Drug treatment of macular oedema secondary to central retinal vein occlusion: a network meta-analysis

John A Ford,1 Deepson Shyangdan,2 Olalekan A Uthman,2 Noemi Lois,3 Norman Waugh2

ABSTRACT

Objective: To indirectly compare aflibercept, bevacizumab, dexamethasone, ranibizumab and triamcinolone for treatment of macular oedema secondary to central retinal vein occlusion using a network meta-analysis (NMA).

Design: NMA.

Data sources: The following databases were searched from January 2005 to March 2013: MEDLINE, MEDLINE In-process, EMBASE, CDSR, DARE, HTA, NHSEED, CENTRAL, Science Citation Index and Conference Proceedings Citation Index-Science.

Eligibility criteria for selecting studies: Only randomised controlled trials assessing patients with macular oedema secondary to central retinal vein occlusion were included. Studies had to report either proportions of patients gaining ≥3 lines, losing ≥3 lines, or the mean change in best corrected visual acuity. Two authors screened titles and abstracts, extracted data and undertook risk of bias assessment. Bayesian NMA was used to compare the different interventions.

Results: Seven studies, assessing five drugs, were judged to be sufficiently comparable for inclusion in the NMA. For the proportions of patients gaining ≥3 lines, triamcinolone 4 mg, ranibizumab 0.5 mg, bevacizumab 1.25 mg and aflibercept 2 mg had a higher probability of being more effective than sham and dexamethasone. A smaller proportion of patients treated with triamcinolone 4 mg, ranibizumab 0.5 mg or aflibercept 2 mg lost ≥3 lines of vision compared to those treated with sham. Patients treated with triamcinolone 4 mg, ranibizumab 0.5 mg, bevacizumab 1.25 mg and aflibercept 2 mg had a higher probability of improvement in the mean best corrected visual acuity compared to those treated with sham injections.

Conclusions: We found no evidence of differences between ranibizumab, aflibercept, bevacizumab and triamcinolone for improving vision. The antivascular endothelial growth factors (VEGFs) are likely to be favoured because they are not associated with steroid-induced cataract formation. Aflibercept may be preferred by clinicians because it might require fewer injections.

Strengths and limitations of this study

- Important topic area, with significant policy implications.
- Robust method used to identify studies.
- Network meta-analyses are based on a number of assumptions.
- Network meta-analysis is the best method to compare interventions in the absence of head-to-head trials.

INTRODUCTION

Central retinal vein occlusion (CRVO) dramatically reduces an individual’s functioning and quality of life.1 It is estimated that the 15-year cumulative incidence of CRVO is 0.5%.2 Visual loss is caused by thrombosis of the central retinal vein which leads to a rise in venous pressure and an increase in vascular endothelial growth factor (VEGF), consequently causing an increase in vascular permeability. Macular oedema subsequently ensues with varying degrees of ischaemia and neovascularisation. Although CRVO is generally classified as ischaemic or non-ischaemic, ischaemia should be regarded as a spectrum.3 Cases with ischaemia carry a considerably worse prognosis as, in around one-third of them, neovascular glaucoma, the most devastating complication of CRVO, may develop.4

CRVO is more common in older people with risk factors such as diabetes, hypertension or hyperlipidaemia, but can occur in young people with inflammatory disorders. Hayreh et al, in a 27-year cohort study, found that only 13% of people with CRVO were under 45 years of age.5 In 95% of cases, CRVO affects only one eye.3 However, visual loss in this already comorbid patient group significantly compounds their already impaired functioning and quality of life. Patients can lose confidence, struggle with...
daily activities and become increasingly dependent on
friends and family.1

For many years, laser photocoagulation was the only
effective therapeutic strategy that could be used in the
management of patients with CRVO. It was only useful
for reducing the risk of neovascular glaucoma, but not
effective for the treatment of macular oedema in
CRVO.5 Over the past decade, a number of drugs to
Treat macular oedema have been introduced, including
the steroids, triamcinolone and dexamethasone, and the
anti-VEGFs, ranibizumab, bevacizumab, pegaptanib and
afibercept. Dexamethasone, ranibizumab and afibercept
have been assessed in large commercially funded
trials.6–13 Bevacizumab was originally developed as an
anticancer drug and has been found to be effective in
treating macular oedema secondary to age-related
macular degeneration,14 diabetic macular oedema,15
branch retinal vein occlusion16 and CRVO.17 Like triam-
cinolone, bevacizumab is used off license in the eye.
Ranibizumab is derived from the same parent molecule
of the bevacizumab monoclonal antibody and was devel-
oped and commercially marketed specifically for use in
the eye.

