March 4, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 15637-review.doc).

Title: DIABETIC MACULAR EDEMA: the role of anti-VEGF therapy

Author: Emre Güler, Ramazan Yağcı

Name of Journal: *World Journal of Ophthalmology*

ESPS Manuscript NO: 15637

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewers.

3 References and typesetting were corrected.

Thank you again for publishing our manuscript in the *World Journal of Ophthalmology*.

Sincerely yours,

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Reviewer 1

1. ABSTRACT: Diabetes is the leading cause of blindness among working-aged individuals in industrialized countries but probably not in underdeveloped countries.

Response: We have revised the statement to:

"Diabetic retinopathy is the leading cause of vision loss in the working-age population in industrialized countries and is related to 1%-5% of cases of blindness in the world."

2. This manuscript is incorrectly titled since it does not discuss all treatment options for DME. It should be entitled something such as "Treatment of Diabetic Macular Edema with VEGF inhibiting Drugs".

Response: We have revised the title to:

"**DIABETIC MACULAR EDEMA: the role of anti-VEGF therapy**"

3. In Core Tip, diabetes is not the leading cause of blindness.

Response: We have revised the statement to:

"Diabetic retinopathy is one of the leading causes of vision loss in the industries countries."

4. At this time there is no ongoing phase III trial for pegaptanib, and because of its minimal use by physicians there will not likely be one.

Response: We have added the following phase 2/3 randomized controlled, multicenter trial:

"Sultan MB, Zhou D, Loftus J, Dombi T, Ice KS, Macugen Study G. A phase 2/3, multicenter, randomized, double-masked, 2-year trial of pegaptanib sodium for the treatment of diabetic macular edema. Ophthalmology 2011;118:1107-1118."

5. The READ-2 did not show improved VA at 36 months in patients treated with laser or laser + ranibizumab? I believe this statement is incorrect.

Response: We have revised the 36 month results of READ-2 study to:

"The 36 month results demonstrated that the mean improvement from the baseline BCVA in the ranibizumab group was 10.3 letters at month 36 vs 7.2 letters at month 24 (ΔBCVA letters = 3.1, P = .009), and CFT at month 36 was 282 μm vs 352 μm at month 24 (ΔFTH = 70 μm, P = .006). Changes in BCVA and CFT in the laser group (-1.6 letters and -36 μm, respectively) and the ranibizumab + laser group (+2.0 letters and -24 μm) were not statistically significant. They concluded that long-term visual outcomes for treatment

of diabetic macular edema with ranibizumab are excellent, but many patients require frequent injections to optimally control edema and maximize vision."

6-7. DRCR.net Protocol I did not contain a ranibizumab monotherapy arm. Include more detail about Protocol I, such as letters improved and retreatment rates through 3 years

Response: We have given the following studies:

Diabetic Retinopathy Clinical Research N EM, Aiello LP, Beck RW, Bressler NM, Bressler SB, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 2010:1064-1077 e1035.

Diabetic Retinopathy Clinical Research N EM, Qin H, Aiello LP, Beck RW, Bressler NM, et al. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: three-year randomized trial results. Ophthalmology 2010:2312-2318.

In addition the results were revised to:

"The 1-year mean change (+/-standard deviation) in the visual acuity letter score from baseline was significantly greater in the ranibizumab + prompt laser group (+9+/-11, P<0.001) and ranibizumab + deferred laser group (+9+/-12, P<0.001) but not in the triamcinolone + prompt laser group (+4+/-13, P=0.31) compared with the sham + prompt laser group (+3+/-13). Reduction in mean central subfield thickness in the triamcinolone + prompt laser group was similar to both ranibizumab groups and greater than in the sham + prompt laser group. Regarding the 3 years results, focal/grid laser treatment at the initiation of intravitreal ranibizumab is no better, and possibly worse, for vision outcomes than deferring laser treatment for 24 weeks or more in eyes with DME involving the fovea and with vision impairment. They suggested these differences in visual acuity at 3 years may be related to fewer cumulative ranibizumab injections during follow-up in the prompt laser treatment group. Follow-up through 5 years continues."

