Peer Review File

Reviewer 1:

Comments:

1. Overall, the manuscript reviews the potential therapies for dry AMD and is fairly complete overview but does not provide enough detailed review in each case (MOA, trial size, potential impact, etc).

Reply 1: Mentioned paragraphs were revised by adding required data and recent updates on each therapy. Page 11, line 215

2. There were some mistakes in the review of various developing non-gene therapy technologies, so data needs to be checked, hence the need to verify all approaches for a good review. For example, PBM using the Valeda Light Delivery System as a mitochondrial approach to improve vision and slow disease progression was poorly presented.

Reply 2: The section was revised adding required data and recent updates on each therapy. Page 11, line 215

3. The LIGHTSITE I (Markowitz et al) manuscript and results was not discussed in any detail and mistakenly cited as a preclinical study along with another PBM laser clinical study by Ivandic.

Reply 3: The revision was performed. Page 12, line 247.

4. The LIGHTISITE II was mentioned but not the ongoing US FDA-approved LIGHTSITE III pivotal Clinical trial.

Reply 4: The revision was performed. Page 12, line 247.

5. This review clearly wants to discuss the future of gene therapy, but a better overall job needs to be made to compare and verify the multiple approaches besides listing the clintrials summary.

Reply 5: Required explanations were added under the title "future perspectives". Page 22, line 463.

Reviewer 2:

Comments:

The article gives a brief introduction to genetics of AMD and a broad overview of novel genetic therapies under investigation for this disease. The authors have done a thorough study of available published material on the subject, and present it in a succinct manner. The topic would be relevant to both clinicians interested in retinal diseases and researchers in this field.

As a general comment, it would be of value to revise the language in the article, which at times is hard to follow. Some specific cases of this are mentioned below, but this comment could apply to the text in general. Please find these and other specific comments below.

1) The authors state that no language restrictions were applied to filter the search results. A remark should be made on how foreign language articles were reviewed (were they translated?). In case no non-English articles were found, this should be explicitly mentioned.

Reply 1: The explanation was added. Page 5, line 80.

2) Line 169 should read "vitamins and minerals" instead of "vitamins and materials". If the authors are talking about antioxidants in general here (which is not entirely clear, see next comment), the term "antioxidants" is sufficient.

Repy 2: The correction was performed and the paragraph was revised and inserted in the end of the section. Page 10, line 197.

3) Supplementation with vitamins and minerals to prevent development of neovascular AMD has been studied in the AREDS and AREDS2 trials, and is currently the only therapy option available. As such, referring to it as "some antioxidant vitamins and minerals", if that is indeed what the authors are attempting, seems to be an understatement. These regiments are so well-known, that they should be mentioned by name. If this is not what the authors are referring to, it is advised to add references to the studies in question.

Reply 3: The section was revised and adequate data were presented. Page 10, line 197.

4) Lines 313-314. It would seem that the authors here refer to voretigene neparvovec (Luxturna) for the treatment

of Leber congenital amaurosis, although it is not mentioned directly. The reader might be left under an impression that all such therapies are in trial stages of development. In fact, Luxturna was the first gene therapy to be approved by the FDA (and subsequently the EMA) to treat an inherited disease, an enormous achievement that should be acknowledged in a review concerning viability of such therapies in other retinal disorders.

Reply 4: An explanation was added to the paragraph. Page 16, line 337.

5) For clinicians reading the review, it would be of interest to know whether any markers exist to stratify patient response to treatment with the currently used anti-VEGF agents - which would be a helpful addition to the paragraph about genetics of AMD.

Reply 5: Some paragraphs on the topic were added to the end of the genetic section. Page 8, line 162.

6) Some structural inconsistencies can be seen in the text. Under the title "Novel treatments of AMD; the alternatives of gene therapy", dry AMD is discussed first, followed by wet AMD , while under "Gene therapy", the order is reversed. A reader would find the structure easier to follow if the structure was consistent throughout the paper.

Reply 6: The correction was performed. Gene therapy for dry AMD is now disscussed first. Page 17, line 357.

7) The paragraph starting at line 421 brings up some relevant discussion points considering cost versus benefit of the disease. The language, especially in the first part of the paragraph, is somewhat hard to follow. A revision for clarity would be highly advised.

Reply 7: A revision was performed. Page 21, line 439

8) A short paragraph on future perspectives would be a logical approach to conclude the review. Do authors believe any new therapies or trials to be especially promising? Are there any pathophysiological avenues left unexplored that should attract more attention from researchers?

Reply 8: The future perspective section was added before the summary. Page 22, line 463.

9) I do appreciate the summary in the tables 1 and 2. The split between complement and non-complement related genes seems warranted. However, perhaps more relevant than chromosome numbers would be the gene function (where known), as this might inform the reader on where the genes might fit in the pathogenesis of AMD.

Reply 9: The chromosome numbers were removed. Phenotypic significance are presented in related column, and the details of the genes are presented in the text.