In the UK, the National Institute of Health and Care
Excellence (NICE) has recommended the use of dexa-
methasone, ranibizumab and afibercept for the treat-
ment of macular oedema secondary to CRVO in
separate appraisals.18–20 Therefore clinicians have three
NICE-recommended treatments for CRVO without
head-to-head trials or clear guidance in which one may
be best for their patients. On this basis, the aim of this
study was to indirectly compare, in a network
meta-analysis (NMA), the clinical effectiveness of afiber-
cept, ranibizumab, bevacizumab, dexamethasone and
triamcinolone for the treatment of macular oedema sec-
ondary to CRVO.

METHODS

Information sources and search strategy
To identify suitable studies, initially for a systematic
review of treatment of macular oedema after CRVO
(submitted for publication), the following databases
were searched from January 2005 to March 2013:
MEDLINE, MEDLINE In-process, EMBASE (all via
OVID); CDSR, DARE, HTA, NHSEED, CENTRAL (all
via The Cochrane Library); Science Citation Index and
Conference Proceedings Citation Index-Science (via
Web of Knowledge). The MEDLINE search strategy is
shown in the online supplementary appendix 1. This
search strategy was modified for other databases. In
addition to the bibliographic database searching, supple-
mental searches were undertaken to look for recent
and unpublished studies in the WHO International
Clinical Trials Registry Platform and ophthalmology con-
ference websites (American Academy of Ophthalmology,
Association for Research in Vision and Ophthalmology
from 2010 to 2012).

Study selection

Only randomised controlled trials which included
patients with macular oedema secondary to CRVO were
included. It was acceptable for a study to include branch
retinal vein occlusion and CRVO provided that the
CRVO group was reported separately. The following
drugs were included: dexamethasone, triamcinolone,
ranibizumab, bevacizumab and afibercept. Pegaptanib
was not included because it is not used routinely in clin-
cal practice. Only doses that are used in clinical practice
were included. Studies had to report at least one of the
following outcomes: proportions of patients gaining ≥3
lines from baseline to 6 months, proportions of patients
losing ≥3 lines from baseline to 6 months and the mean
change in best corrected visual acuity (BCVA) from base-
line to 6 months.

Risk of bias assessment

The Cochrane Collaboration’s tool was used for assessing
risk of bias.21 The trials were graded (unclear, high or
low risk of bias) based on: (1) sequence generation, (2)
allocation concealment, (3) blinding of outcome asses-
or, (4) incomplete outcome data and (5) selective
outcome reporting.

Study selection and data abstraction
Two authors independently assessed the eligibility and
methodological quality of the studies identified during
the literature search. Two authors extracted and com-
pared the data. For each study identified that met the
selection criteria, details on study design, study popula-
tion characteristics, intervention, outcome measures and
study quality were extracted. Discrepancies were resolved
by consensus through discussion. Studies were assessed
for comparability based on the populations included,
trial arms, outcome measures and duration of follow-up.
Common comparators were identified from the trials
and a network diagram was created.

Summary measures

The primary measures of treatment effects were relative
risk (RR) for the proportions of patients gaining ≥3
lines of vision, proportions of patients losing ≥3 lines
of vision and the weighted mean difference (WMD) for
mean change BCVA. We used the following methods to
calculate SDs when incompletely reported: (1) contact
with the corresponding author or (2) estimation of the
SD on the basis of the sample size, median and range as
suggested by Hozo et al22 or on the basis of the sample
size and p value.

