BMJ open

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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-004120
Article Type:	Research
Date Submitted by the Author:	26-Sep-2013
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Primary Subject Heading:	Ophthalmology
Secondary Subject Heading:	Ophthalmology, Public health
Keywords:	Medical ophthalmology < OPHTHALMOLOGY, systematic review, anti-VEGF, Central retinal vein occlusion, macular oedema

Treatments for macular oedema following central retinal vein occlusion: systematic review

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Protocol: Not published

Words: 5750 words

Key words: central retinal vein occlusion, aflibercept, ranibizumab, bevacizumab, dexamethasone, pegaptanib, triamcinolone, systematic review, anti-VEGF, macular oedema

Disclosure

No additional data available.

Abstract

Objectives

To review systematically the randomised controlled trial (RCT) evidence for treatment of macular oedema due to central retinal vein occlusion (CRVO).

Data sources

MEDLINE, EMBASE, CDSR, DARE, HTA, NHSEED, CENTRAL and meeting abstracts (January 2005 to March 2013).

Study eligibility criteria, participants and interventions

RCTs with at least 12 months' follow-up assessing pharmacological treatments for CRVO were included with no language restrictions.

Study appraisal and synthesis methods

Two authors screened titles and abstracts and conducted data extracted and Cochrane risk of bias assessment. Meta-analysis was not possible due to lack of comparable studies.

Results

Eight studies (35 articles, 1714 eyes) were included, assessing aflibercept (n=2), triamcinolone (n=2), bevacizumab (n=1), pegaptanib (n=1), dexamethasone (n=1) and ranibizumab (n=1). In general, bevacizumab, ranibizumab, aflibercept and triamcinolone resulted in clinically significant increases in the proportion of participants with an improvement in visual acuity of ≥15 letters, with 40-60% gaining ≥15 letters on active drugs, compared to 12-28% with sham. Results for pegaptanib and dexamethasone were mixed. Steroids were associated with cataract formation and increased intra-ocular pressure. No overall increase in adverse events was found with bevacizumab, ranibizumab, aflibercept or pegaptanib compared to control. Quality of life was poorly reported. All studies had a low or unclear risk of bias.

Limitations

All studies evaluated a relatively short primary follow-up (1 year or less). Most had an unmasked extension phase. There was no head-to-head evidence. The majority of participants included had non-ischaemic CRVO.

Conclusions and implications of key findings

Bevacizumab, ranibizumab, aflibercept and triamcinolone appear to be effective in treating macular oedema secondary to CRVO. Long-term data on effectiveness and safety are needed. Head-to-head trials and research to identify “responders” is needed to help clinicians make the right choices for their patients. Research aimed to improve sight in people with ischaemic CRVO is required.

Article summary

Article focus

To review the clinical effectiveness of pharmacological treatments for central retinal vein occlusion.

Key messages

Bevacizumab, ranibizumab, aflibercept and triamcinolone have demonstrated good short-term clinical effectiveness in randomised controlled trials for the treatment of macular oedema secondary to central retinal vein occlusion.

Dexamethasone and pegaptanib have shown mixed results.

Strengths and limitations of this study

A robust systematic review method was used which only included randomised controlled trials.

There were no head-to-head trials and there was a lack of long-term data on both effectiveness and safety.

Introduction

Central retinal vein occlusion (CRVO) is a vascular disorder of the retina with often catastrophic consequences to vision and quality of life.[1;2] The incidence of CRVO increases with age; most individuals affected are 50 years of age or older.[3] It has been estimated that there are around 80 new cases of CRVO per million population per year.[4;5] Although CRVO most commonly affects one eye, in around 10% of patients the disease affects both eyes.[2] Approximately 20% of patients with CRVO will develop large areas of retinal non-perfusion (ischaemia).[6] Furthermore, a small proportion (around 8%) of patients with non-ischaemic CRVO may convert into the ischaemic type during follow-up.[6] Retinal ischaemia may lead to the development of neovascularisation in the retina, iris or anterior chamber angle. Complications of neovascularisation include vitreous haemorrhage and neovascular glaucoma.[6] Currently there is no treatment for ischaemic CRVO other than that aimed at ameliorating the severity of complications, with treatments such as panretinal photocoagulation. Even with the use of current therapies, some eyes with ischaemic CRVO end up blind and painful and, ultimately, enucleation (removal of the eye) is necessary to provide comfort to patients.

Not all people with CRVO will require treatment and macular oedema will resolve in about a third of those with non-ischaemic CRVO.[2;7] However most will need treatment and the number of options has increased in recent years. Laser photocoagulation has been for many years the standard therapy for patients with macular oedema secondary to branch retinal vein obstruction (BRVO).[8] However, laser treatment was not found to be beneficial to those with macular oedema secondary to CRVO;[9] for these patients, no therapeutic modalities could be offered. Recently, several studies have demonstrated the benefit of anti-vascular endothelial growth factor (VEGF) therapies and steroids for the management of patients with macular oedema secondary to CRVO.[10;11] Steroids, such as triamcinolone and dexamethasone, have anti-inflammatory and anti-proliferative attributes (as well as some anti-VEGF effects) and therefore are primarily effective by reducing the oedema of the macula.[12] Anti-VEGF treatments, such as bevacizumab, ranibizumab, aflibercept and pegaptanib, inhibit vascular endothelial growth factor A. In CRVO there is an increase in vascular endothelial growth factor A which leads to neovascularization and oedema.[13] In the UK, NICE has approved dexamethasone (in the long-acting form, Ozurdex) and ranibizumab (Lucentis) and an appraisal of aflibercept is currently underway. Bevacizumab is also used, but is not licensed for use in the eye; however this is because the manufacturer has never sought a licence, preferring to market ranibizumab. Triamcinolone has also been used off-licence.

An up-to-date review incorporating all drug treatments for macular oedema secondary to CRVO is needed. The purpose of this study is to review systematically the randomised controlled evidence for drug treatments of macular oedema secondary to CRVO.

Methods

A systematic review was conducted. The following databases were searched: 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). In addition to the bibliographic database searching, supplementary searches were undertaken to look for recent and unpublished studies in the WHO International Clinical Trials Registry Platform and ophthalmology conference websites (American Academy of Ophthalmology, Association for Research in Vision and Ophthalmology from 2010 to 2012).

Search strategy

An iterative procedure was used to develop two search strategies with input from previous systematic reviews.[14;15] The first search strategy was designed to retrieve articles reporting RCTs or systematic reviews about CRVO published from 2005 onwards (the publication date of the first RCT on triamcinolone in Medline). Terms for retinal vein occlusion were included to ensure identification of articles in which both BRVO and CRVO were covered, but were reported separately. The second strategy focussed on retrieving articles where adverse events of relevant pharmacological treatments for CRVO were reported. This second search was limited by condition (age-related macular degeneration (AMD) or RVO), study type (RCTs, SRs or observational studies) and date (published from 2010 onwards). Searches were conducted in March 2013. The strategies used in each database are provided in appendix 1. Auto alerts of searches were set up to capture relevant articles published after the dates of the searches.

Reference lists from the included studies and identified systematic reviews were screened.

Inclusion and exclusion criteria

RCTs were used to assess the clinical effectiveness and adverse events.

Only RCTs examining pharmacological treatment compared with laser treatment, observation, placebo (sham injection) or another pharmacological intervention with at least 12 months follow-up were included. Comparisons of different doses of drugs were not included unless there was an additional comparator group as defined above. Studies including CRVO and BRVO were included

providing participants with CRVO were reported as a subgroup. Studies assessing treatments aimed at restoring circulation to the occluded vein shortly after onset (<30 days) were excluded. There were no language restrictions.

Outcomes

The primary outcome was visual acuity measured as mean change in best corrected visual acuity (BCVA) or as proportion of patients improving by 15 ETDRS (Early Treatment for Diabetic Retinopathy Study) letters or more. Secondary outcomes included mean change in macular thickness using optical coherence tomography (OCT), quality of life and adverse events.

Screening and data extraction

Search results were screened independently by two authors (CC, JF and ST). Differences were resolved through discussion or by consulting a third author (JF). Data were extracted by one author (CC and DS) and checked by a second (ST, CC). Data extraction included inclusion/exclusion criteria, baseline demographics, mean change in BCVA, proportion of patients with 15 letters improvement, central retinal thickness (CRT) and adverse events. Risk of bias was assessed by two reviewers using the Cochrane risk of bias tool.[16]

Meta-analysis was not possible because of a lack of comparable studies.

Results

Search results

The study flow is shown in figure 1. The electronic searches yielded 518 records. 475 were eliminated based on information in the titles and abstract. The full text of the remaining 43 records was checked, and a further eight were eliminated. Reasons for exclusion included the trial being a commentary rather than an RCT, the study having no relevant comparison group (dose ranging only), the participants did not have macular oedema secondary to CRVO, or the interventions being ineligible (non-pharmacological). The remaining 35 records (including conference abstracts) reported on eight RCTs of six different pharmacological agents, and these were included in the analysis. The Geneva study (2010)[11;17;18] technically consists of two RCTs, but as these were analysed and reported together, it was counted as one RCT in this analysis.

We also identified three relevant ongoing trials, one investigating minocycline (http://clinicaltrials.gov/ct2/show/study/NCT01468844), one investigating a combination of bevacizumab and triamcinolone (http://clinicaltrials.gov/show/NCT00566761), and one investigating ranibizumab (http://clinicaltrials.gov/show/NCT01123564).

Study characteristics

Detailed study characteristics of the included studies are shown in table 1.

Study design

Of the eight included RCTs, six were described as double-blind and seven were sham-controlled. All but one were multicentre. Only one was not funded by industry. Four trials were international trials, two came from the USA, and one each from Austria and Sweden. Six of the trials measured primary end-points at around six months (24 to 30 weeks), whereas two measured primary end-points at 12 months. Five studies reported follow-up data for up to 12 months, and two reported data for follow-up periods of up to two years.

Participants

The trials randomised a total of 1714 eyes (one eye per person). The number of eyes per study ranged between 60 and 437. Follow-up at the primary end-point ranged from 77 to 98% (generally over 90% in the intervention groups). The participants had a mean age of between 59.0 and 70.5

years, and between 36 and 49% were female. Only two studies reported mean duration of macular oedema (4.3 and 4.9 months). Five studies reported mean time since CRVO diagnosis (range 2.4 to 2.9 months). Mean baseline BCVA was between 44 and 52.5 ETDRS letters, baseline CRT was between 569 and 721 µm. In most trials, the focus was on macular oedema secondary to CRVO only, but in the Geneva trial macular oedema secondary to BRVO and CRVO was included and only limited data were available on the CRVO-only group.

Interventions

The Geneva trial (2010 ff.)[11;17;18] compared a 0.35 mg (n=136) and a 0.7 mg dexamethasone (n=154) intravitreal implant with sham treatment (n=147). After the initial 6 month study period, patients could enter a 6 month open label extension, where they received a 0.7 mg dexamethasone intravitreal implant.

The SCORE trial (2009 ff.)[19-32] compared intravitreal injections of 1 or 4 mg of triamcinolone (~2 injections over 12 months, n= 92 and 91 for 1 and 4 mg respectively) with an observation group (n=88). The ROVO trial (2013)[33] compared a single intravitreal injection of 4 mg of triamcinolone (over 12 months, n=25) with radial optic neurotomy (n=38) or sham injection (n=20).

In the COPERNICUS trial (2012)[34;35], intravitreal injections of 2 mg of aflibercept (n=114) were given every 4 weeks over 24 weeks to the intervention group and the comparison group received a sham injection (n=75). During weeks 24 to 52, patients in both groups received aflibercept if they met protocol-specified retreatment criteria, and received a sham injection if retreatment was not indicated (3.9 standard error 0.3 injections in the sham group and 2.7 standard error 0.2 injections in the aflibercept group); after the first year, patients continued in a one-year extension phase with as needed dosing. In the GALILEO trial (2012)[36;37], intervention patients also received intravitreal injections of 2 mg of aflibercept (n=103) every 4 weeks over 24 weeks, while the comparison group was given sham injections (n=71). During weeks 24 to 52, patients remained in their original treatment groups but received their allocated treatment as needed; beginning from week 52 to week 76, both groups received the study drug every 8 weeks.

In a trial by Wroblewski and colleagues (2009)[38-44], patients received 0.3 or 1 mg intravitreal injections of pegaptanib sodium every 6 weeks for 24 weeks (n=33 and 33), compared with a sham injection group (n=32). Patients were followed up to 52 weeks.

The CRUISE trial (2010 ff.)[10;45;46] compared monthly injections of 0.3 or 0.5 mg of ranibizumab (n=132 and 130) over 6 months with sham injection (n=130). During months 6 to 12, all patients could receive intraocular ranibizumab (previously assigned dose or 0.5 mg for the sham group) if they met

prespecified functional and anatomic criteria; after 12 months' follow-up patients could continue in the HORIZON trial for another 12 months, where they were eligible to receive intravitreal injections of 0.5 mg ranibizumab if they fulfilled prespecified criteria.

Epstein and colleagues (2012)[47-49] conducted an RCT in which they compared patients receiving four intravitreal injections of 1.25 mg of bevacizumab (n=30) over 6 months with patients receiving sham injection (n=30). From 6 to 12 months, all patients received intravitreal bevacizumab injections every 6 weeks.

Outcomes. The primary endpoint of all but one study was the proportion with a gain of 15 or more ETDRS letters. The primary endpoint of the remaining study was mean change in BCVA. Studies also reported gains or losses of ETDRS letters at various cut-off points, absolute BCVA, CRT, and safety parameters. The COPERNICUS, the GALILEO and the CRUISE studies also measured vision-related quality of life (National Eye Institute Visual Functioning Questionnaire, NEI-VFQ).[10;34-37;45;46] EQ5D was also used in GALILEO.

Ongoing studies. Of the ongoing trials, the first (clinicaltrials.gov NCT01468844) is a 24 month double-blind RCT from the USA. It set out to test the safety and effectiveness of minocycline as a treatment for CRVO in around 20 patients with macular oedema secondary to CRVO. Both groups received monthly intravitreal bevacizumab injections over three months (and afterwards as needed), and the intervention group also received 100 mg oral minocycline twice daily over 24 months. The second trial (clinicaltrials.gov NCT00566761) is an open-label RCT from Mexico in only around 10 patients assessing whether combined treatment with bevacizumab and triamcinolone is more effective than bevacizumab alone. The combination group received 2.5 mg of bevacizumab plus 4 mg of triamcinolone as a first dose and then two doses of bevacizumab alone at monthly intervals, while the monotherapy group received three monthly doses of 2.5 mg bevacizumab alone. Follow-up will be 12 months. A third RCT from Hungary compares monthly injections of ranibizumab for three months (and as needed thereafter) with Argon laser treatment in around 40 patients with macular oedema secondary to CRVO. Follow-up will also be 12 months. The primary endpoint in all studies is BCVA over 12 months.

Risk of bias

Details of risk of bias assessment are shown in Table 3.

Most studies (except GALILEO (2012) and Epstein 2012)[36;37;47-49] adequately described the generation of the allocation sequence, but only half the studies gave enough details to confirm adequate allocation concealment. Most studies (unclear in the ROVO 2013 study)[33] used at least partial masking, and most studies appeared to have had masking of outcome assessment. Intention-to-treat analysis was used in all studies. Where reported separately for comparison groups, losses to follow-up tended to be slightly higher for the control groups than the interventions groups (79 to 88.5% follow-up in the control groups and 90 to 98% in the intervention groups). All studies appeared to have been free of selective reporting. Most studies included a power analysis (not reported for the CRUISE study)[10;45;46], but in two cases (the SCORE and the ROVO studies)[19-33] the numbers randomised were considerably below the numbers indicated in the power calculations. As far as reported, there were no significant differences between comparison groups in baseline characteristics.

Clinical effectiveness

Detailed study results can be found in Table 2.

Visual acuity. Figure 2 shows the primary endpoint in most studies, which was the proportion of participants with a gain of 15 or more ETDRS letters. As there were no significant differences in visual acuity results between groups using different dosages of the given pharmacological treatment, intervention groups were combined for the sake of the plot.

In the Geneva trial (2010 ff.)[11;17;18], treatment of macular oedema secondary to CRVO with a 0.7 mg intravitreal dexamethasone implant resulted in a 0.1 letter gain in BCVA compared to a loss of 1.8 in the sham group ($p < 0.001$). The difference persisted in the extension period where all patients received the 0.7 mg dexamethasone implant. However, there was no significant difference in the proportion of patients gaining or losing 15 letters at either 6 or 12 months (0.35 or 0.7 mg dexamethasone). This may reflect the timing of peak effect at 90 days with dexamethasone.

In the SCORE trial (2009 ff.)[19-32], patients in the triamcinolone groups lost significantly fewer ETDRS letters (triamcinolone 1mg 1.2 letters loss, 4mg 1.2 letters loss and observation 12.1 letters loss) over both 12 and 24 months than patients in the observation group. The proportion of patients gaining 15 letters or more was also significantly larger in the intervention groups at 12 and 24 months (25.6% compared with 6.8% and 31% compared with 9%, respectively). The proportion of patients receiving triamcinolone and losing 15 letters or more was smaller (25.6%) than in the observation group (43.8%), but this difference was not statistically significant (p=0.06).

There was some overall improvement in BCVA in both intervention groups at 12 months in the ROVO trial (2013)[33], (triamcinolone 20%, radial optic neurotomy 47% and sham 10%) however it was unclear whether there were any statistically significant differences between the 4 mg triamcinolone, the radial optic neurotomy, or the sham group. However, there were significantly more patients with an improvement of more than or equal to 15 letters in the neurotomy group than in the sham group (47% versus 10%), but no significant difference to sham after one dose of triamcinolone.

In both the COPERNICUS (2012)[34;35] and GALILEO (2012)[36;37]trialspatients in the aflibercept group had a significant improvement in BCVA at 6 months of 18 and 17.3 letters (compared to 4 letters loss and 3.3 letter gain in sham groups respectively), and this was maintained at 12 months and was significantly greater than the improvements in the sham groups. This was paralleled by a significantly greater proportion of patients(56.1% compared with 12.3% and 60.2% compared with 22.1%, respectively) gaining 15 letters or more. Patients treated sooner after diagnosis (less than versus more than two months) seemed to benefit more (in terms of proportion of patients with 15 letters or more gain) in both trials.

The increase in mean change in BCVA with 0.3 mg pegaptanib compared with sham did not reach significance at 30 weeks in the trial by Wroblewski and colleagues (2009)[38-44], but there was a greater increase in BCVA with 1 mg pegaptanib compared with sham (9.9 letter gain compare with 3.2 letter loss). These differences were not statistically significant at 52 weeks. There was no significant difference between any of the groups in the proportion of patients gaining 15 letters or more at 30 weeks, but significantly fewer patients in both dosage groups lost 15 letters or more than in the sham group (6% compared with 31%).

In the CRUISE trial (2010 ff.)[10;45;46], mean change in BCVA was significantly increased in the ranibizumab groups (no difference between doses) compared with the sham group at both 6 and 12 months (12.0 letters gained in the 0.5 mg group compared to 7.6 in the sham group). After the one year extension with ranibizumab as needed in all groups, there was no difference between the doses of ranibizumab at 24 months. The pattern was similar for the proportion of patients gaining 15 letters or more.

In the trial by Epstein and colleagues (2012)[47-49], treatment with intravitreal bevacizumab , compared with sham treatment significantly increased mean change in BCVA (14.1 letters gain compared to 2.0 letters lost) and the proportion of patients gaining 15 letters or more (60% compared to 20%) at 24 weeks. This difference was maintained in the extension period, even though both groups had been

receiving bevacizumab. Younger patients (<70 years) tended to have better visual outcomes than older patients (>70 years).

Central retinal thickness. In the Geneva trial (2010 ff.)[11;17;18], no significant difference was found in the reduction of CRT after 6 months' treatment in patients with macular oedema secondary to CRVO with the 0.7 mg intravitreal dexamethasone implant (no data given for the 0.35 mg implant) compared with sham.

In the SCORE trial (2009 ff.)[19-32], CRT decreased in all study groups, but there was no significant difference between groups at either 12 or 24 months. Similarly, there was no clear difference in the proportion of patients achieving a CRT of less than 250 µm. CRT decreased in all comparison groups in the ROVO trial (2013)[33], but there was no significant difference between groups.

Both in the COPERNICUS trial (2012)[34;35] and in the GALILEO trial (2012)[36;37] there was a significantly greater reduction in CRT at 6 months in the aflibercept group than in the control group. However the significant difference was maintained in the longer term only in the GALILEO trial, where patients continued their assigned treatment up to 12 months. In the COPERNICUS trial, patients in the sham group also received aflibercept in the extension period, which caused a similar decrease in CRT as in the original intervention group.

After 30 weeks of treatment with pegaptanib (Wroblewski and colleagues 2009)[38-44], differences in decrease of CRT versus sham did not reach significance, but at 52 weeks, the decrease in CRT was significantly greater in both the 0.3 mg and the 1 mg pegaptanib groups compared with sham.

After treatment with ranibizumab in the CRUISE trial (2010 ff.)[10;45;46], a significant reduction in CRT was observed and significantly more patients achieved a CRT of 250 µm or less in the intervention groups (no difference between doses) than in the sham group at 6 months. This difference did not persist at 12 and 24 months because all groups received ranibizumab as needed.

In the trial by Epstein and colleagues (2012)[47-49], treatment with intravitreal bevacizumab significantly decreased CRT and the proportion of patients with no residual oedema (CRT <300 µm) at 24 weeks, compared with sham treatment. When both groups received bevacizumab in the extension period, similar decreases in CRT and increases in the proportion of patients with no residual oedema were seen.

Vision-related quality of life. Vision-related quality of life (NEI-VFQ25) was significantly higher in the aflibercept group, compared with sham injection, at 6 months in both the COPERNICUS trial (+7.2 compared with +0.8)[34;35] and the GALILEO trial (+7.5 compared with +3.5)[36;37]. In the COPERNICUS

trial, patients in the sham group who received aflibercept in the extension period had a similar increase in vision-related quality of life as patients in the original intervention group by 12 months.

In the CRUISE trial (2010 ff.)[10;45;46], vision-related quality of life (NEI-VFQ) was similarly increased in both ranibizumab groups and statistically significantly more than in the sham group at 6 months (+6.2 compared with +2.8). At 12 months, with all groups receiving ranibizumab as needed, the increases were similar in all three groups.

Adverse events. The 0.7 mg dexamethasone intravitreal implant caused significantly more increased intraocular pressure (IOP) than sham treatment (30.1%, versus 1.4% in the control group) in patients with CRVO in the Geneva trial (2010 ff.)[11;17;18] (not reported for 0.35 mg). The incidence of cataract was also slightly higher in the dexamethasone group but numbers were small because of the short duration . There were no other differences in adverse events between groups.

In the triamcinolone group (especially 4 mg, SCORE trial 2009 ff.)[19-32], there was a higher increase in IOP, lens opacity onset or progression (at 12 months) and cataract surgery (12 to 24 months) than in the control group. There were no other differences in adverse events between groups. A similar tendency was seen in the ROVO trial (2013)[33].

Aflibercept did not appear to increase the incidence of ocular or non-ocular adverse events compared with sham in both the COPERNICUS trial (2012)[34;35] and the GALILEO trial (2012)[36;37].

In the trial by Wroblewski and colleagues (2009)[38-44], adverse events in response to pegaptanib were not reported in detail, but there do not appear to have been any serious ocular or systemic adverse events.

After treatment with ranibizumab in the CRUISE trial (2010 ff.)[10;45;46], there were no consistent differences in ocular or systemic adverse events between the intervention groups. None of the ocular adverse events appeared to have increased substantially after all patients received ranibizumab up to 24 months.

Epstein and colleagues (2012)[47-49] did not report adverse events in response to bevacizumab in detail, but the treatment appears not to have caused any serious ocular adverse events over 48 weeks.

Discussion

Statement of principal findings

Compared to control, intravitreal steroids and anti-VEGF therapies increase the proportion of patients whose vision improves by 15 or more letters in patients with macular oedema secondary to CRVO. The most effective drugs result in over 60% of patients gaining 15 letters compared to only about 20% of the control groups. RCT evidence demonstrates the short-term effectiveness of ranibizumab, bevacizumab, aflibercept and triamcinolone. Results from trials of dexamethasone and pegaptanib were mixed. Long-term evidence is awaited.

Strengths and limitations

A robust systematic review methodology was used. A broad search strategy was implemented, which included not restricting the search strategy with drug terms. Grey literature was searched by screening meeting abstracts from relevant conferences. There were no language restrictions. Two reviewers screened titles and abstracts and conducted data extraction and risk of bias assessment. Risk of bias was assessed using the Cochrane Risk of Bias Tool and was generally judged to be low or unclear. Only studies with one year follow up were included to exclude studies with very short follow-up RCTs were identified for all the new ophthalmological drugs, except for the steroid, fluocinolone.

The main limitation is the short duration of follow-up. The primary outcome for most trials was measured at 6 months, with an extension phase up to 12 months. Hence, it is not known whether the benefit of these treatments will be maintained long-term. Furthermore, potential side effects of these treatments may not be captured in these studies as a result of their short follow-up. Patients and clinicians would like sustained, life-long improvement in visual acuity, but of all included studies only one of them had a follow-up of over 24 months.

The sample size of some studies was small. For example, the evidence for pegaptanib and bevacizumab comes from studies with around 30 participants per arm which substantially increases the risk of a type II error. Only three trials included quality of life data, arguably one of the most important outcomes.

The proportion of participants and severity of ischemia within the trials was not clear. Whilst ischaemia is not mentioned in the inclusion/exclusion criteria of most studies, these participants

were unlikely included in these studies, especially if the diagnosis of ischaemic CRVO is based on strict criteria. Furthermore patients were entered into the trials relatively soon after diagnosis (mean 4.3 to 4.9 months) and the it is not clear if the effects would be similar in patients who present with long standing disease.

Another weakness was that patients were not asked at the of trials, what treatment they thought they had received, which would have provided data on the success of masking of allocation.

In the case of dexamethasone, the results at six months were not as good as at 90 days, because of the duration of action. Earlier re-treatment, at say 120 days, would have improved results, but many clinicians might be reluctant to repeat injections of dexamethasone implant often because of the large needle size and risk of adverse effects.

Adverse events

Results from the included studies clearly demonstrate that steroids (triamcinolone and dexamethasone) are associated with clinically meaningful increases in IOP and cataract progression. Anti-VEGF therapy ocular adverse events reported in the trials were similar in both placebo and intervention arms.

There is limited evidence of the safety of these drugs specifically in CRVO, but it would not be unreasonable to look to trials in neovascular age-related macular degeneration (AMD) and diabetic macular oedema (DMO) for safety data, where there is more experience. The CATT trial, which compared bevacizumab with ranibizumab in AMD, suggested that there was a higher incidence (RR 1.29 95%CI 1.01 to 1.66) of serious systematic adverse events (primarily hospitalisations) in the bevacizumab arm.[50]Some have raised concerns about arterial thromboembolic events with bevacizumab, but none of these has been demonstrated in the published literature.[51-54] Micieli and colleagues (2010) undertook a systematic review of the adverse events associated with bevacizumab. 22 studies were reviewed, representing 12,699 participants.[55] Adverse events in patients treated with bevacizumab were cerebrovascular events (0.21%), myocardial infarction (0.19%) and increased blood pressure (0.46%). Most of these represent the background burden of disease in patients with advanced eye disease. The proportion of these directly attributable to bevacizumab is likely to be very small. Campbell and colleagues (2012) undertook a nested case-control study of over 7,000 cases and 37,000 controls.[51] Ranibizumab and bevacizumab injection was the exposure and cardiovascular events were the outcome. The authors found that ranibizumab and bevacizumab were not associated with increased cardiovascular events.

Increased IOP has been associated with ranibizumab, bevacizumab and pegaptanib. Sustained increased in IOP has estimated to be 5.5-6.0% with these drugs.[56;57]

Robust evidence on the long-term safety of aflibercept is awaited.

What do these results mean?

Until very recently, patients with macular oedema as a result of CRVO could only be offered visual rehabilitation and visual aids in an attempt to help them to deal better with their reduced vision and its implications in their daily activities and quality of life. Their future is brighter now as new options to treat macular oedema have become available. Triamcinolone is likely to be a cost-effective treatment at least in selected groups of patients, such as pseudophakic individuals or those with pre-existing cataracts that may require cataract surgery in the near future. The lack of a commercially available licensed product for intraocular administration may restrict its use in clinical practice.

Some anti-VEGF therapies, including bevacizumab, ranibizumab and aflibercept, have been also shown to be effective in short term studies for the treatment of patients with macular oedema and CRVO. Bevacizumab has the advantage of having a low cost with an apparently similar effect to other anti-VEGF therapies[50;58;59]but there is some reluctance to use it as it is not licensed for use in the eye. This has been seen in other eye conditions, such as AMD and DMO. Aflibercept, requiring potentially fewer injections than other anti-VEGF agents, could represent an advantage to patients and may relieve pressure on ophthalmology clinics. As more options have become available, ophthalmologists will need to decide, together with their patients, which may be the best treatment option for them based on their visual requirements and life circumstances. Health care systems will need to evaluate the cost-effectiveness of these new treatments and support affordable ones. The National Institute for Health and Care Excellence is currently appraising aflibercept. Policy makers are left in a difficult position because of bevacizumab. It is cheaper than all other drugs[60] and appears to be as effective, but is unlicensed and unlike ranibizumab and aflibercept does not have evidence from large, well-funded RCTs in CRVO. The use of bevacizumab would result in considerable savings for the NHS.

It is important to note that the evidence of benefit of these new therapies is likely to only apply to patients with non-ischaemic CRVO. Although some patients with ischaemic CRVO were included, these individuals are likely to have mild ischaemic CRVO. Thus, for patients with established ischaemic CRVO, there are no proven treatments available and further research into this area is very much needed.

What is the context of these results

Earlier systematic reviews identified limited evidence on the clinical effectiveness of treatments. A review by Braithwaite and colleagues (search date August 2010)[61] on anti-VEGF agents identified one RCT[10;45;46] comparing two doses of ranibizumab and one RCT[38-44] comparing two doses of pegaptanib sodium versus placebo or no treatment. In both RCTs, the higher dose of the anti-VEGF significantly improved BCVA compared with sham injection in the short term (~6 months), but the effects in the longer term were unclear. Braithwaite and colleagues concluded that data from the two RCTs could not be synthesised because ranibizumab and pegaptanib sodium might not be directly comparable. Subsequent RCTs identified in this review also suggest benefit in ocular outcomes in macular oedema secondary to non-ischaemic CRVO for the anti-VEGFs bevacizumab, and aflibercept.[34-37;47-49]

Gewaily and Greenberg reviewed the literature on intravitreal corticosteroids (search date November 2008) versus observation in macular oedema secondary to CRVO and identified no relevant RCTs.[62] Results from two observational studies suggested that triamcinolone acetonide might be beneficial in the treatment of macular oedema secondary to non-ischaemic CRVO. However, as the authors of the review caution because conclusions are primarily drawn from small case series and case reports with short follow up. Results from the SCORE 2009 RCT corroborate the observational studies.[19-32] The effects of triamcinolone acetonide in people with non-ischaemic CRVO without associated macular oedema are less clear. Data from four observational studies led Gewaily and Greenberg to conclude that intravitreal corticosteroids are associated with transient anatomical and functional improvements.

Immediate treatment aimed at relieving the blocked vein and surgical interventions were outwith the remit of this review. Antithrombotics, such as low-molecular weight heparin (LMWH), and fibrinolytics have also been found to benefit visual acuity in retinal vein occlusion with no associated macular oedema. Two systematic reviews[63;64] identifying the same three RCTs in recent onset (≤30 days) BRVO or CRVO found that LMWH improved visual acuity compared with aspirin and that the associated benefit was larger in CRVO; only one of the three RCTs included people solely with CRVO. One review[64]also included one RCT comparing ticlopidine with placebo and two RCTs assessing intravenous fibrinolytic therapy followed by warfarin or aspirin with either haemodilution or no treatment. The authors of the reviews conclude that no definitive recommendations can be made on clinical effectiveness of LMWH in CRVO given the limited evidence available.

Radial optic neurotomy involves the performance of a radial cut using a microvitreoretinal (MVR) blade through the lamina cribrosa, scleral ring and adjacent sclera at a selected point in the optic nerve head with the goal of "decompressing" the scleral outlet (space confined by the scleral ring and containing the lamina cribrosa, the central retinal artery, central retinal vein and the optic nerve. The SCORE trial found radial optic neurotomy to be more effective than sham.

Further research

Large adequately powered RCTs comparing ranibizumab, bevacizumab, aflibercept and triamcinolone are needed. Part of the problem is that the US the Food and Drug Administration requires pharmaceutical companies to present data establishing a drug's safety and effectiveness. Whilst this does not specifically require a placebo-controlled trial, it is the most efficient study design for demonstrating effectiveness and safety. Clinicians and researchers are left with placebo-controlled trials demonstrating effectiveness for individual drugs, but a lack of evidence to help them decide which is best for their patients.

Given the cost of these treatments and the burden of repeated injections to patients and health care systems, research aiming to predict "responders" would be useful as at present this is done by therapeutic trial. Treatments could then be targeted to patients likely to benefit. Research is also needed on the frequency and sequences of drugs. As other pathogenic pathways besides inflammation and VEGF-mediated pathways may be implicated in the development of macular oedema in patients with CRVO, these should be investigated in an attempt to develop new therapeutic strategies for this condition. Research is also needed into optimum timing of treatment after CRVO. The cost-effectiveness of diagnostic technologies for determining when retreatment is necessary should be examined.

We also need better treatments since a significant proportion of patients do not improve with all of these drugs

Future RCTs should include longer term outcomes, as functional results observed at six months or even one year may not necessarily be representative of what is likely to be achieved longer term and, furthermore, potential side effects of treatments, such as retinal atrophy after repeated injections of anti-VEGFs, may not be captured in shorter term studies.

Conclusions

Bevacizumab, ranibizumab, aflibercept and triamcinolone appear to be effective in improving the number of patients who gain 15 letters or more in CRVO. There are mixed results for dexamethasone and pegaptanib. Steroids were associated with cataract progression and increased IOP. Long-term data on effectiveness and safety are needed. Head-to-head trials and research to identify “responders” is needed to help clinicians make the right choices for their patients.

Acknowledgments: None

Conflict of interest: None

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

Contributions: NW devised the idea for the review. JF wrote the protocol and all authors contributed to the design of the protocol. RC undertook the literature searches. JF, CC and ST screened titles and abstracts. CC, ST and DS extracted the data. All authors contributed to the interpretation of the results. JF, NL, RC, CC and SB contributed to the first draft of the article. All authors reviewed and commented on the final manuscript.

Figure 1: PRISMA statement

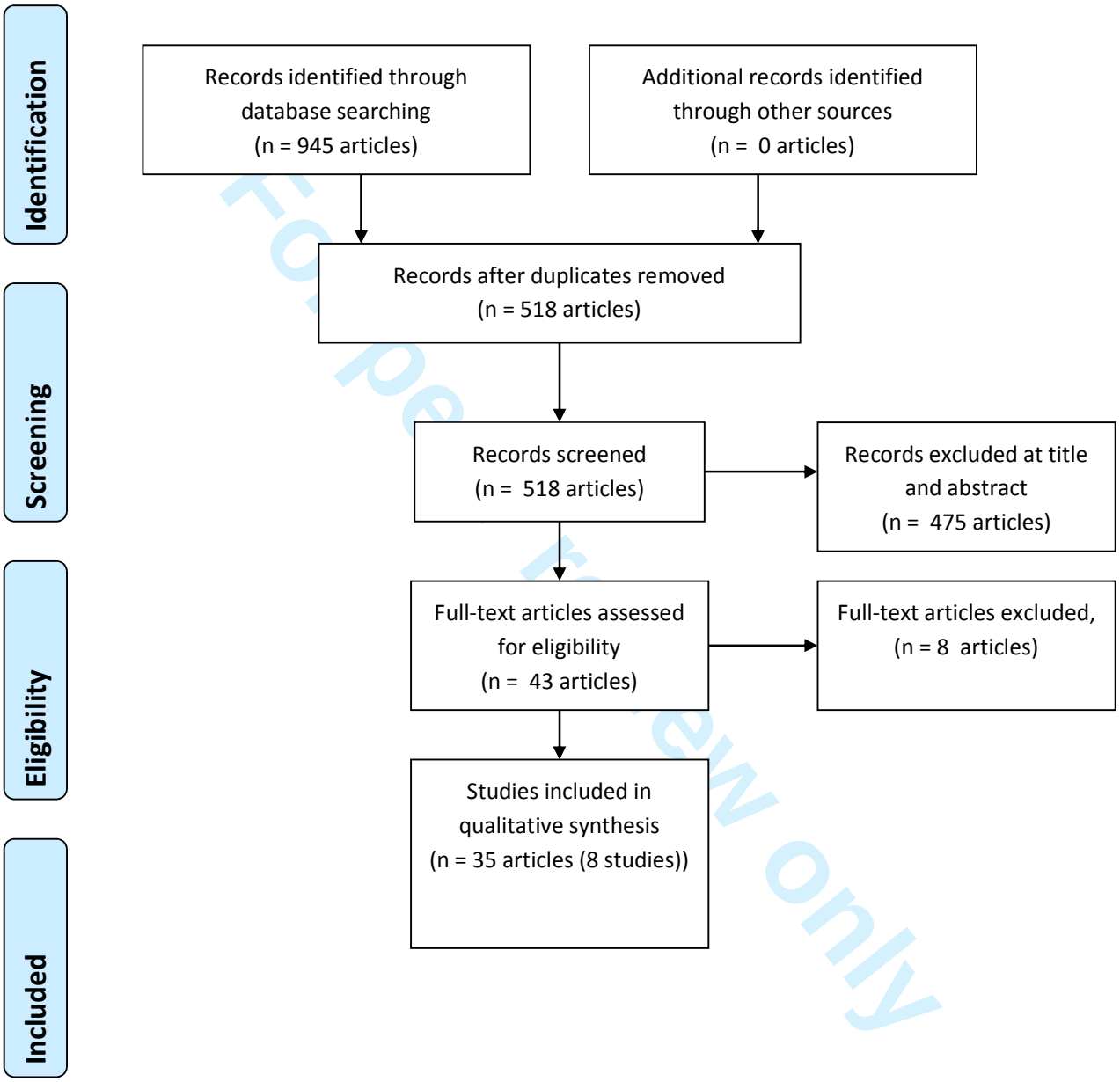

Figure 2. Study results for the primary outcome (≥15 ETDRS letter gain).

