

Report on MSCSE1236

Paper title: The immunosuppressive potency of mTOR inhibitors in solid-organ transplantation

SUMMARY

This review describes the capacity of mTOR inhibitors to influence immune responses in patients undergoing solid-organ transplantation. The scope of the article is broad, covering the effects of these inhibitors on regulatory T cells, advances in methods to measure the potency of immunosuppression, and the anti-cancer properties of these drugs. Although mTOR inhibitors have been in clinical use in the transplant setting for some time, an updated review might be warranted. Nevertheless, the challenge is to produce a cohesive overview when aiming for a dual focus; indeed, we found the primary focus of the paper to be clear while the secondary focus on cancer was less so. Consequently, we have suggested revisions that will help to clarify the scope and emphasise the potential dual advantages of mTOR inhibitors among transplant patients.

Essential issues

- The review lacks an appropriate Introduction. Rather than setting the scene by providing background on solid-organ transplantation – the key clinical issue relevant to the article – the review begins with detailed information on the allo-immune response.
- The reason why such this review is important or topical is not made clear. Timeliness should be emphasised in both the Abstract and the Introduction.
- The article is rather disjointed in terms of its structure. For example, regulatory T cells are discussed in two different sections, both of which included introductory information on this cell type. We have therefore suggested merging these sections into a text box. Other minor rearrangements have been suggested throughout the manuscript. Please note that these changes have resulted in the re-ordering of many references.
- Many clinical studies are described but key details are often lacking, which hampers clear understanding of the results discussed. For this reason, some of the summary statements do not seem well-grounded in the evidence provided.
- References for some factual statements are missing: we recommend checking carefully to ensure that the review is comprehensively referenced.
- The manuscript would benefit from more critical appraisal of the clinical studies.

Other important issues

- Most of the data on immunological effects of mTOR inhibitors focus on rapamycin, but it is not stated whether similar results have been observed (or can be assumed to occur) with everolimus. In addition, it would be helpful to include further detail on mTOR inhibitors in development, if such information is available.
- The figures are lacking suitable legends. We also suggest adding up to three more display items (see below for details).

Possible journals for submission

Submitting your review to a specialist transplantation journal seems a valid strategy given the primary focus of this review on mTOR inhibitors in transplantation. This approach might be more appropriate than targeting a cancer journal, as the anti-cancer effect of these drugs is currently a small, secondary focus of the review. Most journals require a presubmission enquiry together with a brief outline of the review and a statement regarding timeliness before they will consider inviting the full manuscript for a review. The success rate of presubmission queries varies by journal, and often depends on other factors such as previous publications on the topic and whether similar articles have already been commissioned but not yet published. Furthermore, some journals will only consider reviews that have been invited by the Editor or Editorial Board.

- If the review is substantially revised to a high standard, you might consider submission as an 'Overview' to [Transplantation](#), which covers "important advances in transplantation." Overviews are "concise reviews of topics of special timeliness and interest to scientists and clinicians in the field of transplantation" and permit up to 6000 words. A presubmission enquiry is required.
- [Transplant Immunology](#) might be a more realistic target journal than *Transplantation*. It has a broad readership, from basic scientists to transplant physicians, in line with the broad scope of your article. Reviews can be up to 50 typed pages plus 60 references. A presubmission enquiry does not seem to be required. However, as cutting the references to <60 would probably compromise your review (indeed, we have suggested the addition of more), you might consider writing to the journal to ask for guidance on this point before submission
- The article is longer than many journals permit for reviews, which limits the number of potential targets. With the revisions suggested, the review could become even longer (although we have also suggested where information can be condensed). However, if you decide to substantially condense the review (to ~4000 words), and can revise to a very high quality, approaching [Transplant International](#) or [Blood](#) might be an option. Both of these journals require a presubmission enquiry.

FEATURES OF THE PAPER

Organisation and flow

A review can be formatted in many different ways, but there are generally three key elements: a comprehensive Introduction that sets the stage for the article, a central section that reviews the evidence and summarises key concepts in tables and figures, and a closing section that summarises the main points covered and provides directions for future work in the area. As a review often covers a range of subtopics, descriptive section headings and transition sentences, often when moving from one subtopic to another, are crucial to help the reader navigate through the article and to create a coherent and logical flow.

- We have suggested some changes to the structure, mainly in the Introduction and in sections describing regulatory T cells, and some additional subheadings.
- As noted above, the cohesion and flow of the paper can be further improved by emphasising the secondary focus on cancer earlier in the article.

Title and abstract

Many people who encounter your paper will read only the title and the abstract. Therefore, to attract the desired target audience, these sections should be concise and enticing, yet specific enough to clearly communicate what the review is about. The abstract should

provide a brief and self-contained description of the background of the field, the focus of the evidence that will be reviewed, and the most important take-home message(s) of the review.