In one trial (SCORE)23–36 6-month data were not
available because patients were followed up every 4
months. For the dichotomous outcomes, that is, pro-
portions of patients gaining and losing ≥3 lines, we aver-
aged 4 and 8-month data to get the 6 months follow up
data. For the third outcome, that is, mean change
BCVA, again data from two time-points were used. The
weighted mean and SDs for each treatment arm were calculated using the mean and SDs of two time-points.

**Data synthesis and model implementation**

Bayesian NMA was used to compare the different interventions. NMA is a generalisation of meta-analysis methods because it allows comparisons of agents not addressed within individual primary trials. Bayesian statistical inference provides probability distributions for treatment effect parameters (RR and WMD), with 95% credible intervals (95% CrI), rather than 95% CIs (95% CI). A 95% CrI can be interpreted as there being a 95% probability that the parameter takes a value in the specified range.

All analyses were conducted using a Bayesian Markov Chain Monte Carlo (MCMC) method and fitted in the freely available Bayesian software, WinBUGS V.1.4.3. Two Markov chains were run simultaneously using different initial values. Convergence to a stable solution was checked by viewing plots of the sampled simulations and using the Brooks-Gelman-Rubin diagnostic tool. Convergence was found to be adequate after running 20 000 samples for both chains. These samples were then discarded and a further 70 000 sampled simulation was then run, on which the results were based. We also calculated the probability of treatment being the most effective (first best), the second best, the third best and so on, and presented the results graphically with rankograms.

Like standard meta-analysis comparison, an NMA can be either a fixed-effect or a random-effect model. We used the Bayesian Deviation Information Criterion (DIC) to compare fixed-effect and random-effect models. The most appropriate NMA model can be identified as the one with the lowest DIC. The DIC measures the fit of the model while penalising it for the number of effective parameters. The fixed-effect model was chosen because of the small number of trials available for each comparison, and difficulty in estimating between studies variance, if random-effect model, was implemented, and the difference in DIC was less than 5.

**RESULTS**

**Study selection and characteristics**

The literature search identified 945 articles, as shown in figure 1. Seven studies were judged to be sufficiently comparable to be included in the NMA. Tables 1 and 2

---

**Figure 1** Study selection flow diagram.

Table 1 Baseline characteristics and results of all included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Intervention/outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DEXAMETHASONE</strong>&lt;br&gt;GENEVA 2010&lt;sup&gt;6–8&lt;/sup&gt;</td>
<td>CRVO—437 eyes of 437 patients randomised; 94% follow-up at 6 months</td>
<td>1. Dexamethasone 0.7 mg (n=136) Single dose&lt;br&gt;2. Dexamethasone 0.35 mg (n=154) Single dose&lt;br&gt;3. Sham (n=147) Single dose—a needleless applicator was placed against the conjunctiva to simulate the placement of study medication. <strong>Primary end point:</strong> gain of ≥15 ETDRS letters; for the open-label extension: safety</td>
</tr>
<tr>
<td><strong>TRIAMCINOLONE</strong>&lt;br&gt;SCORE 2009&lt;sup&gt;23–36&lt;/sup&gt;</td>
<td>271 eyes of 271 patients randomised; 83% (observation) and 90% (triamcinolone) completed 12 months</td>
<td>1. Triamcinolone 1 mg (n=92) Every 4 months depending on retreatment regimen (average 2.2 injections at 12 months)&lt;br&gt;2. Triamcinolone 4 mg (n=91) Every 4 months depending on retreatment regimen (average 2.0 injections at 12 months) (The form of triamcinolone used was Trivaris, no longer available. It was made by the manufacturer of Ozurdex (Allergan))&lt;br&gt;3. Observation (n=88) <strong>Primary end point:</strong> gain of ≥15 ETDRS letters</td>
</tr>
<tr>
<td><strong>AFLIBERCEPT</strong>&lt;br&gt;COPERNICUS 2012&lt;sup&gt;12&lt;/sup&gt;</td>
<td>189 eyes of 189 patients randomised; 95.7% (aflibercept) and 81.1% (sham) completed 24 weeks; 93% (aflibercept) and 77% (sham) completed 52 weeks</td>
<td>1. Aflibercept 2 mg (n=114) Every 4 weeks for 6 months (average number not available)&lt;br&gt;2. Sham (n=73) Every 4 weeks for 6 months (average number not available) (empty syringe without needle pressed to conjunctival surface) <strong>Primary end point:</strong> gain of ≥15 ETDRS letters</td>
</tr>
<tr>
<td><strong>GALILEO 2012&lt;sup&gt;11&lt;/sup&gt;</strong></td>
<td>177 eyes of 177 patients randomised; 90.6% (aflibercept) and 78.9% (sham) completed 24 weeks</td>
<td>1. Aflibercept 2 mg (n=103) Every 4 weeks for 6 months (average number not available)&lt;br&gt;2. Sham (n=71) Every 4 weeks for 6 months (average number not available) (empty syringe without needle pressed to conjunctival surface) <strong>Primary end point:</strong> gain of ≥15 ETDRS letters</td>
</tr>
<tr>
<td><strong>RANIBIZUMAB</strong>&lt;br&gt;CRUISE 2010&lt;sup&gt;9&lt;/sup&gt;</td>
<td>392 eyes of 392 patients randomised; 97.7% (ranibizumab 0.3 mg), 91.5% (ranibizumab 0.5 mg) and 88.5% (sham) completed 6 months</td>
<td>1. Ranibizumab 0.3 mg (n=132) Every 4 weeks for 6 months (average number not available)&lt;br&gt;2. Ranibizumab 0.5 mg (n=130) Every 4 weeks for 6 months (average number not available)&lt;br&gt;3. Sham (n=130) Every 4 weeks for 6 months (average number not available) (empty syringe without needle pressed to the injection site) <strong>Primary end point:</strong> mean change from baseline BCVA</td>
</tr>
</tbody>
</table>


