Peer Review File

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Reviewer Comments

Your article is very well written and the major aim to reevaluate existing MA concerning SCT considering their quality regarding safety and efficacy reporting is clear. However, to get satisfactory results/recognition, I feel the authors will need to better stratify their approach on a specific example as outlined below. Please consider using this example in your study primer for establishing a good working approach for your actual study and make your approach well understood for your potential readership.

Reply: Thank you for your precious comments during the COVID-19 period. First, "overview of meta-analyses" is a key evidence synthesis method in evidence-based medicine, and this type of method aims to summarize the evidence by including all published meta-analyses (doi: 10.26355/eurrev_201904_17484; doi: 10.1093/infdis/jiaa008; doi: 10.1016/j.jpurol.2019.12.002). And the concept of this method has been given in the background and methodological sections. Second, for clarifying the method, we have cited many typical examples and concept papers (Ref.10, 11, 25, 26, 27, etc.). Therefore, we believe readers could understand our methods and intentions.

1) Revised Title Suggestion & Abstract Background: "Safety and Efficacy of Stem Cell Therapy: An Overview Protocol on Published Meta-Analysis and Evidence Mapping".

Reply: Thank you for your precious suggestions. We believe the present title could reflect the study design and study aim, but we change the title according to your suggestion.

Although your major study aim is kind of clear (To evaluate MA concerning SCT, their quality concerning safety & efficacy analysis/reporting), the definition of your clinical SCT treatment modality (e.g. HSCT or MSCT) and the corresponding clinical target indication to be treated (e.g. BloodCancer or GvHD) is not. To help you out how to solve this problem, here some specific suggestions on a very hot topic that is now also being actively discussed in the ongoing COVID19 crisis and could thus be of interest to you for serving as a good example to illustrate your approach in your study primer, please see Pubmed-ID (PMID) 32574263 Moll et al. "MSC Therapies for COVID19: Importance of Patient Coagulopathy, Thromboprophylaxis, Cell Product Quality and Mode of Delivery for Treatment Safety and Efficacy", published in Frontiers Immunology May 2020 https://doi.org/10.3389/fimmu.2020.01091

Reply: Thank you for your precious suggestions. First, we have stated our research study and study intention, to map the evidence based on an overview of published meta-analyses, your mentioned the paper is interesting but not relevant with our inclusion eligibility; Second, although this evidence synthesis method has been accepted and recognized widely by researchers, policy decision-makers

and clinicians, we given several examples in our manuscript (Ref.10, 11, 25).

SCT is a very broad term and it does not really make sense to evaluate safety/efficacy for many entirely different clinical treatment modalities and indications pooled in one pot, as you will see once you start the study. You may have to focus on one specific treatment modality combined with one specific treatment indications where sufficient MA already exist to conduct your analysis (e.g. Safety/Efficacy of HSCT for HSCT for treatment of a certain type of blood cancer, or Safety/Efficacy of MSC-Infusion for treatment of GvHD). Here, one practical example to illustrate the problem, that could be studied in your analysis: If you would like to focus on MSCT, there are many different treatment indications (e.g. GvHD), different MSC products and also delivery methods you need to take into account. There are many different MSC products that differ greatly in their safety and efficacy profile, depending on the specific target indication (e.g. comorbidities of the patient etc, please see Perspective above on COVID19). For another more detailed review on the matter please also see PMID 30711482 Moll et al. "Intravascular MSC Therapy Product Diversification: Time for New Clinical Guidelines". Here one specific clinical problem is analyzed: "The comparison of intravascular vs. intravenous MSC delivery in the context adverse thrombotic events, which can be lethal to the patient", considering cell delivery PMID 31417542 Caplan et al. "MSC Delivery: Translational Challenges to Clinical Application", gives a very nice outline on local vs. systemic MSC delivery in numerous clinical indications and would support this statement very well. Considering clinical examples of some reported cases please see e.g. PMID 21107396 D. Cyranoski "Korean deaths spark inquiry" already published in 2010, PMID 28838459 Wu et al. "Thromboembolism Induced by Umbilical Cord Mesenchymal Stem Cell Infusion: A Report of Two Cases and Literature Review"; and PMID 24043757 Acosta et al. "Adipose MSC isolated from T2D patients display reduced fibrinolytic activity", as reviewed in PMID 31231366 Soria-Juan et al "Cost-Effective, Safe, and Personalized Therapy for Critical Limb Ischemia in T2DM", summarizing their experience with microthrombosis upon infusion of autologous AT-MSCs in diabetic patients with critical limb ischemia (CLI). Importantly, the review PMID 30711482 by Moll et al. also shows how MSC-products have greatly diversified over the past decade starting with mainly bone marrow (BM)-derived MSCs in 2008 to approximately equal use of BM, adipose tissue (AT), and perinatal tissue (PT)-derived MSCs today, which all three have very different safety and efficacy profiles for intravenous delivery, due to their differential expression of highly procoagulant tissue factor (TF/CD142). Considering comparison of the procoagulant activity of MSCs from different tissue sources, one of the first references with clinical relevance is PMID 26192403 "Different Procoagulant Activity of Therapeutic MSCs derived from Bone Marrow and Placental Decidua, both products studied here have been used in patients, please see studies by Ringdén et al. PMIDs 28744284, 29408819, 29533533, and 31803191. Please see PMID 32133010 "Editorial: Safety, Efficacy and Mechanism of Action (MoA) of Mesenchymal Stem Cell Therapies", which gives a good summary on the interrelationship of the role cell product TF/CD142 expression, the