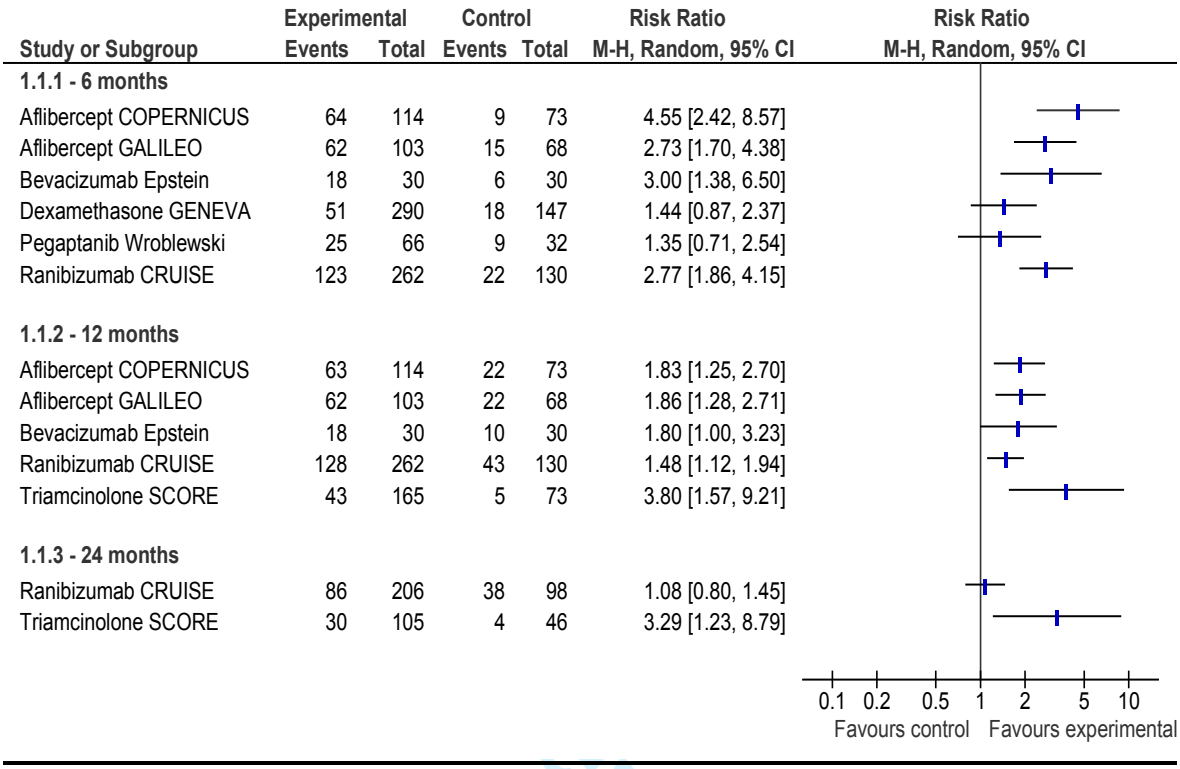

Table 1: Study characteristics

Study	Participants and baseline values	Intervention / Outcomes
DEXAMETHASONE		
GENEVA 2010 ff.[11;17;18] International **Setting:** multicentre (167 centres in 24 countries, so a mean of 2.6 patients per centre) **Study aim:** to evaluate the effects of dexamethasone intravitreal implant in patients with macular oedema secondary to CRVO or BRVO (only data for CRVO reported here) **Design:** 2 identical double-blind, sham-controlled RCTs, phase 3 **Follow-up:** primary endpoint for the masked trial: 6 months; primary endpoint for the open-label extension: 12 months **Overall quality:** 5.5/6	**N:** CRVO – 437 eyes of 437 patients randomised; 94% follow-up at 6 months **Inclusion criteria:** ≥18 years; reduced VA due to macular oedema due to CRVO or BRVO which in the investigator's opinion, is unlikely to be adversely affected if not treated for 6 months; duration of macular oedema 6 weeks to 9 months in patients with CRVO; BCVA 34 to 68 ETDRS letters (~20/200 and 20/50 Snellen equivalent) in the study eye and >34 letters in the non-study eye; CRT ≥300 µm (OCT) **Exclusion criteria:** *study eye:* clinically significant epiretinal membrane; use of periocular corticosteroid within 6 months or topical nonsteroidal anti-inflammatory drug or corticosteroid within 1 month; intraocular surgery or laser within 30 days of study or anticipated; history of intravitreal use of corticosteroid or any other drug; glaucoma; IOP >23 mmHg if untreated or >21 if treated with one medication; treatment with ≥2 IOP-lowering medications; active retinal, optic disc or choroidal neovascularisation; history of herpetic infection; rubeosis iridis, aphakia or anterior-chamber intraocular lens; any ocular condition that would prevent a 15-letter VA improvement; preretinal or vitreous haemorrhage, lens opacity, media opacity that would preclude clinical or photographic evaluation; history of pars plana vitrectomy; *any eye:*	**DEX 0.7 (n=136):** sustained delivery, biodegradable dexamethasone intravitreal implant (Ozurdex), 0.7 mg implant inserted into the vitreous cavity through the pars plana using a customised, single-use, 22-gauge applicator **DEX 0.35 (n=154):** DEX 0.35 mg implant inserted following the same method **Sham (n=147):** a needleless applicator was placed against the conjunctiva to simulate the placement of study medication. **Regimen for all groups:** before inserting the implant, the study eye was anaesthetised with topical and subconjunctival anaesthetics and prepared according to standard clinical practice for eyes undergoing intravitreal injection; patients were treated with a topical ophthalmic antibiotic 4 times daily starting 3 days before the day of their study procedure (day 0) and continuing for 3 days after the procedure **Extension:** patients completing 180 days were eligible to enter a 6 month open label extension where they received DEX 0.7 mg implant **Primary end point:** gain of ≥15 ETDRS letters; for the open-label extension: safety

Study	Participants and baseline values	Intervention / Outcomes
	active ocular infection; history of steroid-induced IOP–increase; diabetic retinopathy; *other:* uncontrolled systemic disease; current or anticipated use of systemic steroids or anticoagulants **Age (years):** 62.7 to 65.2 years **Sex:** 43.7 to 49.2% (CRVO and BRVO together) **Baseline VA (ETDRS letters):**52.4 SD10.6 **Baseline CRT (µm):**DEX 0.7: 648; Sham: 620 **Other ocular information:** phakic status (%): 85 to 88% **Duration of macular oedema:** mean 4.8 to 4.9 months;<90 days: 14.3 to 15.4%; >90 to <180 days: 54.4 to 57.4%, >180 days: 27.1 to 31.3% **Comorbidities:** diabetes mellitus 14 to 15%, hypertension 62 to 64%, coronary artery disease 9 to 13%, IOP-lowering medication at baseline 4 to 6% (all for CRVO and BRVO together)	**Other outcomes:** proportion of eyes achieving at least a 10 and 15 letter improvement from baseline; the proportion of eye exhibiting ≥15 letters of worsening; BCVA; subgroup analysis according to RVO diagnosis (BRVO and CRVO) and duration of macular oedema at baseline; CRT and safety **Outcome assessment:** evaluation at 1, 7, 30, 60, 90 and 180 days after study treatment for both parts of the study
TRIAMCINOLONE		
SCORE 2009 ff.[19-32] USA **Setting:** multicentre **Study aim:** to compare the effects of 1 and 4 mg preservative-free	**N:** 271 eyes of 271 patients randomised; 83% (observation) and 90% (intervention) completed 12 months **Inclusion criteria:** centre-involved macular oedema secondary to CRVO, BCVA 19 to 73 ETDRS letters (Snellen equivalent ~20/400 to 20/40), CRT >250 µm by OCT; media clarity, papillary dilatation and participant	**Tria (1 mg) (n=92):** 1 mg (0.05 ml) of preservative-free, nondispersive formulation of triamcinolone (average number of injections 2.2 at 12 months) **Tria (4 mg) (n=91):** 4 mg (0.05 ml) of preservative-free, nondispersive formulation of triamcinolone(average number of injections 2.0 at 12 months)

Study	Participants and baseline values	Intervention / Outcomes
intravitreal triamcinolone with observation in eyes with vision loss associated with macular oedema secondary to perfused CRVO **Design:** RCT **Follow-up:** primary end point 12 months, FU planned up to 36 months **Overall quality:** 3/6	cooperation sufficient for adequate fundus photographs **Exclusion criteria:** macular oedema due to causes other than CRVO, ocular condition such that visual acuity would not improve from resolution of oedema, substantial cataract, prior treatment with intravitreal corticosteroids or peribulbar steroid injection within 6 months, photocoagulation (prior 4 months or anticipated), prior pars plana vitrectomy, major ocular surgery (prior 6 months or anticipated), IOP ≥25 mmHg, open-angle glaucoma, steroid-induced IOP-elevation requiring IOP-lowering treatment, pseudoexfoliation, aphakia **Age:** 68.0 SD 12.4 years **Sex:** 45% female **Duration of macular oedema:** 4.3 SD3.7 months **Baseline VA (ETDRS letters):** 51.2 SD14.1 **Baseline CRT (µm):** 659 SD229 **Other ocular information:** 81% phakic, IOP 15.5 SD3.2 mmHg **Comorbidities:** 23% diabetes mellitus, 73% hypertension, 21% coronary artery disease, 21% history of cancer	The form of triamcinolone used was Trivaris, no longer available. It was made by the manufacturer of Ozurdex (Allergan) **Obs (n=88):** observation **Regimen for all groups:** all intervention eyes received standardised ocular surface preparation prior to injection (eyelid speculum, topical anaesthetic, topical antibiotics, asepsis with povidone iodine); retreatment every 4 months unless (1) treatment was deemed successful (defined), (2) treatment was contraindicated because of significant adverse effect, (3) additional treatment was considered 'apparently futile' (defined) **Primary end point:** gain of ≥15 ETDRS letters **Other outcomes:** BCVA, intraocular pressure, eye examination including dilated fundus examination, OCT scan for thickness, , lens opacities, , adverse events **Outcome assessment:** follow-up visits every 4 months for 36 months
ROVO 2013[33]	**N:** 90 patients randomised; 82% evaluated **Inclusion criteria:** history of CRVO not longer than 12	**Tria (n=25):** single intravitreal injection of 4 mg triamcinolone acetonide (100 µl) applied after povidone

Study	Participants and baseline values	Intervention / Outcomes
Austria **Setting:** multicentre (7 centres in 7 countries) **Study aim:** to compare the effects of radial optical neurotomy with intravenous triamcinolone and natural history (placebo) in patients with CRVO **Design:** RCT, placebo-controlled **Follow-up:** primary end point 12 months **Overall quality:** 3.5/6	months; VA of ≥0.3 logMAR (≤85 letters) (for perfused CRVO: VA >1 logMAR (>50 letters) or no VA improvement over 4 weeks) **Exclusion criteria:** dense cataract, severe ophthalmologic conditions (severe retinopathy, presence of advanced optic atrophy, uncontrolled glaucoma), pregnancy, allergy against fluoresceine or indocyanine green, any handicap which could prevent patients from attending follow-up visits **Age:** not reported **Sex:** 36% female **Duration of macular oedema:** not reported **Baseline VA (ETDRS letters) :** 1.07 logMAR (interquartile range 0.78 to 1.7) (~46 letters) **Baseline CRT (µm):** 569 to 657 µm **Other ocular information:** not reported **Comorbidities:** 23% diabetes mellitus, 49% hypertension, 17% cardiovascular disease, 4% hypercoagulopathies, 1% leukaemia, 2% anaemia	iodine drops; postoperative topical antibiotics **RON (n=38):**radial optical neurotomy under general anaesthesia (detailed procedure described) **Pla (n=20):** eyes prepared as for triamcinolone injection but sham injection performed (empty syringe without needle pressed against the eye) **Primary end point:** gain of ≥15 ETDRS letters **Other outcomes:** BCVA, CRT, safety **Outcome assessment:** 12 months
AFLIBERCEPT		
COPERNICUS 2012[34;35] International	**N:** 189 eyes of 189 patients randomised; 95.7% (aflibercept) and 81.1% (sham) completed 24 weeks; 93% (aflibercept) and 77% (sham) completed 52 weeks	**VTE (n=114):** intravitreal injections of 2 mg aflibercept (50 µl) every 4 weeks for 24 weeks **Sham (n=73):** sham procedure (empty syringe without

Study	Participants and baseline values	Intervention / Outcomes
Setting: multicentre, 70 sites in North and South America, India and Israel. Mean 2.7 patients per centre. **Study aim:** to evaluate the effects of intravitreal aflibercept in patients with macular oedema secondary to CRVO **Design:** double-blind, sham-controlled RCT, phase 3 **Follow-up:** primary end point 24 weeks, FU 2 years **Overall quality:** 5/6	**Inclusion criteria:** adult patients with centre-involved CRVO for a maximum of 9 months, CRT ≥250 µm with OCT, ETDRS BCVA of 73 to 24 letters (Snellen equivalent 20/40 to 20/320) **Exclusion criteria:** history of vitreoretinal surgery (incl. radial optic neurotomy or sheathotomy); current bilateral retinal vein occlusion; previous pan-retinal or macular laser photocoagulation; other reasons for decreased visual acuity; ocular conditions with poorer prognosis in the fellow eye; history or presence of age-related macular degeneration, diabetic macular oedema, or diabetic retinopathy; any use of intraocular or periocular corticosteroids or antiangiogenic treatment in the study eye at any time or in the fellow eye in the preceding 3 months; iris neovascularisation, vitreous haemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula; vitreomacular traction or epiretinal membrane significantly affecting central vision; ocular inflammation; uveitis; any intraocular surgery in the preceding 3 months; aphakia; uncontrolled glaucoma, hypertension, or diabetes; spherical equivalent of a refractive error of more than -8 diopters; myopia; infectious blepharitis, keratitis, scleritis, or conjunctivitis; cerebral vascular accident or myocardial infarction in the preceding 6 months; and other conditions that could interfere with interpretation of the results or increase the risk of complications; cataract surgery was not allowed during the 3 months before randomisation.	needle pressed to conjunctival surface) every 4 weeks for 24 weeks **Regimen for all groups:** all patients eligible to receive pan-retinal photocoagulation for neovascularisation at any time at the discretion of the investigator; patients were not allowed to use other systemic or local medications for treating CRVO in the study eye over the first 52 weeks of the study; a noninvestigational therapy could be used to treat CRVO in the fellow eye **Extension:** during weeks 24 to 52, patients in both groups were evaluated monthly and received aflibercept if they met protocol-specified retreatment criteria, and received a sham injection if retreatment was not indicated (3.9 SE0.3 injections in the sham group and 2.7 SE0.2 injections in the VTE group); after the first year, patients continued in a 1 year extension phase with as needed dosing **Primary end point:** gain of ≥15 ETDRS letters **Other outcomes:** BCVA, CRT, proportion of patients progressing to neovascularisation of the anterior segment, optic disc or elsewhere in the retina, changes in vision-related quality of life (National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25), safety **Outcome assessment:** examination every 4 weeks up to 24 weeks, 52 weeks

Study	Participants and baseline values	Intervention / Outcomes
	Age: 66.3 SD 13.9 years **Sex:** 43% female **Time since CRVO diagnosis:** 2.4 SD2.8 months; 62.0% ≤2 months, 37.4% >2 months **Baseline VA (ETDRS letters) :** 50.0 SD14.1 ; 75.4% >20/200 **Baseline CRT (µm):** 665.8 SD239.8 **Other ocular information:** 67.9% perfused retinal occlusion, IOP 15.1 SD3.08 mmHg **Comorbidities:** not reported	
GALILEO 2012[36;37] International **Setting:** multicentre, 10 countries in Europe and Asia; 63 centres in total **Study aim:** to evaluate the effects of intravitreal aflibercept in patients with macular oedema secondary to CRVO **Design:** double-blind, sham-controlled RCT, phase 3 **Follow-up:** primary end point 24 weeks, FU up to 12 months, planned	**N:** 177 eyes of 177 patients randomised; 90.6% (aflibercept) and 78.9% (sham) completed 24 weeks **Inclusion criteria:** treatment-naïve patients, age ≥18 years, centre-involved CRVO for a maximum of 9 months, CRT ≥250 µm with OCT, ETDRS BCVA of 73 to 24 letters (Snellen equivalent 20/40 to 20/320) **Exclusion criteria:** uncontrolled glaucoma (IOP≥25 mmHg), filtration surgery, bilateral manifestation of retinal vein occlusion, iris neovascularisation, previous treatment with anti-VEGF agents, pan-retinal or macular laser photocoagulation, intraocular corticosteroids, pregnant **Age:** 61.5 SD 12.9 years	**VTE (n=103):** intravitreal injections of 2 mg aflibercept every 4 weeks for 24 weeks **Sham (n=71):** sham procedure (empty syringe without needle pressed to conjunctival surface) every 4 weeks for 24 weeks **Regimen for all groups:** pan-retinal photocoagulation allowed at any time for all patients if they progressed to neovascularisation of the anterior segment, optic disc or fundus **Extension:** during weeks 24 to 52, patients remained in their original treatment groups but received their allocated treatment as needed; beginning from week 52 to week 76 both groups received treatment every 8

Study	Participants and baseline values	Intervention / Outcomes
up to 76 weeks **Overall quality:** 4/6	**Sex:** 44.4% female **Time since CRVO diagnosis:** 81.8 SD85.4 days; 52.6% <2 months, 46.2% ≥2 months, 1.2% missing **Baseline VA (ETDRS letters) :** 52.2 SD15.7, 83% >20/200 **Baseline CRT (µm):** 665.5 SD231.0 **Other ocular information:** 83.6% perfused retinal occlusion, IOP 14.9 SD2.7 mmHg **Comorbidities:** Renal impairment: 31% mild, 8.2% moderate, 1.2% severe; 2.9% hepatic impairment	weeks **Primary end point:** gain of ≥15 ETDRS letters **Other outcomes:** BCVA, CRT, proportion of patients progressing to neovascularisation of the anterior segment, optic disc or elsewhere in the fundus, changes in vision-related and overall quality of life (National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25), European Quality of Life-5 Dimensions (EQ-5D)), safety **Outcome assessment:** 24 weeks, 52 weeks
PEGAPTANIB		
Wroblewski 2009[38-44] International **Number of sites:** not reported **Setting:** multicentre, practitioners' offices and clinics in Australia, France, Germany, Israel, Spain, USA **Study aim:** to evaluate the effects of intravitreal pegaptanib sodium in patients with macular oedema secondary to CRVO **Design:** double-blind, sham-	**N:** 98 eyes of 98 patients randomised; 93% completed 30 weeks **Inclusion criteria:** age ≥18 years, CRVO with onset within 6 months prior to baseline, CRT ≥250 µm with OCT, ETDRS BCVA of 65 to 20 letters (Snellen equivalent 20/50 to 20/400) and better than 35 letters (20/200) in the fellow eye **Exclusion criteria:** subtenon corticosteroid administration for any ophthalmic condition; prior panretinal or sector scatter photocoagulation; signs of old branch retinal vein occlusion or CRVO in the study eye; any other retinal vascular disease including diabetic retinopathy; eyes with a brisk afferent pupillary defect;	**PS 0.3 mg (n=33):** intravitreal injections of 0.3 mg pegaptanib sodium every 6 weeks for 24 weeks (5 injections) **PS 1 mg (n=33):** intravitreal injections of 1 mg pegaptanib sodium every 6 weeks for 24 weeks (5 injections) **Sham (n=32):** sham procedure (blunt pressure applied to the globe without a needle) every 6 weeks for 24 weeks **Regimen for all groups:** antisepsis procedures were the same for all participants (including those receiving sham); all participants received injected subconjunctival anaesthetic; panretinal photocoagulation permitted at

Study	Participants and baseline values	Intervention / Outcomes
controlled RCT, phase 2 **Follow-up:** primary end point 30 weeks, FU up to 12 months **Overall quality:** 6/6	vitreous haemorrhage except for breakthrough haemorrhage from intraretinal haemorrhage; evidence of any neovascularisation involving the iris, disc, or retina; any other clinically significant concomitant ocular diseases **Age:** 59 to 64 years **Sex:** 47% female **Time from occlusive event to study entry:** 77 to 82 days **Baseline VA (ETDRS letters):** 47.6 to 48.5 letters **Baseline CRT (µm):** 632 to 688 **Other ocular information:** not reported **Comorbidities:** not reported	any time point for neovascularisation according to the Central Vein Occlusion Study protocol; intravitreous steroids not permitted at any time **Extension:** FU to 52 weeks **Primary end point:** gain of ≥15 ETDRS letters **Other outcomes:** BCVA, loss of ≥15 letters, CRT, proportion of eyes progressing to retinal or iris neovascularisation, safety **Outcome assessment:** assessments every 6 weeks up top week 30, FU to week 52
RANIBIZUMAB		
CRUISE 2010 ff.[10;45;46] USA **Number of sites:** not reported **Setting:** multicentre **Study aim:** to evaluate the effects of intravitreal ranibizumab (0.3 or 0.5 mg) in patients with macular oedema secondary to CRVO	**N:** 392 eyes of 392 patients randomised; 97.7% (ran 0.3 mg), 91.5% (ran 0.5 mg), and 88.5% (sham) completed 6 months **Inclusion criteria:** age ≥18 years, foveal centre-involved macular oedema secondary to CRVO diagnosed within 12 months before study began, CRT ≥250 µm with OCT, BCVA 20/40 to 20/320 (ETDRS charts) **Exclusion criteria:** prior episode of retinal vein	**Ran 0.3 mg (n=132):** intravitreal injections of 0.3 mg ranibizumab monthly for 6 months (maximum 6 injections) **Ran 0.5 mg (n=130):** intravitreal injections of 0.5 mg ranibizumab monthly for 6 months (maximum 6 injections) **Sham (n=130):** sham procedure (empty syringe without needle pressed to the injection site) monthly for 6 months

Study	Participants and baseline values	Intervention / Outcomes
Design: double-blind, sham-controlled RCT, phase 3 **Follow-up:** primary end point 6 months, FU up to 12 months **Overall quality:** 4.5/6	occlusion, brisk afferent pupillary defect, >10-letter improvement in BCVA between screening and day 0, history of radial optic neurotomy or sheathotomy, intraocular corticosteroid use in study eye in prior 3 months, history or presence of wet or dry age-related macular oedema, recent or anticipated panretinal scatter photocoagulation or sector laser photocoagulation, laser photocoagulation for macular oedema in prior 4 months, evidence on examination of any diabetic retinopathy, stroke or myocardial infarction in prior 3 months, prior anti-VEGF treatment in study or fellow eye in prior 3 months or systemic anti-VEGF or pro-VEGF treatment in prior 6 months **Age:** 65.4 SD13.1 to 69.7 SD11.6 years **Sex:** 38.5 to 46.2% female **Time since CRVO diagnosis:** 2.9 SD2.9 to 3.6 SD3.2 months; 65.9 to 72.3% ≤3 months **Baseline VA (ETDRS letters):** 47.4 to 49.2 (SD 14.6 to 14.8) (range 9 to 72), 38.5 to 42.3% ≥55 **Baseline CRT (µm):** 679.9 SD242.4 to 688.7 SD253.1 **Other ocular information:** IOP 14.9 SD3.3 to 15.1 SD3.1 mmHg, 10.0 to 16.9% IOP-lowering medication, n=2 >10 disc areas of non-perfusion; fellow eye BCVA 78.8 SD 17.4 to 80.0 SD12.5	**Regimen for all groups:** prior to injection or sham: topical anaesthetic drops, subconjuctival injection of 2% lidocaine, cleaning of injection site with 5% povidone iodine **Extension:** months 6 to 12: all patients could receive intraocular ranibizumab (previously assigned dose or 0.5 mg for the sham group) if they met pre-specified functional and anatomic criteria (3.7 injections sham group, 3.8 injections 0.3 mg ran group, 3.3 injections 0.5 mg ran group); after 12 months' FU, 304 CRUISE patients continued in the HORIZON study for another 12 months, where patients were evaluated at least every 3 months and were eligible to receive an intravitreal injection of 0.5 mg ranibizumab if they fulfilled prespecified criteria (2.9 SD2.7 injections sham group, 3.8 SD2.8 injections 0.3 mg ran group, 3.5 SD2.7 injections 0.5 mg ran group) **Primary end point:** mean change from baseline BCVA **Other outcomes:** percentage gaining ≥15 letters, percentage losing ≥15 letters, CRT, percentage with CRT <250 µm, vision-related quality of life (National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25), safety **Outcome assessment:** monthly visits up to 12 months; 3-monthly evaluation up to 24 months (HORIZON)

Study	Participants and baseline values	Intervention / Outcomes
	Comorbidities: not reported	
BEVACIZUMAB		
Epstein 2012[47-49] Sweden **Setting:** Single centre; St. Eriks Eye Hospital Stockholm **Study aim:** to evaluate the effects of intraocular injections of bevacizumab in patients with macular oedema secondary to CRVO **Design:** sham-injection controlled, double masked RCT **Follow-up:** primary end-point 6 months; open label extension up to 12 months **Overall quality:** 5/6	**N:** 60 eyes of 60 patients randomised; 93% completed open label extension **Inclusion criteria:** CRVO of ≤6 months; BCVA 15 to 65 ETDRS letters (Snellen equivalent ~20/50 to 20/500), CRT ≥300 µm by OCT **Exclusion criteria:** CRVO with neovascularisation; previous treatment for CRVO; intraocular surgery during previous 3 months; vascular retinopathy of other causes; glaucoma with advanced visual field defect or uncontrolled ocular hypertension >25 mmHg despite full therapy; myocardial infarction or stroke during last 12 months **Age:** 70.5 SD 12.6 years **Sex:** 40% female **Time from diagnosis to inclusion:** 8.8 SD 5.7 weeks; 71.7% <90 days, 28.3% >90 days **Baseline VA (ETDRS letters) :** 44.1 SD 15.5 ; 31.7% <34, 68.3% >34	**Bev (n=30):** 1.25 mg (0.05 ml) bevacizumab via pars plana **Sham (n=30):** sham injection (syringe without needle pressed to the globe) **Regimen for all groups:** 4 injections received, one every 6 weeks; eyes treated with topical antibiotics 30 min before injection, topical chlorhexidine, topical anaesthesia with 1% tetracaine **Open label extension:** months 6 to 12, intravitreal bevacizumab injections every 6 weeks (4 injections) for all patients **Primary end point:** gain of ≥15 ETDRS letters **Other outcomes:** BCVA, OCT images, CRT, fluorescein angiogram, colour and red-free photography, slit-lamp examination with dilated fundus-examination, intraocular pressure, adverse events **Outcome assessment:** follow-up visits every 6 weeks up to 24 weeks

Study	Participants and baseline values	Intervention / Outcomes
	Baseline CRT (µm): 721 SD 269 **Comorbidities:** 48.3% hypertension, 6.7% diabetes mellitus	

Abbreviations: BCVA – best corrected visual acuity, CRT – central retinal thickness, CRVO – central retinal vein occlusion, ETDRS – Early Treatment Diabetic Retinopathy Study, FU – follow-up, IOP – intraocular pressure, OCT – optical coherence tomography, SD – standard deviation, SE – standard error

Table 2: Study results and adverse events

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)	Adverse events
DEXAMETHASONE		

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)						Adverse events			
GENEVA 2010 ff.[11;17;18]		**Baseline**	**6 months**	**p**		**12 months**	**p**	**AE**	**DEX 0.35**	**DEX 0.7 (n = 133)**	**Sham (n = 147)**	**p**
	BCVA (mean letters)							**6 months**				
	DEX 0.35	-	-					**Overall incidence of ocular adverse events**				
	DEX 0.7	52.4 SD 10.6	+0.1	< 0.001 vs sham	***DEX 0.7/0.7***	+2 (estimated from graph)				68.4%	49.7%	
	Sham	53.3 SD 10.8	-1.8		***Sham/DEX 0.7***	-1.4 (ditto)		**Common Ocular Adverse Events**				
	≥15 letters gained							Intraocular pressures increased		40 (30.1%)	2 (1.4%)	<0.001
	DEX 0.35		17%	NS vs sham				**Common treatment-related Ocular Adverse Events**				
	DEX 0.7		18.4%	NS vs sham	***DEX 0.7/0.7, day 240***	27%		IOP increased		39 (29.3%)	1 (0.7%)	<0.001
					DEX 0.7 (n=19), day 360	26%		**Cataract adverse events**				
	Sham		12.2%	NS vs sham	***Sham/DEX 0.7, day 240***	21%		Cataract		3 (2.3%)	2 (1.4%)	
	≥15 letters lost							Cataract subcapsular		4 (3.0%)	1 (0.7%)	
	DEX 0.35		-	-				Cataract nuclear		3 (2.3%)	1 (0.7%)	
	DEX 0.7		14.0%	NS				Cataract cortical		1 (0.8%)	3 (2.0%)	
	Sham		20.4%					**Serious adverse events** – not given separately for CRVO				
	Subgroups											
	Duration of macular oedema											
	>90 days	***DEX 0.7***	17.7%									
		Sham	9.6%									
	≤90 days	***DEX 0.7***	26.0%									
		Sham	27.3%									

<table>
<tr><th>Study</th><th>Clinical outcomes (BCVA, CRT; change from baseline at study end)</th><th>Adverse events</th></tr>
<tr><td></td><td>CRT (µm):
<table><tr><th></th><th>Baseline</th><th>6months (mean)</th><th>p</th><th>12 months (mean)</th><th>p</th></tr><tr><td>CRT</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>DEX 0.35</td><td>-</td><td>-</td><td></td><td></td><td></td></tr><tr><td>DEX 0.7</td><td>647.6</td><td>-118.2</td><td>NS vs sham</td><td></td><td></td></tr><tr><td>Sham</td><td>619.8</td><td>-125.3</td><td></td><td></td><td></td></tr></table></td><td></td></tr>
<tr><td colspan="3">TRIAMCINOLONE</td></tr>
<tr><td>SCORE 2009 ff.[19-32]

1 mg intravitreal triamcinolone (2.2 injections over 12 months) (n=92)

versus 4 mg intravitreal triamcinolone (2</td><td>BCVA (ETDRS letters):
<table><tr><th></th><th>Baseline</th><th>12 months</th><th>p</th><th>24 months</th><th>p</th></tr><tr><td>BCVA (letters, 95% CI)</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Tria 1 mg</td><td>50.6 SD 14.9</td><td>-1.2 (-6.4 to +4.1)</td><td><0.05 vs obs</td><td>-4.4 (-11.5 to +2.8)</td><td>NR</td></tr><tr><td>Tria 4 mg</td><td>51.0 SD 14.4</td><td>-1.2 (-6.3 to +4.0)</td><td><0.05 vs obs</td><td>-2.4 (-9.3 to +4.4)</td><td></td></tr></table></td><td>Ocular Adverse Events
<table><tr><th>AE</th><th>Tria 1 mg</th><th>Tria 4 mg</th><th>Obs</th></tr><tr><td>12 months</td><td></td><td></td><td></td></tr><tr><td>Elevated IOP or glaucoma</td><td></td><td></td><td></td></tr><tr><td>Initiation of IOP-lowering medication</td><td>20%</td><td>35%</td><td>8%</td></tr></table></td></tr>
</table>

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)						Adverse events			
injections over 12 months) (n=91) versus observation (n=88)	***Obs***	52.1 SD 13.1	-12.1 (-17.1 to -7.1)		-10.7 (-17.4 to -4.1)		IOP >35 mm Hg (n)	5	8	1
	≥15 letters gained (95% CI)						IOP >10 mm Hg above baseline (n)	15	24	2
	Tria 1 mg		26.5% (17 to 36)	0.001 vs obs	31% (19 to 43)	NR	Laser peripheral iridotomy (n)	0	1	0
	Tria 4 mg		25.6% (16 to 35)	0.001 vs obs	26% (14 to 38)		Trabeculectomy (n)	0	0	0
	Obs		6.8% (1 to 13)		9% (1 to 17)		Tube shunt (n)	2	0	0
	≥15 letters lost						*Cataract*			
	Tria 1 mg		25.3%		31%		Lens opacity onset or progression	26%	33%	18%
	Tria 4 mg		25.6%		26%		Cataract surgery (n)	0	4	0
	Obs		43.8%		48%	NS, p=0.06 tria vs obs	*At least 1 of the following adverse events (n):*	11	6	9
	CRT (µm):						Infectious endophthalmitis (n)	0	0	0
		Baseline	**12 months (median, IQR)**	**p**	**24 months (median, IQR)**	**p**	Non-infectious endophthalmitis (n)	0	0	0

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)						Adverse events			
	CRT						Retinal detachment (n)	0	0	0
	Tria 1 mg	643 SD 226	-196 (-390 to -62)	NR	-286 (-458 to -119)	NR	Iris neovascularisation or neovascular glaucoma	9	4	2
	Tria 4 mg	641 SD 248	-261 (-407 to -79)		-236 (-421 to -63)		Retinal neovascularisation (n)	2	2	4
	Obs	695 SD 208	-277 (-418 to -40)		-304 (-465 to -108)		Vitreous hemorrhage (n)	4	0	4
	CRT <250 µm				**CRT <250 µm**		*Other ocular surgical procedures*			
	Tria 1 mg		32%	NR	50%	NR	YAG capsulotomy	0	0	1
	Tria 4 mg		45%		39%		Sector or panretinal scatter photocoagulation	9	3	5
	Obs		28%		38%		Pars plana vitrectomy	2	0	1
	Results for subgroups (based on baseline BCVA (73 to 59, 58 to 49, 48 to 19), baseline CRT (<500 µm, ≥500 µm), duration of macular oedema (≤3 months, >3 months, pseudophakic at baseline) were consistent with the overall results (significance levels for comparisons not reported)						**Selected Events at 12-24 months**			
							Glaucoma procedures			
							Laser peripheral iridotomy	0	0	0

<table>
<tr><th>Study</th><th>Clinical outcomes (BCVA, CRT; change from baseline at study end)</th><th>Adverse events</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>Trabeculectomy</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Tube shunt</td><td>0</td><td>2</td><td>0</td></tr>
<tr><td>Cataract</td><td></td><td></td><td></td></tr>
<tr><td>Cataract surgery</td><td>3</td><td>21</td><td>0</td></tr>
<tr><td colspan="4">Reports of systemic adverse events were similar between groups</td></tr>
</table>
</td></tr>
<tr><td>ROVO 2013[33]

4 mg intravitreal triamcinolone acetonide (single injection)

versus radial optical neurotomy

versus sham injection</td><td>BCVA (logMAR):
<table>
<tr><th></th><th>Baseline</th><th>12 months</th><th>p</th></tr>
<tr><td>BCVA (logMAR, interquartile range)</td><td></td><td></td><td></td></tr>
<tr><td>Tria 4 mg</td><td>1.02 (0.75, 2.0</td><td>0.86 (0.51, 1.78) (-0.16)</td><td>NR</td></tr>
<tr><td>RON</td><td>1.46 (0.84, 2.0)</td><td>0.75 (46, 1.22) (-0.71)</td><td></td></tr>
<tr><td>Sham</td><td>1.02 (0.9, 1.36)</td><td>1.02 (0.85, 3.0) (0)</td><td></td></tr>
<tr><td>% with VA improvement</td><td></td><td></td><td></td></tr>
<tr><td>Tria 4 mg</td><td></td><td>20%</td><td>0.034 vs RON, NS vs placebo</td></tr>
<tr><td>RON</td><td></td><td>47%</td><td></td></tr>
</table>
</td><td>Ocular Adverse Events, 12 months
<table>
<tr><th>AE</th><th>Tria 4 mg</th><th>RON</th><th>Pla</th></tr>
<tr><td>Retinal detachment</td><td></td><td>7.9%</td><td></td></tr>
<tr><td>Subretinal haemorrhages</td><td></td><td>5.3%</td><td></td></tr>
<tr><td>Vitreous haemorrhage</td><td></td><td>2.6%</td><td>10%</td></tr>
<tr><td>Subretinal membrane formation</td><td></td><td>2.6%</td><td></td></tr>
<tr><td>Retinal tear</td><td></td><td>2.6%</td><td></td></tr>
<tr><td>IOP increase</td><td>32%</td><td></td><td></td></tr>
<tr><td>Cataract progression</td><td>24%</td><td>13%</td><td>15%</td></tr>
<tr><td>Neovascular glaucoma</td><td>12%</td><td>5%</td><td>15%</td></tr>
</table>
</td></tr>
</table>

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)				Adverse events	
	Sham		10%	0.009 vs RON	Rubeosis iridis	15%
	% with VA deterioration				No cases of phthisis, enucleation, endophthalmitis, injury of central vessels, injury of optic nerve	
	Tria 4 mg		NR			
	RON		8%			
	Sham		35%	0.007 vs RON		
	CRT (µm):					
		Baseline	**12 months**	**p**		
	CRT					
	Tria 4 mg	657	-235	NS		
	RON	569	-263	NS		
	Sham	615	-206			
AFLIBERCEPT						
COPERNICUS 2012[34;35]	**BCVA (ETDRS letters):**				**Adverse Events**	
		Baseline	**24 weeks**	**p**	**52 weeks (all VTE PRN)**	**p**
2 mg intravitreal aflibercept(every 4 weeks over 24	**BCVA (letters)**					

AE (24 weeks)	VTE	Sham
Discontinued treatment before week 24 because of AE	0	4.1%
At least one AE	83.3%	85.1%