Open Access
present the characteristics and results of the included trials. Two studies\textsuperscript{11–13} compared aflibercept 2 mg against sham; two identical studies\textsuperscript{6–8} compared dexamethasone 0.7 mg (Ozurdex) against sham; one study\textsuperscript{9–10} compared ranibizumab 0.5 mg against sham; one study\textsuperscript{12–44} compared bevacizumab 1.25 mg against sham and, finally, one study\textsuperscript{25–36} compared triamcinolone 4 mg against observation. Sham or observation was used as the common comparator. The number of included participants varied from 60\textsuperscript{42–44} to 437.\textsuperscript{5–8} Most studies required patients to be treatment naïve and have macular oedema with retinal thickness measuring at least 250 or 300 μm on optical coherence tomography. Sham injection was undertaken by placing a needleless syringe on the eye. All studies, except for Epstein \textit{et al.}\textsuperscript{42–44} were multi-centre, international studies. Most studies had an extension phase after the primary outcome, but this was not included in the NMA.

The sufficiently comparable studies were combined into a network analysis based on a common comparator. The network for the proportions of patients gaining ≥3 lines is shown in figure 2. This network is the same for the other two outcomes, but without dexamethasone, because the trial did not report these outcomes.

Risk of bias of included trials
Risk of bias is shown in table 3. Included studies were generally of high quality, with all studies being judged to be of low or unclear bias for all criteria. The non-commercially funded bevacizumab trial had fewer patients and, inevitably, results had wider CIs.\textsuperscript{42–44} In no study does it appear that patients were asked at the end of the trial which arm they thought they had been assigned. It is unclear how many could distinguish injections (intervention arm) from punctureless pressure (sham arm).

Effects of interventions on proportions of patients gaining ≥3 lines

Figure 3 displays a forest plot of the risk ratio and 95% CrI in proportions of patients gaining ≥3 lines for all the possible pairwise comparisons. In terms of proportions of patients gaining ≥3 lines, triamcinolone 4 mg, ranibizumab 0.5 mg, bevacizumab 1.25 mg and aflibercept 2 mg had a higher probability of being more effective than a sham and dexamethasone (figure 4). There was no difference in the proportions of patients gaining ≥3 lines between triamcinolone 4 mg, ranibizumab 0.5 mg, bevacizumab 1.25 mg and aflibercept 2 mg.

