as ICA, GADA, IA2 and ZnT8, normoglycemia and absence of diabetic symptoms. In stage 2, the β -cell volume is critically decreased, and metabolic markers become detectable in asymptomatic patients."*

7) At least one Ref. should be added after these sentences. Page 7, line 6: Lately, stage-specific therapies have been in the focus of clinical trials for modifying disease progression [add references]. Page 11, line 10: Over the past decade, mesenchymal stem cell (MSC) transplantation has received increased attention in clinical trials as a promising therapy within regenerative medicine for type 1 diabetes mellitus [add references].

References have been added.

8) The term "disease-modifying therapies" should be consistent with the title and should not be written as "disease modifying therapies". Check the whole manuscript and revise it to be consistent.

Terminology of the manuscript had been revised to be consistent.

9) Page 14, paragraph 3: Cai et al. investigated.....The author should not just extract the results and conclusions of others, but use 1-2 sentences to comment on the content.

Additional comments to the paragraph has been added.

Reviewer 2

T1DM was featured with insulin deficiency resulting from autoimmune-induced β cell destruction. Disease-modifying therapies, such as immuno- and regenerative therapies are promising methods to delay clinical onset of T1DM. This mini-review is interesting and I recommend to be published.

Thank you to Reviewer 2 for their kind words.

Reviewer 3

The author should better quote references from the last 5 years in order to reflect the latest developments in type 1 diabetes.

Thank you for the kind suggestion. We searched through PubMed and ClinTrials.gov again and several additional finished/currently running studies were identified. Their results were implemented into the manuscript.

Reviewer 4

This article introduces the pathogenesis, various treatment methods and clinical attempts of type 1 diabetes. However, most of the treatments mentioned in the article belong to the preclinical phase, with early detection and early treatment, while ignoring the treatment in the middle and late stages. As well as the treatment and improvement of diabetic complications. Adding this point will make the content of the article more complete.

Thank you for your kind criticism. We agree with our Reviewer that significant results have recently been achieved in later stages of the disease and diabetic complications with the introduction of various novel therapies. The presentation of these would significantly exceed the limits of a minireview, therefore, the following was added to Introduction:

"This minireview, focuses on the clinical applications of novel disease-modifying therapeutic intervention options in early stages of T1DM that may prevent or reverse clinically overt symptomatic T1DM. The presentation of the latest improvements available for middle and late stage disease, and diabetic complications is out of the scope of the current review."

Company editor-in-chief:

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Diabetes, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: <https://www.referencecitationanalysis.com/>.

Thank you for the suggestion. As suggested by the Reviewers the manuscript was extended with further research results. A total of 43 additional references were added, and the text of the manuscript was significantly extended.

Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file.

Figures were saved as a decomposable PowerPoint file.

Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

Table 1 was redrawn as per Author Guidelines of the World Journal of Diabetes.

Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022.

As per the suggestions by the Reviewers Figure 2 was significantly redrawn. We confirm, that all figures within the manuscript were de novo generated by the Authors for this article; and all references, if necessary, were cited in the figure captions.

Yours sincerely,

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