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)					
weeks)(n=114) versus sham injection (n=73) extension up to 52 weeks with aflibercept PRN in both groups	***VTE***	50.7 SD 13.9	+17.3	<0.001	+16.2	<0.001
	Sham	48.9 SD 14.4	-4.0		+3.8	
	≥15 letters gained					
	VTE		56.1%	<0.001	55.3%	<0.001
	Sham		12.3%		30.1%	
	≥10 letters lost					
	VTE		1.8%	NR		
	Sham		30.1%			
	Subgroups					
	Baseline VA		**≥15 letters gained**			
	VTE ≤20/200	*VTE*	67.9%	NR	60.7%	NR
		Sham	16.7%		22.2%	
	VTE >20/200	*VTE*	52.3%		53.5%	
		Sham	10.9%		32.7%	
	Time since diagnosis					
	VTE <2 mo	*VTE*	68.8%	NR	64.1%	NR

Adverse events		
Ocular AEs	68.4%	68.9%
Patients with at least one serious adverse event	3.5%	13.5%
Vitreous haemorrhage	0	5.4%
Neovascular glaucoma	0	2.7%
Iris neovascularisation	0	2.7%
Retinal haemorrhage	0	2.7%
Visual acuity reduced	0.9%	1.4%
Retinal artery occlusion	0.9%	0
Retinal tear	0	1.4%
Retinal vein occlusion	0	1.4%
Endophthalmitis	0.9%	0
Corneal abrasion	0.9%	0

AE (24 to 52 weeks)	**VTE**	**Sham**
Patients with at least one serious adverse event	2.7%	3.3%
Vitreous haemorrhage	0.9%	1.7%
Glaucoma	0	1.7%

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)						Adverse events		
		Sham	15.4%		34.6%		Iris neovascularisation	0	0
	VTE ≥2 mo	*VTE*	38.8%		42.9%		Retinal haemorrhage	0	0
		Sham	4.8%		19.0%		Visual acuity reduced	0	0
	Perfusion status						Retinal artery occlusion	0	0
	VTE perfused	*VTE*	58.4%	NS	58.4%	NR	Retinal tear	0	1.7%
		Sham	16%		30.0%		Retinal vein occlusion	0.9%	0
	VTE non-perfused	*VTE*	51.4%		48.6%		Cataract	0.9%	0
		Sham	4.3%		30.4%		Cystoid macular oedema	0.9%	0
							Endophthalmitis	0	0
							Corneal abrasion	0	0
	CRT (µm):								
		Baseline	**24 weeks**	**p**	**52 weeks (all VTE PRN)**	**p**	Reports of systemic adverse events were similar between groups; 2 deaths in the sham group by 24 weeks; 2.7% arterial thromboembolic events in the sham group and 0.9% in the intervention group		
	CRT								
	VTE	661.7 SD 237.4	-457.2	<0.001	-413.0	NS			
	Sham	672.4 SD 245.3	-144.8		-381.8				
	QoL								
		Baseline	**24 weeks**	**p**	**52 weeks (all VTE**	**p**			

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)					Adverse events
					PRN)	
	NEI-VFQ-25 total					
	VTE	77.76 SD 15.96	+7.2 SD 12.1	0.001	+7.5	NS
	Sham	77.78 SD 16.25	+0.8 SD 9.8		+5.1	
	NEI-VFQ-25 near activities					
	VTE	69.96 SD 21.94	+8.3 SD 22.0	<0.05	+11.4	NS
	Sham	70.72 SD 20.22	+1.84 SD 19.75		+8.3	
	NEI-VFQ-25 distance activities					
	VTE	75.99 SD 21.26	+6.1 SD 20.0	<0.05	+8.5	NS
	Sham	78.08 SD 21.25	-0.64 SD 15.2		+3.8	
	NEI-VFQ-25 vision dependency					
	VTE	83.26 SD 25.51	+7.1 SD 20.5	<0.05	+6.0	NS
	Sham	82.76 SD 27.41	+1.1 SD 20.5		+3.4	

<table>
<tr><th>Study</th><th>Clinical outcomes (BCVA, CRT; change from baseline at study end)</th><th>Adverse events</th></tr>
<tr><td></td><td>Progression to neovascularisation: 0 with aflibercept, 6.8% with sham treatment over 52 weeks, p=0.006

Perfused status at week 24: 78.9% with aflibercept, 46.6% with sham treatment</td><td></td></tr>
<tr><td>GALILEO 2012[36;37]

2 mg intravitreal aflibercept (every 4 weeks over 24 weeks) (n=103)

versus sham injection (n=71)

extension up to 52 weeks</td><td>BCVA (ETDRS letters):
<table>
<tr><th></th><th>Baseline</th><th>24 weeks</th><th>p</th><th>52 weeks</th><th>p</th></tr>
<tr><td>BCVA (letters)</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>VTE</td><td>53.6 SD15.8</td><td>+18.0</td><td><0.0001</td><td>+16.9</td><td><0.0001</td></tr>
<tr><td>Sham</td><td>50.9 SD15.4</td><td>+3.3</td><td></td><td>+3.8</td><td></td></tr>
<tr><td>≥15 letters gained</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>VTE</td><td></td><td>60.2%</td><td><0.0001</td><td>60.2%</td><td>0.0004</td></tr>
<tr><td>Sham</td><td></td><td>22.1%</td><td></td><td>32.4%</td><td></td></tr>
<tr><td>≥10 letters lost</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>VTE</td><td></td><td>7.8%</td><td>0.0033</td><td></td><td></td></tr>
<tr><td>Sham</td><td></td><td>25.0%</td><td></td><td></td><td></td></tr>
<tr><td>Subgroups</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Time since diagnosis</td><td></td><td>≥15 letters gained</td><td></td><td></td><td></td></tr>
<tr><td>VTE <2 mo</td><td></td><td>70.9%</td><td>NR</td><td></td><td></td></tr>
</table></td><td>Ocular Adverse Events
<table>
<tr><th>AE</th><th>VTE</th><th>Sham</th></tr>
<tr><td>Discontinued treatment before week 24 because of AE</td><td>1.9%</td><td>11.3%</td></tr>
<tr><td>Eye pain</td><td>11.5%</td><td>4.4%</td></tr>
<tr><td>Conjunctival haemorrhage</td><td>8.7%</td><td>4.4%</td></tr>
<tr><td>Retinal exudates</td><td>6.7%</td><td>7.4%</td></tr>
<tr><td>Foreign body sensation</td><td>5.8%</td><td>7.4%</td></tr>
<tr><td>Retinal vascular disorder</td><td>5.8%</td><td>8.8%</td></tr>
<tr><td>Ocular hyperaemia</td><td>4.8%</td><td>5.9%</td></tr>
<tr><td>Vitreous floaters</td><td>4.8%</td><td>0</td></tr>
<tr><td>Macular oedema</td><td>3.8%</td><td>16.2%</td></tr>
<tr><td>Macular ischaemia</td><td>3.8%</td><td>4.4%</td></tr>
<tr><td>Optic disc vascular disorder</td><td>3.8%</td><td>4.4%</td></tr>
<tr><td>Eye irritation</td><td>2.9%</td><td>10.3%</td></tr>
<tr><td>Lacrimation increased</td><td>2.9%</td><td>5.9%</td></tr>
</table></td></tr>
</table>

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)					Adverse events		
	VTE ≥2 mo		50.0%			Papilloedema	1.9%	4.4%
						Retinal ischaemia	1.0%	4.4%
	CRT (µm):					Visual acuity reduced	0	10.3%
		Baseline	**24 weeks**	**p**	**52 weeks**	**p**	IOP increased	9.6%	5.9%
	CRT						Injection site pain	4.8%	2.9%
	VTE	683.2 SD234.5	-448.6	<0.0001	-423.5	<0.0001	**Serious adverse events**		
	Sham	638.7 SD224.7	-169.3		-219.3		At least 1 SAE	1.9%	5.9%
							Glaucoma	0	2.9%
	QoL						Macular oedema	1.0%	1.5%
		Baseline	**24 weeks**	**p**	**52 weeks**	**p**	Retinal tear	1.0%	0
	NEI-VFQ						Vitreous detachment	1.0%	0
	VTE		+7.5	0.0013					
	Sham		+3.5				Reports of systemic adverse events were similar between groups; no arterial thromboembolic events or deaths during 24 weeks		
	Percentage of any patients progressing to any neovascularisation by week 24, difference between groups -1.5 (95% CI: -7.4 to 4.4)						No endophthalmitis or cases of rhegmatogenous detachment, one incidence of uveitis in VTE group considered mild and resolved without change in therapy		
	No significant differences on the EQ-5D score between groups								

<table>
<tr><th>Study</th><th>Clinical outcomes (BCVA, CRT; change from baseline at study end)</th><th>Adverse events</th></tr>
<tr><td colspan="3">PEGAPTANIB</td></tr>
<tr><td>Wroblewski 2009[38-44]

0.3 mg intravitreal pegaptanib sodium (every 6 weeks over 24 weeks) (n=33)

versus 1 mg intravitreal pegaptanib sodium (every 6 weeks over 24 weeks) (n=33)

versus sham injection (n=32)

FU up to 52 weeks</td><td>BCVA (ETDRS letters):

<table>
<tr><th></th><th>Baseline</th><th>30 weeks</th><th>p</th><th>52 weeks</th><th>p</th></tr>
<tr><td>BCVA (letters)</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>PS 0.3 mg</td><td>47.6</td><td>+7.1</td><td>NS, 0.09 vs sham</td><td>+7.5</td><td>NS vs sham</td></tr>
<tr><td>PS 1 mg</td><td>48.4</td><td>+9.9</td><td>0.02 vs sham</td><td>+6.3</td><td>NS vs sham</td></tr>
<tr><td>Sham</td><td>48.5</td><td>-3.2</td><td></td><td>-2.4</td><td></td></tr>
<tr><td>≥15 letters gained</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>PS 0.3 mg</td><td></td><td>36%</td><td>NS, p=0.48</td><td></td><td></td></tr>
<tr><td>PS 1 mg</td><td></td><td>39%</td><td></td><td></td><td></td></tr>
<tr><td>Sham</td><td></td><td>28%</td><td></td><td></td><td></td></tr>
<tr><td>≥15 letters lost</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>PS 0.3 mg</td><td></td><td>9%</td><td>0.03 vs sham</td><td></td><td></td></tr>
<tr><td>PS 1 mg</td><td></td><td>6%</td><td>0.01 vs sham</td><td></td><td></td></tr>
<tr><td>Sham</td><td></td><td>31%</td><td></td><td></td><td></td></tr>
</table>

CRT (µm):</td><td>No serious ocular adverse events up to week 30

No endophthalmitis, traumatic cataract or retinal detachment (30 weeks)

No evidence of sustained effect on intraocular pressure (30 weeks)

No evidence of increased risk of systemic adverse events (30 weeks)</td></tr>
</table>

<table>
<tr><th>Study</th><th>Clinical outcomes (BCVA, CRT; change from baseline at study end)</th><th>Adverse events</th></tr>
<tr><td></td><td>
<table>
<tr><th></th><th>Baseline</th><th>30 weeks</th><th>p</th><th>52 weeks</th><th>p</th></tr>
<tr><td>CRT</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>PS 0.3 mg</td><td>688</td><td>-243</td><td>NS, p=0.13</td><td>-295</td><td><0.05 vs sham</td></tr>
<tr><td>PS 1 mg</td><td>632</td><td>-179</td><td>NS, p=0.06</td><td>-216</td><td></td></tr>
<tr><td>Sham</td><td>674</td><td>-148</td><td></td><td>-183</td><td></td></tr>
</table>
3 patients in the sham arm and 1 patient in each of the pegaptanib sodium arms developed ocular neovascularisation (p=0.29 (NS))
</td><td></td></tr>
<tr><td colspan="3">RANIBIZUMAB</td></tr>
<tr><td>CRUISE 2010 ff.[10;45;46]

0.3 mg intravitreal ranibizumab (monthly for 6 months)

versus 0.5 mg intravitreal ranibizumab (monthly for 6 months)</td><td>
BCVA (ETDRS letters):
<table>
<tr><th></th><th>Baseline</th><th>6 months</th><th>12 months (ran PRN)</th><th>24 months (ran PRN, HORIZON)</th></tr>
<tr><td>BCVA (letters, 95% CI)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Ran 0.3 mg</td><td>47.4 SD14.8</td><td>+12.7 (9.9, 15.4), p<0.0001 vs sham</td><td>+13.9 SD15.2, p=0.0007 vs sham</td><td>+8.2</td></tr>
<tr><td>Ran 0.5 mg</td><td>48.1 SD14.6</td><td>+14.9 (12.6, 17.2), p<0.0001 vs sham</td><td>+13.9 SD14.2, p=0.0006 vs sham</td><td>+12.0</td></tr>
<tr><td>Sham</td><td>49.2 SD14.7</td><td>+0.8 (-2.0, 3.6)</td><td>+7.3 SD15.9</td><td>+7.6</td></tr>
</table>
</td><td>
6 months
<table>
<tr><th>AE</th><th>Ran 0.3 mg</th><th>Ran 0.5 mg</th><th>Sham</th></tr>
<tr><td>Any intraocular inflammation event</td><td>2.3 %</td><td>1.6%</td><td>3.9%</td></tr>
<tr><td>Iridocyclitis</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Iritis</td><td>1.5%</td><td>1.6%</td><td>2.3%</td></tr>
<tr><td>Vitritis</td><td>0.8%</td><td>0.8%</td><td>1.6%</td></tr>
<tr><td>Endophthalmitis</td><td>0</td><td>0</td><td>0</td></tr>
</table>
</td></tr>
</table>

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)				Adverse events			
versus sham extension 6 to 12 months 0.3 or 0.5 mg ranibizumab PRN extension ≥12 to 24 months 0.5 mg ranibizumab PRN	**≥15 letters gained**				Lens damage	0	0	0
	Ran 0.3 mg	46.2%, p<0.0001 vs sham	47.0%	38.6%	Cataract	1.5%	1.6%	0
	Ran 0.5 mg	47.7%, p<0.0001 vs sham	50.8%	45.1%	Iris neovascularisation	1.5%	0.8%	7.0%
	Sham	16.9%	33.1%	38.3%	Neovascular glaucoma	0	0	1.6%
	≥15 letters lost				Rhegmatogenous retinal detachment	0	0	0
	Ran 0.3 mg	3.8%	3.8%	12.9%	Retinal tear	0	0	0
	Ran 0.5 mg	1.5%	2.3%	5.9%	Vitreous haemorrhage	3.8%	5.4%	7.0%
	Sham	15.4%	10.%	13.3%	Systemic adverse events balanced across groups; 1 myocardial infarction in each group, 1 transient ischaemic attack and angina pectoris in the same person in ran 0.5 mg group			
	Subgroups ***Time of diagnosis (6 month outcomes):***<3 months: +13.2 letters (both ran groups), ≥3 months: +10.5 letters (0.3 mg ran), +15.3 letters (0.5 mg ran), p=? Mean change in BCVA was greater for patients with worse baseline BCVA and CRT >450 µm				**12 months, sham for months 6 to 12** **Ocular AE** / **Ran 0.3 mg** / **Ran 0.5 mg** / **Sham** Any intraocular inflammation: 2.3 % / 1.6% / 1.8%			
	CRT (µm) and anatomic							
	Baseline	**6 months**	**12 months (ran PRN)**	**24 months (ran PRN, HORIZON)**				

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)				
	CRT (µm, 95% CI)				
	Ran 0.3 mg	679.9 SD 242.4	-433.7 (-484.9, -382.6), p<0.0001 vs sham	-462.1, p= NS vs sham	-370.9
	Ran 0.5 mg	688.7 SD 253.1	-452.3 (-497.0, -407.6), p<0.0001 vs sham	-452.8, p=NS vs sham	-412.2
	Sham	687.0 SD 237.6	-167.7 (-221.5 -114.0)	-427.2	-418.7
	CRT ≤250 µm				
	Ran 0.3 mg		75.0%, p<0.0001 vs sham	75.8%	58.0%
	Ran 0.5 mg		76.9%, p<0.0001 vs sham	77.7%	56.9%
	Sham		23.1%	70.8%	70.2%
	No retinal haemorrhages				
	Ran 0.3 mg	0.8%	31.5%	41.3%	
	Ran 0.5 mg	1.5%	39.3%	47.8%	
	Sham	1.5%	5.4%	36.7%	
	QoL				

Adverse events			
event			
Endophthalmitis	0	0	0
Lens damage	0	0	0
Cataract	3.8%	7.0%	1.8%
Iris neovascularisation	1.5%	3.9%	1.8%
Neovascular glaucoma	0	0.8%	0
Rhegmatogenous retinal detachment	0	0	0
Retinal tear	0	1.6%	1.8%
Vitreous haemorrhage	5.3%	5.4%	1.8%
Arterial thromboembolic events	0.8%	2.3%	0

HORIZON, 12 to 24 months

AE	**Ran 0.3/0.5**	**Ran 0.5**	**Sham/ran 0.5 mg**

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)					Adverse events			
		Baseline	6 months	p	12 months (ran PRN)	p		mg	mg	
	NEI-VFQ (95% CI)						Any ocular AE	62.6%	66.7%	62.5%
	Ran 0.3 mg		+7.1 (5.2, 9.0)	<0.05 vs sham	+7.1	NS vs sham	Ocular AEs leading to discontinuation	1.9%	2.0%	0
	Ran 0.5 mg		+6.2 (4.3, 8.0)	<0.05 vs sham	+6.6	NS vs sham	Cataract	5.6%	5.1%	3.1%
	Sham		+2.8 (0.8, 4.7)		+5.0		Ocular serious adverse events	9.3%	3.0%	5.2%
							Cystoid macular oedema	0.9%	0	0
							Endophthalmitis	1.9%	0	0
							IOP increased	0.9%	0	0
							Macular oedema	1.9%	2.0%	1.0%
							Ischaemic optic neuropathy	0.9%	0	0
							VA reduced	1.9%	1.0%	3.1%
							VA reduced transiently	0.9%	0	0
							Vitreous haemorrhage	0	0	1.0%
							Arterial thromboembolic	1.9%	3.0%	2.1%

<table>
<tr><th>Study</th><th>Clinical outcomes (BCVA, CRT; change from baseline at study end)</th><th>Adverse events</th></tr>
<tr><td></td><td></td><td>events
(potentially
related to drug)</td></tr>
<tr><td colspan="3">BEVACIZUMAB</td></tr>
<tr><td>Epstein 2012[47-49]

1.25 mg intravitreal bevacizumab (4 injections over 6 months) (n=30)

versus sham injection (n=30)

6 month open label extension (1.25 mg intravitreal bevacizumab (4 injections over 6 months) for all patients)</td><td>BCVA (ETDRS letters):

<table>
<tr><th></th><th>Baseline</th><th>24 weeks</th><th>p</th><th>48 weeks (bev/bev vs sham/bev)</th><th>p</th></tr>
<tr><td>BCVA (letters)</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Bev</td><td>44.4 SD15.3; 30% <34, 70% >34</td><td>+14.1</td><td><0.01</td><td>+16.1</td><td><0.05</td></tr>
<tr><td>Sham</td><td>43.9 SD16.0; 33.3% <34, 66.7% >34</td><td>-2.0</td><td></td><td>+4.6</td><td></td></tr>
<tr><td>≥15 letters gained</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Bev</td><td></td><td>60%</td><td>0.003</td><td>60%</td><td><0.05</td></tr>
<tr><td>Sham</td><td></td><td>20%</td><td></td><td>33.3%</td><td></td></tr>
<tr><td>>15 letters lost</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Bev</td><td></td><td>6.7%</td><td>NS, p=0.146</td><td>6.7%</td><td>NS</td></tr>
</table></td><td>Adverse events:

Neovascularisation: 16.7% (sham) versus 0 (bev) had developed iris rubeosis at week 24; iris rubeosis regressed in all patients at week 48, no new cases in either group

No events of endophthalmitis, retinal tear, retinal detachment; no serious non-ocular adverse events</td></tr>
</table>

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)					Adverse events
	Sham	23.3%		6.7%		
	Subgroups					
	Disease duration	**BCVA (letters)**				
	Bev <90 days	+18.7	0.039			
	Bev >90 days	+9.8				
	Age			**BCVA (letters)**		
	<70 years			+14.2	NS, >0.05	
	>70 years			+7.4		
	<70 years sham/bev			-1.4	<0.003	
	>70 years sham/bev			+20.1		
	CRT (µm):					
		Baseline	**24 weeks**	**p**	**48 weeks (bev/bev vs sham/bev)**	**p**

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)					Adverse events
	CRT					
	Bev/bev	712 SD330	-426	<0.001	-435	NS, >0.05
	Sham/bev	729 SD195	-102		-404	
	No residual oedema (CRT <300 µm)					
	Bev/bev		86.7%	<0.001	83.3%	NS
	Sham/bev		20%		60%	

Abbreviations: AE – adverse event, BCVA – best corrected visual acuity, CI – confidence interval, CRT – central retinal thickness, CRVO – central retinal vein occlusion, ETDRS – Early Treatment Diabetic Retinopathy Study, FU – follow-up, IQR – interquartile range, IOP – intraocular pressure, mo – months, NR – not reported, NS – non-significant, OCT – optical coherence tomography, PRN – pro re nata (as needed), QoL – quality of life, SD – standard deviation

Table 3: Study quality

Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
DEXAMETHASONE							
GENEVA 2010 ff.	Low	Low	Partial: patients and assessors of efficacy variables	Low: ITT analysis, 94% FU at 6 months	Low	*Power:* 81% power to detect difference in primary outcome with n=495 for each trial *Similarity at baseline:* yes	Allergan Inc.
TRIAMCINOLONE							
SCORE 2009 ff	Low	Unclear	Partial (physicians and patients masked to dose but not triamcinolone versus observation)	Low: ITT analysis, 83 to 90% FU at 12 months	Low	*Power:* 80% power to detect difference in primary outcome with n=486 (but only 271 randomised) *Similarity at baseline:* yes	National Eye Institute grants, Allergan

Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
ROVO 2013	Low	Low	Unclear	Low: ITT analysis (?), 92% FU at 12 months	Low	*Power:* 80% power to detect difference in primary outcome with n=53 per group (but only 20 to 38 per group) *Similarity at baseline:* unclear *Other:* limited baseline data	Jubiläumsfonds der Österreichischen Nationalbank, Ludwig Boltzmann Institute for Retinology and Biomicroscopic Laser Surgery (non-commercial)
AFLIBERCEPT							
COPERNICUS 2012	Low	Unclear	Low: double-blind	Low: ITT analysis, 89.9% assessed at primary end point	Low	*Power:* 90% power to detect difference in primary outcome with n=165 *Similarity at baseline:* yes	Bayer HealthCare, Regeneron Pharmaceuticals

Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
GALILEO 2012	Unclear	Unclear	Low: double-blind	Low: ITT analysis, 86% assessed at primary end point	Low	*Power:* 90% power to detect difference in primary outcome with n=150 *Similarity at baseline:* yes	Bayer HealthCare, Regeneron Pharmaceuticals
PEGAPTANIB							
Wroblewski 2009	Low	Low	Low: patients and ophthalmologist responsible for patients care and assessments	Low: ITT analysis, 7% withdrawals	Low	*Power:* 80% power to detect difference in primary outcome with n=30 per group *Similarity at baseline:* yes	Eyetech Inc, Pfizer Inc.
RANIBIZUMAB							
CRUISE 2010 ff	Low	Unclear	Low: patients and evaluating examiners, injecting physicians masked to dose	Low: ITT analysis, 88.5 to 97.7% completed 6 months	Low	*Power:* not reported *Similarity at baseline:* yes	Genentech Inc.

Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
BEVACIZUMAB							
Epstein 2012	Unclear	Low	Low: patients, outcome assessors	Low: ITT analysis; missing data for 2 patients (primary endpoint)	Low	*Power:* 80% power to detect difference in primary outcome with n=24 per group *Similarity at baseline:* yes	Unclear; authors are consultants for Allergan, Novartis, Alcon, Bayer

Table 4: On-going trials

Study	Participants and baseline values	Intervention / Outcomes
MINOCYCLINE		
http://clinicaltrials.gov/ct2/show/study/NCT01468844 USA **Study aim:** to test the safety and effectiveness of minocycline as a treatment for CRVO **Design:** RCT, double-blind **Follow-up:** 24 months	**N:** ~20 **Inclusion criteria:**>18 years, macular oedema secondary to CRVO, CRT >350 µm, media clarity and pupillary dilatation sufficient for fundus photographs **Exclusion criteria:** macular oedema due to causes other than CRVO, history of recurrent RVO or RVO >18 months, any other ocular condition that could affect macular oedema or BCVA, substantial cataract, photocoagulation within 4 months before study, pars plana vitrectomy within 6 months, major ocular surgery within 3 months, study eye treated with intravitreal or periocular steroid injections within 3 months, study eye treated with intravitreal anti-VEGF agents within 28 days; significant systemic disease (details given)	**Mino:** 100 mg oral minocycline twice daily over 24 months; monthly bevacizumab injection over 3 months, then PRN **Placebo:** oral placebo twice daily over 24 months; monthly bevacizumab injection over 3 months, then PRN **Primary end point:** BCVA over 12 months **Other outcomes:** number of bevacizumab injections, CRT, safety **Outcome assessment:** 6, 12, 18, 24 months

Study	Participants and baseline values	Intervention / Outcomes
BEVACIZUMAB / TRIAMCINOLONE		
http://clinicaltrials.gov/show/NCT00566761 Mexico **Study aim:** to assess if treatment of macular oedema secondary to CRVO is more effective with combined therapy of bevacizumab and triamcinolone compared to bevacizumab alone **Design:** RCT, open-label, phase 4 **Follow-up:** 12 months	**N:** ~10 **Inclusion criteria:** macular oedema secondary to CRVO; BCVA <20/40; CRT >250 µm (OCT) **Exclusion criteria:** diabetic retinopathy or other retinopathy; media opacity that does not allow follow-up; steroid responder; diagnosed glaucoma or IOP > 21 mmHg	**Bev:** bevacizumab 2.5 mg for (3 applications, administered monthly) **Bev/Tria:** bevacizumab 2.5 mg + triamcinolone 4 mg first dose followed by two doses of bevacizumab alone **Primary end point:** BCVA over 12 months **Other outcomes:** treatment complications **Outcome assessment:** 3, 6 and 12 months
RANIBIZUMAB		

Study	Participants and baseline values	Intervention / Outcomes
http://clinicaltrials.gov/show/NCT01123564 Hungary **Study aim:** to assess if ranibizumab (Lucentis) injection applied into the eye is superior to conventional treatment concerning the prevention of visual loss in patients having clinically significant macular oedema secondary to retinal vein occlusion **Design:** RCT, open-label, phase 2 **Follow-up:** 12 months	**N:** ~40 **Inclusion criteria:**>18 years, macular oedema persisting for >3 months despite conventional medication; CRVO confirmed by slit-lamp biomicroscopy and fluorescein angiography (FLAG); patient in ranibizumab group do not receive macular laser treatment; CRT > 280 µm and/or retinal thickness is >330 µm at any region of the macula; baseline VA <64 ETDRS letters (or 0.4 decimal equivalent) **Exclusion criteria:** diabetes mellitus; additional vitreoretinal diseases; history of pars plana vitrectomy; previous macular grid laser treatment; intravitreal triamcinolone acetonide treatment; complicated cataract surgery; advanced glaucomatous damage of optic nerve head; cataract (except mild, defined as grade 1 nuclear sclerosis and/or grade 1 posterior subcapsular cataract); age-related macular degeneration; pregnancy and lactation; women in childbearing potential who are not using double safe contraception	**Rani:** intravitreal ranibizumab, applied monthly in the first 3 months, and after this only if visual acuity (VA) decreases with more than 5 letters at any monthly visits **Laser:** Argon laser treatment; conventional grid pattern argon laser treatment and panretinal argon laser photocoagulation in an as needed basis **Primary end point:** BCVA over 12 months **Other outcomes:** CRT **Outcome assessment:** monthly visits

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Appendix 1: Search strategy

CRVO: Clinical effectiveness search for RCTs and SRs

Ovid MEDLINE(R) 1946 to March Week 1 2013, searched on 20 March 2013

1 CRVO.mp.

2 Retinal Vein Occlusion/

3 retinal vein occlusion.mp.

4 retinal vein obstruction.mp.

5 retinal venous occlusion.mp.

6 retinal venous obstruction.mp.

7 retina*.mp.

8 ("central vein occlusion" or "central vein obstruction" or "central venous occlusion" or "central venous obstruction").mp.

9 7 and 8

10 1 or 2 or 3 or 4 or 5 or 6 or 9

11 randomized controlled trial.pt.

12 (random* or "controlled trial*" or "clinical trial*" or rct).tw.

13 11 or 12

14 (metaanalys* or "meta analys*" or "meta-analys*").tw.

15 "systematic review*".tw.

16 meta analysis.pt.

17 14 or 15 or 16

18 10 and 13

19 10 and 17

20 18 or 19

21 limit 20 to yr="2005 -Current"

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations March 19, 2013, searched on 20 March 2013

1 CRVO.mp.

2 retinal vein occlusion.mp.

3 retinal vein obstruction.mp.

4 retinal venous occlusion.mp.

5 retinal venous obstruction.mp.

6 retina*.mp.

7 ("central vein occlusion" or "central vein obstruction" or "central venous occlusion" or "central venous obstruction").mp.

8 6 and 7

9 1 or 2 or 3 or 4 or 5 or 8

10 (random* or "controlled trial*" or "clinical trial*" or rct).tw.

11 (metaanalys* or "meta analys*" or "meta-analys*").tw.

12 "systematic review*".tw.

13 11 or 12

14 9 and 10

15 9 and 13

16 14 or 15

Embase 1980 to 2013 Week 11, searched on 20 March 2013

1 CRVO.mp.

2 Retina Vein Occlusion/

3 Central Retina Vein Occlusion/

4 retinal vein occlusion.mp.

5 retinal vein obstruction.mp.

6 retinal venous occlusion.mp.

7 retinal venous obstruction.mp.

8 retina*.mp.

9 ("central vein occlusion" or "central vein obstruction" or "central venous occlusion" or "central venous obstruction").mp.

10 8 and 9

11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 10

12 randomized controlled trial/

13 (random* or "controlled trial*" or "clinical trial*" or rct).tw.

14 12 or 13

15 systematic review/

16 meta analysis/

17 (metaanalys* or "meta analys*" or "meta-analys*").tw.

18 "systematic review*".tw.

19 15 or 16 or 17 or 18

20 11 and 14

21 11 and 19

22 20 or 21

23 limit 22 to yr="2005 -Current"

Cochrane Library (including CDSR, CENTRAL, DARE, HTA, NHS EED), searched on 20 March 2013

#1 CRVO

#2 MeSH descriptor: [Retinal Vein Occlusion] this term only

#3 "retinal vein occlusion"

#4 "retinal vein obstruction"

#5 "retinal venous occlusion"

#6 "retinal venous obstruction"

#7 retina*

#8 "central vein occlusion" or "central vein obstruction" or "central venous occlusion" or "central venous obstruction"

#9 #7 and #8

#10 #1 or #2 or #3 or #4 or #5 or #6 or #9

#11 #10 from 2005

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7-8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	68-71
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7-8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7-8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7-8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	23
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	25-35
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	56-59
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	N/A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16-20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16-20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	22

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ open

Treatments for macular oedema following central retinal vein occlusion: systematic review

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-004120.R1
Article Type:	Research
Date Submitted by the Author:	03-Jan-2014
Complete List of Authors:	Ford, John; University of East Anglia, Public Health Clar, Christine; Warwick University, Warwick Evidence Lois, Noemi; Centre for Vision and Vascular Science, Barton, Samantha; BMJ Technology Assessment Group, Thomas, Sian; Warwick University, Warwick Evidence Court, Rachel; Warwick University, Division of Health Sciences Shyangdan, Deepson; University of Warwick, Warwick Evidence, Warwick Medical School Waugh, Norman; University of Warwick, Warwick Evidence
Primary Subject Heading:	Ophthalmology
Secondary Subject Heading:	Ophthalmology, Public health
Keywords:	Medical ophthalmology < OPHTHALMOLOGY, systematic review, anti-VEGF, Central retinal vein occlusion, macular oedema

Treatments for macular oedema following central retinal vein occlusion: systematic review

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Protocol: Not published

Words: 5750 words

Key words: central retinal vein occlusion, aflibercept, ranibizumab, bevacizumab, dexamethasone, pegaptanib, triamcinolone, systematic review, anti-VEGF, macular oedema

Disclosure

No additional data available.

Abstract

Objectives

To review systematically the randomised controlled trial (RCT) evidence for treatment of macular oedema due to central retinal vein occlusion (CRVO).

Data sources

MEDLINE, EMBASE, CDSR, DARE, HTA, NHSEED, CENTRAL and meeting abstracts (January 2005 to March 2013).

Study eligibility criteria, participants and interventions

RCTs with at least 12 months' follow-up assessing pharmacological treatments for CRVO were included with no language restrictions.

Study appraisal and synthesis methods

Two authors screened titles and abstracts and conducted data extracted and Cochrane risk of bias assessment. Meta-analysis was not possible due to lack of comparable studies.

Results

Eight studies (35 articles, 1714 eyes) were included, assessing aflibercept (n=2), triamcinolone (n=2), bevacizumab (n=1), pegaptanib (n=1), dexamethasone (n=1) and ranibizumab (n=1). In general, bevacizumab, ranibizumab, aflibercept and triamcinolone resulted in clinically significant increases in the proportion of participants with an improvement in visual acuity of ≥15 letters, with 40-60% gaining ≥15 letters on active drugs, compared to 12-28% with sham. Results for pegaptanib and dexamethasone were mixed. Steroids were associated with cataract formation and increased intra-ocular pressure. No overall increase in adverse events was found with bevacizumab, ranibizumab, aflibercept or pegaptanib compared to control. Quality of life was poorly reported. All studies had a low or unclear risk of bias.

Limitations

All studies evaluated a relatively short primary follow-up (1 year or less). Most had an unmasked extension phase. There was no head-to-head evidence. The majority of participants included had non-ischaemic CRVO.

Conclusions and implications of key findings

Bevacizumab, ranibizumab, aflibercept and triamcinolone appear to be effective in treating macular oedema secondary to CRVO. Long-term data on effectiveness and safety are needed. Head-to-head trials and research to identify “responders” is needed to help clinicians make the right choices for their patients. Research aimed to improve sight in people with ischaemic CRVO is required.

Article summary

Article focus

To review the clinical effectiveness of pharmacological treatments for central retinal vein occlusion.

Key messages

Bevacizumab, ranibizumab, aflibercept and triamcinolone have demonstrated good short-term clinical effectiveness in randomised controlled trials for the treatment of macular oedema secondary to central retinal vein occlusion.

Dexamethasone and pegaptanib have shown mixed results.

Strengths and limitations of this study

A robust systematic review method was used which only included randomised controlled trials.

There were no head-to-head trials and there was a lack of long-term data on both effectiveness and safety.

Introduction

Central retinal vein occlusion (CRVO) is a vascular disorder of the retina with often catastrophic consequences to vision and quality of life.[1;2] The incidence of CRVO increases with age; most individuals affected are 50 years of age or older.[3] It has been estimated that there are around 80 new cases of CRVO per million population per year.[4;5] Although CRVO most commonly affects one eye, in around 10% of patients the disease affects both eyes.[2] Approximately 20% of patients with CRVO will develop large areas of retinal non-perfusion (ischaemia).[6] Furthermore, a small proportion (around 8%) of patients with non-ischaemic CRVO may convert into the ischaemic type during follow-up.[6] Retinal ischaemia may lead to the development of neovascularisation in the retina, iris or anterior chamber angle. Complications of neovascularisation include vitreous haemorrhage and neovascular glaucoma.[6] Currently there is no treatment for ischaemic CRVO other than that aimed at ameliorating the severity of complications, with treatments such as panretinal photocoagulation. Even with the use of current therapies, some eyes with ischaemic CRVO end up blind and painful and, ultimately, enucleation (removal of the eye) is necessary to provide comfort to patients.

Not all people with CRVO will require treatment and macular oedema will resolve in about a third of those with non-ischaemic CRVO.[2;7] However most will need treatment and the number of options has increased in recent years. Laser photocoagulation has been for many years the standard therapy for patients with macular oedema secondary to branch retinal vein obstruction (BRVO).[8] However, laser treatment was not found to be beneficial to those with macular oedema secondary to CRVO;[9] for these patients, no therapeutic modalities could be offered. Recently, several studies have demonstrated the benefit of anti-vascular endothelial growth factor (VEGF) therapies and steroids for the management of patients with macular oedema secondary to CRVO.[10;11] Steroids, such as triamcinolone and dexamethasone, have anti-inflammatory and anti-proliferative attributes (as well as some anti-VEGF effects) and therefore are primarily effective by reducing the oedema of the macula.[12] Anti-VEGF treatments, such as bevacizumab, ranibizumab, aflibercept and pegaptanib, inhibit vascular endothelial growth factor A. In CRVO there is an increase in vascular endothelial growth factor A which leads to neovascularization and oedema.[13] In the UK, NICE has approved dexamethasone (in the long-acting form, Ozurdex) and ranibizumab (Lucentis) and an appraisal of aflibercept is currently underway. Bevacizumab is also used, but is not licensed for use in the eye; however this is because the manufacturer has never sought a licence, preferring to market ranibizumab. Triamcinolone has also been used off-licence.

An up-to-date review incorporating all drug treatments for macular oedema secondary to CRVO is needed. The purpose of this study is to review systematically the randomised controlled evidence for drug treatments of macular oedema secondary to CRVO.

Methods

A systematic review was conducted. The following databases were searched: 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). In addition to the bibliographic database searching, supplementary searches were undertaken to look for recent and unpublished studies in the WHO International Clinical Trials Registry Platform and ophthalmology conference websites (American Academy of Ophthalmology, Association for Research in Vision and Ophthalmology from 2010 to 2012).

