Peer Review File

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Reviewer 1:

Comments:
Overall, it is a well-written summary of the current treatments for wet AMD and dry AMD. If authors provide a table to summarize therapies, it will help readers to understand.
We thank the reviewers for their insightful comments. We have additionally included 2 figures to summarize the therapeutic classes for neovascular and non-neovascular AMD.

1.Can you discuss more pros and cons of each therapy? For example, rate of response, side effects, and resistance are important piece of information.

Reply 1: We thank the reviewer for this comment. We thoroughly describe the pros and cons of different treatments in Table 1, and added more information in lines 195-197. Intravitreal Anti-VEGF therapy has been well studied for wet AMD. Apart from this, unfortunately, gene therapies, suprachoroidal therapies, nano particle drug delivery systems and other therapeutics are in early stage clinical trials with overall limited sample sizes. This makes evaluation of response rate, and especially resistance in the case of viral gene therapies, and unknown variable and an important subject of investigation.

2. Regarding intravitreal gene therapy and subretinal gene therapy, different anti-VEGF drugs were applied by a different route. Is there any reason or advantage to choosing a different route for different therapy?

Reply 2: We thank the reviewer for this question. We have added Table 1 which tabulates pros and cons of different treatment routes including intravitreal, subretinal, and other routes. In short, intravitreal injection is advantageous due to its minimally invasive nature and low cost. On the other hand, the biggest advantage of subretinal injection is its favorable immune response as the subretinal space has the greatest immune privilege. Also, subretinal injection has historically yielded the highest expression of the gene product at the level of RPE and photoreceptors.

3. Authors summarized intravitreal injection, subretinal injection, suprachoroidal approach, drug delivery systems, and oral therapies. However, there are also eye drops in development for wet AMD, which are not discussed. Please discuss.

Reply 3: Thank you for this comment. Please see lines 570-585 for this newly added information.

4. Minor point, page 5 line 10 and page 9 line 16, “bimonthly” can mean either twice per month or every 2 months. Please clarify.

Reply 4: Thank you for pointing this out. We have changed “bimonthly” to “four to eight week” in line 124 and “every other month” in line 535.

Reviewer 2:

Comments:
This is a solid and well-written review highlighting the routes of ocular drug delivery for age-related macular degeneration (AMD). The review focuses on currently available and future promising treatments for age-related macular degeneration (AMD). Overall, the manuscript is logically organized and is a good updated review of AMD's potential therapeutic targets and therapies.

The manuscript's main focus is on what is coming down the pipeline for both wet and dry AMD.

1. The authors performed a thorough review of the literature and cited the majority of the landmark studies. We are currently witnessing a considerable drive to revolutionize AMD treatment. Regardless of having available rather successful therapies for wet AMD, due to a socio-economic burden to patients and the health care system, identifying novel treatments that would be more cost and clinically effective is very attractive for ophthalmic research. Besides, choosing the most accountable targets, drug administration routes are another exciting venue for exploration. The still unmet need is dry AMD treatment. Besides, supplementation with the AREDS formulation and lifestyle modification, no other treatments are currently available.

Reply 1: Thank you for this comment, we completely agree. Our ability to preserve vision in neovascular AMD is excellent, although the burden to patients is very significant and a more durable treatment is needed. Dry AMD and GA are the subject of numerous drug therapies which hopefully make it down the pipeline and enter clinical use. The drive for new routes of administration has in part been driven by gene therapy, especially with subretinal and suprachoroidal-to-subretinal delivery.

2. The authors primarily focus on wet AMD treatments, but to a lesser degree, reflect on some of the dry AMD treatments coming down the pipeline. Nonetheless, many dry AMD treatments, successfully or less successfully advanced in the trials, remain unmentioned (e.g., Lampalizumab, Eculizumab, FHTR2163). Indeed, the review provides a reasonably comprehensive update on recent clinical trials in the field and highlights some shortcomings of the different therapeutic targets and routes of administration but barely mentions unresolved knowledge gaps.

Reply 2: Thank you for this comment. We have added information on the mechanisms of

action and clinical trial outcomes of Lampalizumab, Eculizumab, and FHTR2163 in lines 503-513, 541-549, and 563-567. We also added a statement on unresolved knowledge gaps in lines 619-621.

3. The authors made commendable efforts in summarizing recent literature, mainly discussing the most up-to-date approved therapeutics and therapeutic pipeline while focusing on delivery routes. However, the pathogenesis of AMD is very superficially described and could be significantly improved. The manuscript would benefit from emphasizing the disease's multifactorial character and explaining its pathogenesis in more detail. Additionally, it would be good to summarize different treatment routes in a table format, emphasizing their differences.

Reply 3: Thank you for this comment. More information on the pathogenesis was added in lines 76-80, and is elaborated further within each treatment modality and drug target. To help summarize the ocular routes of delivery, we have created a new Table 1 which summarizes the advantages and disadvantages of each route.

4. A few similar reviews came out in 2020 (e.g., doi: 10.3389/fbioe.2020.549089, doi: 10.3389/fbioe.2020.588014, doi: 10.3389/fcell.2020.612812, doi: 10.1177/25158414211003381), that should be referenced, and the differences between this one and the other should be emphasized.

Reply 4: Thank you for this comment. There are many similarities between our review and the aforementioned reviews. We have referenced them and made a statement in lines 102-105 regarding this.