PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Treatments for macular oedema following central retinal vein occlusion: systematic review
AUTHORS	Ford, John; Clar, Christine; Lois, Noemi; Barton, Samantha; Thomas, Sian; Court, Rachel; Shyangdan, Deepson; Waugh, Norman

VERSION 1 - REVIEW

REVIEWER	Y C Yang Royal Wolverhampton Hospitals NHS Trust UK Received honoraria from Novartis, Genetech, Allergan, Bayer, Pfizer.
REVIEW RETURNED	20-Oct-2013

GENERAL COMMENTS	Line 52-54- Avastin is actually a very expensive drug and is only cheap because it is aliquoted. May need to state this and comment on how the lisensing authorities can approve the use of aliqouted drug in a registrations study as aliquoting has never been achieved before in an industry sponsored phase III study for the purpose of product registration with licensing authorities. Detailed description of method of literure search and inclusion criteria of articles. line 49- need to specify triamcinolone used in Score was not Kenalog but Trivaris (a presevative free version of Triamcinolone). Kenalog is rare used for RVO now despite the data from SCORE in 2009. ROVO study should not be included due to methodological flaws in it. Patients were not masked. line 9-17 I found it diffcult to see how the statement of pricipal findings related to the preceeding results section where the finidngs of each study was summarised without much comparison. On its own, this paragraph does not add to new knowledge and should have some opinion on how the RCT data should be used to guide treatment selection. HORIZON has 2 year data on ranibizumab. page 17 line 19 - large needle now improved. Line 38- I found it disappointing to see that the article still recommends that the individual ophthalmologists has to decide on whihc drug to use. can this be improved? page 20 line 9 - SCORE trial did not evaluate RON.

REVIEWER	Franz Prager MD Hospital Barmherzige Brüder Wien Johannes von Gott Platz 1 Austria
REVIEW RETURNED	11-Dec-2013

GENERAL COMMENTS	Main limitation of this systematic review is its lack of novelty, since another already puplished systematic review on intravitreal therapy in macular edema due to branch and central retinal vein occlusion (A. Pielen, N. Feltgen et al. Efficacy and safety of intravitreal Therapy in macular edema due to branch and central retinal vein occlusion: a systematic review. PLoS One. 2013) covers the same topic and reviews the same RCTs. This systematic review evaluates the evidence for treatments of macular oedema following central retinal vein occlusion according to several recent randomized controlled clinical trials (RCTs). The review focuses on 8 RCT with at least 12 months of follow-up. However, main limitation of this systematic review is its lack of novelty, since another already puplished systematic review on intravitreal therapy in macular edema due to branch and central retinal vein occlusion (A. Pielen, N. Feltgen et al. Efficacy and safety of intravitreal Therapy in macular edema due to branch and central retinal vein occlusion: a systematic review. PLoS One. 2013) covers the same topic and reviews the same RCTs.

VERSION 1 – AUTHOR RESPONSE

Yit Yang
Line 52-54- Avastin is actually a very expensive drug and is only cheap because it is aliquoted. May need to state this and comment on how the licensing authorities can approve the use of aliqouted drug in a registrations study as aliquoting has never been achieved before in an industry sponsored phase III study for the purpose of product registration with licensing authorities.

RESPONSE - As the referee says, it is not expensive once the cancer dose is converted to 300 eye doses. This has been stated in the discussion. Bevacizumab has never been licensed for eye use because the manufacturers have never submitted it – because they also manufacture ranibizumab. There is no reason why a licensing authority could not approve bevacizumab based on the safety and efficacy data that already exists.

Detailed description of method of literature search and inclusion criteria of articles. line 49- need to specify triamcinolone used in Score was not Kenalog but Trivaris (a preservative free version of Triamcinolone). Kenalog is rare used for RVO now despite the data from SCORE in 2009.

RESPONSE - This has been clarified in the manuscript

ROVO study should not be included due to methodological flaws in it. Patients were not masked.

RESPONSE -Methodological quality was not part of the inclusion/exclusion criteria and it is not appropriate to exclude studies post-hoc despite meeting the pre-defined inclusion criteria as this has the potential to bias.

line 9-17 I found it difficult to see how the statement of principal findings related to the preceding results section where the findings of each study was summarised without much comparison. On its

own, this paragraph does not add to new knowledge and should have some opinion on how the RCT data should be used to guide treatment selection. HORIZON has 2 year data on ranibizumab.

RESPONSE -HORIZON included patients with age-related macular degeneration and therefore was not included. The statement of principal findings has been amended to improve clarity.

page 17 line 19 - large needle now improved.

RESPONSE -We believe this remains an issue of concern to clinicians and do not feel that the text should be changed.

Line 38- I found it disappointing to see that the article still recommends that the individual ophthalmologists has to decide on whihc drug to use. can this be improved?

RESPONSE - Accepted. We have removed this statement.

page 20 line 9 - SCORE trial did not evaluate RON.

RESPONSE -Accepted. This was supposed to read “ROVO trial”

Franz Prager
Main limitation of this systematic review is its lack of novelty, since another already published systematic review on intravitreal therapy in macular edema due to branch and central retinal vein occlusion (A. Pielen, N. Feltgen et al. Efficacy and safety of intravitreal Therapy in macular edema due to branch and central retinal vein occlusion: a systematic review. PLoS One. 2013) covers the same topic and reviews the same RCTs.

RESPONSE - We have included a paragraph citing this review in the discussion. We feel that publication is merited because:
Firstly, independent confirmation is important because it improves validity of both reviews which is useful to readers.
Secondly, different methods and inclusions were used for the two reviews.
Thirdly, our review just includes CRVO and is more up to date by inclusion of GALILEO.