Search strategy

An iterative procedure was used to develop two search strategies with input from previous systematic reviews.[14;15] The first search strategy was designed to retrieve articles reporting RCTs or systematic reviews about CRVO published from 2005 onwards (the publication date of the first RCT on triamcinolone in Medline). Terms for retinal vein occlusion were included to ensure identification of articles in which both BRVO and CRVO were covered, but were reported separately. The second strategy focussed on retrieving articles where adverse events of relevant pharmacological treatments for CRVO were reported. This second search was limited by condition (age-related macular degeneration (AMD) or RVO), study type (RCTs, SRs or observational studies) and date (published from 2010 onwards). Searches were conducted in March 2013. The strategies used in each database are provided in appendix 1. Auto alerts of searches were set up to capture relevant articles published after the dates of the searches.

Reference lists from the included studies and identified systematic reviews were screened.

Inclusion and exclusion criteria

RCTs were used to assess the clinical effectiveness and adverse events.

Only RCTs examining pharmacological treatment compared with laser treatment, observation, placebo (sham injection) or another pharmacological intervention with at least 12 months follow-up were included. Comparisons of different doses of drugs were not included unless there was an additional comparator group as defined above. Studies including CRVO and BRVO were included

providing participants with CRVO were reported as a subgroup. Studies assessing treatments aimed at restoring circulation to the occluded vein shortly after onset (<30 days) were excluded. There were no language restrictions.

Outcomes

The primary outcome was visual acuity measured as mean change in best corrected visual acuity (BCVA) or as proportion of patients improving by 15 ETDRS (Early Treatment for Diabetic Retinopathy Study) letters or more. Secondary outcomes included mean change in macular thickness using optical coherence tomography (OCT), quality of life and adverse events.

Screening and data extraction

Search results were screened independently by two authors (CC, JF and ST). Differences were resolved through discussion or by consulting a third author (JF). Data were extracted by one author (CC and DS) and checked by a second (ST, CC). Data extraction included inclusion/exclusion criteria, baseline demographics, mean change in BCVA, proportion of patients with 15 letters improvement, central retinal thickness (CRT) and adverse events. Risk of bias was assessed by two reviewers using the Cochrane risk of bias tool.[16]

Meta-analysis was not possible because of a lack of comparable studies.

Results

Search results

The study flow is shown in figure 1. The electronic searches yielded 518 records. 475 were eliminated based on information in the titles and abstract. The full text of the remaining 43 records was checked, and a further eight were eliminated. Reasons for exclusion included the trial being a commentary rather than an RCT, the study having no relevant comparison group (dose ranging only), the participants did not have macular oedema secondary to CRVO, or the interventions being ineligible (non-pharmacological). The remaining 35 records (including conference abstracts) reported on eight RCTs of six different pharmacological agents, and these were included in the analysis. The Geneva study (2010)[11;17;18] technically consists of two RCTs, but as these were analysed and reported together, it was counted as one RCT in this analysis.

We also identified three relevant ongoing trials, one investigating minocycline (http://clinicaltrials.gov/ct2/show/study/NCT01468844), one investigating a combination of bevacizumab and triamcinolone (http://clinicaltrials.gov/show/NCT00566761), and one investigating ranibizumab (http://clinicaltrials.gov/show/NCT01123564).

Study characteristics

Detailed study characteristics of the included studies are shown in table 1.

Study design

Of the eight included RCTs, six were described as double-blind and seven were sham-controlled. All but one were multicentre. Only one was not funded by industry. Four trials were international trials, two came from the USA, and one each from Austria and Sweden. Six of the trials measured primary end-points at around six months (24 to 30 weeks), whereas two measured primary end-points at 12 months. Five studies reported follow-up data for up to 12 months, and two reported data for follow-up periods of up to two years.

Participants

The trials randomised a total of 1714 eyes (one eye per person). The number of eyes per study ranged between 60 and 437. Follow-up at the primary end-point ranged from 77 to 98% (generally over 90% in the intervention groups). The participants had a mean age of between 59.0 and 70.5

years, and between 36 and 49% were female. Only two studies reported mean duration of macular oedema (4.3 and 4.9 months). Five studies reported mean time since CRVO diagnosis (range 2.4 to 2.9 months). Mean baseline BCVA was between 44 and 52.5 ETDRS letters, baseline CRT was between 569 and 721 µm. In most trials, the focus was on macular oedema secondary to CRVO only, but in the Geneva trial macular oedema secondary to BRVO and CRVO was included and only limited data were available on the CRVO-only group.

Interventions

The Geneva trial (2010 ff.)[11;17;18] compared a 0.35 mg (n=136) and a 0.7 mg dexamethasone (n=154) intravitreal implant with sham treatment (n=147). After the initial 6 month study period, patients could enter a 6 month open label extension, where they received a 0.7 mg dexamethasone intravitreal implant.

The SCORE trial (2009 ff.)[19-32] compared intravitreal injections of 1 or 4 mg of triamcinolone (~2 injections over 12 months, n= 92 and 91 for 1 and 4 mg respectively) with an observation group (n=88). Two forms of triamcinolone have been used in trial; the SCORE trial used Trivaris, rather than Kenalog. Trivaris is no longer available because its manufacturer has promoted an alternative steroid (dexamethasone). The ROVO trial (2013)[33] compared a single intravitreal injection of 4 mg of triamcinolone (over 12 months, n=25) with radial optic neurotomy (n=38) or sham injection (n=20).

In the COPERNICUS trial (2012)[34;35], intravitreal injections of 2 mg of aflibercept (n=114) were given every 4 weeks over 24 weeks to the intervention group and the comparison group received a sham injection (n=75). During weeks 24 to 52, patients in both groups received aflibercept if they met protocol-specified retreatment criteria, and received a sham injection if retreatment was not indicated (3.9 standard error 0.3 injections in the sham group and 2.7 standard error 0.2 injections in the aflibercept group); after the first year, patients continued in a one-year extension phase with as needed dosing. In the GALILEO trial (2012)[36;37], intervention patients also received intravitreal injections of 2 mg of aflibercept (n=103) every 4 weeks over 24 weeks, while the comparison group was given sham injections (n=71). During weeks 24 to 52, patients remained in their original treatment groups but received their allocated treatment as needed; beginning from week 52 to week 76, both groups received the study drug every 8 weeks.

In a trial by Wroblewski and colleagues (2009)[38-44], patients received 0.3 or 1 mg intravitreal injections of pegaptanib sodium every 6 weeks for 24 weeks (n=33 and 33), compared with a sham injection group (n=32). Patients were followed up to 52 weeks.

The CRUISE trial (2010 ff.)[10;45;46] compared monthly injections of 0.3 or 0.5 mg of ranibizumab (n=132 and 130) over 6 months with sham injection (n=130). During months 6 to 12, all patients could receive intraocular ranibizumab (previously assigned dose or 0.5 mg for the sham group) if they met prespecified functional and anatomic criteria; after 12 months' follow-up patients could continue in the HORIZON trial for another 12 months, where they were eligible to receive intravitreal injections of 0.5 mg ranibizumab if they fulfilled prespecified criteria.

Epstein and colleagues (2012)[47-49] conducted an RCT in which they compared patients receiving four intravitreal injections of 1.25 mg of bevacizumab (n=30) over 6 months with patients receiving sham injection (n=30). From 6 to 12 months, all patients received intravitreal bevacizumab injections every 6 weeks.

Outcomes. The primary endpoint of all but one study was the proportion with a gain of 15 or more ETDRS letters. The primary endpoint of the remaining study was mean change in BCVA. Studies also reported gains or losses of ETDRS letters at various cut-off points, absolute BCVA, CRT, and safety parameters. The COPERNICUS, the GALILEO and the CRUISE studies also measured vision-related quality of life (National Eye Institute Visual Functioning Questionnaire, NEI-VFQ).[10;34-37;45;46] EQ5D was also used in GALILEO.

Ongoing studies. Of the ongoing trials, the first (clinicaltrials.gov NCT01468844) is a 24 month double-blind RCT from the USA. It set out to test the safety and effectiveness of minocycline as a treatment for CRVO in around 20 patients with macular oedema secondary to CRVO. Both groups received monthly intravitreal bevacizumab injections over three months (and afterwards as needed), and the intervention group also received 100 mg oral minocycline twice daily over 24 months. The second trial (clinicaltrials.gov NCT00566761) is an open-label RCT from Mexico in only around 10 patients assessing whether combined treatment with bevacizumab and triamcinolone is more effective than bevacizumab alone. The combination group received 2.5 mg of bevacizumab plus 4 mg of triamcinolone as a first dose and then two doses of bevacizumab alone at monthly intervals, while the monotherapy group received three monthly doses of 2.5 mg bevacizumab alone. Follow-up will be 12 months. A third RCT from Hungary compares monthly injections of ranibizumab for three months (and as needed thereafter) with Argon laser treatment in around 40 patients with macular oedema secondary to CRVO. Follow-up will also be 12 months. The primary endpoint in all studies is BCVA over 12 months.

Risk of bias

Details of risk of bias assessment are shown in Table 3.

Most studies (except GALILEO (2012) and Epstein 2012)[36;37;47-49] adequately described the generation of the allocation sequence, but only half the studies gave enough details to confirm adequate allocation concealment. Most studies (unclear in the ROVO 2013 study)[33] used at least partial masking, and most studies appeared to have had masking of outcome assessment. Intention-to-treat analysis was used in all studies. Where reported separately for comparison groups, losses to follow-up tended to be slightly higher for the control groups than the interventions groups (79 to 88.5% follow-up in the control groups and 90 to 98% in the intervention groups). All studies appeared to have been free of selective reporting. Most studies included a power analysis (not reported for the CRUISE study)[10;45;46], but in two cases (the SCORE and the ROVO studies)[19-33] the numbers randomised were considerably below the numbers indicated in the power calculations. As far as reported, there were no significant differences between comparison groups in baseline characteristics.

Clinical effectiveness

Detailed study results can be found in Table 2.

Visual acuity. Figure 2 shows the primary endpoint in most studies, which was the proportion of participants with a gain of 15 or more ETDRS letters. As there were no significant differences in visual acuity results between groups using different dosages of the given pharmacological treatment, intervention groups were combined for the sake of the plot.

In the Geneva trial (2010 ff.)[11;17;18], treatment of macular oedema secondary to CRVO with a 0.7 mg intravitreal dexamethasone implant resulted in a 0.1 letter gain in BCVA compared to a loss of 1.8 in the sham group ($p < 0.001$). The difference persisted in the extension period where all patients received the 0.7 mg dexamethasone implant. However, there was no significant difference in the proportion of patients gaining or losing 15 letters at either 6 or 12 months (0.35 or 0.7 mg dexamethasone). This may reflect the timing of peak effect at 90 days with dexamethasone.

In the SCORE trial (2009 ff.)[19-32], patients in the triamcinolone groups lost significantly fewer ETDRS letters (triamcinolone 1mg 1.2 letters loss, 4mg 1.2 letters loss and observation 12.1 letters loss) over both 12 and 24 months than patients in the observation group. The proportion of patients gaining 15 letters or more was also significantly larger in the intervention groups at 12 and 24 months (25.6% compared with 6.8% and 31% compared with 9%, respectively). The proportion of

patients receiving triamcinolone and losing 15 letters or more was smaller (25.6%) than in the observation group (43.8%), but this difference was not statistically significant (p=0.06).

There was some overall improvement in BCVA in both intervention groups at 12 months in the ROVO trial (2013)[33], (triamcinolone 20%, radial optic neurotomy 47% and sham 10%) however it was unclear whether there were any statistically significant differences between the 4 mg triamcinolone, the radial optic neurotomy, or the sham group. However, there were significantly more patients with an improvement of more than or equal to 15 letters in the neurotomy group than in the sham group (47% versus 10%), but no significant difference to sham after one dose of triamcinolone.

In both the COPERNICUS (2012)[34;35] and GALILEO (2012)[36;37]trialspatients in the aflibercept group had a significant improvement in BCVA at 6 months of 18 and 17.3 letters (compared to 4 letters loss and 3.3 letter gain in sham groups respectively), and this was maintained at 12 months and was significantly greater than the improvements in the sham groups. This was paralleled by a significantly greater proportion of patients(56.1% compared with 12.3% and 60.2% compared with 22.1%, respectively) gaining 15 letters or more. Patients treated sooner after diagnosis (less than versus more than two months) seemed to benefit more (in terms of proportion of patients with 15 letters or more gain) in both trials.

The increase in mean change in BCVA with 0.3 mg pegaptanib compared with sham did not reach significance at 30 weeks in the trial by Wroblewski and colleagues (2009)[38-44], but there was a greater increase in BCVA with 1 mg pegaptanib compared with sham (9.9 letter gain compare with 3.2 letter loss). These differences were not statistically significant at 52 weeks. There was no significant difference between any of the groups in the proportion of patients gaining 15 letters or more at 30 weeks, but significantly fewer patients in both dosage groups lost 15 letters or more than in the sham group (6% compared with 31%).

In the CRUISE trial (2010 ff.)[10;45;46], mean change in BCVA was significantly increased in the ranibizumab groups (no difference between doses) compared with the sham group at both 6 and 12 months (12.0 letters gained in the 0.5 mg group compared to 7.6 in the sham group). After the one year extension with ranibizumab as needed in all groups, there was no difference between the doses of ranibizumab at 24 months. The pattern was similar for the proportion of patients gaining 15 letters or more.

In the trial by Epstein and colleagues (2012)[47-49], treatment with intravitreal bevacizumab , compared with sham treatment significantly increased mean change in BCVA (14.1 letters gain compared to 2.0 letters lost) and the proportion of patients gaining 15 letters or more (60% compared to 20%) at 24

weeks. This difference was maintained in the extension period, even though both groups had been receiving bevacizumab. Younger patients (<70 years) tended to have better visual outcomes than older patients (>70 years).

Central retinal thickness. In the Geneva trial (2010 ff.)[11;17;18], no significant difference was found in the reduction of CRT after 6 months' treatment in patients with macular oedema secondary to CRVO with the 0.7 mg intravitreal dexamethasone implant (no data given for the 0.35 mg implant) compared with sham.

In the SCORE trial (2009 ff.)[19-32], CRT decreased in all study groups, but there was no significant difference between groups at either 12 or 24 months. Similarly, there was no clear difference in the proportion of patients achieving a CRT of less than 250 µm. CRT decreased in all comparison groups in the ROVO trial (2013)[33], but there was no significant difference between groups.

Both in the COPERNICUS trial (2012)[34;35] and in the GALILEO trial (2012)[36;37] there was a significantly greater reduction in CRT at 6 months in the aflibercept group than in the control group. However the significant difference was maintained in the longer term only in the GALILEO trial, where patients continued their assigned treatment up to 12 months. In the COPERNICUS trial, patients in the sham group also received aflibercept in the extension period, which caused a similar decrease in CRT as in the original intervention group.

After 30 weeks of treatment with pegaptanib (Wroblewski and colleagues 2009)[38-44], differences in decrease of CRT versus sham did not reach significance, but at 52 weeks, the decrease in CRT was significantly greater in both the 0.3 mg and the 1 mg pegaptanib groups compared with sham.

After treatment with ranibizumab in the CRUISE trial (2010 ff.)[10;45;46], a significant reduction in CRT was observed and significantly more patients achieved a CRT of 250 µm or less in the intervention groups (no difference between doses) than in the sham group at 6 months. This difference did not persist at 12 and 24 months because all groups received ranibizumab as needed.

In the trial by Epstein and colleagues (2012)[47-49], treatment with intravitreal bevacizumab significantly decreased CRT and the proportion of patients with no residual oedema (CRT <300 µm) at 24 weeks, compared with sham treatment. When both groups received bevacizumab in the extension period, similar decreases in CRT and increases in the proportion of patients with no residual oedema were seen.

Vision-related quality of life. Vision-related quality of life (NEI-VFQ25) was significantly higher in the aflibercept group, compared with sham injection, at 6 months in both the COPERNICUS trial (+7.2

compared with +0.8)[34;35] and the GALILEO trial (+7.5 compared with +3.5)[36;37]. In the COPERNICUS trial, patients in the sham group who received aflibercept in the extension period had a similar increase in vision-related quality of life as patients in the original intervention group by 12 months.

In the CRUISE trial (2010 ff.)[10;45;46], vision-related quality of life (NEI-VFQ) was similarly increased in both ranibizumab groups and statistically significantly more than in the sham group at 6 months (+6.2 compared with +2.8). At 12 months, with all groups receiving ranibizumab as needed, the increases were similar in all three groups.

Adverse events. The 0.7 mg dexamethasone intravitreal implant caused significantly more increased intraocular pressure (IOP) than sham treatment (30.1%, versus 1.4% in the control group) in patients with CRVO in the Geneva trial (2010 ff.)[11;17;18] (not reported for 0.35 mg). The incidence of cataract was also slightly higher in the dexamethasone group but numbers were small because of the short duration . There were no other differences in adverse events between groups.

In the triamcinolone group (especially 4 mg, SCORE trial 2009 ff.)[19-32], there was a higher increase in IOP, lens opacity onset or progression (at 12 months) and cataract surgery (12 to 24 months) than in the control group. There were no other differences in adverse events between groups. A similar tendency was seen in the ROVO trial (2013)[33].

Aflibercept did not appear to increase the incidence of ocular or non-ocular adverse events compared with sham in both the COPERNICUS trial (2012)[34;35] and the GALILEO trial (2012)[36;37].

In the trial by Wroblewski and colleagues (2009)[38-44], adverse events in response to pegaptanib were not reported in detail, but there do not appear to have been any serious ocular or systemic adverse events.

After treatment with ranibizumab in the CRUISE trial (2010 ff.)[10;45;46], there were no consistent differences in ocular or systemic adverse events between the intervention groups. None of the ocular adverse events appeared to have increased substantially after all patients received ranibizumab up to 24 months.

Epstein and colleagues (2012)[47-49] did not report adverse events in response to bevacizumab in detail, but the treatment appears not to have caused any serious ocular adverse events over 48 weeks.

Discussion

Statement of principal findings

Evidence from good quality RCTs shows that intravitreal steroids and anti-VEGF therapies increase the proportion of patients whose vision improves by 15 or more letters in patients with macular oedema secondary to CRVO. The most effective drugs result in over 60% of patients gaining 15 letters compared to only about 20% of the control groups. The RCT evidence shows only short-term effectiveness of ranibizumab, bevacizumab, aflibercept and triamcinolone. Results from trials of dexamethasone and pegaptanib were mixed. Long-term evidence is awaited.

Strengths and limitations

A robust systematic review methodology was used. A broad search strategy was implemented, which included not restricting the search strategy with drug terms. Grey literature was searched by screening meeting abstracts from relevant conferences. There were no language restrictions. Two reviewers screened titles and abstracts and conducted data extraction and risk of bias assessment. Risk of bias was assessed using the Cochrane Risk of Bias Tool and was generally judged to be low or unclear. Only studies with one year follow up were included to exclude studies with very short follow-up RCTs were identified for all the new ophthalmological drugs, except for the steroid, fluocinolone.

The main limitation is the short duration of follow-up. The primary outcome for most trials was measured at 6 months, with an extension phase up to 12 months. Hence, it is not known whether the benefit of these treatments will be maintained long-term. Furthermore, potential side effects of these treatments may not be captured in these studies as a result of their short follow-up. Patients and clinicians would like sustained, life-long improvement in visual acuity, but of all included studies only one of them had a follow-up of over 24 months.

The sample size of some studies was small. For example, the evidence for pegaptanib and bevacizumab comes from studies with around 30 participants per arm which substantially increases the risk of a type II error. Only three trials included quality of life data, arguably one of the most important outcomes.

The proportion of participants and severity of ischemia within the trials was not clear. Whilst ischaemia is not mentioned in the inclusion/exclusion criteria of most studies, these participants

were unlikely included in these studies, especially if the diagnosis of ischaemic CRVO is based on strict criteria. Furthermore patients were entered into the trials relatively soon after diagnosis (mean 4.3 to 4.9 months) and the it is not clear if the effects would be similar in patients who present with long standing disease.

Another weakness was that patients were not asked at the of trials, what treatment they thought they had received, which would have provided data on the success of masking of allocation.

In the case of dexamethasone, the results at six months were not as good as at 90 days, because of the duration of action. Earlier re-treatment, at say 120 days, would have improved results, but many clinicians might be reluctant to repeat injections of dexamethasone implant often because of the large needle size and risk of adverse effects.

Adverse events

Results from the included studies clearly demonstrate that steroids (triamcinolone and dexamethasone) are associated with clinically meaningful increases in IOP and cataract progression. Anti-VEGF therapy ocular adverse events reported in the trials were similar in both placebo and intervention arms.

There is limited evidence of the safety of these drugs specifically in CRVO, but it would not be unreasonable to look to trials in neovascular age-related macular degeneration (AMD) and diabetic macular oedema (DMO) for safety data, where there is more experience. The CATT trial, which compared bevacizumab with ranibizumab in AMD, suggested that there was a higher incidence (RR 1.29 95%CI 1.01 to 1.66) of serious systematic adverse events (primarily hospitalisations) in the bevacizumab arm.[50]Some have raised concerns about arterial thromboembolic events with bevacizumab, but none of these has been demonstrated in the published literature.[51-54] Micieli and colleagues (2010) undertook a systematic review of the adverse events associated with bevacizumab. 22 studies were reviewed, representing 12,699 participants.[55] Adverse events in patients treated with bevacizumab were cerebrovascular events (0.21%), myocardial infarction (0.19%) and increased blood pressure (0.46%). Most of these represent the background burden of disease in patients with advanced eye disease. The proportion of these directly attributable to bevacizumab is likely to be very small. Campbell and colleagues (2012) undertook a nested case-control study of over 7,000 cases and 37,000 controls.[51] Ranibizumab and bevacizumab injection was the exposure and cardiovascular events were the outcome. The authors found that ranibizumab and bevacizumab were not associated with increased cardiovascular events.

Increased IOP has been associated with ranibizumab, bevacizumab and pegaptanib. Sustained increased in IOP has estimated to be 5.5-6.0% with these drugs.[56;57]

Robust evidence on the long-term safety of aflibercept is awaited.

What do these results mean?

Until very recently, patients with macular oedema as a result of CRVO could only be offered visual rehabilitation and visual aids in an attempt to help them to deal better with their reduced vision and its implications in their daily activities and quality of life. Their future is brighter now as new options to treat macular oedema have become available. Triamcinolone is likely to be a cost-effective treatment at least in selected groups of patients, such as pseudophakic individuals or those with pre-existing cataracts that may require cataract surgery in the near future. The lack of a commercially available licensed product for intraocular administration may restrict its use in clinical practice.

Some anti-VEGF therapies, including bevacizumab, ranibizumab and aflibercept, have been also shown to be effective in short term studies for the treatment of patients with macular oedema and CRVO. Bevacizumab has the advantage of having a low cost , with an apparently similar effect to other anti-VEGF therapies[50;58;59]but there is some reluctance to use it as it is not licensed for use in the eye. This has been seen in other eye conditions, such as AMD and DMO. Aflibercept, requiring potentially fewer injections than other anti-VEGF agents, could represent an advantage to patients and may relieve pressure on ophthalmology clinics. Health care systems will need to evaluate the cost-effectiveness of these new treatments and support affordable ones. The National Institute for Health and Care Excellence is currently appraising aflibercept. Policy makers are left in a difficult position because of bevacizumab. It is cheaper than all other drugs[60] and appears to be as effective, but is unlicensed and unlike ranibizumab and aflibercept does not have evidence from large, well-funded RCTs in CRVO. The use of bevacizumab would result in considerable savings for the NHS.

It is important to note that the evidence of benefit of these new therapies is likely to only apply to patients with non-ischaemic CRVO. Although some patients with ischaemic CRVO were included, these individuals are likely to have mild ischaemic CRVO. Thus, for patients with established ischaemic CRVO, there are no proven treatments available and further research into this area is very much needed.

What is the context of these results

Earlier systematic reviews identified limited evidence on the clinical effectiveness of treatments. A review by Braithwaite and colleagues (search date August 2010)[61] on anti-VEGF agents identified one RCT[10;45;46] comparing two doses of ranibizumab and one RCT[38-44] comparing two doses of pegaptanib sodium versus placebo or no treatment. In both RCTs, the higher dose of the anti-VEGF significantly improved BCVA compared with sham injection in the short term (~6 months), but the effects in the longer term were unclear. Braithwaite and colleagues concluded that data from the two RCTs could not be synthesised because ranibizumab and pegaptanib sodium might not be directly comparable. Subsequent RCTs identified in this review also suggest benefit in ocular outcomes in macular oedema secondary to non-ischaemic CRVO for the anti-VEGFs bevacizumab, and aflibercept.[34-37;47-49]

Gewaily and Greenberg reviewed the literature on intravitreal corticosteroids (search date November 2008) versus observation in macular oedema secondary to CRVO and identified no relevant RCTs.[62] Results from two observational studies suggested that triamcinolone acetonide might be beneficial in the treatment of macular oedema secondary to non-ischaemic CRVO. However, as the authors of the review caution because conclusions are primarily drawn from small case series and case reports with short follow up. Results from the SCORE 2009 RCT corroborate the observational studies.[19-32] The effects of triamcinolone acetonide in people with non-ischaemic CRVO without associated macular oedema are less clear. Data from four observational studies led Gewaily and Greenberg to conclude that intravitreal corticosteroids are associated with transient anatomical and functional improvements.

Immediate treatment aimed at relieving the blocked vein and surgical interventions were outwith the remit of this review. Antithrombotics, such as low-molecular weight heparin (LMWH), and fibrinolytics have also been found to benefit visual acuity in retinal vein occlusion with no associated macular oedema. Two systematic reviews[63;64] identifying the same three RCTs in recent onset (≤30 days) BRVO or CRVO found that LMWH improved visual acuity compared with aspirin and that the associated benefit was larger in CRVO; only one of the three RCTs included people solely with CRVO. One review[64]also included one RCT comparing ticlopidine with placebo and two RCTs assessing intravenous fibrinolytic therapy followed by warfarin or aspirin with either haemodilution or no treatment. The authors of the reviews conclude that no definitive recommendations can be made on clinical effectiveness of LMWH in CRVO given the limited evidence available.

Radial optic neurotomy involves the performance of a radial cut using a microvitreoretinal (MVR) blade through the lamina cribrosa, scleral ring and adjacent sclera at a selected point in the optic nerve head with the goal of "decompressing" the scleral outlet (space confined by the scleral ring

and containing the lamina cribrosa, the central retinal artery, central retinal vein and the optic nerve. The ROVO trial found radial optic neurotomy to be more effective than sham.

While this review was being considered for publication, another was published, with differences in scope (BRVO and CRVO) and inclusions (this review is more up to date).[65] The reviewers found that aflibercept and bevacizumab resulted in greatest gain, followed by ranibizumab and triamcinolone. The overall conclusions in both reviews were similar.

Further research

Large adequately powered RCTs comparing ranibizumab, bevacizumab, aflibercept and triamcinolone are needed. Part of the problem is that the US the Food and Drug Administration requires pharmaceutical companies to present data establishing a drug's safety and effectiveness. Whilst this does not specifically require a placebo-controlled trial, it is the most efficient study design for demonstrating effectiveness and safety. Clinicians and researchers are left with placebo-controlled trials demonstrating effectiveness for individual drugs, but a lack of evidence to help them decide which is best for their patients.

Given the cost of these treatments and the burden of repeated injections to patients and health care systems, research aiming to predict "responders" would be useful as at present this is done by therapeutic trial. Treatments could then be targeted to patients likely to benefit. Research is also needed on the frequency and sequences of drugs. As other pathogenic pathways besides inflammation and VEGF-mediated pathways may be implicated in the development of macular oedema in patients with CRVO, these should be investigated in an attempt to develop new therapeutic strategies for this condition. Research is also needed into optimum timing of treatment after CRVO. The cost-effectiveness of diagnostic technologies for determining when retreatment is necessary should be examined.

We also need better treatments since a significant proportion of patients do not improve with all of these drugs

Future RCTs should include longer term outcomes, as functional results observed at six months or even one year may not necessarily be representative of what is likely to be achieved longer term and, furthermore, potential side effects of treatments, such as retinal atrophy after repeated injections of anti-VEGFs, may not be captured in shorter term studies.

Conclusions

Bevacizumab, ranibizumab, aflibercept and triamcinolone appear to be effective in improving the number of patients who gain 15 letters or more in CRVO. There are mixed results for dexamethasone and pegaptanib. Steroids were associated with cataract progression and increased IOP. Long-term data on effectiveness and safety are needed. Head-to-head trials and research to identify “responders” is needed to help clinicians make the right choices for their patients.

Figure legends

Figure 1: PRISMA statement

Figure 2.**Study results for the primary outcome (≥15 ETDRS letter gain).**

Acknowledgments: None

Conflict of interest: None

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

Contributions: NW devised the idea for the review. JF wrote the protocol and all authors contributed to the design of the protocol. RC undertook the literature searches. JF, CC and ST screened titles and abstracts. CC, ST and DS extracted the data. All authors contributed to the interpretation of the results. JF, NL, RC, CC and SB contributed to the first draft of the article. All authors reviewed and commented on the final manuscript.

Data sharing: No additional data available

1 Table 1: Study characteristics

Study	Participants and baseline values	Intervention / Outcomes
DEXAMETHASONE		
GENEVA 2010 ff.[11;17;18] International **Setting:** multicentre (167 centres in 24 countries, so a mean of 2.6 patients per centre) **Study aim:** to evaluate the effects of dexamethasone intravitreal implant in patients with macular oedema secondary to CRVO or BRVO (only data for CRVO reported here) **Design:** 2 identical double-blind, sham-controlled RCTs, phase 3 **Follow-up:** primary endpoint for the masked trial: 6 months; primary endpoint for the open-label extension: 12 months **Overall quality:** 5.5/6	**N:** CRVO – 437 eyes of 437 patients randomised; 94% follow-up at 6 months **Inclusion criteria:** ≥18 years; reduced VA due to macular oedema due to CRVO or BRVO which in the investigator's opinion, is unlikely to be adversely affected if not treated for 6 months; duration of macular oedema 6 weeks to 9 months in patients with CRVO; BCVA 34 to 68 ETDRS letters (~20/200 and 20/50 Snellen equivalent) in the study eye and >34 letters in the non-study eye; CRT ≥300 µm (OCT) **Exclusion criteria:** *study eye:* clinically significant epiretinal membrane; use of periocular corticosteroid within 6 months or topical nonsteroidal anti-inflammatory drug or corticosteroid within 1 month; intraocular surgery or laser within 30 days of study or anticipated; history of intravitreal use of corticosteroid or any other drug; glaucoma; IOP >23 mmHg if untreated or >21 if treated with one medication; treatment with ≥2 IOP-lowering medications; active retinal, optic disc or choroidal neovascularisation; history of herpetic infection; rubeosis iridis, aphakia or anterior-chamber intraocular lens; any ocular condition that would prevent a 15-letter VA improvement; preretinal or vitreous haemorrhage, lens opacity, media opacity that would preclude clinical or photographic evaluation; history of pars plana vitrectomy; *any eye:*	**DEX 0.7 (n=136):** sustained delivery, biodegradable dexamethasone intravitreal implant (Ozurdex), 0.7 mg implant inserted into the vitreous cavity through the pars plana using a customised, single-use, 22-gauge applicator **DEX 0.35 (n=154):** DEX 0.35 mg implant inserted following the same method **Sham (n=147):** a needleless applicator was placed against the conjunctiva to simulate the placement of study medication. **Regimen for all groups:** before inserting the implant, the study eye was anaesthetised with topical and subconjunctival anaesthetics and prepared according to standard clinical practice for eyes undergoing intravitreal injection; patients were treated with a topical ophthalmic antibiotic 4 times daily starting 3 days before the day of their study procedure (day 0) and continuing for 3 days after the procedure **Extension:** patients completing 180 days were eligible to enter a 6 month open label extension where they received DEX 0.7 mg implant **Primary end point:** gain of ≥15 ETDRS letters; for the open-label extension: safety

Study	Participants and baseline values	Intervention / Outcomes
	active ocular infection; history of steroid-induced IOP–increase; diabetic retinopathy; *other:* uncontrolled systemic disease; current or anticipated use of systemic steroids or anticoagulants **Age (years):** 62.7 to 65.2 years **Sex:** 43.7 to 49.2% (CRVO and BRVO together) **Baseline VA (ETDRS letters):**52.4 SD10.6 **Baseline CRT (µm):**DEX 0.7: 648; Sham: 620 **Other ocular information:** phakic status (%): 85 to 88% **Duration of macular oedema:** mean 4.8 to 4.9 months;<90 days: 14.3 to 15.4%; >90 to <180 days: 54.4 to 57.4%, >180 days: 27.1 to 31.3% **Comorbidities:** diabetes mellitus 14 to 15%, hypertension 62 to 64%, coronary artery disease 9 to 13%, IOP-lowering medication at baseline 4 to 6% (all for CRVO and BRVO together)	**Other outcomes:** proportion of eyes achieving at least a 10 and 15 letter improvement from baseline; the proportion of eye exhibiting ≥15 letters of worsening; BCVA; subgroup analysis according to RVO diagnosis (BRVO and CRVO) and duration of macular oedema at baseline; CRT and safety **Outcome assessment:** evaluation at 1, 7, 30, 60, 90 and 180 days after study treatment for both parts of the study
TRIAMCINOLONE		
SCORE 2009 ff.[19-32] USA **Setting:** multicentre **Study aim:** to compare the effects of 1 and 4 mg preservative-free	**N:** 271 eyes of 271 patients randomised; 83% (observation) and 90% (intervention) completed 12 months **Inclusion criteria:** centre-involved macular oedema secondary to CRVO, BCVA 19 to 73 ETDRS letters (Snellen equivalent ~20/400 to 20/40), CRT >250 µm by OCT; media clarity, papillary dilatation and participant	**Tria (1 mg) (n=92):** 1 mg (0.05 ml) of preservative-free, nondispersive formulation of triamcinolone (average number of injections 2.2 at 12 months) **Tria (4 mg) (n=91):** 4 mg (0.05 ml) of preservative-free, nondispersive formulation of triamcinolone(average number of injections 2.0 at 12 months)

Study	Participants and baseline values	Intervention / Outcomes
intravitreal triamcinolone with observation in eyes with vision loss associated with macular oedema secondary to perfused CRVO **Design:** RCT **Follow-up:** primary end point 12 months, FU planned up to 36 months **Overall quality:** 3/6	cooperation sufficient for adequate fundus photographs **Exclusion criteria:** macular oedema due to causes other than CRVO, ocular condition such that visual acuity would not improve from resolution of oedema, substantial cataract, prior treatment with intravitreal corticosteroids or peribulbar steroid injection within 6 months, photocoagulation (prior 4 months or anticipated), prior pars plana vitrectomy, major ocular surgery (prior 6 months or anticipated), IOP ≥25 mmHg, open-angle glaucoma, steroid-induced IOP-elevation requiring IOP-lowering treatment, pseudoexfoliation, aphakia **Age:** 68.0 SD 12.4 years **Sex:** 45% female **Duration of macular oedema:** 4.3 SD3.7 months **Baseline VA (ETDRS letters):** 51.2 SD14.1 **Baseline CRT (µm):** 659 SD229 **Other ocular information:** 81% phakic, IOP 15.5 SD3.2 mmHg **Comorbidities:** 23% diabetes mellitus, 73% hypertension, 21% coronary artery disease, 21% history of cancer	The form of triamcinolone used was Trivaris, no longer available. It was made by the manufacturer of Ozurdex (Allergan) **Obs (n=88):** observation **Regimen for all groups:** all intervention eyes received standardised ocular surface preparation prior to injection (eyelid speculum, topical anaesthetic, topical antibiotics, asepsis with povidone iodine); retreatment every 4 months unless (1) treatment was deemed successful (defined), (2) treatment was contraindicated because of significant adverse effect, (3) additional treatment was considered 'apparently futile' (defined) **Primary end point:** gain of ≥15 ETDRS letters **Other outcomes:** BCVA, intraocular pressure, eye examination including dilated fundus examination, OCT scan for thickness, , lens opacities, , adverse events **Outcome assessment:** follow-up visits every 4 months for 36 months
ROVO 2013[33]	**N:** 90 patients randomised; 82% evaluated **Inclusion criteria:** history of CRVO not longer than 12	**Tria (n=25):** single intravitreal injection of 4 mg triamcinolone acetonide (100 µl) applied after povidone

Study	Participants and baseline values	Intervention / Outcomes
Austria **Setting:** multicentre (7 centres in 7 countries) **Study aim:** to compare the effects of radial optical neurotomy with intravenous triamcinolone and natural history (placebo) in patients with CRVO **Design:** RCT, placebo-controlled **Follow-up:** primary end point 12 months **Overall quality:** 3.5/6	months; VA of ≥0.3 logMAR (≤85 letters) (for perfused CRVO: VA >1 logMAR (>50 letters) or no VA improvement over 4 weeks) **Exclusion criteria:** dense cataract, severe ophthalmologic conditions (severe retinopathy, presence of advanced optic atrophy, uncontrolled glaucoma), pregnancy, allergy against fluoresceine or indocyanine green, any handicap which could prevent patients from attending follow-up visits **Age:** not reported **Sex:** 36% female **Duration of macular oedema:** not reported **Baseline VA (ETDRS letters) :** 1.07 logMAR (interquartile range 0.78 to 1.7) (~46 letters) **Baseline CRT (µm):** 569 to 657 µm **Other ocular information:** not reported **Comorbidities:** 23% diabetes mellitus, 49% hypertension, 17% cardiovascular disease, 4% hypercoagulopathies, 1% leukaemia, 2% anaemia	iodine drops; postoperative topical antibiotics **RON (n=38):**radial optical neurotomy under general anaesthesia (detailed procedure described) **Pla (n=20):** eyes prepared as for triamcinolone injection but sham injection performed (empty syringe without needle pressed against the eye) **Primary end point:** gain of ≥15 ETDRS letters **Other outcomes:** BCVA, CRT, safety **Outcome assessment:** 12 months
AFLIBERCEPT		
COPERNICUS 2012[34;35] International	**N:** 189 eyes of 189 patients randomised; 95.7% (aflibercept) and 81.1% (sham) completed 24 weeks; 93% (aflibercept) and 77% (sham) completed 52 weeks	**VTE (n=114):** intravitreal injections of 2 mg aflibercept (50 µl) every 4 weeks for 24 weeks **Sham (n=73):** sham procedure (empty syringe without