Effects of interventions on proportions of patients losing ≥3 lines

Figure 5 displays forest plot of the risk ratio and 95% CrI of proportions of patients losing ≥3 lines for all the possible pairwise comparisons. A smaller proportion of patients treated with triamcinolone 4 mg, ranibizumab 0.5 mg or aflibercept 2 mg lost ≥3 lines of vision than those treated with sham. There was no difference in the proportions of patients losing ≥3 lines between triamcinolone 4 mg, ranibizumab 0.5 mg, bevacizumab 1.25 mg and aflibercept 2 mg. Figure 6 shows ranking for efficacy in terms of proportions of patients losing ≥3 lines.

Effects of interventions on mean change in BCVA

Figure 7 displays a forest plot of the mean changes and 95% CrIs of improvement in BCVA for all the possible pairwise comparisons. Patients treated with triamcinolone 4 mg, ranibizumab 0.5 mg, bevacizumab 1.25 mg or aflibercept 2 mg had a higher probability of improvement in BCVA compared to those treated with sham injections. Patients treated with aflibercept 2 mg had a higher probability of improvement in BCVA compared with those treated with triamcinolone 4 mg (figure 8). There was no difference in the mean change in BCVA from baseline between patients treated with ranibizumab 0.5 mg, bevacizumab 1.25 mg and aflibercept 2 mg.

DISCUSSION
Statement of principal findings
Our results show no evidence of a difference in effectiveness between aflibercept, ranibizumab and triamcinolone. Bevacizumab was similar to these drugs in terms of
### Table 2 Baseline characteristics and results of included trials

<table>
<thead>
<tr>
<th>Copernicus</th>
<th>Galileo</th>
<th>Cruise</th>
<th>Geneva</th>
<th>Epstein et al</th>
<th>Score</th>
</tr>
</thead>
</table>

#### Baseline similarities

<table>
<thead>
<tr>
<th>Number (%) of patients</th>
<th>Aflib 2 mg: 114</th>
<th>Aflib 2 mg: 103</th>
<th>Rani 0.5 mg: 130</th>
<th>Dexe 0.7 mg: 136</th>
<th>Beva 1.25 mg: 30</th>
<th>Triam 4 mg: 91</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Aflib 2 mg: 65.5 SD 13.6</td>
<td>Aflib 2 mg: 59.9 SD 12.4</td>
<td>Rani 0.5 mg: 67.6 SD 12.4</td>
<td>Dexe 0.7 mg: NR</td>
<td>Beva 1.25 mg: 70.6 SD 12.6</td>
<td>Triam 4 mg: 67.5 SD 12.0</td>
</tr>
<tr>
<td>bcva at baseline (SD)</td>
<td>Aflib 2 mg: 50.7 SD 13.9</td>
<td>Aflib 2 mg: 53.6 SD 15.8</td>
<td>Rani 0.5 mg: 48.1 SD 14.6</td>
<td>Dexe 0.7 mg: NR</td>
<td>Beva 1.25 mg: 44.4 SD 15.3</td>
<td>Triam 4 mg: 51.0 SD 14.4</td>
</tr>
</tbody>
</table>

#### Results

| Number (%) of patients gaining ≥15 letters improvement from baseline to 6 months | Aflib 2 mg: 64 (56.1) | Aflib 2 mg: 62 (60.2) | Rani 0.5 mg: 62 (47.7) | Dexe 0.7 mg: 25 (18) | Beva 1.25 mg: 18 (60%) | Triam 4 mg: 18 (19.5%) (average of 4 and 8 months) |
| Number (%) of patients losing ≥15 letters of BCVA from baseline to 6 months | Aflib 2 mg: 9 (12.3) | Sham: 15 (22.1) | Rani 0.5 mg: 2 (1.5) | Dexe 0.7 mg: NR | Beva 1.25 mg: 2 (6.7%) | Triam 4 mg: 19 (20.5%) (average of 4 and 8 months) |
| Mean change (SD) from baseline in BCVA | Aflib 2 mg: 17.3 (12.8) | Aflib 2 mg: 18.0 (12.2) | Rani 0.5 mg: 14.9 (13.2) | Dexe 0.7 mg: 0.1 (13.2) | Beva 1.25 mg: 14.1 SD 18.7 | Triam 4 mg: −0.15 SD 20.67 (n=85) (weight mean and SD of 4 and 8 months) |
| Sham: −4 (18) | Sham: 3.3 (14.1) | Sham: 0.8 (16.2) | Sham: −1.8 (NR) | Sham: −2.0 SD 20.5 | Sham: −9.66 SD 18.04 (n=75) (weighted mean and SD of 4 and 8 months) |