8. Sham groups in RIDE/RIDE as well as treatment groups were eligible for laser rescue at 3 months.

Response: We have added the following statement:

"Macular laser was available per-protocol–specified criteria."

9. The RESTORE study also included a laser group.

Response: We have added the following statement:

"The RESTORE study evaluated the superiority of ranibizumab 0.5 mg monotherapy or combined with laser over laser alone based on mean average change in BCVA over 12 months in 345 DME patients."

10. We have no data to say that aflibercept has the longest half-life in the human eye.

Response: We have excluded the data.

11. There was only one laser group in DA VINCI so why were there 2 thickness averages.

Response: We have revised the statement to:

"Regarding the decrease in CFT, it was ranged from -165.4 to 227.4 μm in the aflibercept groups and 227.4 to 58.4 μm in the laser groups."

12. Phase III results from VIVID and VISTA have been published and need to be described.

Response: We have added and given detail for these studies.

13. Bevacizumab binds only VEGF-A isoforms, not those from other families.

Response: We have revised the statement to:

"Bevacizumab is a full-size, humanized, recombinant monoclonal immunoglobulin G which combines all VEGF A isoforms."

14. Bevacizumab is the poorest studied anti-VEGF for DME because research has not been supported by industry. There is no level I evidence supporting its use as has been established with ranibizumab and aflibercept.

Response: We have excluded the statement:

"Currently it is the most common used anti-VEGF substance."

15. The DRCR.net evaluated many previously treated DME eyes but not those that were refractory to therapy.

Response: We have revised the statement to:

"In summary, DRCR.net trial revealed that bevacizumab is a favorable agent for treatment of DME in primary cases and also in previously treated DME eyes."

16. Safety results need to focus on DME trials, not those from AMD.

Response: We have excluded the safety results from AMD trials.

17. Since pegaptanib is rarely used it should only be briefly mentioned.

Response: We have given a brief paragraph to mention its safety in DME.

18. Where is DME safety data on ranibizumab? Results from RISE/RIDE showed higher incidences of stroke in the 0.5 mg group. Therefore, the FDA approved only the 0.3 mg dose.

Response: We have given the safety data from the major trials for ranibizumab in DME.

19. The Mason manuscript talks about post-vitrectomy endophthalmitis, not post-bevacizumab.

Response: We have excluded the mentioned study.

20. The incidence of bevacizumab related side effects in cancer is not relevant to this manuscript.

Response: We have excluded its safety results in cancer.

21. Why is the cost of bevacizumab treatment high? Provide comparative data from cost-effectiveness analyses.

Response: We have discussed the cost effectiveness for ranibizumab and bevacizumab in DME treatment.

22. What are the pertinent comparative studies? Protocol T?

Response: We have added the following paragraph:

Protocol T, phase 3 study sponsored by the DRCR will compare the safety and efficacy of intravitreal aflibercept (2.0 mg), bevacizumab (1.25 mg) and ranibizumab (0.5 mg) for DME in 660 patients recruited from different clinical centers in the US. The primary outcome in this study is to evaluate the changes in BCVA at month 12. Protocol T is currently recruiting patients

23. A chart listing the most important trials with top line results would be helpful.

Response: We have given the table 1.

Reviewer 2

This is an interesting review; title should change in "**DIABETIC MACULAR EDEMA: the role of anti-VEGF therapy**" or similar, since the authors do not discuss other treatment modalities (sub-treshold laser and so on). English editing is required.

Response: We have revised the title to: "**DIABETIC MACULAR EDEMA: the role of anti-VEGF therapy**"

Answer to chief editor:

We have added the latest information for the following studies regarding the recommend of the chief editor:

<!--[if !supportLists]--> · <!--[endif]-->DRCR.net 5 year results

<!--[if !supportLists]--> · <!--[endif]-->The RISE and RIDE 36 month results

<!--[if !supportLists]--> · <!--[endif]-->The RESTORE study 2 and 3 years results

<!--[if !supportLists]--> · <!--[endif]-->The VIVID study 2 year results

<!--[if !supportLists]--> · <!--[endif]-->DRCR.net Protocol T 12 month results

Best Regards.