Study	Participants and baseline values	Intervention / Outcomes
Setting: multicentre, 70 sites in North and South America, India and Israel. Mean 2.7 patients per centre. **Study aim:** to evaluate the effects of intravitreal aflibercept in patients with macular oedema secondary to CRVO **Design:** double-blind, sham-controlled RCT, phase 3 **Follow-up:** primary end point 24 weeks, FU 2 years **Overall quality:** 5/6	**Inclusion criteria:** adult patients with centre-involved CRVO for a maximum of 9 months, CRT ≥250 µm with OCT, ETDRS BCVA of 73 to 24 letters (Snellen equivalent 20/40 to 20/320) **Exclusion criteria:** history of vitreoretinal surgery (incl. radial optic neurotomy or sheathotomy); current bilateral retinal vein occlusion; previous pan-retinal or macular laser photocoagulation; other reasons for decreased visual acuity; ocular conditions with poorer prognosis in the fellow eye; history or presence of age-related macular degeneration, diabetic macular oedema, or diabetic retinopathy; any use of intraocular or periocular corticosteroids or antiangiogenic treatment in the study eye at any time or in the fellow eye in the preceding 3 months; iris neovascularisation, vitreous haemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula; vitreomacular traction or epiretinal membrane significantly affecting central vision; ocular inflammation; uveitis; any intraocular surgery in the preceding 3 months; aphakia; uncontrolled glaucoma, hypertension, or diabetes; spherical equivalent of a refractive error of more than -8 diopters; myopia; infectious blepharitis, keratitis, scleritis, or conjunctivitis; cerebral vascular accident or myocardial infarction in the preceding 6 months; and other conditions that could interfere with interpretation of the results or increase the risk of complications; cataract surgery was not allowed during the 3 months before randomisation.	needle pressed to conjunctival surface) every 4 weeks for 24 weeks **Regimen for all groups:** all patients eligible to receive pan-retinal photocoagulation for neovascularisation at any time at the discretion of the investigator; patients were not allowed to use other systemic or local medications for treating CRVO in the study eye over the first 52 weeks of the study; a noninvestigational therapy could be used to treat CRVO in the fellow eye **Extension:** during weeks 24 to 52, patients in both groups were evaluated monthly and received aflibercept if they met protocol-specified retreatment criteria, and received a sham injection if retreatment was not indicated (3.9 SE0.3 injections in the sham group and 2.7 SE0.2 injections in the VTE group); after the first year, patients continued in a 1 year extension phase with as needed dosing **Primary end point:** gain of ≥15 ETDRS letters **Other outcomes:** BCVA, CRT, proportion of patients progressing to neovascularisation of the anterior segment, optic disc or elsewhere in the retina, changes in vision-related quality of life (National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25), safety **Outcome assessment:** examination every 4 weeks up to 24 weeks, 52 weeks

Study	Participants and baseline values	Intervention / Outcomes
	Age: 66.3 SD 13.9 years **Sex:** 43% female **Time since CRVO diagnosis:** 2.4 SD2.8 months; 62.0% ≤2 months, 37.4% >2 months **Baseline VA (ETDRS letters) :** 50.0 SD14.1 ; 75.4% >20/200 **Baseline CRT (µm):** 665.8 SD239.8 **Other ocular information:** 67.9% perfused retinal occlusion, IOP 15.1 SD3.08 mmHg **Comorbidities:** not reported	
GALILEO 2012[36;37] International **Setting:** multicentre, 10 countries in Europe and Asia; 63 centres in total **Study aim:** to evaluate the effects of intravitreal aflibercept in patients with macular oedema secondary to CRVO **Design:** double-blind, sham-controlled RCT, phase 3 **Follow-up:** primary end point 24 weeks, FU up to 12 months, planned	**N:** 177 eyes of 177 patients randomised; 90.6% (aflibercept) and 78.9% (sham) completed 24 weeks **Inclusion criteria:** treatment-naïve patients, age ≥18 years, centre-involved CRVO for a maximum of 9 months, CRT ≥250 µm with OCT, ETDRS BCVA of 73 to 24 letters (Snellen equivalent 20/40 to 20/320) **Exclusion criteria:** uncontrolled glaucoma (IOP≥25 mmHg), filtration surgery, bilateral manifestation of retinal vein occlusion, iris neovascularisation, previous treatment with anti-VEGF agents, pan-retinal or macular laser photocoagulation, intraocular corticosteroids, pregnant **Age:** 61.5 SD 12.9 years	**VTE (n=103):** intravitreal injections of 2 mg aflibercept every 4 weeks for 24 weeks **Sham (n=71):** sham procedure (empty syringe without needle pressed to conjunctival surface) every 4 weeks for 24 weeks **Regimen for all groups:** pan-retinal photocoagulation allowed at any time for all patients if they progressed to neovascularisation of the anterior segment, optic disc or fundus **Extension:** during weeks 24 to 52, patients remained in their original treatment groups but received their allocated treatment as needed; beginning from week 52 to week 76 both groups received treatment every 8

Study	Participants and baseline values	Intervention / Outcomes
up to 76 weeks **Overall quality:** 4/6	**Sex:** 44.4% female **Time since CRVO diagnosis:** 81.8 SD85.4 days; 52.6% <2 months, 46.2% ≥2 months, 1.2% missing **Baseline VA (ETDRS letters) :** 52.2 SD15.7, 83% >20/200 **Baseline CRT (µm):** 665.5 SD231.0 **Other ocular information:** 83.6% perfused retinal occlusion, IOP 14.9 SD2.7 mmHg **Comorbidities:** Renal impairment: 31% mild, 8.2% moderate, 1.2% severe; 2.9% hepatic impairment	weeks **Primary end point:** gain of ≥15 ETDRS letters **Other outcomes:** BCVA, CRT, proportion of patients progressing to neovascularisation of the anterior segment, optic disc or elsewhere in the fundus, changes in vision-related and overall quality of life (National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25), European Quality of Life-5 Dimensions (EQ-5D)), safety **Outcome assessment:** 24 weeks, 52 weeks
PEGAPTANIB		
Wroblewski 2009[38-44] International **Number of sites:** not reported **Setting:** multicentre, practitioners' offices and clinics in Australia, France, Germany, Israel, Spain, USA **Study aim:** to evaluate the effects of intravitreal pegaptanib sodium in patients with macular oedema secondary to CRVO **Design:** double-blind, sham-	**N:** 98 eyes of 98 patients randomised; 93% completed 30 weeks **Inclusion criteria:** age ≥18 years, CRVO with onset within 6 months prior to baseline, CRT ≥250 µm with OCT, ETDRS BCVA of 65 to 20 letters (Snellen equivalent 20/50 to 20/400) and better than 35 letters (20/200) in the fellow eye **Exclusion criteria:** subtenon corticosteroid administration for any ophthalmic condition; prior panretinal or sector scatter photocoagulation; signs of old branch retinal vein occlusion or CRVO in the study eye; any other retinal vascular disease including diabetic retinopathy; eyes with a brisk afferent pupillary defect;	**PS 0.3 mg (n=33):** intravitreal injections of 0.3 mg pegaptanib sodium every 6 weeks for 24 weeks (5 injections) **PS 1 mg (n=33):** intravitreal injections of 1 mg pegaptanib sodium every 6 weeks for 24 weeks (5 injections) **Sham (n=32):** sham procedure (blunt pressure applied to the globe without a needle) every 6 weeks for 24 weeks **Regimen for all groups:** antisepsis procedures were the same for all participants (including those receiving sham); all participants received injected subconjunctival anaesthetic; panretinal photocoagulation permitted at

Study	Participants and baseline values	Intervention / Outcomes
controlled RCT, phase 2 **Follow-up:** primary end point 30 weeks, FU up to 12 months **Overall quality:** 6/6	vitreous haemorrhage except for breakthrough haemorrhage from intraretinal haemorrhage; evidence of any neovascularisation involving the iris, disc, or retina; any other clinically significant concomitant ocular diseases **Age:** 59 to 64 years **Sex:** 47% female **Time from occlusive event to study entry:** 77 to 82 days **Baseline VA (ETDRS letters):** 47.6 to 48.5 letters **Baseline CRT (µm):** 632 to 688 **Other ocular information:** not reported **Comorbidities:** not reported	any time point for neovascularisation according to the Central Vein Occlusion Study protocol; intravitreous steroids not permitted at any time **Extension:** FU to 52 weeks **Primary end point:** gain of ≥15 ETDRS letters **Other outcomes:** BCVA, loss of ≥15 letters, CRT, proportion of eyes progressing to retinal or iris neovascularisation, safety **Outcome assessment:** assessments every 6 weeks up top week 30, FU to week 52
RANIBIZUMAB		
CRUISE 2010 ff.[10;45;46] USA **Number of sites:** not reported **Setting:** multicentre **Study aim:** to evaluate the effects of intravitreal ranibizumab (0.3 or 0.5 mg) in patients with macular oedema secondary to CRVO	**N:** 392 eyes of 392 patients randomised; 97.7% (ran 0.3 mg), 91.5% (ran 0.5 mg), and 88.5% (sham) completed 6 months **Inclusion criteria:** age ≥18 years, foveal centre-involved macular oedema secondary to CRVO diagnosed within 12 months before study began, CRT ≥250 µm with OCT, BCVA 20/40 to 20/320 (ETDRS charts) **Exclusion criteria:** prior episode of retinal vein	**Ran 0.3 mg (n=132):** intravitreal injections of 0.3 mg ranibizumab monthly for 6 months (maximum 6 injections) **Ran 0.5 mg (n=130):** intravitreal injections of 0.5 mg ranibizumab monthly for 6 months (maximum 6 injections) **Sham (n=130):** sham procedure (empty syringe without needle pressed to the injection site) monthly for 6 months

Study	Participants and baseline values	Intervention / Outcomes
Design: double-blind, sham-controlled RCT, phase 3 **Follow-up:** primary end point 6 months, FU up to 12 months **Overall quality:** 4.5/6	occlusion, brisk afferent pupillary defect, >10-letter improvement in BCVA between screening and day 0, history of radial optic neurotomy or sheathotomy, intraocular corticosteroid use in study eye in prior 3 months, history or presence of wet or dry age-related macular oedema, recent or anticipated panretinal scatter photocoagulation or sector laser photocoagulation, laser photocoagulation for macular oedema in prior 4 months, evidence on examination of any diabetic retinopathy, stroke or myocardial infarction in prior 3 months, prior anti-VEGF treatment in study or fellow eye in prior 3 months or systemic anti-VEGF or pro-VEGF treatment in prior 6 months **Age:** 65.4 SD13.1 to 69.7 SD11.6 years **Sex:** 38.5 to 46.2% female **Time since CRVO diagnosis:** 2.9 SD2.9 to 3.6 SD3.2 months; 65.9 to 72.3% ≤3 months **Baseline VA (ETDRS letters):** 47.4 to 49.2 (SD 14.6 to 14.8) (range 9 to 72), 38.5 to 42.3% ≥55 **Baseline CRT (µm):** 679.9 SD242.4 to 688.7 SD253.1 **Other ocular information:** IOP 14.9 SD3.3 to 15.1 SD3.1 mmHg, 10.0 to 16.9% IOP-lowering medication, n=2 >10 disc areas of non-perfusion; fellow eye BCVA 78.8 SD 17.4 to 80.0 SD12.5	**Regimen for all groups:** prior to injection or sham: topical anaesthetic drops, subconjuctival injection of 2% lidocaine, cleaning of injection site with 5% povidone iodine **Extension:** months 6 to 12: all patients could receive intraocular ranibizumab (previously assigned dose or 0.5 mg for the sham group) if they met pre-specified functional and anatomic criteria (3.7 injections sham group, 3.8 injections 0.3 mg ran group, 3.3 injections 0.5 mg ran group); after 12 months' FU, 304 CRUISE patients continued in the HORIZON study for another 12 months, where patients were evaluated at least every 3 months and were eligible to receive an intravitreal injection of 0.5 mg ranibizumab if they fulfilled prespecified criteria (2.9 SD2.7 injections sham group, 3.8 SD2.8 injections 0.3 mg ran group, 3.5 SD2.7 injections 0.5 mg ran group) **Primary end point:** mean change from baseline BCVA **Other outcomes:** percentage gaining ≥15 letters, percentage losing ≥15 letters, CRT, percentage with CRT <250 µm, vision-related quality of life (National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25), safety **Outcome assessment:** monthly visits up to 12 months; 3-monthly evaluation up to 24 months (HORIZON)

Study	Participants and baseline values	Intervention / Outcomes
	Comorbidities: not reported	
BEVACIZUMAB		
Epstein 2012[47-49] Sweden **Setting:** Single centre; St. Eriks Eye Hospital Stockholm **Study aim:** to evaluate the effects of intraocular injections of bevacizumab in patients with macular oedema secondary to CRVO **Design:** sham-injection controlled, double masked RCT **Follow-up:** primary end-point 6 months; open label extension up to 12 months **Overall quality:** 5/6	**N:** 60 eyes of 60 patients randomised; 93% completed open label extension **Inclusion criteria:** CRVO of ≤6 months; BCVA 15 to 65 ETDRS letters (Snellen equivalent ~20/50 to 20/500), CRT ≥300 µm by OCT **Exclusion criteria:** CRVO with neovascularisation; previous treatment for CRVO; intraocular surgery during previous 3 months; vascular retinopathy of other causes; glaucoma with advanced visual field defect or uncontrolled ocular hypertension >25 mmHg despite full therapy; myocardial infarction or stroke during last 12 months **Age:** 70.5 SD 12.6 years **Sex:** 40% female **Time from diagnosis to inclusion:** 8.8 SD 5.7 weeks; 71.7% <90 days, 28.3% >90 days **Baseline VA (ETDRS letters) :** 44.1 SD 15.5 ; 31.7% <34, 68.3% >34	**Bev (n=30):** 1.25 mg (0.05 ml) bevacizumab via pars plana **Sham (n=30):** sham injection (syringe without needle pressed to the globe) **Regimen for all groups:** 4 injections received, one every 6 weeks; eyes treated with topical antibiotics 30 min before injection, topical chlorhexidine, topical anaesthesia with 1% tetracaine **Open label extension:** months 6 to 12, intravitreal bevacizumab injections every 6 weeks (4 injections) for all patients **Primary end point:** gain of ≥15 ETDRS letters **Other outcomes:** BCVA, OCT images, CRT, fluorescein angiogram, colour and red-free photography, slit-lamp examination with dilated fundus-examination, intraocular pressure, adverse events **Outcome assessment:** follow-up visits every 6 weeks up to 24 weeks

Study	Participants and baseline values	Intervention / Outcomes
	Baseline CRT (µm): 721 SD 269 **Comorbidities:** 48.3% hypertension, 6.7% diabetes mellitus	

Abbreviations: BCVA – best corrected visual acuity, CRT – central retinal thickness, CRVO – central retinal vein occlusion, ETDRS – Early Treatment Diabetic Retinopathy Study, FU – follow-up, IOP – intraocular pressure, OCT – optical coherence tomography, SD – standard deviation, SE – standard error

Table 2: Study results and adverse events

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)	Adverse events
DEXAMETHASONE		

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)						Adverse events			
GENEVA 2010 ff.[11;17;18]		**Baseline**	**6 months**	**p**		**12 months**	**p**	**AE**	**DEX 0.35**	**DEX 0.7 (n = 133)**	**Sham (n = 147)**	**p**
	BCVA (mean letters)							**6 months**				
	DEX 0.35	-	-					**Overall incidence of ocular adverse events**				
	DEX 0.7	52.4 SD 10.6	+0.1	< 0.001 vs sham	***DEX 0.7/0.7***	+2 (estimated from graph)				68.4%	49.7%	
	Sham	53.3 SD 10.8	-1.8		***Sham/DEX 0.7***	-1.4 (ditto)		**Common Ocular Adverse Events**				
	≥15 letters gained							Intraocular pressures increased		40 (30.1%)	2 (1.4%)	<0.001
	DEX 0.35		17%	NS vs sham				**Common treatment-related Ocular Adverse Events**				
	DEX 0.7		18.4%	NS vs sham	***DEX 0.7/0.7, day 240***	27%		IOP increased		39 (29.3%)	1 (0.7%)	<0.001
					DEX 0.7 (n=19), day 360	26%		**Cataract adverse events**				
	Sham		12.2%	NS vs sham	***Sham/DEX 0.7, day 240***	21%		Cataract		3 (2.3%)	2 (1.4%)	
	≥15 letters lost							Cataract subcapsular		4 (3.0%)	1 (0.7%)	
	DEX 0.35		-	-				Cataract nuclear		3 (2.3%)	1 (0.7%)	
	DEX 0.7		14.0%	NS				Cataract cortical		1 (0.8%)	3 (2.0%)	
	Sham		20.4%					**Serious adverse events** – not given separately for CRVO				
	Subgroups											
	Duration of macular oedema											
	>90 days	***DEX 0.7***	17.7%									
		Sham	9.6%									
	≤90 days	***DEX 0.7***	26.0%									
		Sham	27.3%									

<table>
<tr><th>Study</th><th>Clinical outcomes (BCVA, CRT; change from baseline at study end)</th><th>Adverse events</th></tr>
<tr><td></td><td>CRT (µm):
<table><tr><th></th><th>Baseline</th><th>6months (mean)</th><th>p</th><th>12 months (mean)</th><th>p</th></tr><tr><td>CRT</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>DEX 0.35</td><td>-</td><td>-</td><td></td><td></td><td></td></tr><tr><td>DEX 0.7</td><td>647.6</td><td>-118.2</td><td>NS vs sham</td><td></td><td></td></tr><tr><td>Sham</td><td>619.8</td><td>-125.3</td><td></td><td></td><td></td></tr></table></td><td></td></tr>
<tr><td colspan="3">TRIAMCINOLONE</td></tr>
<tr><td>SCORE 2009 ff.[19-32]

1 mg intravitreal triamcinolone (2.2 injections over 12 months) (n=92)

versus 4 mg intravitreal triamcinolone (2</td><td>BCVA (ETDRS letters):
<table><tr><th></th><th>Baseline</th><th>12 months</th><th>p</th><th>24 months</th><th>p</th></tr><tr><td>BCVA (letters, 95% CI)</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Tria 1 mg</td><td>50.6 SD 14.9</td><td>-1.2 (-6.4 to +4.1)</td><td><0.05 vs obs</td><td>-4.4 (-11.5 to +2.8)</td><td>NR</td></tr><tr><td>Tria 4 mg</td><td>51.0 SD 14.4</td><td>-1.2 (-6.3 to +4.0)</td><td><0.05 vs obs</td><td>-2.4 (-9.3 to +4.4)</td><td></td></tr></table></td><td>Ocular Adverse Events
<table><tr><th>AE</th><th>Tria 1 mg</th><th>Tria 4 mg</th><th>Obs</th></tr><tr><td>12 months</td><td></td><td></td><td></td></tr><tr><td>Elevated IOP or glaucoma</td><td></td><td></td><td></td></tr><tr><td>Initiation of IOP-lowering medication</td><td>20%</td><td>35%</td><td>8%</td></tr></table></td></tr>
</table>

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)						Adverse events			
injections over 12 months) (n=91) versus observation (n=88)	***Obs***	52.1 SD 13.1	-12.1 (-17.1 to -7.1)		-10.7 (-17.4 to -4.1)		IOP >35 mm Hg (n)	5	8	1
	≥15 letters gained (95% CI)						IOP >10 mm Hg above baseline (n)	15	24	2
	Tria 1 mg		26.5% (17 to 36)	0.001 vs obs	31% (19 to 43)	NR	Laser peripheral iridotomy (n)	0	1	0
	Tria 4 mg		25.6% (16 to 35)	0.001 vs obs	26% (14 to 38)		Trabeculectomy (n)	0	0	0
	Obs		6.8% (1 to 13)		9% (1 to 17)		Tube shunt (n)	2	0	0
	≥15 letters lost						*Cataract*			
	Tria 1 mg		25.3%		31%		Lens opacity onset or progression	26%	33%	18%
	Tria 4 mg		25.6%		26%		Cataract surgery (n)	0	4	0
	Obs		43.8%		48%	NS, p=0.06 tria vs obs	*At least 1 of the following adverse events (n):*	11	6	9
	CRT (µm):						Infectious endophthalmitis (n)	0	0	0
		Baseline	**12 months (median, IQR)**	**p**	**24 months (median, IQR)**	**p**	Non-infectious endophthalmitis (n)	0	0	0

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)						Adverse events			
	CRT						Retinal detachment (n)	0	0	0
	Tria 1 mg	643 SD 226	-196 (-390 to -62)	NR	-286 (-458 to -119)	NR	Iris neovascularisation or neovascular glaucoma	9	4	2
	Tria 4 mg	641 SD 248	-261 (-407 to -79)		-236 (-421 to -63)		Retinal neovascularisation (n)	2	2	4
	Obs	695 SD 208	-277 (-418 to -40)		-304 (-465 to -108)		Vitreous hemorrhage (n)	4	0	4
	CRT <250 µm				**CRT <250 µm**		*Other ocular surgical procedures*			
	Tria 1 mg		32%	NR	50%	NR	YAG capsulotomy	0	0	1
	Tria 4 mg		45%		39%		Sector or panretinal scatter photocoagulation	9	3	5
	Obs		28%		38%		Pars plana vitrectomy	2	0	1
	Results for subgroups (based on baseline BCVA (73 to 59, 58 to 49, 48 to 19), baseline CRT (<500 µm, ≥500 µm), duration of macular oedema (≤3 months, >3 months, pseudophakic at baseline) were consistent with the overall results (significance levels for comparisons not reported)						**Selected Events at 12-24 months**			
							Glaucoma procedures			
							Laser peripheral iridotomy	0	0	0

<table>
<tr><th>Study</th><th>Clinical outcomes (BCVA, CRT; change from baseline at study end)</th><th>Adverse events</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>Trabeculectomy</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Tube shunt</td><td>0</td><td>2</td><td>0</td></tr>
<tr><td>Cataract</td><td></td><td></td><td></td></tr>
<tr><td>Cataract surgery</td><td>3</td><td>21</td><td>0</td></tr>
<tr><td colspan="4">Reports of systemic adverse events were similar between groups</td></tr>
</table>
</td></tr>
<tr><td>ROVO 2013[33]

4 mg intravitreal triamcinolone acetonide (single injection)

versus radial optical neurotomy

versus sham injection</td><td>BCVA (logMAR):
<table>
<tr><th></th><th>Baseline</th><th>12 months</th><th>p</th></tr>
<tr><td>BCVA (logMAR, interquartile range)</td><td></td><td></td><td></td></tr>
<tr><td>Tria 4 mg</td><td>1.02 (0.75, 2.0</td><td>0.86 (0.51, 1.78) (-0.16)</td><td>NR</td></tr>
<tr><td>RON</td><td>1.46 (0.84, 2.0)</td><td>0.75 (46, 1.22) (-0.71)</td><td></td></tr>
<tr><td>Sham</td><td>1.02 (0.9, 1.36)</td><td>1.02 (0.85, 3.0) (0)</td><td></td></tr>
<tr><td>% with VA improvement</td><td></td><td></td><td></td></tr>
<tr><td>Tria 4 mg</td><td></td><td>20%</td><td>0.034 vs RON, NS vs placebo</td></tr>
<tr><td>RON</td><td></td><td>47%</td><td></td></tr>
</table>
</td><td>Ocular Adverse Events, 12 months
<table>
<tr><th>AE</th><th>Tria 4 mg</th><th>RON</th><th>Pla</th></tr>
<tr><td>Retinal detachment</td><td></td><td>7.9%</td><td></td></tr>
<tr><td>Subretinal haemorrhages</td><td></td><td>5.3%</td><td></td></tr>
<tr><td>Vitreous haemorrhage</td><td></td><td>2.6%</td><td>10%</td></tr>
<tr><td>Subretinal membrane formation</td><td></td><td>2.6%</td><td></td></tr>
<tr><td>Retinal tear</td><td></td><td>2.6%</td><td></td></tr>
<tr><td>IOP increase</td><td>32%</td><td></td><td></td></tr>
<tr><td>Cataract progression</td><td>24%</td><td>13%</td><td>15%</td></tr>
<tr><td>Neovascular glaucoma</td><td>12%</td><td>5%</td><td>15%</td></tr>
</table>
</td></tr>
</table>

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)				Adverse events	
	Sham		10%	0.009 vs RON	Rubeosis iridis	15%
	% with VA deterioration				No cases of phthisis, enucleation, endophthalmitis, injury of central vessels, injury of optic nerve	
	Tria 4 mg		NR			
	RON		8%			
	Sham		35%	0.007 vs RON		
	CRT (µm):					
		Baseline	**12 months**	**p**		
	CRT					
	Tria 4 mg	657	-235	NS		
	RON	569	-263	NS		
	Sham	615	-206			
AFLIBERCEPT						
COPERNICUS 2012[34;35]	**BCVA (ETDRS letters):**				**Adverse Events**	
		Baseline	**24 weeks**	**p**	**52 weeks (all VTE PRN)**	**p**
2 mg intravitreal aflibercept(every 4 weeks over 24	**BCVA (letters)**					

AE (24 weeks)	VTE	Sham
Discontinued treatment before week 24 because of AE	0	4.1%
At least one AE	83.3%	85.1%

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)					
weeks)(n=114) versus sham injection (n=73) extension up to 52 weeks with aflibercept PRN in both groups	***VTE***	50.7 SD 13.9	+17.3	<0.001	+16.2	<0.001
	Sham	48.9 SD 14.4	-4.0		+3.8	
	≥15 letters gained					
	VTE		56.1%	<0.001	55.3%	<0.001
	Sham		12.3%		30.1%	
	≥10 letters lost					
	VTE		1.8%	NR		
	Sham		30.1%			
	Subgroups					
	Baseline VA		**≥15 letters gained**			
	VTE ≤20/200	*VTE*	67.9%	NR	60.7%	NR
		Sham	16.7%		22.2%	
	VTE >20/200	*VTE*	52.3%		53.5%	
		Sham	10.9%		32.7%	
	Time since diagnosis					
	VTE <2 mo	*VTE*	68.8%	NR	64.1%	NR

Adverse events		
Ocular AEs	68.4%	68.9%
Patients with at least one serious adverse event	3.5%	13.5%
Vitreous haemorrhage	0	5.4%
Neovascular glaucoma	0	2.7%
Iris neovascularisation	0	2.7%
Retinal haemorrhage	0	2.7%
Visual acuity reduced	0.9%	1.4%
Retinal artery occlusion	0.9%	0
Retinal tear	0	1.4%
Retinal vein occlusion	0	1.4%
Endophthalmitis	0.9%	0
Corneal abrasion	0.9%	0

AE (24 to 52 weeks)	**VTE**	**Sham**
Patients with at least one serious adverse event	2.7%	3.3%
Vitreous haemorrhage	0.9%	1.7%
Glaucoma	0	1.7%

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)						Adverse events		
		Sham	15.4%		34.6%		Iris neovascularisation	0	0
	VTE ≥2 mo	*VTE*	38.8%		42.9%		Retinal haemorrhage	0	0
		Sham	4.8%		19.0%		Visual acuity reduced	0	0
	Perfusion status						Retinal artery occlusion	0	0
	VTE perfused	*VTE*	58.4%	NS	58.4%	NR	Retinal tear	0	1.7%
		Sham	16%		30.0%		Retinal vein occlusion	0.9%	0
	VTE non-perfused	*VTE*	51.4%		48.6%		Cataract	0.9%	0
		Sham	4.3%		30.4%		Cystoid macular oedema	0.9%	0
							Endophthalmitis	0	0
							Corneal abrasion	0	0
	CRT (µm):								
		Baseline	**24 weeks**	**p**	**52 weeks (all VTE PRN)**	**p**	Reports of systemic adverse events were similar between groups; 2 deaths in the sham group by 24 weeks; 2.7% arterial thromboembolic events in the sham group and 0.9% in the intervention group		
	CRT								
	VTE	661.7 SD 237.4	-457.2	<0.001	-413.0	NS			
	Sham	672.4 SD 245.3	-144.8		-381.8				
	QoL								
		Baseline	**24 weeks**	**p**	**52 weeks (all VTE**	**p**			

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)					Adverse events
					PRN)	
	NEI-VFQ-25 total					
	VTE	77.76 SD 15.96	+7.2 SD 12.1	0.001	+7.5	NS
	Sham	77.78 SD 16.25	+0.8 SD 9.8		+5.1	
	NEI-VFQ-25 near activities					
	VTE	69.96 SD 21.94	+8.3 SD 22.0	<0.05	+11.4	NS
	Sham	70.72 SD 20.22	+1.84 SD 19.75		+8.3	
	NEI-VFQ-25 distance activities					
	VTE	75.99 SD 21.26	+6.1 SD 20.0	<0.05	+8.5	NS
	Sham	78.08 SD 21.25	-0.64 SD 15.2		+3.8	
	NEI-VFQ-25 vision dependency					
	VTE	83.26 SD 25.51	+7.1 SD 20.5	<0.05	+6.0	NS
	Sham	82.76 SD 27.41	+1.1 SD 20.5		+3.4	

<table>
<tr><th>Study</th><th>Clinical outcomes (BCVA, CRT; change from baseline at study end)</th><th>Adverse events</th></tr>
<tr><td></td><td>Progression to neovascularisation: 0 with aflibercept, 6.8% with sham treatment over 52 weeks, p=0.006

Perfused status at week 24: 78.9% with aflibercept, 46.6% with sham treatment</td><td></td></tr>
<tr><td>GALILEO 2012[36;37]

2 mg intravitreal aflibercept (every 4 weeks over 24 weeks) (n=103)

versus sham injection (n=71)

extension up to 52 weeks</td><td>BCVA (ETDRS letters):
<table>
<tr><th></th><th>Baseline</th><th>24 weeks</th><th>p</th><th>52 weeks</th><th>p</th></tr>
<tr><td>BCVA (letters)</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>VTE</td><td>53.6 SD15.8</td><td>+18.0</td><td><0.0001</td><td>+16.9</td><td><0.0001</td></tr>
<tr><td>Sham</td><td>50.9 SD15.4</td><td>+3.3</td><td></td><td>+3.8</td><td></td></tr>
<tr><td>≥15 letters gained</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>VTE</td><td></td><td>60.2%</td><td><0.0001</td><td>60.2%</td><td>0.0004</td></tr>
<tr><td>Sham</td><td></td><td>22.1%</td><td></td><td>32.4%</td><td></td></tr>
<tr><td>≥10 letters lost</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>VTE</td><td></td><td>7.8%</td><td>0.0033</td><td></td><td></td></tr>
<tr><td>Sham</td><td></td><td>25.0%</td><td></td><td></td><td></td></tr>
<tr><td>Subgroups</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Time since diagnosis</td><td></td><td>≥15 letters gained</td><td></td><td></td><td></td></tr>
<tr><td>VTE <2 mo</td><td></td><td>70.9%</td><td>NR</td><td></td><td></td></tr>
</table></td><td>Ocular Adverse Events
<table>
<tr><th>AE</th><th>VTE</th><th>Sham</th></tr>
<tr><td>Discontinued treatment before week 24 because of AE</td><td>1.9%</td><td>11.3%</td></tr>
<tr><td>Eye pain</td><td>11.5%</td><td>4.4%</td></tr>
<tr><td>Conjunctival haemorrhage</td><td>8.7%</td><td>4.4%</td></tr>
<tr><td>Retinal exudates</td><td>6.7%</td><td>7.4%</td></tr>
<tr><td>Foreign body sensation</td><td>5.8%</td><td>7.4%</td></tr>
<tr><td>Retinal vascular disorder</td><td>5.8%</td><td>8.8%</td></tr>
<tr><td>Ocular hyperaemia</td><td>4.8%</td><td>5.9%</td></tr>
<tr><td>Vitreous floaters</td><td>4.8%</td><td>0</td></tr>
<tr><td>Macular oedema</td><td>3.8%</td><td>16.2%</td></tr>
<tr><td>Macular ischaemia</td><td>3.8%</td><td>4.4%</td></tr>
<tr><td>Optic disc vascular disorder</td><td>3.8%</td><td>4.4%</td></tr>
<tr><td>Eye irritation</td><td>2.9%</td><td>10.3%</td></tr>
<tr><td>Lacrimation increased</td><td>2.9%</td><td>5.9%</td></tr>
</table></td></tr>
</table>

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)					Adverse events		
	VTE ≥2 mo	50.0%				Papilloedema	1.9%	4.4%
						Retinal ischaemia	1.0%	4.4%
	CRT (µm):					Visual acuity reduced	0	10.3%
		Baseline	**24 weeks**	**p**	**52 weeks**	**p**	IOP increased	9.6%	5.9%
	CRT						Injection site pain	4.8%	2.9%
	VTE	683.2 SD234.5	-448.6	<0.0001	-423.5	<0.0001	**Serious adverse events**		
	Sham	638.7 SD224.7	-169.3		-219.3		At least 1 SAE	1.9%	5.9%
							Glaucoma	0	2.9%
	QoL						Macular oedema	1.0%	1.5%
		Baseline	**24 weeks**	**p**	**52 weeks**	**p**	Retinal tear	1.0%	0
	NEI-VFQ						Vitreous detachment	1.0%	0
	VTE		+7.5	0.0013					
	Sham		+3.5				Reports of systemic adverse events were similar between groups; no arterial thromboembolic events or deaths during 24 weeks		
	Percentage of any patients progressing to any neovascularisation by week 24, difference between groups -1.5 (95% CI: -7.4 to 4.4)						No endophthalmitis or cases of rhegmatogenous detachment, one incidence of uveitis in VTE group considered mild and resolved without change in therapy		
	No significant differences on the EQ-5D score between groups								

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)					Adverse events
PEGAPTANIB						
Wroblewski 2009[38-44] 0.3 mg intravitreal pegaptanib sodium (every 6 weeks over 24 weeks) (n=33) versus 1 mg intravitreal pegaptanib sodium (every 6 weeks over 24 weeks) (n=33) versus sham injection (n=32) FU up to 52 weeks	**BCVA (ETDRS letters):**					No serious ocular adverse events up to week 30 No endophthalmitis, traumatic cataract or retinal detachment (30 weeks) No evidence of sustained effect on intraocular pressure (30 weeks) No evidence of increased risk of systemic adverse events (30 weeks)
		Baseline	**30 weeks**	**p**	**52 weeks**	**p**
	BCVA (letters)					
	PS 0.3 mg	47.6	+7.1	NS, 0.09 vs sham	+7.5	NS vs sham
	PS 1 mg	48.4	+9.9	0.02 vs sham	+6.3	NS vs sham
	Sham	48.5	-3.2		-2.4	
	≥15 letters gained					
	PS 0.3 mg		36%	NS, p=0.48		
	PS 1 mg		39%			
	Sham		28%			
	≥15 letters lost					
	PS 0.3 mg		9%	0.03 vs sham		
	PS 1 mg		6%	0.01 vs sham		
	Sham		31%			
	CRT (µm):					

<table>
<tr><th>Study</th><th>Clinical outcomes (BCVA, CRT; change from baseline at study end)</th><th>Adverse events</th></tr>
<tr><td></td><td>
<table>
<tr><th></th><th>Baseline</th><th>30 weeks</th><th>p</th><th>52 weeks</th><th>p</th></tr>
<tr><td>CRT</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>PS 0.3 mg</td><td>688</td><td>-243</td><td>NS, p=0.13</td><td>-295</td><td><0.05 vs sham</td></tr>
<tr><td>PS 1 mg</td><td>632</td><td>-179</td><td>NS, p=0.06</td><td>-216</td><td></td></tr>
<tr><td>Sham</td><td>674</td><td>-148</td><td></td><td>-183</td><td></td></tr>
</table>
3 patients in the sham arm and 1 patient in each of the pegaptanib sodium arms developed ocular neovascularisation (p=0.29 (NS))
</td><td></td></tr>
<tr><td colspan="3">RANIBIZUMAB</td></tr>
<tr><td>CRUISE 2010 ff.[10;45;46]

0.3 mg intravitreal ranibizumab (monthly for 6 months)

versus 0.5 mg intravitreal ranibizumab (monthly for 6 months)</td><td>
BCVA (ETDRS letters):
<table>
<tr><th></th><th>Baseline</th><th>6 months</th><th>12 months (ran PRN)</th><th>24 months (ran PRN, HORIZON)</th></tr>
<tr><td>BCVA (letters, 95% CI)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Ran 0.3 mg</td><td>47.4 SD14.8</td><td>+12.7 (9.9, 15.4), p<0.0001 vs sham</td><td>+13.9 SD15.2, p=0.0007 vs sham</td><td>+8.2</td></tr>
<tr><td>Ran 0.5 mg</td><td>48.1 SD14.6</td><td>+14.9 (12.6, 17.2), p<0.0001 vs sham</td><td>+13.9 SD14.2, p=0.0006 vs sham</td><td>+12.0</td></tr>
<tr><td>Sham</td><td>49.2 SD14.7</td><td>+0.8 (-2.0, 3.6)</td><td>+7.3 SD15.9</td><td>+7.6</td></tr>
</table>
</td><td>
6 months
<table>
<tr><th>AE</th><th>Ran 0.3 mg</th><th>Ran 0.5 mg</th><th>Sham</th></tr>
<tr><td>Any intraocular inflammation event</td><td>2.3 %</td><td>1.6%</td><td>3.9%</td></tr>
<tr><td>Iridocyclitis</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Iritis</td><td>1.5%</td><td>1.6%</td><td>2.3%</td></tr>
<tr><td>Vitritis</td><td>0.8%</td><td>0.8%</td><td>1.6%</td></tr>
<tr><td>Endophthalmitis</td><td>0</td><td>0</td><td>0</td></tr>
</table>
</td></tr>
</table>