Aflib, aflibercept; BCVA, best corrected visual acuity; Dexe, dexamethasone; NR, not reported; Obser, observation; Rani, ranibizumab; Triam, triamcinolone.
letters gained and the mean change in BCVA. Dexamethasone was less effective compared with these drugs.

Strengths and limitations
This is the first study providing an indirect comparison of drugs to treat macular oedema secondary to CRVO. A robust search strategy, screening process and data extraction were used, and this analysis drew on a systematic review. The studies included had, in general, a low risk of bias. Safety was not considered in this study but is described in detail elsewhere. Five different drugs were suitable for NMA. Unpublished data were obtained from one author. Bayesian methods were used for the NMA. There was good model fit and convergence within the analysis.

However, pre-specified outcomes were not reported in all studies and the sample size varied considerably. For example, Epstein et al., assessing bevacizumab, only included 30 participants in each arm. This resulted in wide CrIs from the NMA, which could have led to a type 1 error, especially with regard to the proportions of patients losing ≥3 lines. The SCORE study compared triamcinolone to observation. The NMA assumes a similar effect of sham and observation and this may result in a small degree of bias. Only 6 months of data were included, and the long-term effects are not known. Using a 6-month follow-up period may disadvantage dexamethasone because peak effect in the GENEVA trials was seen at 90 days, and by 6 months, benefits had been largely lost.

As with most network meta-analyses, methodological heterogeneity was present. There were some differences among the trials. For example, CRUISE, assessing ranibizumab, did not include as many patients with ischaemic CRVO as the aflibercept trials. There were also some small differences in the chronicity of macular oedema and the mean BCVA at baseline.

Meaning of the study: possible explanations and implications for clinicians and policymakers
No head-to-head trials comparing aflibercept, bevacizumab, ranibizumab, triamcinolone and dexamethasone have been published in CRVO. Part of the reason for this is that the Food and Drug Administration requires proof of the safety and effectiveness of a drug. The easiest and quickest method for pharmaceutical companies to produce this proof is through placebo-controlled trials. Trials comparing new medications to current best treatment would be considerably more useful to clinicians and patients.

Head-to-head trials comparing some of these drugs are available in other conditions. For example, a comparison of ranibizumab and bevacizumab was undertaken in age-related macular degeneration in the Comparison of Age-related macular degeneration Treatment Trials (CATT) and alternative treatments to Inhibit VEGF in patients with Age-related choroidal Neovascularisation (IVAN) trials. Both of these trials found no difference in effectiveness between ranibizumab and bevacizumab. Furthermore, an indirect comparison of ranibizumab and bevacizumab found no evidence of a difference between these drugs. Thus, it is highly probable that this may also apply in CRVO. The difference seen in our results regarding bevacizumab may be due to the low number of patients included in Epstein et al. In the CATT trial, more patients were hospitalised in the bevacizumab arm, but the authors did not believe that this was explained by a direct effect of bevacizumab. The 2-year results from the IVAN showed little difference in cardiovascular events, with the number being insignificantly lower with bevacizumab. Ranibizumab and aflibercept were directly compared in two similarly designed trials, VEGF Trap-eye: investigation of Efficacy and safety in Wet age-related macular degeneration (VIEW 1 and 2). Similar efficacy and safety was found in both drugs.