use of fresh vs. thawed cells, their optimal washing / reconstitution / formulation, and the corresponding patient anticoagulation protocols for best clinical safety and efficacy in appreciation of the implicated underlying MoA of the cell product, which would fit very well at this point.

Reply: Thank you for your precious suggestions. First, overview is a key evidence synthesis approach to map the evidence based on an overview of published meta-analyses, it is different with any other secondary research or primary study. Second, SCT is a promising treatment method and is complex, but many meta-analyses only include preclinical primary studies. This indicating SCT is still need more studies to provide evidence. Therefore, the present manuscript was designed to map all published meta-analyses concerning on SCT. Third, according to our knowledge, many published overviews focusing on a wide topic (doi: 10.1016/j.ctim.2019.06.002; doi:10.1186/s12911-020-01298-5).

2) Introduction / Background Section: Again, I understand the problem you wish to address in your study that has also greatly concerned our study team in the past: That most MA available on safety/efficacy in particular for MSC-therapies is rather misleading so far, since the quality of the analysis has been insufficient. From your introduction I would suggest you should either focus on MSCT matched with suitable target indications and clinical aspect (as outlined above), or in your main study conduct several different sub-analysis for different treatment modalities as indicated below in the comments on search methods. Two recent reviews from Germany conducted with assistance of the German regulatory organization (Paul Ehrlich Institute, PEI) both summarize that adverse events in MSCT are highly underreported in existing MA and much more common than initially thought. In addition, efficacy data based on early phase clinical trials without randomization etc. are mainly anecdotal. These very important review articles should be mentioned in your study primer introduction and discussion: PMID 30063299 Bauer et al. “Concise Review: A Comprehensive Analysis of Reported Adverse Events in Patients Receiving Unproven Stem Cell-Based Interventions” published in Stem Cells Translational Medicine in 2018, which gives a broader overview on various reported adverse events, and PMID 30711482 Moll et al. “Intravascular MSC Therapy Product Diversification: Time for New Clinical Guidelines”, which is a followup to this review and focuses on one specific problem, which is now discussed to be integrated in national and international WHO-guidelines for stem cell therapies: 32574263 Moll et al. “MSC Therapies for COVID19: Importance of Patient Coagulopathy, Thromboprophylaxis, Cell Product Quality and Mode of Delivery for Treatment Safety and Efficacy”, published in Frontiers Immunology May 2020 https://doi.org/10.3389/fimmu.2020.01091.

Reply: Thank you for your precious suggestions. First, we have stated our research study and study intention, to map the evidence based on an overview of published meta-analyses. The data regarding safety and efficacy will be summarized descriptively, will include effect size and 95%CI. Second, we know the different SCTs may have different effectiveness for different diseases, and our study is to address this question; Third, scoping review is the other method to synthesis the evidence on

regarding a given area or topic, and it can include all available types evidence. Considering our study aim, we select overview method. But if you are interested in all available types evidence concerning on SCT, your team could make a scoping review.

3) Search Method: In your PUBMED and EMBASE search your keywords include: “stem cells”, “mesenchymal stem cells”, “Stem cell transplantation”, “peripheral blood stem cell transplantation”, “cord blood stem cell transplantation”, “hematopoietic stem cell transplantation”, “systematic review”, “meta-analysis”, and “meta”. The problem here is that the stratification is way too broad and may not work since you have two or three major categories in here that are interrelated, but their safety and efficacy evaluation differ greatly. The need for search-terms for meta-analysis it is clear, but then you really need to separate the different major groups and categorize / sub-stratify either:

a) E.g. Meta-analysis + Stem Cells or SCT + Mesenchymal stem cells

b) E.g. Meta-analysis + Stem Cells or SCT + either HSCT, PBSCT, CBST

Reply: Thank you for your precious suggestions. First, the present research is an overview protocol, and based on our study aims, we will include published meta-analyses concerning SCT. Therefore, the search strategy is consisting of “SCT” section and “meta-analysis” section, and this is common in overviews (doi: 10.1016/j.ctim.2019.06.002; doi: 10.1111/wvn.12459; doi:10.1186/s13643-019-1191-5). Second, for avoiding missing some important, we will use MESH terms and keywords. Third, the present manuscript is only a protocol, many situations are remaining unknown before competition of literature screening. According to common practice in overview conduct, we will select eligible meta-analyses.