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)				Adverse events			
versus sham extension 6 to 12 months 0.3 or 0.5 mg ranibizumab PRN extension ≥12 to 24 months 0.5 mg ranibizumab PRN	**≥15 letters gained**				Lens damage	0	0	0
	Ran 0.3 mg	46.2%, p<0.0001 vs sham	47.0%	38.6%	Cataract	1.5%	1.6%	0
	Ran 0.5 mg	47.7%, p<0.0001 vs sham	50.8%	45.1%	Iris neovascularisation	1.5%	0.8%	7.0%
	Sham	16.9%	33.1%	38.3%	Neovascular glaucoma	0	0	1.6%
	≥15 letters lost				Rhegmatogenous retinal detachment	0	0	0
	Ran 0.3 mg	3.8%	3.8%	12.9%	Retinal tear	0	0	0
	Ran 0.5 mg	1.5%	2.3%	5.9%	Vitreous haemorrhage	3.8%	5.4%	7.0%
	Sham	15.4%	10.%	13.3%				
	Subgroups ***Time of diagnosis (6 month outcomes):***<3 months: +13.2 letters (both ran groups), ≥3 months: +10.5 letters (0.3 mg ran), +15.3 letters (0.5 mg ran), p=? Mean change in BCVA was greater for patients with worse baseline BCVA and CRT >450 µm				Systemic adverse events balanced across groups; 1 myocardial infarction in each group, 1 transient ischaemic attack and angina pectoris in the same person in ran 0.5 mg group			
	CRT (µm) and anatomic				**12 months, sham for months 6 to 12**			
	Baseline	**6 months**	**12 months (ran PRN)**	**24 months (ran PRN, HORIZON)**	**Ocular AE**	**Ran 0.3 mg**	**Ran 0.5 mg**	**Sham**
					Any intraocular inflammation	2.3 %	1.6%	1.8%

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)				
	CRT (µm, 95% CI)				
	Ran 0.3 mg	679.9 SD 242.4	-433.7 (-484.9, -382.6), p<0.0001 vs sham	-462.1, p= NS vs sham	-370.9
	Ran 0.5 mg	688.7 SD 253.1	-452.3 (-497.0, -407.6), p<0.0001 vs sham	-452.8, p=NS vs sham	-412.2
	Sham	687.0 SD 237.6	-167.7 (-221.5 -114.0)	-427.2	-418.7
	CRT ≤250 µm				
	Ran 0.3 mg		75.0%, p<0.0001 vs sham	75.8%	58.0%
	Ran 0.5 mg		76.9%, p<0.0001 vs sham	77.7%	56.9%
	Sham		23.1%	70.8%	70.2%
	No retinal haemorrhages				
	Ran 0.3 mg	0.8%	31.5%	41.3%	
	Ran 0.5 mg	1.5%	39.3%	47.8%	
	Sham	1.5%	5.4%	36.7%	
	QoL				

Adverse events			
event			
Endophthalmitis	0	0	0
Lens damage	0	0	0
Cataract	3.8%	7.0%	1.8%
Iris neovascularisation	1.5%	3.9%	1.8%
Neovascular glaucoma	0	0.8%	0
Rhegmatogenous retinal detachment	0	0	0
Retinal tear	0	1.6%	1.8%
Vitreous haemorrhage	5.3%	5.4%	1.8%
Arterial thromboembolic events	0.8%	2.3%	0

HORIZON, 12 to 24 months

AE	**Ran 0.3/0.5**	**Ran 0.5**	**Sham/ran 0.5 mg**

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)					Adverse events			
		Baseline	6 months	p	12 months (ran PRN)	p		mg	mg	
	NEI-VFQ (95% CI)						Any ocular AE	62.6%	66.7%	62.5%
	Ran 0.3 mg		+7.1 (5.2, 9.0)	<0.05 vs sham	+7.1	NS vs sham	Ocular AEs leading to discontinuation	1.9%	2.0%	0
	Ran 0.5 mg		+6.2 (4.3, 8.0)	<0.05 vs sham	+6.6	NS vs sham	Cataract	5.6%	5.1%	3.1%
	Sham		+2.8 (0.8, 4.7)		+5.0		Ocular serious adverse events	9.3%	3.0%	5.2%
							Cystoid macular oedema	0.9%	0	0
							Endophthalmitis	1.9%	0	0
							IOP increased	0.9%	0	0
							Macular oedema	1.9%	2.0%	1.0%
							Ischaemic optic neuropathy	0.9%	0	0
							VA reduced	1.9%	1.0%	3.1%
							VA reduced transiently	0.9%	0	0
							Vitreous haemorrhage	0	0	1.0%
							Arterial thromboembolic	1.9%	3.0%	2.1%

<table>
<tr><th>Study</th><th>Clinical outcomes (BCVA, CRT; change from baseline at study end)</th><th>Adverse events</th></tr>
<tr><td></td><td></td><td>events
(potentially
related to drug)</td></tr>
<tr><td colspan="3">BEVACIZUMAB</td></tr>
<tr><td>Epstein 2012[47-49]

1.25 mg intravitreal bevacizumab (4 injections over 6 months) (n=30)

versus sham injection (n=30)

6 month open label extension (1.25 mg intravitreal bevacizumab (4 injections over 6 months) for all patients)</td><td>BCVA (ETDRS letters):

<table>
<tr><th></th><th>Baseline</th><th>24 weeks</th><th>p</th><th>48 weeks (bev/bev vs sham/bev)</th><th>p</th></tr>
<tr><td>BCVA (letters)</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Bev</td><td>44.4 SD15.3; 30% <34, 70% >34</td><td>+14.1</td><td><0.01</td><td>+16.1</td><td><0.05</td></tr>
<tr><td>Sham</td><td>43.9 SD16.0; 33.3% <34, 66.7% >34</td><td>-2.0</td><td></td><td>+4.6</td><td></td></tr>
<tr><td>≥15 letters gained</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Bev</td><td></td><td>60%</td><td>0.003</td><td>60%</td><td><0.05</td></tr>
<tr><td>Sham</td><td></td><td>20%</td><td></td><td>33.3%</td><td></td></tr>
<tr><td>>15 letters lost</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Bev</td><td></td><td>6.7%</td><td>NS, p=0.146</td><td>6.7%</td><td>NS</td></tr>
</table></td><td>Adverse events:

Neovascularisation: 16.7% (sham) versus 0 (bev) had developed iris rubeosis at week 24; iris rubeosis regressed in all patients at week 48, no new cases in either group

No events of endophthalmitis, retinal tear, retinal detachment; no serious non-ocular adverse events</td></tr>
</table>

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)					Adverse events
	Sham	23.3%		6.7%		
	Subgroups					
	Disease duration	**BCVA (letters)**				
	Bev <90 days	+18.7	0.039			
	Bev >90 days	+9.8				
	Age			**BCVA (letters)**		
	<70 years			+14.2	NS, >0.05	
	>70 years			+7.4		
	<70 years sham/bev			-1.4	<0.003	
	>70 years sham/bev			+20.1		

CRT (µm):

	Baseline	**24 weeks**	**p**	**48 weeks (bev/bev vs sham/bev)**	**p**

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)					Adverse events
	CRT					
	Bev/bev	712 SD330	-426	<0.001	-435	NS, >0.05
	Sham/bev	729 SD195	-102		-404	
	No residual oedema (CRT <300 µm)					
	Bev/bev		86.7%	<0.001	83.3%	NS
	Sham/bev		20%		60%	

Abbreviations: AE – adverse event, BCVA – best corrected visual acuity, CI – confidence interval, CRT – central retinal thickness, CRVO – central retinal vein occlusion, ETDRS – Early Treatment Diabetic Retinopathy Study, FU – follow-up, IQR – interquartile range, IOP – intraocular pressure, mo – months, NR – not reported, NS – non-significant, OCT – optical coherence tomography, PRN – pro re nata (as needed), QoL – quality of life, SD – standard deviation

11 Table 3: Study quality

Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
DEXAMETHASONE							
GENEVA 2010 ff.	Low	Low	Partial: patients and assessors of efficacy variables	Low: ITT analysis, 94% FU at 6 months	Low	*Power:* 81% power to detect difference in primary outcome with n=495 for each trial *Similarity at baseline:* yes	Allergan Inc.
TRIAMCINOLONE							
SCORE 2009 ff	Low	Unclear	Partial (physicians and patients masked to dose but not triamcinolone versus observation)	Low: ITT analysis, 83 to 90% FU at 12 months	Low	*Power:* 80% power to detect difference in primary outcome with n=486 (but only 271 randomised) *Similarity at baseline:* yes	National Eye Institute grants, Allergan

Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
ROVO 2013	Low	Low	Unclear	Low: ITT analysis (?), 92% FU at 12 months	Low	*Power:* 80% power to detect difference in primary outcome with n=53 per group (but only 20 to 38 per group) *Similarity at baseline:* unclear *Other:* limited baseline data	Jubiläumsfonds der Österreichischen Nationalbank, Ludwig Boltzmann Institute for Retinology and Biomicroscopic Laser Surgery (non-commercial)
AFLIBERCEPT							
COPERNICUS 2012	Low	Unclear	Low: double-blind	Low: ITT analysis, 89.9% assessed at primary end point	Low	*Power:* 90% power to detect difference in primary outcome with n=165 *Similarity at baseline:* yes	Bayer HealthCare, Regeneron Pharmaceuticals

Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
GALILEO 2012	Unclear	Unclear	Low: double-blind	Low: ITT analysis, 86% assessed at primary end point	Low	*Power:* 90% power to detect difference in primary outcome with n=150 *Similarity at baseline:* yes	Bayer HealthCare, Regeneron Pharmaceuticals
PEGAPTANIB							
Wroblewski 2009	Low	Low	Low: patients and ophthalmologist responsible for patients care and assessments	Low: ITT analysis, 7% withdrawals	Low	*Power:* 80% power to detect difference in primary outcome with n=30 per group *Similarity at baseline:* yes	Eyetech Inc, Pfizer Inc.
RANIBIZUMAB							
CRUISE 2010 ff	Low	Unclear	Low: patients and evaluating examiners, injecting physicians masked to dose	Low: ITT analysis, 88.5 to 97.7% completed 6 months	Low	*Power:* not reported *Similarity at baseline:* yes	Genentech Inc.

Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
BEVACIZUMAB							
Epstein 2012	Unclear	Low	Low: patients, outcome assessors	Low: ITT analysis; missing data for 2 patients (primary endpoint)	Low	*Power:* 80% power to detect difference in primary outcome with n=24 per group *Similarity at baseline:* yes	Unclear; authors are consultants for Allergan, Novartis, Alcon, Bayer

Table 4: On-going trials

Study	Participants and baseline values	Intervention / Outcomes
MINOCYCLINE		
http://clinicaltrials.gov/ct2/show/study/NCT01468844 USA **Study aim:** to test the safety and effectiveness of minocycline as a treatment for CRVO **Design:** RCT, double-blind **Follow-up:** 24 months	**N:** ~20 **Inclusion criteria:**>18 years, macular oedema secondary to CRVO, CRT >350 µm, media clarity and pupillary dilatation sufficient for fundus photographs **Exclusion criteria:** macular oedema due to causes other than CRVO, history of recurrent RVO or RVO >18 months, any other ocular condition that could affect macular oedema or BCVA, substantial cataract, photocoagulation within 4 months before study, pars plana vitrectomy within 6 months, major ocular surgery within 3 months, study eye treated with intravitreal or periocular steroid injections within 3 months, study eye treated with intravitreal anti-VEGF agents within 28 days; significant systemic disease (details given)	**Mino:** 100 mg oral minocycline twice daily over 24 months; monthly bevacizumab injection over 3 months, then PRN **Placebo:** oral placebo twice daily over 24 months; monthly bevacizumab injection over 3 months, then PRN **Primary end point:** BCVA over 12 months **Other outcomes:** number of bevacizumab injections, CRT, safety **Outcome assessment:** 6, 12, 18, 24 months

Study	Participants and baseline values	Intervention / Outcomes
BEVACIZUMAB / TRIAMCINOLONE		
http://clinicaltrials.gov/show/NCT00566761 Mexico **Study aim:** to assess if treatment of macular oedema secondary to CRVO is more effective with combined therapy of bevacizumab and triamcinolone compared to bevacizumab alone **Design:** RCT, open-label, phase 4 **Follow-up:** 12 months	**N:** ~10 **Inclusion criteria:** macular oedema secondary to CRVO; BCVA <20/40; CRT >250 µm (OCT) **Exclusion criteria:** diabetic retinopathy or other retinopathy; media opacity that does not allow follow-up; steroid responder; diagnosed glaucoma or IOP > 21 mmHg	**Bev:** bevacizumab 2.5 mg for (3 applications, administered monthly) **Bev/Tria:** bevacizumab 2.5 mg + triamcinolone 4 mg first dose followed by two doses of bevacizumab alone **Primary end point:** BCVA over 12 months **Other outcomes:** treatment complications **Outcome assessment:** 3, 6 and 12 months
RANIBIZUMAB		

Study	Participants and baseline values	Intervention / Outcomes
http://clinicaltrials.gov/show/NCT01123564 Hungary **Study aim:** to assess if ranibizumab (Lucentis) injection applied into the eye is superior to conventional treatment concerning the prevention of visual loss in patients having clinically significant macular oedema secondary to retinal vein occlusion **Design:** RCT, open-label, phase 2 **Follow-up:** 12 months	**N:** ~40 **Inclusion criteria:**>18 years, macular oedema persisting for >3 months despite conventional medication; CRVO confirmed by slit-lamp biomicroscopy and fluorescein angiography (FLAG); patient in ranibizumab group do not receive macular laser treatment; CRT > 280 µm and/or retinal thickness is >330 µm at any region of the macula; baseline VA <64 ETDRS letters (or 0.4 decimal equivalent) **Exclusion criteria:** diabetes mellitus; additional vitreoretinal diseases; history of pars plana vitrectomy; previous macular grid laser treatment; intravitreal triamcinolone acetonide treatment; complicated cataract surgery; advanced glaucomatous damage of optic nerve head; cataract (except mild, defined as grade 1 nuclear sclerosis and/or grade 1 posterior subcapsular cataract); age-related macular degeneration; pregnancy and lactation; women in childbearing potential who are not using double safe contraception	**Rani:** intravitreal ranibizumab, applied monthly in the first 3 months, and after this only if visual acuity (VA) decreases with more than 5 letters at any monthly visits **Laser:** Argon laser treatment; conventional grid pattern argon laser treatment and panretinal argon laser photocoagulation in an as needed basis **Primary end point:** BCVA over 12 months **Other outcomes:** CRT **Outcome assessment:** monthly visits

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Treatments for macular oedema following central retinal vein occlusion: systematic review

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Protocol: Not published

Words: 5750 words

Key words: central retinal vein occlusion, aflibercept, ranibizumab, bevacizumab, dexamethasone, pegaptanib, triamcinolone, systematic review, anti-VEGF, macular oedema

Disclosure

No additional data available.

Abstract

Objectives

To review systematically the randomised controlled trial (RCT) evidence for treatment of macular oedema due to central retinal vein occlusion (CRVO).

Data sources

MEDLINE, EMBASE, CDSR, DARE, HTA, NHSEED, CENTRAL and meeting abstracts (January 2005 to March 2013).

Study eligibility criteria, participants and interventions

RCTs with at least 12 months' follow-up assessing pharmacological treatments for CRVO were included with no language restrictions.

Study appraisal and synthesis methods

Two authors screened titles and abstracts and conducted data extracted and Cochrane risk of bias assessment. Meta-analysis was not possible due to lack of comparable studies.

Results

Eight studies (35 articles, 1714 eyes) were included, assessing aflibercept (n=2), triamcinolone (n=2), bevacizumab (n=1), pegaptanib (n=1), dexamethasone (n=1) and ranibizumab (n=1). In general, bevacizumab, ranibizumab, aflibercept and triamcinolone resulted in clinically significant increases in the proportion of participants with an improvement in visual acuity of ≥15 letters, with 40-60% gaining ≥15 letters on active drugs, compared to 12-28% with sham. Results for pegaptanib and dexamethasone were mixed. Steroids were associated with cataract formation and increased intra-ocular pressure. No overall increase in adverse events was found with bevacizumab, ranibizumab, aflibercept or pegaptanib compared to control. Quality of life was poorly reported. All studies had a low or unclear risk of bias.

Limitations

All studies evaluated a relatively short primary follow-up (1 year or less). Most had an unmasked extension phase. There was no head-to-head evidence. The majority of participants included had non-ischaemic CRVO.

Conclusions and implications of key findings

Bevacizumab, ranibizumab, aflibercept and triamcinolone appear to be effective in treating macular oedema secondary to CRVO. Long-term data on effectiveness and safety are needed. Head-to-head trials and research to identify “responders” is needed to help clinicians make the right choices for their patients. Research aimed to improve sight in people with ischaemic CRVO is required.

Article summary

Article focus

To review the clinical effectiveness of pharmacological treatments for central retinal vein occlusion.

Key messages

Bevacizumab, ranibizumab, aflibercept and triamcinolone have demonstrated good short-term clinical effectiveness in randomised controlled trials for the treatment of macular oedema secondary to central retinal vein occlusion.

Dexamethasone and pegaptanib have shown mixed results.

Strengths and limitations of this study

A robust systematic review method was used which only included randomised controlled trials.

There were no head-to-head trials and there was a lack of long-term data on both effectiveness and safety.

Introduction

Central retinal vein occlusion (CRVO) is a vascular disorder of the retina with often catastrophic consequences to vision and quality of life.[1;2] The incidence of CRVO increases with age; most individuals affected are 50 years of age or older.[3] It has been estimated that there are around 80 new cases of CRVO per million population per year.[4;5] Although CRVO most commonly affects one eye, in around 10% of patients the disease affects both eyes.[2] Approximately 20% of patients with CRVO will develop large areas of retinal non-perfusion (ischaemia).[6] Furthermore, a small proportion (around 8%) of patients with non-ischaemic CRVO may convert into the ischaemic type during follow-up.[6] Retinal ischaemia may lead to the development of neovascularisation in the retina, iris or anterior chamber angle. Complications of neovascularisation include vitreous haemorrhage and neovascular glaucoma.[6] Currently there is no treatment for ischaemic CRVO other than that aimed at ameliorating the severity of complications, with treatments such as panretinal photocoagulation. Even with the use of current therapies, some eyes with ischaemic CRVO end up blind and painful and, ultimately, enucleation (removal of the eye) is necessary to provide comfort to patients.

Not all people with CRVO will require treatment and macular oedema will resolve in about a third of those with non-ischaemic CRVO.[2;7] However most will need treatment and the number of options has increased in recent years. Laser photocoagulation has been for many years the standard therapy for patients with macular oedema secondary to branch retinal vein obstruction (BRVO).[8] However, laser treatment was not found to be beneficial to those with macular oedema secondary to CRVO;[9] for these patients, no therapeutic modalities could be offered. Recently, several studies have demonstrated the benefit of anti-vascular endothelial growth factor (VEGF) therapies and steroids for the management of patients with macular oedema secondary to CRVO.[10;11] Steroids, such as triamcinolone and dexamethasone, have anti-inflammatory and anti-proliferative attributes (as well as some anti-VEGF effects) and therefore are primarily effective by reducing the oedema of the macula.[12] Anti-VEGF treatments, such as bevacizumab, ranibizumab, aflibercept and pegaptanib, inhibit vascular endothelial growth factor A. In CRVO there is an increase in vascular endothelial growth factor A which leads to neovascularization and oedema.[13] In the UK, NICE has approved dexamethasone (in the long-acting form, Ozurdex) and ranibizumab (Lucentis) and an appraisal of aflibercept is currently underway. Bevacizumab is also used, but is not licensed for use in the eye; however this is because the manufacturer has never sought a licence, preferring to market ranibizumab. Triamcinolone has also been used off-licence.

An up-to-date review incorporating all drug treatments for macular oedema secondary to CRVO is needed. The purpose of this study is to review systematically the randomised controlled evidence for drug treatments of macular oedema secondary to CRVO.

Methods

A systematic review was conducted. The following databases were searched: 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). In addition to the bibliographic database searching, supplementary searches were undertaken to look for recent and unpublished studies in the WHO International Clinical Trials Registry Platform and ophthalmology conference websites (American Academy of Ophthalmology, Association for Research in Vision and Ophthalmology from 2010 to 2012).

Search strategy

An iterative procedure was used to develop two search strategies with input from previous systematic reviews.[14;15] The first search strategy was designed to retrieve articles reporting RCTs or systematic reviews about CRVO published from 2005 onwards (the publication date of the first RCT on triamcinolone in Medline). Terms for retinal vein occlusion were included to ensure identification of articles in which both BRVO and CRVO were covered, but were reported separately. The second strategy focussed on retrieving articles where adverse events of relevant pharmacological treatments for CRVO were reported. This second search was limited by condition (age-related macular degeneration (AMD) or RVO), study type (RCTs, SRs or observational studies) and date (published from 2010 onwards). Searches were conducted in March 2013. The strategies used in each database are provided in appendix 1. Auto alerts of searches were set up to capture relevant articles published after the dates of the searches.

Reference lists from the included studies and identified systematic reviews were screened.

Inclusion and exclusion criteria

RCTs were used to assess the clinical effectiveness and adverse events.

Only RCTs examining pharmacological treatment compared with laser treatment, observation, placebo (sham injection) or another pharmacological intervention with at least 12 months follow-up were included. Comparisons of different doses of drugs were not included unless there was an additional comparator group as defined above. Studies including CRVO and BRVO were included

providing participants with CRVO were reported as a subgroup. Studies assessing treatments aimed at restoring circulation to the occluded vein shortly after onset (<30 days) were excluded. There were no language restrictions.

Outcomes

The primary outcome was visual acuity measured as mean change in best corrected visual acuity (BCVA) or as proportion of patients improving by 15 ETDRS (Early Treatment for Diabetic Retinopathy Study) letters or more. Secondary outcomes included mean change in macular thickness using optical coherence tomography (OCT), quality of life and adverse events.

Screening and data extraction

Search results were screened independently by two authors (CC, JF and ST). Differences were resolved through discussion or by consulting a third author (JF). Data were extracted by one author (CC and DS) and checked by a second (ST, CC). Data extraction included inclusion/exclusion criteria, baseline demographics, mean change in BCVA, proportion of patients with 15 letters improvement, central retinal thickness (CRT) and adverse events. Risk of bias was assessed by two reviewers using the Cochrane risk of bias tool.[16]

Meta-analysis was not possible because of a lack of comparable studies.

Results

Search results

The study flow is shown in figure 1. The electronic searches yielded 518 records. 475 were eliminated based on information in the titles and abstract. The full text of the remaining 43 records was checked, and a further eight were eliminated. Reasons for exclusion included the trial being a commentary rather than an RCT, the study having no relevant comparison group (dose ranging only), the participants did not have macular oedema secondary to CRVO, or the interventions being ineligible (non-pharmacological). The remaining 35 records (including conference abstracts) reported on eight RCTs of six different pharmacological agents, and these were included in the analysis. The Geneva study (2010)[11;17;18] technically consists of two RCTs, but as these were analysed and reported together, it was counted as one RCT in this analysis.

We also identified three relevant ongoing trials, one investigating minocycline (http://clinicaltrials.gov/ct2/show/study/NCT01468844), one investigating a combination of bevacizumab and triamcinolone (http://clinicaltrials.gov/show/NCT00566761), and one investigating ranibizumab (http://clinicaltrials.gov/show/NCT01123564).

Study characteristics

Detailed study characteristics of the included studies are shown in table 1.

Study design

Of the eight included RCTs, six were described as double-blind and seven were sham-controlled. All but one were multicentre. Only one was not funded by industry. Four trials were international trials, two came from the USA, and one each from Austria and Sweden. Six of the trials measured primary end-points at around six months (24 to 30 weeks), whereas two measured primary end-points at 12 months. Five studies reported follow-up data for up to 12 months, and two reported data for follow-up periods of up to two years.

Participants

The trials randomised a total of 1714 eyes (one eye per person). The number of eyes per study ranged between 60 and 437. Follow-up at the primary end-point ranged from 77 to 98% (generally over 90% in the intervention groups). The participants had a mean age of between 59.0 and 70.5

years, and between 36 and 49% were female. Only two studies reported mean duration of macular oedema (4.3 and 4.9 months). Five studies reported mean time since CRVO diagnosis (range 2.4 to 2.9 months). Mean baseline BCVA was between 44 and 52.5 ETDRS letters, baseline CRT was between 569 and 721 µm. In most trials, the focus was on macular oedema secondary to CRVO only, but in the Geneva trial macular oedema secondary to BRVO and CRVO was included and only limited data were available on the CRVO-only group.

Interventions

The Geneva trial (2010 ff.)[11;17;18] compared a 0.35 mg (n=136) and a 0.7 mg dexamethasone (n=154) intravitreal implant with sham treatment (n=147). After the initial 6 month study period, patients could enter a 6 month open label extension, where they received a 0.7 mg dexamethasone intravitreal implant.

The SCORE trial (2009 ff.)[19-32] compared intravitreal injections of 1 or 4 mg of triamcinolone (~2 injections over 12 months, n= 92 and 91 for 1 and 4 mg respectively) with an observation group (n=88). Two forms of triamcinolone have been used in trial~~exist~~; the SCORE trial used Trivaris, rather than Kenalog. Trivaris is no longer available ~~t used as much~~ because its manufacturer has promoted an alternative steroid (dexamethasone). The ROVO trial (2013)[33] compared a single intravitreal injection of 4 mg of triamcinolone (over 12 months, n=25) with radial optic neurotomy (n=38) or sham injection (n=20).

In the COPERNICUS trial (2012)[34;35], intravitreal injections of 2 mg of aflibercept (n=114) were given every 4 weeks over 24 weeks to the intervention group and the comparison group received a sham injection (n=75). During weeks 24 to 52, patients in both groups received aflibercept if they met protocol-specified retreatment criteria, and received a sham injection if retreatment was not indicated (3.9 standard error 0.3 injections in the sham group and 2.7 standard error 0.2 injections in the aflibercept group); after the first year, patients continued in a one-year extension phase with as needed dosing. In the GALILEO trial (2012)[36;37], intervention patients also received intravitreal injections of 2 mg of aflibercept (n=103) every 4 weeks over 24 weeks, while the comparison group was given sham injections (n=71). During weeks 24 to 52, patients remained in their original treatment groups but received their allocated treatment as needed; beginning from week 52 to week 76, both groups received the study drug every 8 weeks.

In a trial by Wroblewski and colleagues (2009)[38-44], patients received 0.3 or 1 mg intravitreal injections of pegaptanib sodium every 6 weeks for 24 weeks (n=33 and 33), compared with a sham injection group (n=32). Patients were followed up to 52 weeks.

The CRUISE trial (2010 ff.)[10;45;46] compared monthly injections of 0.3 or 0.5 mg of ranibizumab (n=132 and 130) over 6 months with sham injection (n=130). During months 6 to 12, all patients could receive intraocular ranibizumab (previously assigned dose or 0.5 mg for the sham group) if they met prespecified functional and anatomic criteria; after 12 months' follow-up patients could continue in the HORIZON trial for another 12 months, where they were eligible to receive intravitreal injections of 0.5 mg ranibizumab if they fulfilled prespecified criteria.

Epstein and colleagues (2012)[47-49] conducted an RCT in which they compared patients receiving four intravitreal injections of 1.25 mg of bevacizumab (n=30) over 6 months with patients receiving sham injection (n=30). From 6 to 12 months, all patients received intravitreal bevacizumab injections every 6 weeks.

Outcomes. The primary endpoint of all but one study was the proportion with a gain of 15 or more ETDRS letters. The primary endpoint of the remaining study was mean change in BCVA. Studies also reported gains or losses of ETDRS letters at various cut-off points, absolute BCVA, CRT, and safety parameters. The COPERNICUS, the GALILEO and the CRUISE studies also measured vision-related quality of life (National Eye Institute Visual Functioning Questionnaire, NEI-VFQ).[10;34-37;45;46] EQ5D was also used in GALILEO.

Ongoing studies. Of the ongoing trials, the first (clinicaltrials.gov NCT01468844) is a 24 month double-blind RCT from the USA. It set out to test the safety and effectiveness of minocycline as a treatment for CRVO in around 20 patients with macular oedema secondary to CRVO. Both groups received monthly intravitreal bevacizumab injections over three months (and afterwards as needed), and the intervention group also received 100 mg oral minocycline twice daily over 24 months. The second trial (clinicaltrials.gov NCT00566761) is an open-label RCT from Mexico in only around 10 patients assessing whether combined treatment with bevacizumab and triamcinolone is more effective than bevacizumab alone. The combination group received 2.5 mg of bevacizumab plus 4 mg of triamcinolone as a first dose and then two doses of bevacizumab alone at monthly intervals, while the monotherapy group received three monthly doses of 2.5 mg bevacizumab alone. Follow-up will be 12 months. A third RCT from Hungary compares monthly injections of ranibizumab for three months (and as needed thereafter) with Argon laser treatment in around 40 patients with macular oedema secondary to CRVO. Follow-up will also be 12 months. The primary endpoint in all studies is BCVA over 12 months.

Risk of bias

Details of risk of bias assessment are shown in Table 3.

Most studies (except GALILEO (2012) and Epstein 2012)[36;37;47-49] adequately described the generation of the allocation sequence, but only half the studies gave enough details to confirm adequate allocation concealment. Most studies (unclear in the ROVO 2013 study)[33] used at least partial masking, and most studies appeared to have had masking of outcome assessment. Intention-to-treat analysis was used in all studies. Where reported separately for comparison groups, losses to follow-up tended to be slightly higher for the control groups than the interventions groups (79 to 88.5% follow-up in the control groups and 90 to 98% in the intervention groups). All studies appeared to have been free of selective reporting. Most studies included a power analysis (not reported for the CRUISE study)[10;45;46], but in two cases (the SCORE and the ROVO studies)[19-33] the numbers randomised were considerably below the numbers indicated in the power calculations. As far as reported, there were no significant differences between comparison groups in baseline characteristics.

Clinical effectiveness

Detailed study results can be found in Table 2.

Visual acuity. Figure 2 shows the primary endpoint in most studies, which was the proportion of participants with a gain of 15 or more ETDRS letters. As there were no significant differences in visual acuity results between groups using different dosages of the given pharmacological treatment, intervention groups were combined for the sake of the plot.

In the Geneva trial (2010 ff.)[11;17;18], treatment of macular oedema secondary to CRVO with a 0.7 mg intravitreal dexamethasone implant resulted in a 0.1 letter gain in BCVA compared to a loss of 1.8 in the sham group ($p < 0.001$). The difference persisted in the extension period where all patients received the 0.7 mg dexamethasone implant. However, there was no significant difference in the proportion of patients gaining or losing 15 letters at either 6 or 12 months (0.35 or 0.7 mg dexamethasone). This may reflect the timing of peak effect at 90 days with dexamethasone.

In the SCORE trial (2009 ff.)[19-32], patients in the triamcinolone groups lost significantly fewer ETDRS letters (triamcinolone 1mg 1.2 letters loss, 4mg 1.2 letters loss and observation 12.1 letters loss) over both 12 and 24 months than patients in the observation group. The proportion of patients gaining 15 letters or more was also significantly larger in the intervention groups at 12 and 24 months (25.6% compared with 6.8% and 31% compared with 9%, respectively). The proportion of

patients receiving triamcinolone and losing 15 letters or more was smaller (25.6%) than in the observation group (43.8%), but this difference was not statistically significant (p=0.06).

There was some overall improvement in BCVA in both intervention groups at 12 months in the ROVO trial (2013)[33], (triamcinolone 20%, radial optic neurotomy 47% and sham 10%) however it was unclear whether there were any statistically significant differences between the 4 mg triamcinolone, the radial optic neurotomy, or the sham group. However, there were significantly more patients with an improvement of more than or equal to 15 letters in the neurotomy group than in the sham group (47% versus 10%), but no significant difference to sham after one dose of triamcinolone.

In both the COPERNICUS (2012)[34;35] and GALILEO (2012)[36;37]trialspatients in the aflibercept group had a significant improvement in BCVA at 6 months of 18 and 17.3 letters (compared to 4 letters loss and 3.3 letter gain in sham groups respectively), and this was maintained at 12 months and was significantly greater than the improvements in the sham groups. This was paralleled by a significantly greater proportion of patients(56.1% compared with 12.3% and 60.2% compared with 22.1%, respectively) gaining 15 letters or more. Patients treated sooner after diagnosis (less than versus more than two months) seemed to benefit more (in terms of proportion of patients with 15 letters or more gain) in both trials.

The increase in mean change in BCVA with 0.3 mg pegaptanib compared with sham did not reach significance at 30 weeks in the trial by Wroblewski and colleagues (2009)[38-44], but there was a greater increase in BCVA with 1 mg pegaptanib compared with sham (9.9 letter gain compare with 3.2 letter loss). These differences were not statistically significant at 52 weeks. There was no significant difference between any of the groups in the proportion of patients gaining 15 letters or more at 30 weeks, but significantly fewer patients in both dosage groups lost 15 letters or more than in the sham group (6% compared with 31%).

In the CRUISE trial (2010 ff.)[10;45;46], mean change in BCVA was significantly increased in the ranibizumab groups (no difference between doses) compared with the sham group at both 6 and 12 months (12.0 letters gained in the 0.5 mg group compared to 7.6 in the sham group). After the one year extension with ranibizumab as needed in all groups, there was no difference between the doses of ranibizumab at 24 months. The pattern was similar for the proportion of patients gaining 15 letters or more.

In the trial by Epstein and colleagues (2012)[47-49], treatment with intravitreal bevacizumab , compared with sham treatment significantly increased mean change in BCVA (14.1 letters gain compared to 2.0 letters lost) and the proportion of patients gaining 15 letters or more (60% compared to 20%) at 24

weeks. This difference was maintained in the extension period, even though both groups had been receiving bevacizumab. Younger patients (<70 years) tended to have better visual outcomes than older patients (>70 years).

Central retinal thickness. In the Geneva trial (2010 ff.)[11;17;18], no significant difference was found in the reduction of CRT after 6 months' treatment in patients with macular oedema secondary to CRVO with the 0.7 mg intravitreal dexamethasone implant (no data given for the 0.35 mg implant) compared with sham.

In the SCORE trial (2009 ff.)[19-32], CRT decreased in all study groups, but there was no significant difference between groups at either 12 or 24 months. Similarly, there was no clear difference in the proportion of patients achieving a CRT of less than 250 µm. CRT decreased in all comparison groups in the ROVO trial (2013)[33], but there was no significant difference between groups.

Both in the COPERNICUS trial (2012)[34;35] and in the GALILEO trial (2012)[36;37] there was a significantly greater reduction in CRT at 6 months in the aflibercept group than in the control group. However the significant difference was maintained in the longer term only in the GALILEO trial, where patients continued their assigned treatment up to 12 months. In the COPERNICUS trial, patients in the sham group also received aflibercept in the extension period, which caused a similar decrease in CRT as in the original intervention group.

After 30 weeks of treatment with pegaptanib (Wroblewski and colleagues 2009)[38-44], differences in decrease of CRT versus sham did not reach significance, but at 52 weeks, the decrease in CRT was significantly greater in both the 0.3 mg and the 1 mg pegaptanib groups compared with sham.

After treatment with ranibizumab in the CRUISE trial (2010 ff.)[10;45;46], a significant reduction in CRT was observed and significantly more patients achieved a CRT of 250 µm or less in the intervention groups (no difference between doses) than in the sham group at 6 months. This difference did not persist at 12 and 24 months because all groups received ranibizumab as needed.

In the trial by Epstein and colleagues (2012)[47-49], treatment with intravitreal bevacizumab significantly decreased CRT and the proportion of patients with no residual oedema (CRT <300 µm) at 24 weeks, compared with sham treatment. When both groups received bevacizumab in the extension period, similar decreases in CRT and increases in the proportion of patients with no residual oedema were seen.

Vision-related quality of life. Vision-related quality of life (NEI-VFQ25) was significantly higher in the aflibercept group, compared with sham injection, at 6 months in both the COPERNICUS trial (+7.2

compared with +0.8)[34;35] and the GALILEO trial (+7.5 compared with +3.5)[36;37]. In the COPERNICUS trial, patients in the sham group who received aflibercept in the extension period had a similar increase in vision-related quality of life as patients in the original intervention group by 12 months.

In the CRUISE trial (2010 ff.)[10;45;46], vision-related quality of life (NEI-VFQ) was similarly increased in both ranibizumab groups and statistically significantly more than in the sham group at 6 months (+6.2 compared with +2.8). At 12 months, with all groups receiving ranibizumab as needed, the increases were similar in all three groups.

Adverse events. The 0.7 mg dexamethasone intravitreal implant caused significantly more increased intraocular pressure (IOP) than sham treatment (30.1%, versus 1.4% in the control group) in patients with CRVO in the Geneva trial (2010 ff.)[11;17;18] (not reported for 0.35 mg). The incidence of cataract was also slightly higher in the dexamethasone group but numbers were small because of the short duration . There were no other differences in adverse events between groups.

In the triamcinolone group (especially 4 mg, SCORE trial 2009 ff.)[19-32], there was a higher increase in IOP, lens opacity onset or progression (at 12 months) and cataract surgery (12 to 24 months) than in the control group. There were no other differences in adverse events between groups. A similar tendency was seen in the ROVO trial (2013)[33].

Aflibercept did not appear to increase the incidence of ocular or non-ocular adverse events compared with sham in both the COPERNICUS trial (2012)[34;35] and the GALILEO trial (2012)[36;37].

In the trial by Wroblewski and colleagues (2009)[38-44], adverse events in response to pegaptanib were not reported in detail, but there do not appear to have been any serious ocular or systemic adverse events.

After treatment with ranibizumab in the CRUISE trial (2010 ff.)[10;45;46], there were no consistent differences in ocular or systemic adverse events between the intervention groups. None of the ocular adverse events appeared to have increased substantially after all patients received ranibizumab up to 24 months.

Epstein and colleagues (2012)[47-49] did not report adverse events in response to bevacizumab in detail, but the treatment appears not to have caused any serious ocular adverse events over 48 weeks.