From the included trials it is clear that intraocular steroids are associated with complications, including increased intraocular pressure and cataract formation. These are substantial drawbacks for using steroids to treat macular oedema in CRVO. However, many affected patients may already be pseudophakic and, on these, the use of intraocular steroids may be reasonable. Steroids may have a place in the treatment pathway of patients who have failed on anti-VEGF therapy, but this is yet to be tested. The anti-VEGF drugs have a good safety profile and do not cause cataract formation. For this reason they are more likely to be favoured by clinicians than steroids.

Aflibercept, compared with ranibizumab and bevacizumab, targets a wider range of cytokines and may have a stronger binding affinity. Initial results suggested that aflibercept would require fewer injections than ranibizumab. Heier and colleagues compared aflibercept and ranibizumab in two similarly designed randomised controlled trials in age-related macular degeneration. They found that 2 mg aflibercept administered every 8 weeks produced similar effects at 96 weeks to 0.5 mg ranibizumab administered every 4 weeks. This was reflected in the FDA Dermatologic and Ophthalmic Drugs Advisory Committee recommendation that aflibercept should be given every
<table>
<thead>
<tr>
<th>Study (author and year)</th>
<th>Adequate sequence generation</th>
<th>Allocation concealment</th>
<th>Masking</th>
<th>Incomplete outcome data addressed</th>
<th>Free of selective reporting</th>
<th>Free of other bias (eg, similarity at baseline, power assessment)</th>
<th>Funder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geneva 2010(^{6,8})</td>
<td>Low</td>
<td>Low</td>
<td>Partial: patients and assessors of efficacy variables</td>
<td>Low: ITT analysis, 94% FU at 6 months</td>
<td>Low</td>
<td>Power: 81% power to detect difference in primary outcome with n=495 for each trial</td>
<td>Allergan Inc</td>
</tr>
<tr>
<td>Score 2009(^{23-36})</td>
<td>Low</td>
<td>Unclear</td>
<td>Partial (physicians and patients masked to dose but not triamcinolone vs observation)</td>
<td>Low: ITT analysis, 83–90% FU at 12 months</td>
<td>Low</td>
<td>Power: 80% power to detect difference in primary outcome with n=486 (but only 271 randomised)</td>
<td>National Eye Institute grants, Allergan</td>
</tr>
<tr>
<td>Copernicus 2012(^{12,13})</td>
<td>Low</td>
<td>Unclear</td>
<td>Low: double-blind</td>
<td>Low: ITT analysis, 89.9% assessed at primary end point</td>
<td>Low</td>
<td>Power: 90% power to detect difference in primary outcome with n=165</td>
<td>Bayer HealthCare, Regeneron Pharmaceuticals</td>
</tr>
<tr>
<td>Galileo 2012(^{11})</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Low: double-blind</td>
<td>Low: ITT analysis, 86% assessed at primary end point</td>
<td>Low</td>
<td>Power: 90% power to detect difference in primary outcome with n=150</td>
<td>Bayer HealthCare, Regeneron Pharmaceuticals</td>
</tr>
<tr>
<td>Cruise 2010(^{9,10})</td>
<td>Low</td>
<td>Unclear</td>
<td>Low: patients and evaluating examiners, injecting physicians masked to dose</td>
<td>Low: ITT analysis, 88.5–97.7% completed 6 months</td>
<td>Low</td>
<td>Power: not reported</td>
<td>Genentech Inc.</td>
</tr>
<tr>
<td>Epstein 2012(^{22-44})</td>
<td>Unclear</td>
<td>Low</td>
<td>Low: patients, outcome assessors</td>
<td>Low: ITT analysis; missing data for 2 patients (primary endpoint)</td>
<td>Low</td>
<td>Power: 80% power to detect difference in primary outcome with n=24 per group</td>
<td>Unclear; authors are consultants for Allergan, Novartis, Alcon, Bayer</td>
</tr>
</tbody>
</table>

FU, follow-up; ITT, intention to treat.
2 months following three initial monthly doses in age-related macular oedema. This may be because aflibercept also appears to last longer in the eye than ranibizumab. Age-related macular degeneration is a more aggressive condition than CRVO and so it is unlikely that more frequent dosing would be needed. Therefore, aflibercept may be preferred because it would reduce pressure on outpatient clinics.

