Author’s response to reviews

Title: Efficacy and safety of widely used treatments for macular oedema secondary to retinal vein occlusion: a systematic review

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Author’s response to reviews: see over
Dear Dr Harold,

On behalf of the authors, I am pleased to submit the following revised manuscript for publication in **BMC Ophthalmology**:

**Title:** Efficacy and safety of widely used treatments for macular oedema secondary to retinal vein occlusion: a systematic review

**Authors:** Julie Glanville, Jacoby Patterson, Rachael McCool, Alberto Ferreira, Kerry Gairy and Ian Pearce

**Ref:** MS 2039420465926535

We thank the reviewers for their constructive and largely positive comments. We have revised the manuscript according to the comments received and have prepared a full list of responses. There were three comments that required significant work:

In response to the comments about clarifying the inclusion and exclusion criteria for RCTs selected for this review, we have amended the title, abstract and methods to clarify that the review includes widely used treatments available at the time of the review, specifically ranibizumab, bevacizumab, dexamethasone IVT and laser photocoagulation.

In response to the comment about mentioning the two large aflibercept RCTs (GALILEO and COPERNICUS), we have added background information on aflibercept (approved since the review was carried out), a short discussion of the RCT results and a proposal that future reviews include these data.

In response to the comment about improving the description of the mode of action for dexamethasone, we have included more details on the effect of this treatment on the other cytokines mentioned by the reviewer.

We believe that our research meets the high standards of your journal and will be of interest to your readership. We look forward to hearing from you regarding our submission.

Yours faithfully

JULIE GLANVILLE
Associate Director
Response to reviewers’ comments

We thank the reviewers for their constructive and largely positive comments. We have revised the manuscript according to the comments received and have prepared a full list of responses. Reviewers’ comments are numbered with our responses given as bullet points below:

Specific comments by Reviewer 1

1. Please clarify the inclusion and exclusion criteria for RCTs selected for this review. Table 1 only specifies Ranibizumab, Bevacizumab, Dexamethasone IVT, and Laser Photocoagulation- Does that mean all other treatment modalities were excluded? If this is the case it needs to be clarified in the title, abstract and the main methods section, and potential limitations of the review mentioned in the discussion.

   • [Title] We have amended the title of the manuscript to reflect the focus of the review on widely used treatments available at the time of the review: “Efficacy and safety of widely used treatments for macular oedema secondary to retinal vein occlusion: a systematic review.”

   • [Page 3, line 5] We have updated the 2nd sentence of the abstract to read: “This systematic review assessed the efficacies of widely used treatments for macular oedema secondary to RVO.”

   • [Page 6, line 30–page 7, line 3] We have updated the methods to state: “The main interventions included in searches were ranibizumab, bevacizumab, dexamethasone IVT and laser photocoagulation. Data for other interventions were included only for comparisons with the main interventions.”

   • [Page 19, lines 17–25] We have also added reference to the two large aflibercept (approved since the review was carried out) RCTs (GALILEO and COPERNICUS), a short discussion of the RCT results, and a proposal that future reviews include these data.

2. The systematic search was performed on 18th Nov 2010 - this date should be included in the main abstract so readers are aware that the review may not be up to date and would not cover or include the many RCTs published in the last 55 months. It may be worth mentioning this as a potential limitation in the discussion.

   • [Page 3, line 8] We have added the date of the review (November 2010) to the methods section of the abstract.
   • [Page 19, lines 17–25] We have also added a discussion of the aflibercept RCTs, published since the review was carried out.

3. (Discretionary revision) I note that the Ranibizumab studies (BRAVO/CRUISE) are described as “high-quality” in the text but similar mention of level of quality is not present for the Dex IV study GENEVA. I note the quality scores were fairly equal - 6/8 for Lucentis studies and 7/8 for GENEVA. To avoid bias can you call both studies high quality or exclude this comment.

   • [Page 3, line 18] We have removed the phrase “high-quality” from the abstract.
[Page 10, line 17] We have added the phrase “high-quality” to the line: “The efficacy of dexamethasone IVT in patients with BRVO or CRVO has been investigated in two large, high-quality, prospective, multicentre, masked, parallel-group RCTs...”

4. (Discretionary revision) I feel the review would be incomplete without at least a mention of the large aflibercept RCTs (GALILEO and COPERNICUS) which is currently undergoing NICE review, especially as other papers published after the systematic review date which are non RCTs e.g. HORIZON are quoted in the discussion.

[Page 6, line 8] In the introduction, we have added reference to aflibercept (approved since the review was carried out) to the discussion of available therapies.

[Page 19, lines 17–25] In the discussion, we comment on the efficacy and safety results from the two large aflibercept RCTs (GALILEO and COPERNICUS) and make a proposal that future reviews include these data.

Specific comments by Reviewer 2:

1. Mechanisms of action of ranibizumab (anti-VEGF) is well described. However, the other actions (mechanisms) of dexamethasone need to be clearly stated rather than a bland statement e.g. on Pg. 5-6 that it is anti-inflammatory. Specifically, the effects on other cytokines e.g. IL-6, IL-8, ICAM-1 and MCP-1, some of which are elevated in RVO should be stated. This is especially as the anti-VEGF effect of dexamethasone is limited. Mechanisms of triamcinolone need to be mentioned as well.

[Page 6, lines 1–4] We have included more details on the effect of this treatment on the other cytokines mentioned by the reviewer in the background discussion of available treatments: “Dexamethasone IVT is a sustained-biodegradable implant containing the corticosteroid dexamethasone. Corticosteroids including dexamethasone are known to have anti-inflammatory, anti-angiogenic properties and may inhibit the expression of VEGF and other proinflammatory cytokines such as IL-6, ICAM-1 and MCP-1; it is prescribed at a dose of 0.7 mg.”

2. The referencing needs to be improved. E.g.:
   i) On Pg. 9, 2nd paragraph: cite BRAVO
      • [Page 9, line 16] We have added the reference (Campochario et al. 2010).
   ii) Pg. 9, 3rd paragraph: Insert ref. for ROCC
      • [Page 9, lines 25 and 28] ROCC is referenced along with CRUISE earlier in this paragraph, but we have added further reference to both for clarity.
   iii) Last paragraph: ditto
      • [Page 10, line 8] We have added references for CRUISE (Brown et al. 2010) and ROCC (Kinge et al. 2010).
   iv) Pg. 14 1st paragraph: reference in text
      • [Page 14, lines 13 and 15] We have added references for GENEVA (Haller et al. 2010; Shyangdan et al. 2010), for BRAVO (Campochario et al. 2010) and CRUISE (Brown et al. 2010).