Discussion

Statement of principal findings

~~Compared to control,~~ Evidence from good quality RCTs shows that intravitreal steroids and anti-VEGF therapies increase the proportion of patients whose vision improves by 15 or more letters in patients with macular oedema secondary to CRVO. The most effective drugs result in over 60% of patients gaining 15 letters compared to only about 20% of the control groups. The RCT evidence shows only ~~demonstrates the~~ short-term effectiveness of ranibizumab, bevacizumab, aflibercept and triamcinolone. Results from trials of dexamethasone and pegaptanib were mixed. Long-term evidence is awaited.

Strengths and limitations

A robust systematic review methodology was used. A broad search strategy was implemented, which included not restricting the search strategy with drug terms. Grey literature was searched by screening meeting abstracts from relevant conferences. There were no language restrictions. Two reviewers screened titles and abstracts and conducted data extraction and risk of bias assessment. Risk of bias was assessed using the Cochrane Risk of Bias Tool and was generally judged to be low or unclear. Only studies with one year follow up were included to exclude studies with very short follow-up RCTs were identified for all the new ophthalmological drugs, except for the steroid, fluocinolone.

The main limitation is the short duration of follow-up. The primary outcome for most trials was measured at 6 months, with an extension phase up to 12 months. Hence, it is not known whether the benefit of these treatments will be maintained long-term. Furthermore, potential side effects of these treatments may not be captured in these studies as a result of their short follow-up. Patients and clinicians would like sustained, life-long improvement in visual acuity, but of all included studies only one of them had a follow-up of over 24 months.

The sample size of some studies was small. For example, the evidence for pegaptanib and bevacizumab comes from studies with around 30 participants per arm which substantially increases the risk of a type II error. Only three trials included quality of life data, arguably one of the most important outcomes.

The proportion of participants and severity of ischemia within the trials was not clear. Whilst ischaemia is not mentioned in the inclusion/exclusion criteria of most studies, these participants were unlikely included in these studies, especially if the diagnosis of ischaemic CRVO is based on strict criteria. Furthermore patients were entered into the trials relatively soon after diagnosis (mean 4.3 to 4.9 months) and the it is not clear if the effects would be similar in patients who present with long standing disease.

Another weakness was that patients were not asked at the of trials, what treatment they thought they had received, which would have provided data on the success of masking of allocation.

In the case of dexamethasone, the results at six months were not as good as at 90 days, because of the duration of action. Earlier re-treatment, at say 120 days, would have improved results, but many clinicians might be reluctant to repeat injections of dexamethasone implant often because of the large needle size and risk of adverse effects.

Adverse events

Results from the included studies clearly demonstrate that steroids (triamcinolone and dexamethasone) are associated with clinically meaningful increases in IOP and cataract progression. Anti-VEGF therapy ocular adverse events reported in the trials were similar in both placebo and intervention arms.

There is limited evidence of the safety of these drugs specifically in CRVO, but it would not be unreasonable to look to trials in neovascular age-related macular degeneration (AMD) and diabetic macular oedema (DMO) for safety data, where there is more experience. The CATT trial, which compared bevacizumab with ranibizumab in AMD, suggested that there was a higher incidence (RR 1.29 95%CI 1.01 to 1.66) of serious systematic adverse events (primarily hospitalisations) in the bevacizumab arm.[50]Some have raised concerns about arterial thromboembolic events with bevacizumab, but none of these has been demonstrated in the published literature.[51-54] Micieli and colleagues (2010) undertook a systematic review of the adverse events associated with bevacizumab. 22 studies were reviewed, representing 12,699 participants.[55] Adverse events in patients treated with bevacizumab were cerebrovascular events (0.21%), myocardial infarction (0.19%) and increased blood pressure (0.46%). Most of these represent the background burden of disease in patients with advanced eye disease. The proportion of these directly attributable to bevacizumab is likely to be very small. Campbell and colleagues (2012) undertook a nested case-control study of over 7,000 cases and 37,000 controls.[51] Ranibizumab and bevacizumab injection was

the exposure and cardiovascular events were the outcome. The authors found that ranibizumab and bevacizumab were not associated with increased cardiovascular events.

Increased IOP has been associated with ranibizumab, bevacizumab and pegaptanib. Sustained increased in IOP has estimated to be 5.5-6.0% with these drugs.[56;57]

Robust evidence on the long-term safety of aflibercept is awaited.

What do these results mean?

Until very recently, patients with macular oedema as a result of CRVO could only be offered visual rehabilitation and visual aids in an attempt to help them to deal better with their reduced vision and its implications in their daily activities and quality of life. Their future is brighter now as new options to treat macular oedema have become available. Triamcinolone is likely to be a cost-effective treatment at least in selected groups of patients, such as pseudophakic individuals or those with pre-existing cataracts that may require cataract surgery in the near future. The lack of a commercially available licensed product for intraocular administration may restrict its use in clinical practice.

Some anti-VEGF therapies, including bevacizumab, ranibizumab and aflibercept, have been also shown to be effective in short term studies for the treatment of patients with macular oedema and CRVO. Bevacizumab has the advantage of having a low cost~~, because it is aliquoted~~ , with an apparently similar effect to other anti-VEGF therapies[50;58;59] but there is some reluctance to use it as it is not licensed for use in the eye. This has been seen in other eye conditions, such as AMD and DMO. Aflibercept, requiring potentially fewer injections than other anti-VEGF agents, could represent an advantage to patients and may relieve pressure on ophthalmology clinics. ~~As more options have become available, ophthalmologists will need to decide, together with their patients, which may be the best treatment option for them based on their visual requirements and life circumstances.~~ Health care systems will need to evaluate the cost-effectiveness of these new treatments and support affordable ones. The National Institute for Health and Care Excellence is currently appraising aflibercept. Policy makers are left in a difficult position because of bevacizumab. It is cheaper than all other drugs[60] and appears to be as effective, but is unlicensed and unlike ranibizumab and aflibercept does not have evidence from large, well-funded RCTs in CRVO. The use of bevacizumab would result in considerable savings for the NHS.

It is important to note that the evidence of benefit of these new therapies is likely to only apply to patients with non-ischaemic CRVO. Although some patients with ischaemic CRVO were included,

these individuals are likely to have mild ischaemic CRVO. Thus, for patients with established ischaemic CRVO, there are no proven treatments available and further research into this area is very much needed.

What is the context of these results

Earlier systematic reviews identified limited evidence on the clinical effectiveness of treatments. A review by Braithwaite and colleagues (search date August 2010)[61] on anti-VEGF agents identified one RCT[10;45;46] comparing two doses of ranibizumab and one RCT[38-44] comparing two doses of pegaptanib sodium versus placebo or no treatment. In both RCTs, the higher dose of the anti-VEGF significantly improved BCVA compared with sham injection in the short term (~6 months), but the effects in the longer term were unclear. Braithwaite and colleagues concluded that data from the two RCTs could not be synthesised because ranibizumab and pegaptanib sodium might not be directly comparable. Subsequent RCTs identified in this review also suggest benefit in ocular outcomes in macular oedema secondary to non-ischaemic CRVO for the anti-VEGFs bevacizumab, and aflibercept.[34-37;47-49]

Gewaily and Greenberg reviewed the literature on intravitreal corticosteroids (search date November 2008) versus observation in macular oedema secondary to CRVO and identified no relevant RCTs.[62] Results from two observational studies suggested that triamcinolone acetonide might be beneficial in the treatment of macular oedema secondary to non-ischaemic CRVO. However, as the authors of the review caution because conclusions are primarily drawn from small case series and case reports with short follow up. Results from the SCORE 2009 RCT corroborate the observational studies.[19-32] The effects of triamcinolone acetonide in people with non-ischaemic CRVO without associated macular oedema are less clear. Data from four observational studies led Gewaily and Greenberg to conclude that intravitreal corticosteroids are associated with transient anatomical and functional improvements.

Immediate treatment aimed at relieving the blocked vein and surgical interventions were outwith the remit of this review. Antithrombotics, such as low-molecular weight heparin (LMWH), and fibrinolytics have also been found to benefit visual acuity in retinal vein occlusion with no associated macular oedema. Two systematic reviews[63;64] identifying the same three RCTs in recent onset (≤30 days) BRVO or CRVO found that LMWH improved visual acuity compared with aspirin and that the associated benefit was larger in CRVO; only one of the three RCTs included people solely with CRVO. One review[64]also included one RCT comparing ticlopidine with placebo and two RCTs assessing intravenous fibrinolytic therapy followed by warfarin or aspirin with either haemodilution or no

treatment. The authors of the reviews conclude that no definitive recommendations can be made on clinical effectiveness of LMWH in CRVO given the limited evidence available.

Radial optic neurotomy involves the performance of a radial cut using a microvitreoretinal (MVR) blade through the lamina cribrosa, scleral ring and adjacent sclera at a selected point in the optic nerve head with the goal of "decompressing" the scleral outlet (space confined by the scleral ring and containing the lamina cribrosa, the central retinal artery, central retinal vein and the optic nerve. The ~~SCORE~~ ROVO trial found radial optic neurotomy to be more effective than sham.

While this review was being considered for publication, another was published, with differences in scope (BRVO and CRVO) and inclusions (this review is more up to date).[65] The reviewers found that aflibercept and bevacizumab resulted in greatest gain, followed by ranibizumab and triamcinolone. The overall conclusions in both reviews were similar.

Further research

Large adequately powered RCTs comparing ranibizumab, bevacizumab, aflibercept and triamcinolone are needed. Part of the problem is that the US the Food and Drug Administration requires pharmaceutical companies to present data establishing a drug's safety and effectiveness. Whilst this does not specifically require a placebo-controlled trial, it is the most efficient study design for demonstrating effectiveness and safety. Clinicians and researchers are left with placebo-controlled trials demonstrating effectiveness for individual drugs, but a lack of evidence to help them decide which is best for their patients.

Given the cost of these treatments and the burden of repeated injections to patients and health care systems, research aiming to predict "responders" would be useful as at present this is done by therapeutic trial. Treatments could then be targeted to patients likely to benefit. Research is also needed on the frequency and sequences of drugs. As other pathogenic pathways besides inflammation and VEGF-mediated pathways may be implicated in the development of macular oedema in patients with CRVO, these should be investigated in an attempt to develop new therapeutic strategies for this condition. Research is also needed into optimum timing of treatment after CRVO. The cost-effectiveness of diagnostic technologies for determining when retreatment is necessary should be examined.

We also need better treatments since a significant proportion of patients do not improve with all of these drugs

Future RCTs should include longer term outcomes, as functional results observed at six months or even one year may not necessarily be representative of what is likely to be achieved longer term and, furthermore, potential side effects of treatments, such as retinal atrophy after repeated injections of anti-VEGFs, may not be captured in shorter term studies.

Conclusions

Bevacizumab, ranibizumab, aflibercept and triamcinolone appear to be effective in improving the number of patients who gain 15 letters or more in CRVO. There are mixed results for dexamethasone and pegaptanib. Steroids were associated with cataract progression and increased IOP. Long-term data on effectiveness and safety are needed. Head-to-head trials and research to identify “responders” is needed to help clinicians make the right choices for their patients.

Acknowledgments: None

Conflict of interest: None

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

Contributions: NW devised the idea for the review. JF wrote the protocol and all authors contributed to the design of the protocol. RC undertook the literature searches. JF, CC and ST screened titles and abstracts. CC, ST and DS extracted the data. All authors contributed to the interpretation of the results. JF, NL, RC, CC and SB contributed to the first draft of the article. All authors reviewed and commented on the final manuscript.

Figure 1: PRISMA statement

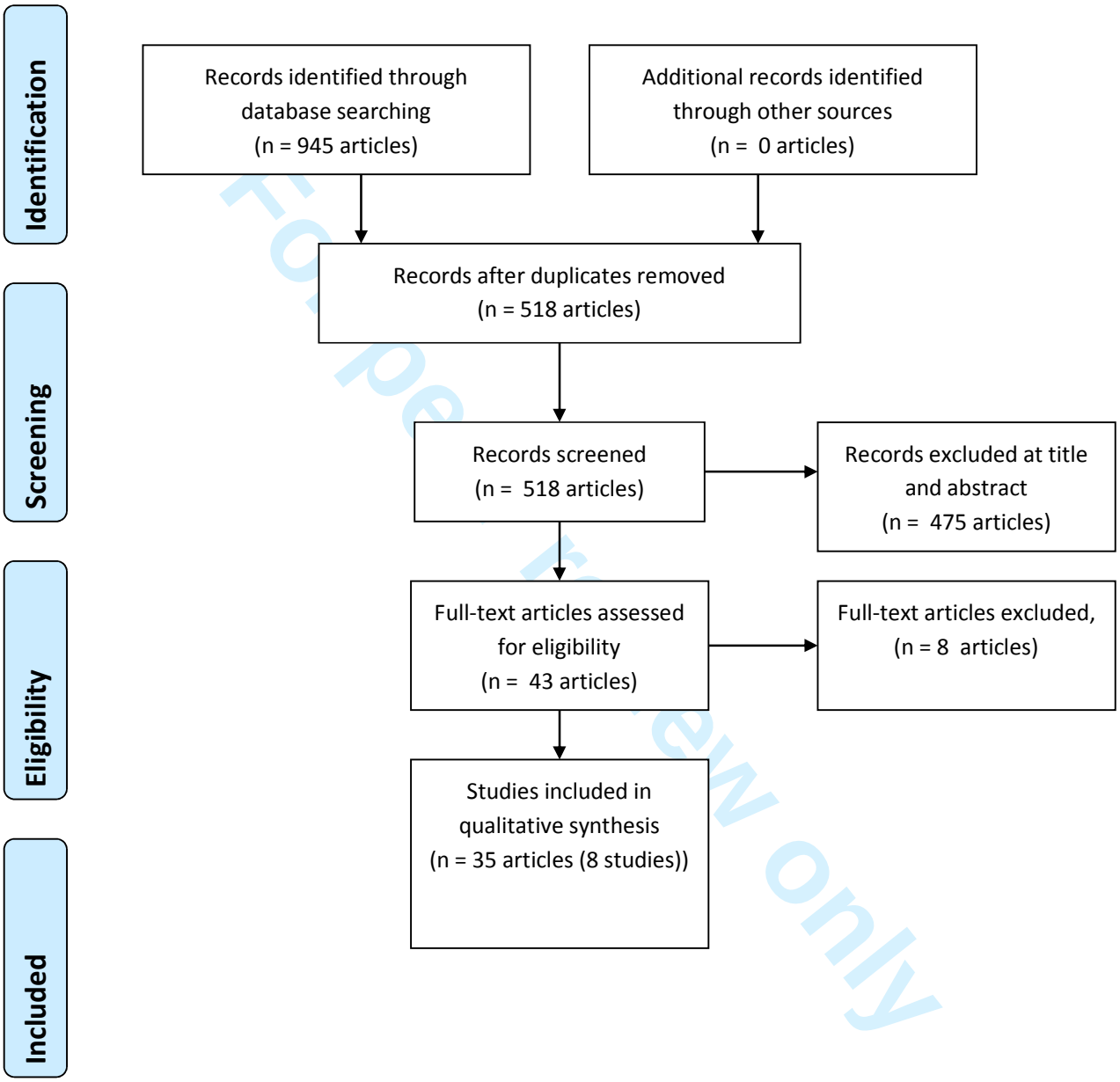
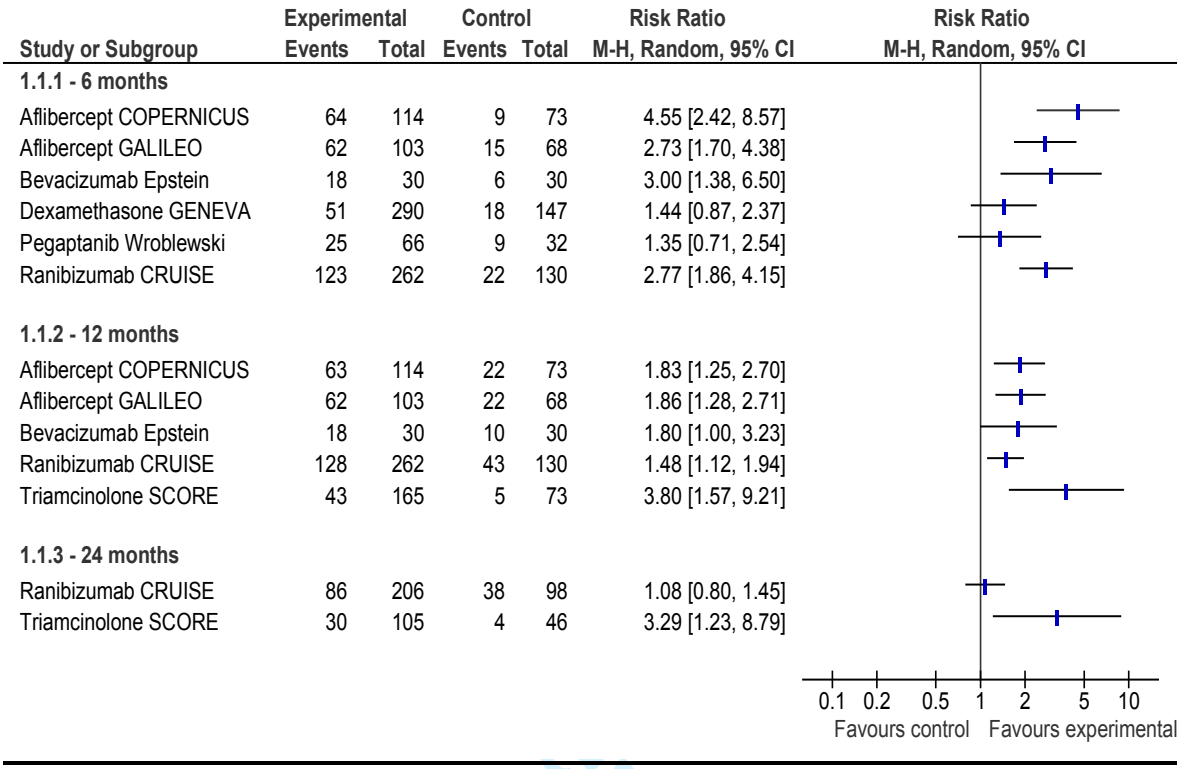


Figure 2. Study results for the primary outcome (≥15 ETDRS letter gain).



1 Table 1: Study characteristics

Study	Participants and baseline values	Intervention / Outcomes
DEXAMETHASONE		
GENEVA 2010 ff.[11;17;18] International **Setting:** multicentre (167 centres in 24 countries, so a mean of 2.6 patients per centre) **Study aim:** to evaluate the effects of dexamethasone intravitreal implant in patients with macular oedema secondary to CRVO or BRVO (only data for CRVO reported here) **Design:** 2 identical double-blind, sham-controlled RCTs, phase 3 **Follow-up:** primary endpoint for the masked trial: 6 months; primary endpoint for the open-label extension: 12 months **Overall quality:** 5.5/6	**N:** CRVO – 437 eyes of 437 patients randomised; 94% follow-up at 6 months **Inclusion criteria:** ≥18 years; reduced VA due to macular oedema due to CRVO or BRVO which in the investigator's opinion, is unlikely to be adversely affected if not treated for 6 months; duration of macular oedema 6 weeks to 9 months in patients with CRVO; BCVA 34 to 68 ETDRS letters (~20/200 and 20/50 Snellen equivalent) in the study eye and >34 letters in the non-study eye; CRT ≥300 µm (OCT) **Exclusion criteria:** *study eye:* clinically significant epiretinal membrane; use of periocular corticosteroid within 6 months or topical nonsteroidal anti-inflammatory drug or corticosteroid within 1 month; intraocular surgery or laser within 30 days of study or anticipated; history of intravitreal use of corticosteroid or any other drug; glaucoma; IOP >23 mmHg if untreated or >21 if treated with one medication; treatment with ≥2 IOP-lowering medications; active retinal, optic disc or choroidal neovascularisation; history of herpetic infection; rubeosis iridis, aphakia or anterior-chamber intraocular lens; any ocular condition that would prevent a 15-letter VA improvement; preretinal or vitreous haemorrhage, lens opacity, media opacity that would preclude clinical or photographic evaluation; history of pars plana vitrectomy; *any eye:*	**DEX 0.7 (n=136):** sustained delivery, biodegradable dexamethasone intravitreal implant (Ozurdex), 0.7 mg implant inserted into the vitreous cavity through the pars plana using a customised, single-use, 22-gauge applicator **DEX 0.35 (n=154):** DEX 0.35 mg implant inserted following the same method **Sham (n=147):** a needleless applicator was placed against the conjunctiva to simulate the placement of study medication. **Regimen for all groups:** before inserting the implant, the study eye was anaesthetised with topical and subconjunctival anaesthetics and prepared according to standard clinical practice for eyes undergoing intravitreal injection; patients were treated with a topical ophthalmic antibiotic 4 times daily starting 3 days before the day of their study procedure (day 0) and continuing for 3 days after the procedure **Extension:** patients completing 180 days were eligible to enter a 6 month open label extension where they received DEX 0.7 mg implant **Primary end point:** gain of ≥15 ETDRS letters; for the open-label extension: safety

Study	Participants and baseline values	Intervention / Outcomes
	active ocular infection; history of steroid-induced IOP–increase; diabetic retinopathy; *other:* uncontrolled systemic disease; current or anticipated use of systemic steroids or anticoagulants **Age (years):** 62.7 to 65.2 years **Sex:** 43.7 to 49.2% (CRVO and BRVO together) **Baseline VA (ETDRS letters):**52.4 SD10.6 **Baseline CRT (µm):**DEX 0.7: 648; Sham: 620 **Other ocular information:** phakic status (%): 85 to 88% **Duration of macular oedema:** mean 4.8 to 4.9 months;<90 days: 14.3 to 15.4%; >90 to <180 days: 54.4 to 57.4%, >180 days: 27.1 to 31.3% **Comorbidities:** diabetes mellitus 14 to 15%, hypertension 62 to 64%, coronary artery disease 9 to 13%, IOP-lowering medication at baseline 4 to 6% (all for CRVO and BRVO together)	**Other outcomes:** proportion of eyes achieving at least a 10 and 15 letter improvement from baseline; the proportion of eye exhibiting ≥15 letters of worsening; BCVA; subgroup analysis according to RVO diagnosis (BRVO and CRVO) and duration of macular oedema at baseline; CRT and safety **Outcome assessment:** evaluation at 1, 7, 30, 60, 90 and 180 days after study treatment for both parts of the study
TRIAMCINOLONE		
SCORE 2009 ff.[19-32] USA **Setting:** multicentre **Study aim:** to compare the effects of 1 and 4 mg preservative-free	**N:** 271 eyes of 271 patients randomised; 83% (observation) and 90% (intervention) completed 12 months **Inclusion criteria:** centre-involved macular oedema secondary to CRVO, BCVA 19 to 73 ETDRS letters (Snellen equivalent ~20/400 to 20/40), CRT >250 µm by OCT; media clarity, papillary dilatation and participant	**Tria (1 mg) (n=92):** 1 mg (0.05 ml) of preservative-free, nondispersive formulation of triamcinolone (average number of injections 2.2 at 12 months) **Tria (4 mg) (n=91):** 4 mg (0.05 ml) of preservative-free, nondispersive formulation of triamcinolone(average number of injections 2.0 at 12 months)

Study	Participants and baseline values	Intervention / Outcomes
intravitreal triamcinolone with observation in eyes with vision loss associated with macular oedema secondary to perfused CRVO **Design:** RCT **Follow-up:** primary end point 12 months, FU planned up to 36 months **Overall quality:** 3/6	cooperation sufficient for adequate fundus photographs **Exclusion criteria:** macular oedema due to causes other than CRVO, ocular condition such that visual acuity would not improve from resolution of oedema, substantial cataract, prior treatment with intravitreal corticosteroids or peribulbar steroid injection within 6 months, photocoagulation (prior 4 months or anticipated), prior pars plana vitrectomy, major ocular surgery (prior 6 months or anticipated), IOP ≥25 mmHg, open-angle glaucoma, steroid-induced IOP-elevation requiring IOP-lowering treatment, pseudoexfoliation, aphakia **Age:** 68.0 SD 12.4 years **Sex:** 45% female **Duration of macular oedema:** 4.3 SD3.7 months **Baseline VA (ETDRS letters):** 51.2 SD14.1 **Baseline CRT (µm):** 659 SD229 **Other ocular information:** 81% phakic, IOP 15.5 SD3.2 mmHg **Comorbidities:** 23% diabetes mellitus, 73% hypertension, 21% coronary artery disease, 21% history of cancer	The form of triamcinolone used was Trivaris, no longer available. It was made by the manufacturer of Ozurdex (Allergan) **Obs (n=88):** observation **Regimen for all groups:** all intervention eyes received standardised ocular surface preparation prior to injection (eyelid speculum, topical anaesthetic, topical antibiotics, asepsis with povidone iodine); retreatment every 4 months unless (1) treatment was deemed successful (defined), (2) treatment was contraindicated because of significant adverse effect, (3) additional treatment was considered 'apparently futile' (defined) **Primary end point:** gain of ≥15 ETDRS letters **Other outcomes:** BCVA, intraocular pressure, eye examination including dilated fundus examination, OCT scan for thickness, , lens opacities, , adverse events **Outcome assessment:** follow-up visits every 4 months for 36 months
ROVO 2013[33]	**N:** 90 patients randomised; 82% evaluated **Inclusion criteria:** history of CRVO not longer than 12	**Tria (n=25):** single intravitreal injection of 4 mg triamcinolone acetonide (100 µl) applied after povidone

Study	Participants and baseline values	Intervention / Outcomes
Austria **Setting:** multicentre (7 centres in 7 countries) **Study aim:** to compare the effects of radial optical neurotomy with intravenous triamcinolone and natural history (placebo) in patients with CRVO **Design:** RCT, placebo-controlled **Follow-up:** primary end point 12 months **Overall quality:** 3.5/6	months; VA of ≥0.3 logMAR (≤85 letters) (for perfused CRVO: VA >1 logMAR (>50 letters) or no VA improvement over 4 weeks) **Exclusion criteria:** dense cataract, severe ophthalmologic conditions (severe retinopathy, presence of advanced optic atrophy, uncontrolled glaucoma), pregnancy, allergy against fluoresceine or indocyanine green, any handicap which could prevent patients from attending follow-up visits **Age:** not reported **Sex:** 36% female **Duration of macular oedema:** not reported **Baseline VA (ETDRS letters) :** 1.07 logMAR (interquartile range 0.78 to 1.7) (~46 letters) **Baseline CRT (µm):** 569 to 657 µm **Other ocular information:** not reported **Comorbidities:** 23% diabetes mellitus, 49% hypertension, 17% cardiovascular disease, 4% hypercoagulopathies, 1% leukaemia, 2% anaemia	iodine drops; postoperative topical antibiotics **RON (n=38):**radial optical neurotomy under general anaesthesia (detailed procedure described) **Pla (n=20):** eyes prepared as for triamcinolone injection but sham injection performed (empty syringe without needle pressed against the eye) **Primary end point:** gain of ≥15 ETDRS letters **Other outcomes:** BCVA, CRT, safety **Outcome assessment:** 12 months
AFLIBERCEPT		
COPERNICUS 2012[34;35] International	**N:** 189 eyes of 189 patients randomised; 95.7% (aflibercept) and 81.1% (sham) completed 24 weeks; 93% (aflibercept) and 77% (sham) completed 52 weeks	**VTE (n=114):** intravitreal injections of 2 mg aflibercept (50 µl) every 4 weeks for 24 weeks **Sham (n=73):** sham procedure (empty syringe without

Study	Participants and baseline values	Intervention / Outcomes
Setting: multicentre, 70 sites in North and South America, India and Israel. Mean 2.7 patients per centre. **Study aim:** to evaluate the effects of intravitreal aflibercept in patients with macular oedema secondary to CRVO **Design:** double-blind, sham-controlled RCT, phase 3 **Follow-up:** primary end point 24 weeks, FU 2 years **Overall quality:** 5/6	**Inclusion criteria:** adult patients with centre-involved CRVO for a maximum of 9 months, CRT ≥250 µm with OCT, ETDRS BCVA of 73 to 24 letters (Snellen equivalent 20/40 to 20/320) **Exclusion criteria:** history of vitreoretinal surgery (incl. radial optic neurotomy or sheathotomy); current bilateral retinal vein occlusion; previous pan-retinal or macular laser photocoagulation; other reasons for decreased visual acuity; ocular conditions with poorer prognosis in the fellow eye; history or presence of age-related macular degeneration, diabetic macular oedema, or diabetic retinopathy; any use of intraocular or periocular corticosteroids or antiangiogenic treatment in the study eye at any time or in the fellow eye in the preceding 3 months; iris neovascularisation, vitreous haemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula; vitreomacular traction or epiretinal membrane significantly affecting central vision; ocular inflammation; uveitis; any intraocular surgery in the preceding 3 months; aphakia; uncontrolled glaucoma, hypertension, or diabetes; spherical equivalent of a refractive error of more than -8 diopters; myopia; infectious blepharitis, keratitis, scleritis, or conjunctivitis; cerebral vascular accident or myocardial infarction in the preceding 6 months; and other conditions that could interfere with interpretation of the results or increase the risk of complications; cataract surgery was not allowed during the 3 months before randomisation.	needle pressed to conjunctival surface) every 4 weeks for 24 weeks **Regimen for all groups:** all patients eligible to receive pan-retinal photocoagulation for neovascularisation at any time at the discretion of the investigator; patients were not allowed to use other systemic or local medications for treating CRVO in the study eye over the first 52 weeks of the study; a noninvestigational therapy could be used to treat CRVO in the fellow eye **Extension:** during weeks 24 to 52, patients in both groups were evaluated monthly and received aflibercept if they met protocol-specified retreatment criteria, and received a sham injection if retreatment was not indicated (3.9 SE0.3 injections in the sham group and 2.7 SE0.2 injections in the VTE group); after the first year, patients continued in a 1 year extension phase with as needed dosing **Primary end point:** gain of ≥15 ETDRS letters **Other outcomes:** BCVA, CRT, proportion of patients progressing to neovascularisation of the anterior segment, optic disc or elsewhere in the retina, changes in vision-related quality of life (National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25), safety **Outcome assessment:** examination every 4 weeks up to 24 weeks, 52 weeks

Study	Participants and baseline values	Intervention / Outcomes
	Age: 66.3 SD 13.9 years **Sex:** 43% female **Time since CRVO diagnosis:** 2.4 SD2.8 months; 62.0% ≤2 months, 37.4% >2 months **Baseline VA (ETDRS letters) :** 50.0 SD14.1 ; 75.4% >20/200 **Baseline CRT (µm):** 665.8 SD239.8 **Other ocular information:** 67.9% perfused retinal occlusion, IOP 15.1 SD3.08 mmHg **Comorbidities:** not reported	
GALILEO 2012[36;37] International **Setting:** multicentre, 10 countries in Europe and Asia; 63 centres in total **Study aim:** to evaluate the effects of intravitreal aflibercept in patients with macular oedema secondary to CRVO **Design:** double-blind, sham-controlled RCT, phase 3 **Follow-up:** primary end point 24 weeks, FU up to 12 months, planned	**N:** 177 eyes of 177 patients randomised; 90.6% (aflibercept) and 78.9% (sham) completed 24 weeks **Inclusion criteria:** treatment-naïve patients, age ≥18 years, centre-involved CRVO for a maximum of 9 months, CRT ≥250 µm with OCT, ETDRS BCVA of 73 to 24 letters (Snellen equivalent 20/40 to 20/320) **Exclusion criteria:** uncontrolled glaucoma (IOP≥25 mmHg), filtration surgery, bilateral manifestation of retinal vein occlusion, iris neovascularisation, previous treatment with anti-VEGF agents, pan-retinal or macular laser photocoagulation, intraocular corticosteroids, pregnant **Age:** 61.5 SD 12.9 years	**VTE (n=103):** intravitreal injections of 2 mg aflibercept every 4 weeks for 24 weeks **Sham (n=71):** sham procedure (empty syringe without needle pressed to conjunctival surface) every 4 weeks for 24 weeks **Regimen for all groups:** pan-retinal photocoagulation allowed at any time for all patients if they progressed to neovascularisation of the anterior segment, optic disc or fundus **Extension:** during weeks 24 to 52, patients remained in their original treatment groups but received their allocated treatment as needed; beginning from week 52 to week 76 both groups received treatment every 8

Study	Participants and baseline values	Intervention / Outcomes
up to 76 weeks **Overall quality:** 4/6	**Sex:** 44.4% female **Time since CRVO diagnosis:** 81.8 SD85.4 days; 52.6% <2 months, 46.2% ≥2 months, 1.2% missing **Baseline VA (ETDRS letters) :** 52.2 SD15.7, 83% >20/200 **Baseline CRT (µm):** 665.5 SD231.0 **Other ocular information:** 83.6% perfused retinal occlusion, IOP 14.9 SD2.7 mmHg **Comorbidities:** Renal impairment: 31% mild, 8.2% moderate, 1.2% severe; 2.9% hepatic impairment	weeks **Primary end point:** gain of ≥15 ETDRS letters **Other outcomes:** BCVA, CRT, proportion of patients progressing to neovascularisation of the anterior segment, optic disc or elsewhere in the fundus, changes in vision-related and overall quality of life (National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25), European Quality of Life-5 Dimensions (EQ-5D)), safety **Outcome assessment:** 24 weeks, 52 weeks
PEGAPTANIB		
Wroblewski 2009[38-44] International **Number of sites:** not reported **Setting:** multicentre, practitioners' offices and clinics in Australia, France, Germany, Israel, Spain, USA **Study aim:** to evaluate the effects of intravitreal pegaptanib sodium in patients with macular oedema secondary to CRVO **Design:** double-blind, sham-	**N:** 98 eyes of 98 patients randomised; 93% completed 30 weeks **Inclusion criteria:** age ≥18 years, CRVO with onset within 6 months prior to baseline, CRT ≥250 µm with OCT, ETDRS BCVA of 65 to 20 letters (Snellen equivalent 20/50 to 20/400) and better than 35 letters (20/200) in the fellow eye **Exclusion criteria:** subtenon corticosteroid administration for any ophthalmic condition; prior panretinal or sector scatter photocoagulation; signs of old branch retinal vein occlusion or CRVO in the study eye; any other retinal vascular disease including diabetic retinopathy; eyes with a brisk afferent pupillary defect;	**PS 0.3 mg (n=33):** intravitreal injections of 0.3 mg pegaptanib sodium every 6 weeks for 24 weeks (5 injections) **PS 1 mg (n=33):** intravitreal injections of 1 mg pegaptanib sodium every 6 weeks for 24 weeks (5 injections) **Sham (n=32):** sham procedure (blunt pressure applied to the globe without a needle) every 6 weeks for 24 weeks **Regimen for all groups:** antisepsis procedures were the same for all participants (including those receiving sham); all participants received injected subconjunctival anaesthetic; panretinal photocoagulation permitted at

Study	Participants and baseline values	Intervention / Outcomes
controlled RCT, phase 2 **Follow-up:** primary end point 30 weeks, FU up to 12 months **Overall quality:** 6/6	vitreous haemorrhage except for breakthrough haemorrhage from intraretinal haemorrhage; evidence of any neovascularisation involving the iris, disc, or retina; any other clinically significant concomitant ocular diseases **Age:** 59 to 64 years **Sex:** 47% female **Time from occlusive event to study entry:** 77 to 82 days **Baseline VA (ETDRS letters):** 47.6 to 48.5 letters **Baseline CRT (µm):** 632 to 688 **Other ocular information:** not reported **Comorbidities:** not reported	any time point for neovascularisation according to the Central Vein Occlusion Study protocol; intravitreous steroids not permitted at any time **Extension:** FU to 52 weeks **Primary end point:** gain of ≥15 ETDRS letters **Other outcomes:** BCVA, loss of ≥15 letters, CRT, proportion of eyes progressing to retinal or iris neovascularisation, safety **Outcome assessment:** assessments every 6 weeks up top week 30, FU to week 52
RANIBIZUMAB		
CRUISE 2010 ff.[10;45;46] USA **Number of sites:** not reported **Setting:** multicentre **Study aim:** to evaluate the effects of intravitreal ranibizumab (0.3 or 0.5 mg) in patients with macular oedema secondary to CRVO	**N:** 392 eyes of 392 patients randomised; 97.7% (ran 0.3 mg), 91.5% (ran 0.5 mg), and 88.5% (sham) completed 6 months **Inclusion criteria:** age ≥18 years, foveal centre-involved macular oedema secondary to CRVO diagnosed within 12 months before study began, CRT ≥250 µm with OCT, BCVA 20/40 to 20/320 (ETDRS charts) **Exclusion criteria:** prior episode of retinal vein	**Ran 0.3 mg (n=132):** intravitreal injections of 0.3 mg ranibizumab monthly for 6 months (maximum 6 injections) **Ran 0.5 mg (n=130):** intravitreal injections of 0.5 mg ranibizumab monthly for 6 months (maximum 6 injections) **Sham (n=130):** sham procedure (empty syringe without needle pressed to the injection site) monthly for 6 months