Figure 3  Proportions of patients gaining three lines or more from baseline to 6 months.

Figure 4  Rankogram for gaining $\geq 3$ lines—distribution of the probabilities of every treatment being ranked at each of the possible six positions.
Furthermore, there is some evidence from patients with age-related macular degeneration that aflibercept may be effective in patients who have not responded to ranibizumab.\textsuperscript{55, 56} This may be due to the higher affinity and wider number of cytokines that are targeted. There is no reason to suspect that these effects are any different for the macular oedema caused by CRVO. However, we have as yet no evidence as to whether ranibizumab would be effective after aflibercept has failed.

The National Institute of Health and Care Excellence has recommended dexamethasone, ranibizumab and aflibercept as options in the treatment of macular oedema secondary to CRVO.\textsuperscript{18–20} Until these technologies are reviewed together and compared with each other, clinicians are left with three recommended drugs. It should be noted that during the appraisal of ranibizumab the evidence review group found that in the cost-effectiveness analysis dexamethasone was extendedly dominated by ranibizumab (an intervention is judged not be cost-effective because it has an ICER that is greater than that of a more effective intervention). The committee appraising ranibizumab did not re-consider the previous appraisal decision on dexamethasone. Our results show that dexamethasone was not as effective as ranibizumab or aflibercept, at 6 months follow-up and with the dosing regimens in the trials. However, these results do not assess quality of life or cost effectiveness. Bevacizumab is likely to prove more cost effective than both aflibercept and ranibizumab because

**Figure 5** Proportions of patients losing three lines or more from baseline to 6 months.

**Figure 6** Rankogram for losing $\geq$3 lines—distribution of the probabilities of every treatment being ranked at each of the possible six positions.
it is substantially less expensive.\textsuperscript{57} However, the National Institute for Health and Care Excellence has not issued guidance on bevacizumab because it does not have a license for use in the eye.

**Unanswered questions and future research**

Not all patients benefit from the use of anti-VEGF drugs; only about 60\% gain 15 or more letters. It is not clear why some patients benefit more than others. Future
research should focus on identifying subgroups of patients who are likely to benefit. Only a few of the trials included ischaemic patients, and in those trials only a few patients with ischaemia were included.\textsuperscript{11–13} More research assessing the effectiveness of these drugs in severely ischaemic patients is needed.

Head-to-head trials comparing ranibizumab, aflibercept, bevacizumab and triamcinolone are needed. These should include assessment of cost effectiveness. To assist this, a better measure of quality of life is needed for patients with eye conditions. The widely used EQ5D may not be sensitive enough to measure changes that are important to patients, such as the ability to drive.

In conclusion, we have found no evidence of differences between ranibizumab, bevacizumab, aflibercept and triamcinolone for improving vision. The anti-VEGFs are likely to be favoured because they are not associated with steroid-induced cataract formation. Clinicians may prefer Aflibercept because it might require fewer injections.

Acknowledgements The authors thank Christine Clar, Sian Thomas and Rachel Court for assisting with searches, screening and data extraction for the systematic review that precedes this study. They also thank the authors of the Epstein 2012 trial for providing additional data.

Contributors NW conceived the idea. All authors contributed to the design of the study. DS and OAU undertook the statistical analysis. JAF, DS and OAU wrote the first draft of the manuscript. All authors redrafted and agreed on the final article. JAF is the guarantor.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/
Drug treatment of macular oedema secondary to central retinal vein occlusion: a network meta-analysis

John A Ford, Deepson Shyangdan, Olalekan A Uthman, Noemi Lois and Norman Waugh

BMJ Open 2014 4:
doi: 10.1136/bmjopen-2014-005292

Updated information and services can be found at:
http://bmjopen.bmj.com/content/4/7/e005292

Supplementary Material
Supplementary material can be found at:
http://bmjopen.bmj.com/content/suppl/2014/07/23/bmjopen-2014-005292.DC1.html

These include:

References
This article cites 46 articles, 8 of which you can access for free at:
http://bmjopen.bmj.com/content/4/7/e005292#BIBL

Open Access
This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

- Health policy (252)
- Ophthalmology (50)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/