- We suggest referring to mTOR inhibitors in the title (rather than referring specifically to everolimus); you might also consider specifying whether the review is focused on solid-organ transplantation. Finally, to reflect the main focus on the role of mTOR inhibitors in transplantation, you might consider removing 'and cancer' from the title.
- The Abstract is generally good, although the cancer aspect could be emphasised. In particular, we recommend that you highlight that transplant recipients are at increased risk of cancer, which explains the logic of the dual focus of your review.

Introduction

A review's Introduction should consist of background information that provides context for the evidence discussed in the rest of the article – 'setting the stage', so to speak. As many topics tend to be over-reviewed, it is also useful to highlight what sets the review apart from others on a similar topic, and what makes this particular topic important now (timeliness).

- An appropriate Introduction for a review about solid-organ transplantation was lacking. We moved up some pertinent text that could form the basis of a revised Introduction, but the inclusion of further information is recommended. We suggest opening with some statistics about liver transplantation (e.g. incidence and mortality).
- We have suggested moving the background information on agents used in transplantation to the Introduction.
- Please consider emphasising that new immunosuppressive drugs, or new information about existing immunosuppressive drugs, are urgently required to improve the care of transplant recipients, which will highlight the need to review this topic.
- The Introduction lacked background information about cancer risk after transplantation. As the effects of mTOR inhibitors on cancer are a secondary focus of the review, this aspect should be mentioned in the Introduction.
- We have suggested minor modifications to the guiding paragraph at the end of the introduction that reiterates the objective of the review and the approach taken.
- Most of information about the allo-immune response could be moved to a new section.

Main text

The main text of a review should present, in a logical order, the evidence relevant to the article's focus and bring the reader up to date. In presenting the evidence, a review should also interpret it in the context of what is already known, thereby educating the reader. Where appropriate, it should also critically appraise the evidence reviewed – that is, point out key strengths and weaknesses of studies discussed and how they might have affected study results – rather than treating all evidence as equal. Ideally, a review should be comprehensive, citing all recent relevant studies; however, in practice, this is not always possible. If you have taken a particular approach to selecting the evidence reviewed, this should be made clear. The main text should be complemented by display items (figures, tables, and text boxes) that highlight key concepts and provide information in a summary format.

- The main text of the review contains a great deal of information. Overall, this is fairly well organised, although we have suggested some restructuring to improve the flow.

- The role of B cells is covered only briefly early in the review. Later in the article, it becomes clear to the reader that B cells actually have a central role in the rejection response. We recommend describing the role of B cells more comprehensively in the section on the allo-immune response.
- Many clinical studies are discussed, but in most cases key details are missing. For example, it is often unclear whether immune cells were isolated from patients treated with immunosuppressive drugs or whether immune cells were exposed to drugs *in vitro*. In some cases, the comparator group is not described, so the relevance of the reported results is difficult to discern. More detail might be provided so that the setting of each study discussed is clear.
- Many of the clinical studies described used a combination immunosuppressive drug regimen, meaning that mTOR inhibitors were not assessed in isolation, so it could be difficult to disentangle their effects from those of the combination treatment. You might consider commenting on this challenging aspect of research in this area.
- As noted above, we have suggested merging the information on regulatory T cells into a text box. These are a feature of reviews in most journals; however, please check the requirements of your target journal before submitting.
- Approaches that can be used to measure lymphocyte proliferation or B-cell function are not described, even though their use is mentioned extensively in the clinical studies reviewed later.
- The sections describing methods for measuring soluble CD30 and the ImmuKnow assay are quite long. As these methods are barely mentioned elsewhere in the article, you might consider condensing these sections, leaving more space to expand on other elements in the review.
- The evidence presented for the effects of mTOR on regulatory T cells is quite limited. Please consider discussing additional studies here to strengthen this section.

Concluding paragraphs

Ideally, the closing section of a review should provide a summary of what has been presented in the main text. While it can speculate on what might lie ahead in terms of discoveries that are around the corner, take-home messages should be grounded in the scientifically sound evidence that has been reviewed earlier in the article. The closing section of a review can also include some forward-looking comments on what further research might address the unanswered questions or otherwise further understanding about the topic.

- This section does not flow well as it is not clearly organised. We have therefore suggested separating the Conclusions into three main paragraphs (one for each take-home message) that summarise the immunomodulatory effects of mTOR inhibitors in transplantation; methods used to measure the potency of these drugs; and the potential of mTOR inhibitors to reduce cancer risk. The latter paragraph requires some expansion.
- Please also consider adding some additional comments on the future of this field.

Display items

The display items are well-presented and complement the main text of the review.

- For clarity, we recommend adding descriptive legends for all figures.

- The data shown in Figure 3 seem to be from a previously published article. We suggest citing this article in the legend; note that reproduction from another source might require copyright permission. Also, detailed information about the study is lacking.
- We recommend adding one or more references to Table 1.
- You might consider adding a table that summarises the methods used to measure the potency of immunosuppressive agents, perhaps noting the pros and cons of each.
- You might also consider adding a schematic that illustrates the potential dual advantages of mTOR inhibitors in transplant patients (i.e. maintaining immunosuppression/immunomodulation while reducing cancer risk) to capture the dual focus of the review.