Study	Participants and baseline values	Intervention / Outcomes
Design: double-blind, sham-controlled RCT, phase 3 **Follow-up:** primary end point 6 months, FU up to 12 months **Overall quality:** 4.5/6	occlusion, brisk afferent pupillary defect, >10-letter improvement in BCVA between screening and day 0, history of radial optic neurotomy or sheathotomy, intraocular corticosteroid use in study eye in prior 3 months, history or presence of wet or dry age-related macular oedema, recent or anticipated panretinal scatter photocoagulation or sector laser photocoagulation, laser photocoagulation for macular oedema in prior 4 months, evidence on examination of any diabetic retinopathy, stroke or myocardial infarction in prior 3 months, prior anti-VEGF treatment in study or fellow eye in prior 3 months or systemic anti-VEGF or pro-VEGF treatment in prior 6 months **Age:** 65.4 SD13.1 to 69.7 SD11.6 years **Sex:** 38.5 to 46.2% female **Time since CRVO diagnosis:** 2.9 SD2.9 to 3.6 SD3.2 months; 65.9 to 72.3% ≤3 months **Baseline VA (ETDRS letters):** 47.4 to 49.2 (SD 14.6 to 14.8) (range 9 to 72), 38.5 to 42.3% ≥55 **Baseline CRT (µm):** 679.9 SD242.4 to 688.7 SD253.1 **Other ocular information:** IOP 14.9 SD3.3 to 15.1 SD3.1 mmHg, 10.0 to 16.9% IOP-lowering medication, n=2 >10 disc areas of non-perfusion; fellow eye BCVA 78.8 SD 17.4 to 80.0 SD12.5	**Regimen for all groups:** prior to injection or sham: topical anaesthetic drops, subconjuctival injection of 2% lidocaine, cleaning of injection site with 5% povidone iodine **Extension:** months 6 to 12: all patients could receive intraocular ranibizumab (previously assigned dose or 0.5 mg for the sham group) if they met pre-specified functional and anatomic criteria (3.7 injections sham group, 3.8 injections 0.3 mg ran group, 3.3 injections 0.5 mg ran group); after 12 months' FU, 304 CRUISE patients continued in the HORIZON study for another 12 months, where patients were evaluated at least every 3 months and were eligible to receive an intravitreal injection of 0.5 mg ranibizumab if they fulfilled prespecified criteria (2.9 SD2.7 injections sham group, 3.8 SD2.8 injections 0.3 mg ran group, 3.5 SD2.7 injections 0.5 mg ran group) **Primary end point:** mean change from baseline BCVA **Other outcomes:** percentage gaining ≥15 letters, percentage losing ≥15 letters, CRT, percentage with CRT <250 µm, vision-related quality of life (National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25), safety **Outcome assessment:** monthly visits up to 12 months; 3-monthly evaluation up to 24 months (HORIZON)

Study	Participants and baseline values	Intervention / Outcomes
	Comorbidities: not reported	
BEVACIZUMAB		
Epstein 2012[47-49] Sweden **Setting:** Single centre; St. Eriks Eye Hospital Stockholm **Study aim:** to evaluate the effects of intraocular injections of bevacizumab in patients with macular oedema secondary to CRVO **Design:** sham-injection controlled, double masked RCT **Follow-up:** primary end-point 6 months; open label extension up to 12 months **Overall quality:** 5/6	**N:** 60 eyes of 60 patients randomised; 93% completed open label extension **Inclusion criteria:** CRVO of ≤6 months; BCVA 15 to 65 ETDRS letters (Snellen equivalent ~20/50 to 20/500), CRT ≥300 µm by OCT **Exclusion criteria:** CRVO with neovascularisation; previous treatment for CRVO; intraocular surgery during previous 3 months; vascular retinopathy of other causes; glaucoma with advanced visual field defect or uncontrolled ocular hypertension >25 mmHg despite full therapy; myocardial infarction or stroke during last 12 months **Age:** 70.5 SD 12.6 years **Sex:** 40% female **Time from diagnosis to inclusion:** 8.8 SD 5.7 weeks; 71.7% <90 days, 28.3% >90 days **Baseline VA (ETDRS letters) :** 44.1 SD 15.5 ; 31.7% <34, 68.3% >34	**Bev (n=30):** 1.25 mg (0.05 ml) bevacizumab via pars plana **Sham (n=30):** sham injection (syringe without needle pressed to the globe) **Regimen for all groups:** 4 injections received, one every 6 weeks; eyes treated with topical antibiotics 30 min before injection, topical chlorhexidine, topical anaesthesia with 1% tetracaine **Open label extension:** months 6 to 12, intravitreal bevacizumab injections every 6 weeks (4 injections) for all patients **Primary end point:** gain of ≥15 ETDRS letters **Other outcomes:** BCVA, OCT images, CRT, fluorescein angiogram, colour and red-free photography, slit-lamp examination with dilated fundus-examination, intraocular pressure, adverse events **Outcome assessment:** follow-up visits every 6 weeks up to 24 weeks

Study	Participants and baseline values	Intervention / Outcomes
	Baseline CRT (µm): 721 SD 269 **Comorbidities:** 48.3% hypertension, 6.7% diabetes mellitus	

Abbreviations: BCVA – best corrected visual acuity, CRT – central retinal thickness, CRVO – central retinal vein occlusion, ETDRS – Early Treatment Diabetic Retinopathy Study, FU – follow-up, IOP – intraocular pressure, OCT – optical coherence tomography, SD – standard deviation, SE – standard error

Table 2: Study results and adverse events

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)	Adverse events
DEXAMETHASONE		

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)						Adverse events				
GENEVA 2010 ff.[11;17;18]		**Baseline**	**6 months**	**p**		**12 months**	**p**	**AE**	**DEX 0.35**	**DEX 0.7 (n = 133)**	**Sham (n = 147)**	**p**
	BCVA (mean letters)							**6 months**				
	DEX 0.35	-	-					**Overall incidence of ocular adverse events**				
	DEX 0.7	52.4 SD 10.6	+0.1	< 0.001 vs sham	***DEX 0.7/0.7***	+2 (estimated from graph)				68.4%	49.7%	
	Sham	53.3 SD 10.8	-1.8		***Sham/DEX 0.7***	-1.4 (ditto)		**Common Ocular Adverse Events**				
	≥15 letters gained							Intraocular pressures increased		40 (30.1%)	2 (1.4%)	<0.001
	DEX 0.35		17%	NS vs sham				**Common treatment-related Ocular Adverse Events**				
	DEX 0.7		18.4%	NS vs sham	***DEX 0.7/0.7, day 240***	27%		IOP increased		39 (29.3%)	1 (0.7%)	<0.001
					DEX 0.7 (n=19), day 360	26%		**Cataract adverse events**				
	Sham		12.2%	NS vs sham	***Sham/DEX 0.7, day 240***	21%		Cataract		3 (2.3%)	2 (1.4%)	
	≥15 letters lost							Cataract subcapsular		4 (3.0%)	1 (0.7%)	
	DEX 0.35		-	-				Cataract nuclear		3 (2.3%)	1 (0.7%)	
	DEX 0.7		14.0%	NS				Cataract cortical		1 (0.8%)	3 (2.0%)	
	Sham		20.4%					**Serious adverse events** – not given separately for CRVO				
	Subgroups											
	Duration of macular oedema											
	>90 days	***DEX 0.7***	17.7%									
		Sham	9.6%									
	≤90 days	***DEX 0.7***	26.0%									
		Sham	27.3%									

<table>
<tr><th>Study</th><th>Clinical outcomes (BCVA, CRT; change from baseline at study end)</th><th>Adverse events</th></tr>
<tr><td></td><td>
CRT (µm):
<table>
<tr><th></th><th>Baseline</th><th>6months (mean)</th><th>p</th><th>12 months (mean)</th><th>p</th></tr>
<tr><td>CRT</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>DEX 0.35</td><td>-</td><td>-</td><td></td><td></td><td></td></tr>
<tr><td>DEX 0.7</td><td>647.6</td><td>-118.2</td><td>NS vs sham</td><td></td><td></td></tr>
<tr><td>Sham</td><td>619.8</td><td>-125.3</td><td></td><td></td><td></td></tr>
</table>
</td><td></td></tr>
<tr><td colspan="3">TRIAMCINOLONE</td></tr>
<tr><td>SCORE 2009 ff.[19-32]

1 mg intravitreal triamcinolone (2.2 injections over 12 months) (n=92)

versus 4 mg intravitreal triamcinolone (2</td><td>
BCVA (ETDRS letters):
<table>
<tr><th></th><th>Baseline</th><th>12 months</th><th>p</th><th>24 months</th><th>p</th></tr>
<tr><td>BCVA (letters, 95% CI)</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Tria 1 mg</td><td>50.6 SD 14.9</td><td>-1.2 (-6.4 to +4.1)</td><td><0.05 vs obs</td><td>-4.4 (-11.5 to +2.8)</td><td>NR</td></tr>
<tr><td>Tria 4 mg</td><td>51.0 SD 14.4</td><td>-1.2 (-6.3 to +4.0)</td><td><0.05 vs obs</td><td>-2.4 (-9.3 to +4.4)</td><td></td></tr>
</table>
</td><td>
Ocular Adverse Events
<table>
<tr><th>AE</th><th>Tria 1 mg</th><th>Tria 4 mg</th><th>Obs</th></tr>
<tr><td>12 months</td><td></td><td></td><td></td></tr>
<tr><td>Elevated IOP or glaucoma</td><td></td><td></td><td></td></tr>
<tr><td>Initiation of IOP-lowering medication</td><td>20%</td><td>35%</td><td>8%</td></tr>
</table>
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</table>

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)						Adverse events			
injections over 12 months) (n=91) versus observation (n=88)	***Obs***	52.1 SD 13.1	-12.1 (-17.1 to -7.1)		-10.7 (-17.4 to -4.1)		IOP >35 mm Hg (n)	5	8	1
	≥15 letters gained (95% CI)						IOP >10 mm Hg above baseline (n)	15	24	2
	Tria 1 mg		26.5% (17 to 36)	0.001 vs obs	31% (19 to 43)	NR	Laser peripheral iridotomy (n)	0	1	0
	Tria 4 mg		25.6% (16 to 35)	0.001 vs obs	26% (14 to 38)		Trabeculectomy (n)	0	0	0
	Obs		6.8% (1 to 13)		9% (1 to 17)		Tube shunt (n)	2	0	0
	≥15 letters lost						*Cataract*			
	Tria 1 mg		25.3%		31%		Lens opacity onset or progression	26%	33%	18%
	Tria 4 mg		25.6%		26%		Cataract surgery (n)	0	4	0
	Obs		43.8%		48%	NS, p=0.06 tria vs obs	*At least 1 of the following adverse events (n):*	11	6	9
	CRT (µm):						Infectious endophthalmitis (n)	0	0	0
		Baseline	**12 months (median, IQR)**	**p**	**24 months (median, IQR)**	**p**	Non-infectious endophthalmitis (n)	0	0	0

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)						Adverse events			
	CRT						Retinal detachment (n)	0	0	0
	Tria 1 mg	643 SD 226	-196 (-390 to -62)	NR	-286 (-458 to -119)	NR	Iris neovascularisation or neovascular glaucoma	9	4	2
	Tria 4 mg	641 SD 248	-261 (-407 to -79)		-236 (-421 to -63)		Retinal neovascularisation (n)	2	2	4
	Obs	695 SD 208	-277 (-418 to -40)		-304 (-465 to -108)		Vitreous hemorrhage (n)	4	0	4
	CRT <250 µm				**CRT <250 µm**		*Other ocular surgical procedures*			
	Tria 1 mg		32%	NR	50%	NR	YAG capsulotomy	0	0	1
	Tria 4 mg		45%		39%		Sector or panretinal scatter photocoagulation	9	3	5
	Obs		28%		38%		Pars plana vitrectomy	2	0	1
	Results for subgroups (based on baseline BCVA (73 to 59, 58 to 49, 48 to 19), baseline CRT (<500 µm, ≥500 µm), duration of macular oedema (≤3 months, >3 months, pseudophakic at baseline) were consistent with the overall results (significance levels for comparisons not reported)						**Selected Events at 12-24 months**			
							Glaucoma procedures			
							Laser peripheral iridotomy	0	0	0

<table>
<tr><th>Study</th><th>Clinical outcomes (BCVA, CRT; change from baseline at study end)</th><th>Adverse events</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>Trabeculectomy</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Tube shunt</td><td>0</td><td>2</td><td>0</td></tr>
<tr><td>Cataract</td><td></td><td></td><td></td></tr>
<tr><td>Cataract surgery</td><td>3</td><td>21</td><td>0</td></tr>
</table>
Reports of systemic adverse events were similar between groups
</td></tr>
<tr><td>ROVO 2013[33]

4 mg intravitreal triamcinolone acetonide (single injection)

versus radial optical neurotomy

versus sham injection</td><td>BCVA (logMAR):
<table>
<tr><th></th><th>Baseline</th><th>12 months</th><th>p</th></tr>
<tr><td>BCVA (logMAR, interquartile range)</td><td></td><td></td><td></td></tr>
<tr><td>Tria 4 mg</td><td>1.02 (0.75, 2.0</td><td>0.86 (0.51, 1.78) (-0.16)</td><td>NR</td></tr>
<tr><td>RON</td><td>1.46 (0.84, 2.0)</td><td>0.75 (46, 1.22) (-0.71)</td><td></td></tr>
<tr><td>Sham</td><td>1.02 (0.9, 1.36)</td><td>1.02 (0.85, 3.0) (0)</td><td></td></tr>
<tr><td>% with VA improvement</td><td></td><td></td><td></td></tr>
<tr><td>Tria 4 mg</td><td></td><td>20%</td><td>0.034 vs RON, NS vs placebo</td></tr>
<tr><td>RON</td><td></td><td>47%</td><td></td></tr>
</table>
</td><td>Ocular Adverse Events, 12 months
<table>
<tr><th>AE</th><th>Tria 4 mg</th><th>RON</th><th>Pla</th></tr>
<tr><td>Retinal detachment</td><td></td><td>7.9%</td><td></td></tr>
<tr><td>Subretinal haemorrhages</td><td></td><td>5.3%</td><td></td></tr>
<tr><td>Vitreous haemorrhage</td><td></td><td>2.6%</td><td>10%</td></tr>
<tr><td>Subretinal membrane formation</td><td></td><td>2.6%</td><td></td></tr>
<tr><td>Retinal tear</td><td></td><td>2.6%</td><td></td></tr>
<tr><td>IOP increase</td><td>32%</td><td></td><td></td></tr>
<tr><td>Cataract progression</td><td>24%</td><td>13%</td><td>15%</td></tr>
<tr><td>Neovascular glaucoma</td><td>12%</td><td>5%</td><td>15%</td></tr>
</table>
</td></tr>
</table>

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)				Adverse events	
	Sham		10%	0.009 vs RON	Rubeosis iridis	15%
	% with VA deterioration				No cases of phthisis, enucleation, endophthalmitis, injury of central vessels, injury of optic nerve	
	Tria 4 mg		NR			
	RON		8%			
	Sham		35%	0.007 vs RON		
	CRT (µm):					
		Baseline	**12 months**	**p**		
	CRT					
	Tria 4 mg	657	-235	NS		
	RON	569	-263	NS		
	Sham	615	-206			
AFLIBERCEPT						
COPERNICUS 2012[34;35]	**BCVA (ETDRS letters):**				**Adverse Events**	
		Baseline	**24 weeks**	**p**	**52 weeks (all VTE PRN)**	**p**
2 mg intravitreal aflibercept(every 4 weeks over 24	**BCVA (letters)**					

AE (24 weeks)	VTE	Sham
Discontinued treatment before week 24 because of AE	0	4.1%
At least one AE	83.3%	85.1%

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)					
weeks)(n=114)	***VTE***	50.7 SD 13.9	+17.3	<0.001	+16.2	<0.001
versus sham injection (n=73)	***Sham***	48.9 SD 14.4	-4.0		+3.8	
	≥15 letters gained					
extension up to 52 weeks with aflibercept PRN in both groups	***VTE***		56.1%	<0.001	55.3%	<0.001
	Sham		12.3%		30.1%	
	≥10 letters lost					
	VTE		1.8%	NR		
	Sham		30.1%			
	Subgroups					
	Baseline VA		**≥15 letters gained**			
	VTE ≤20/200	*VTE*	67.9%	NR	60.7%	NR
		Sham	16.7%		22.2%	
	VTE >20/200	*VTE*	52.3%		53.5%	
		Sham	10.9%		32.7%	
	Time since diagnosis					
	VTE <2 mo	*VTE*	68.8%	NR	64.1%	NR

Adverse events		
Ocular AEs	68.4%	68.9%
Patients with at least one serious adverse event	3.5%	13.5%
Vitreous haemorrhage	0	5.4%
Neovascular glaucoma	0	2.7%
Iris neovascularisation	0	2.7%
Retinal haemorrhage	0	2.7%
Visual acuity reduced	0.9%	1.4%
Retinal artery occlusion	0.9%	0
Retinal tear	0	1.4%
Retinal vein occlusion	0	1.4%
Endophthalmitis	0.9%	0
Corneal abrasion	0.9%	0

AE (24 to 52 weeks)	**VTE**	**Sham**
Patients with at least one serious adverse event	2.7%	3.3%
Vitreous haemorrhage	0.9%	1.7%
Glaucoma	0	1.7%

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)						Adverse events		
		Sham	15.4%		34.6%		Iris neovascularisation	0	0
	VTE ≥2 mo	*VTE*	38.8%		42.9%		Retinal haemorrhage	0	0
		Sham	4.8%		19.0%		Visual acuity reduced	0	0
	Perfusion status						Retinal artery occlusion	0	0
	VTE perfused	*VTE*	58.4%	NS	58.4%	NR	Retinal tear	0	1.7%
		Sham	16%		30.0%		Retinal vein occlusion	0.9%	0
	VTE non-perfused	*VTE*	51.4%		48.6%		Cataract	0.9%	0
		Sham	4.3%		30.4%		Cystoid macular oedema	0.9%	0
							Endophthalmitis	0	0
							Corneal abrasion	0	0
	CRT (µm):								
		Baseline	**24 weeks**	**p**	**52 weeks (all VTE PRN)**	**p**	Reports of systemic adverse events were similar between groups; 2 deaths in the sham group by 24 weeks; 2.7% arterial thromboembolic events in the sham group and 0.9% in the intervention group		
	CRT								
	VTE	661.7 SD 237.4	-457.2	<0.001	-413.0	NS			
	Sham	672.4 SD 245.3	-144.8		-381.8				
	QoL								
		Baseline	**24 weeks**	**p**	**52 weeks (all VTE**	**p**			

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)						Adverse events
					PRN)		
	NEI-VFQ-25 total						
	VTE	77.76 SD 15.96	+7.2 SD 12.1	0.001	+7.5	NS	
	Sham	77.78 SD 16.25	+0.8 SD 9.8		+5.1		
	NEI-VFQ-25 near activities						
	VTE	69.96 SD 21.94	+8.3 SD 22.0	<0.05	+11.4	NS	
	Sham	70.72 SD 20.22	+1.84 SD 19.75		+8.3		
	NEI-VFQ-25 distance activities						
	VTE	75.99 SD 21.26	+6.1 SD 20.0	<0.05	+8.5	NS	
	Sham	78.08 SD 21.25	-0.64 SD 15.2		+3.8		
	NEI-VFQ-25 vision dependency						
	VTE	83.26 SD 25.51	+7.1 SD 20.5	<0.05	+6.0	NS	
	Sham	82.76 SD 27.41	+1.1 SD 20.5		+3.4		

<table>
<tr><th>Study</th><th>Clinical outcomes (BCVA, CRT; change from baseline at study end)</th><th>Adverse events</th></tr>
<tr><td></td><td>Progression to neovascularisation: 0 with aflibercept, 6.8% with sham treatment over 52 weeks, p=0.006

Perfused status at week 24: 78.9% with aflibercept, 46.6% with sham treatment</td><td></td></tr>
<tr><td>GALILEO 2012[36;37]

2 mg intravitreal aflibercept (every 4 weeks over 24 weeks) (n=103)

versus sham injection (n=71)

extension up to 52 weeks</td><td>BCVA (ETDRS letters):
<table>
<tr><th></th><th>Baseline</th><th>24 weeks</th><th>p</th><th>52 weeks</th><th>p</th></tr>
<tr><td>BCVA (letters)</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>VTE</td><td>53.6 SD15.8</td><td>+18.0</td><td><0.0001</td><td>+16.9</td><td><0.0001</td></tr>
<tr><td>Sham</td><td>50.9 SD15.4</td><td>+3.3</td><td></td><td>+3.8</td><td></td></tr>
<tr><td>≥15 letters gained</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>VTE</td><td></td><td>60.2%</td><td><0.0001</td><td>60.2%</td><td>0.0004</td></tr>
<tr><td>Sham</td><td></td><td>22.1%</td><td></td><td>32.4%</td><td></td></tr>
<tr><td>≥10 letters lost</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>VTE</td><td></td><td>7.8%</td><td>0.0033</td><td></td><td></td></tr>
<tr><td>Sham</td><td></td><td>25.0%</td><td></td><td></td><td></td></tr>
<tr><td>Subgroups</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Time since diagnosis</td><td></td><td>≥15 letters gained</td><td></td><td></td><td></td></tr>
<tr><td>VTE <2 mo</td><td></td><td>70.9%</td><td>NR</td><td></td><td></td></tr>
</table></td><td>Ocular Adverse Events
<table>
<tr><th>AE</th><th>VTE</th><th>Sham</th></tr>
<tr><td>Discontinued treatment before week 24 because of AE</td><td>1.9%</td><td>11.3%</td></tr>
<tr><td>Eye pain</td><td>11.5%</td><td>4.4%</td></tr>
<tr><td>Conjunctival haemorrhage</td><td>8.7%</td><td>4.4%</td></tr>
<tr><td>Retinal exudates</td><td>6.7%</td><td>7.4%</td></tr>
<tr><td>Foreign body sensation</td><td>5.8%</td><td>7.4%</td></tr>
<tr><td>Retinal vascular disorder</td><td>5.8%</td><td>8.8%</td></tr>
<tr><td>Ocular hyperaemia</td><td>4.8%</td><td>5.9%</td></tr>
<tr><td>Vitreous floaters</td><td>4.8%</td><td>0</td></tr>
<tr><td>Macular oedema</td><td>3.8%</td><td>16.2%</td></tr>
<tr><td>Macular ischaemia</td><td>3.8%</td><td>4.4%</td></tr>
<tr><td>Optic disc vascular disorder</td><td>3.8%</td><td>4.4%</td></tr>
<tr><td>Eye irritation</td><td>2.9%</td><td>10.3%</td></tr>
<tr><td>Lacrimation increased</td><td>2.9%</td><td>5.9%</td></tr>
</table></td></tr>
</table>

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)						Adverse events		
	VTE ≥2 mo		50.0%				Papilloedema	1.9%	4.4%
							Retinal ischaemia	1.0%	4.4%
	CRT (µm):						Visual acuity reduced	0	10.3%
		Baseline	**24 weeks**	**p**	**52 weeks**	**p**	IOP increased	9.6%	5.9%
	CRT						Injection site pain	4.8%	2.9%
	VTE	683.2 SD234.5	-448.6	<0.0001	-423.5	<0.0001	**Serious adverse events**		
	Sham	638.7 SD224.7	-169.3		-219.3		At least 1 SAE	1.9%	5.9%
							Glaucoma	0	2.9%
	QoL						Macular oedema	1.0%	1.5%
		Baseline	**24 weeks**	**p**	**52 weeks**	**p**	Retinal tear	1.0%	0
	NEI-VFQ						Vitreous detachment	1.0%	0
	VTE		+7.5	0.0013					
	Sham		+3.5						
	Percentage of any patients progressing to any neovascularisation by week 24, difference between groups -1.5 (95% CI: -7.4 to 4.4)						Reports of systemic adverse events were similar between groups; no arterial thromboembolic events or deaths during 24 weeks		
	No significant differences on the EQ-5D score between groups						No endophthalmitis or cases of rhegmatogenous detachment, one incidence of uveitis in VTE group considered mild and resolved without change in therapy		

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)					Adverse events
PEGAPTANIB						
Wroblewski 2009[38-44] 0.3 mg intravitreal pegaptanib sodium (every 6 weeks over 24 weeks) (n=33) versus 1 mg intravitreal pegaptanib sodium (every 6 weeks over 24 weeks) (n=33) versus sham injection (n=32) FU up to 52 weeks	**BCVA (ETDRS letters):**					No serious ocular adverse events up to week 30 No endophthalmitis, traumatic cataract or retinal detachment (30 weeks) No evidence of sustained effect on intraocular pressure (30 weeks) No evidence of increased risk of systemic adverse events (30 weeks)
		Baseline	**30 weeks**	**p**	**52 weeks**	**p**
	BCVA (letters)					
	PS 0.3 mg	47.6	+7.1	NS, 0.09 vs sham	+7.5	NS vs sham
	PS 1 mg	48.4	+9.9	0.02 vs sham	+6.3	NS vs sham
	Sham	48.5	-3.2		-2.4	
	≥15 letters gained					
	PS 0.3 mg		36%	NS, p=0.48		
	PS 1 mg		39%			
	Sham		28%			
	≥15 letters lost					
	PS 0.3 mg		9%	0.03 vs sham		
	PS 1 mg		6%	0.01 vs sham		
	Sham		31%			
	CRT (µm):					

<table>
<tr><th>Study</th><th>Clinical outcomes (BCVA, CRT; change from baseline at study end)</th><th>Adverse events</th></tr>
<tr><td></td><td>
<table>
<tr><th></th><th>Baseline</th><th>30 weeks</th><th>p</th><th>52 weeks</th><th>p</th></tr>
<tr><td>CRT</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>PS 0.3 mg</td><td>688</td><td>-243</td><td>NS, p=0.13</td><td>-295</td><td><0.05 vs sham</td></tr>
<tr><td>PS 1 mg</td><td>632</td><td>-179</td><td>NS, p=0.06</td><td>-216</td><td></td></tr>
<tr><td>Sham</td><td>674</td><td>-148</td><td></td><td>-183</td><td></td></tr>
</table>
3 patients in the sham arm and 1 patient in each of the pegaptanib sodium arms developed ocular neovascularisation (p=0.29 (NS))
</td><td></td></tr>
<tr><td colspan="3">RANIBIZUMAB</td></tr>
<tr><td>CRUISE 2010 ff.[10;45;46]

0.3 mg intravitreal ranibizumab (monthly for 6 months)

versus 0.5 mg intravitreal ranibizumab (monthly for 6 months)</td><td>
BCVA (ETDRS letters):
<table>
<tr><th></th><th>Baseline</th><th>6 months</th><th>12 months (ran PRN)</th><th>24 months (ran PRN, HORIZON)</th></tr>
<tr><td>BCVA (letters, 95% CI)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Ran 0.3 mg</td><td>47.4 SD14.8</td><td>+12.7 (9.9, 15.4), p<0.0001 vs sham</td><td>+13.9 SD15.2, p=0.0007 vs sham</td><td>+8.2</td></tr>
<tr><td>Ran 0.5 mg</td><td>48.1 SD14.6</td><td>+14.9 (12.6, 17.2), p<0.0001 vs sham</td><td>+13.9 SD14.2, p=0.0006 vs sham</td><td>+12.0</td></tr>
<tr><td>Sham</td><td>49.2 SD14.7</td><td>+0.8 (-2.0, 3.6)</td><td>+7.3 SD15.9</td><td>+7.6</td></tr>
</table>
</td><td>
6 months
<table>
<tr><th>AE</th><th>Ran 0.3 mg</th><th>Ran 0.5 mg</th><th>Sham</th></tr>
<tr><td>Any intraocular inflammation event</td><td>2.3 %</td><td>1.6%</td><td>3.9%</td></tr>
<tr><td>Iridocyclitis</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Iritis</td><td>1.5%</td><td>1.6%</td><td>2.3%</td></tr>
<tr><td>Vitritis</td><td>0.8%</td><td>0.8%</td><td>1.6%</td></tr>
<tr><td>Endophthalmitis</td><td>0</td><td>0</td><td>0</td></tr>
</table>
</td></tr>
</table>

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)				Adverse events			
versus sham extension 6 to 12 months 0.3 or 0.5 mg ranibizumab PRN extension ≥12 to 24 months 0.5 mg ranibizumab PRN	**≥15 letters gained**				Lens damage	0	0	0
	Ran 0.3 mg	46.2%, p<0.0001 vs sham	47.0%	38.6%	Cataract	1.5%	1.6%	0
	Ran 0.5 mg	47.7%, p<0.0001 vs sham	50.8%	45.1%	Iris neovascularisation	1.5%	0.8%	7.0%
	Sham	16.9%	33.1%	38.3%	Neovascular glaucoma	0	0	1.6%
	≥15 letters lost				Rhegmatogenous retinal detachment	0	0	0
	Ran 0.3 mg	3.8%	3.8%	12.9%	Retinal tear	0	0	0
	Ran 0.5 mg	1.5%	2.3%	5.9%	Vitreous haemorrhage	3.8%	5.4%	7.0%
	Sham	15.4%	10.%	13.3%				
	Subgroups ***Time of diagnosis (6 month outcomes):***<3 months: +13.2 letters (both ran groups), ≥3 months: +10.5 letters (0.3 mg ran), +15.3 letters (0.5 mg ran), p=? Mean change in BCVA was greater for patients with worse baseline BCVA and CRT >450 µm				Systemic adverse events balanced across groups; 1 myocardial infarction in each group, 1 transient ischaemic attack and angina pectoris in the same person in ran 0.5 mg group			
	CRT (µm) and anatomic				**12 months, sham for months 6 to 12**			
	Baseline	**6 months**	**12 months (ran PRN)**	**24 months (ran PRN, HORIZON)**	**Ocular AE**	**Ran 0.3 mg**	**Ran 0.5 mg**	**Sham**
					Any intraocular inflammation	2.3 %	1.6%	1.8%

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)					Adverse events			
	CRT (µm, 95% CI)					event			
	Ran 0.3 mg	679.9 SD 242.4	-433.7 (-484.9, -382.6), p<0.0001 vs sham	-462.1, p= NS vs sham	-370.9	Endophthalmitis	0	0	0
	Ran 0.5 mg	688.7 SD 253.1	-452.3 (-497.0, -407.6), p<0.0001 vs sham	-452.8, p=NS vs sham	-412.2	Lens damage	0	0	0
	Sham	687.0 SD 237.6	-167.7 (-221.5 -114.0)	-427.2	-418.7	Cataract	3.8%	7.0%	1.8%
	CRT ≤250 µm					Iris neovascularisation	1.5%	3.9%	1.8%
	Ran 0.3 mg		75.0%, p<0.0001 vs sham	75.8%	58.0%	Neovascular glaucoma	0	0.8%	0
	Ran 0.5 mg		76.9%, p<0.0001 vs sham	77.7%	56.9%	Rhegmatogenous retinal detachment	0	0	0
	Sham		23.1%	70.8%	70.2%	Retinal tear	0	1.6%	1.8%
	No retinal haemorrhages					Vitreous haemorrhage	5.3%	5.4%	1.8%
	Ran 0.3 mg	0.8%	31.5%	41.3%		**Arterial thromboembolic events**	0.8%	2.3%	0
	Ran 0.5 mg	1.5%	39.3%	47.8%					
	Sham	1.5%	5.4%	36.7%					
	QoL					**HORIZON, 12 to 24 months**			
						AE	**Ran 0.3/0.5**	**Ran 0.5**	**Sham/ran 0.5 mg**

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)					Adverse events			
		Baseline	6 months	p	12 months (ran PRN)	p		mg	mg	
	NEI-VFQ (95% CI)						Any ocular AE	62.6%	66.7%	62.5%
	Ran 0.3 mg		+7.1 (5.2, 9.0)	<0.05 vs sham	+7.1	NS vs sham	Ocular AEs leading to discontinuation	1.9%	2.0%	0
	Ran 0.5 mg		+6.2 (4.3, 8.0)	<0.05 vs sham	+6.6	NS vs sham	Cataract	5.6%	5.1%	3.1%
	Sham		+2.8 (0.8, 4.7)		+5.0		Ocular serious adverse events	9.3%	3.0%	5.2%
							Cystoid macular oedema	0.9%	0	0
							Endophthalmitis	1.9%	0	0
							IOP increased	0.9%	0	0
							Macular oedema	1.9%	2.0%	1.0%
							Ischaemic optic neuropathy	0.9%	0	0
							VA reduced	1.9%	1.0%	3.1%
							VA reduced transiently	0.9%	0	0
							Vitreous haemorrhage	0	0	1.0%
							Arterial thromboembolic	1.9%	3.0%	2.1%

<table>
<tr><th>Study</th><th colspan="5">Clinical outcomes (BCVA, CRT; change from baseline at study end)</th><th>Adverse events</th></tr>
<tr><td></td><td colspan="5"></td><td>events
(potentially
related to drug)</td></tr>
<tr><td colspan="7">BEVACIZUMAB</td></tr>
<tr><td>Epstein 2012[47-49]

1.25 mg intravitreal bevacizumab (4 injections over 6 months) (n=30)

versus sham injection (n=30)

6 month open label extension (1.25 mg intravitreal bevacizumab (4 injections over 6 months) for all patients)</td><td colspan="5">BCVA (ETDRS letters):

Baseline | 24 weeks | p | 48 weeks (bev/bev vs sham/bev) | p

BCVA (letters)

Bev | 44.4 SD15.3; 30% <34, 70% >34 | +14.1 | <0.01 | +16.1 | <0.05

Sham | 43.9 SD16.0; 33.3% <34, 66.7% >34 | -2.0 | | +4.6

≥15 letters gained

Bev | | 60% | 0.003 | 60% | <0.05

Sham | | 20% | | 33.3%

>15 letters lost

Bev | | 6.7% | NS, p=0.146 | 6.7% | NS</td><td>Adverse events:

Neovascularisation: 16.7% (sham) versus 0 (bev) had developed iris rubeosis at week 24; iris rubeosis regressed in all patients at week 48, no new cases in either group

No events of endophthalmitis, retinal tear, retinal detachment; no serious non-ocular adverse events</td></tr>
</table>

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)					Adverse events
	Sham	23.3%		6.7%		
	Subgroups					
	Disease duration	**BCVA (letters)**				
	Bev <90 days	+18.7	0.039			
	Bev >90 days	+9.8				
	Age			**BCVA (letters)**		
	<70 years			+14.2	NS, >0.05	
	>70 years			+7.4		
	<70 years sham/bev			-1.4	<0.003	
	>70 years sham/bev			+20.1		
	CRT (µm):					
		Baseline	**24 weeks**	**p**	**48 weeks (bev/bev vs sham/bev)**	**p**

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)						Adverse events
	CRT						
	Bev/bev	712 SD330	-426	<0.001	-435	NS, >0.05	
	Sham/bev	729 SD195	-102		-404		
	No residual oedema (CRT <300 µm)						
	Bev/bev		86.7%	<0.001	83.3%	NS	
	Sham/bev		20%		60%		

Abbreviations: AE – adverse event, BCVA – best corrected visual acuity, CI – confidence interval, CRT – central retinal thickness, CRVO – central retinal vein occlusion, ETDRS – Early Treatment Diabetic Retinopathy Study, FU – follow-up, IQR – interquartile range, IOP – intraocular pressure, mo – months, NR – not reported, NS – non-significant, OCT – optical coherence tomography, PRN – pro re nata (as needed), QoL – quality of life, SD – standard deviation

11 Table 3: Study quality

Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
DEXAMETHASONE							
GENEVA 2010 ff.	Low	Low	Partial: patients and assessors of efficacy variables	Low: ITT analysis, 94% FU at 6 months	Low	*Power:* 81% power to detect difference in primary outcome with n=495 for each trial *Similarity at baseline:* yes	Allergan Inc.
TRIAMCINOLONE							
SCORE 2009 ff	Low	Unclear	Partial (physicians and patients masked to dose but not triamcinolone versus observation)	Low: ITT analysis, 83 to 90% FU at 12 months	Low	*Power:* 80% power to detect difference in primary outcome with n=486 (but only 271 randomised) *Similarity at baseline:* yes	National Eye Institute grants, Allergan

Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
ROVO 2013	Low	Low	Unclear	Low: ITT analysis (?), 92% FU at 12 months	Low	*Power:* 80% power to detect difference in primary outcome with n=53 per group (but only 20 to 38 per group) *Similarity at baseline:* unclear *Other:* limited baseline data	Jubiläumsfonds der Österreichischen Nationalbank, Ludwig Boltzmann Institute for Retinology and Biomicroscopic Laser Surgery (non-commercial)
AFLIBERCEPT							
COPERNICUS 2012	Low	Unclear	Low: double-blind	Low: ITT analysis, 89.9% assessed at primary end point	Low	*Power:* 90% power to detect difference in primary outcome with n=165 *Similarity at baseline:* yes	Bayer HealthCare, Regeneron Pharmaceuticals

Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
GALILEO 2012	Unclear	Unclear	Low: double-blind	Low: ITT analysis, 86% assessed at primary end point	Low	*Power:* 90% power to detect difference in primary outcome with n=150 *Similarity at baseline:* yes	Bayer HealthCare, Regeneron Pharmaceuticals
PEGAPTANIB							
Wroblewski 2009	Low	Low	Low: patients and ophthalmologist responsible for patients care and assessments	Low: ITT analysis, 7% withdrawals	Low	*Power:* 80% power to detect difference in primary outcome with n=30 per group *Similarity at baseline:* yes	Eyetech Inc, Pfizer Inc.
RANIBIZUMAB							
CRUISE 2010 ff	Low	Unclear	Low: patients and evaluating examiners, injecting physicians masked to dose	Low: ITT analysis, 88.5 to 97.7% completed 6 months	Low	*Power:* not reported *Similarity at baseline:* yes	Genentech Inc.

Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
BEVACIZUMAB							
Epstein 2012	Unclear	Low	Low: patients, outcome assessors	Low: ITT analysis; missing data for 2 patients (primary endpoint)	Low	*Power:* 80% power to detect difference in primary outcome with n=24 per group *Similarity at baseline:* yes	Unclear; authors are consultants for Allergan, Novartis, Alcon, Bayer

14 Table 4: On-going trials

Study	Participants and baseline values	Intervention / Outcomes
MINOCYCLINE		
http://clinicaltrials.gov/ct2/show/study/NCT01468844 USA **Study aim:** to test the safety and effectiveness of minocycline as a treatment for CRVO **Design:** RCT, double-blind **Follow-up:** 24 months	**N:** ~20 **Inclusion criteria:**>18 years, macular oedema secondary to CRVO, CRT >350 µm, media clarity and pupillary dilatation sufficient for fundus photographs **Exclusion criteria:** macular oedema due to causes other than CRVO, history of recurrent RVO or RVO >18 months, any other ocular condition that could affect macular oedema or BCVA, substantial cataract, photocoagulation within 4 months before study, pars plana vitrectomy within 6 months, major ocular surgery within 3 months, study eye treated with intravitreal or periocular steroid injections within 3 months, study eye treated with intravitreal anti-VEGF agents within 28 days; significant systemic disease (details given)	**Mino:** 100 mg oral minocycline twice daily over 24 months; monthly bevacizumab injection over 3 months, then PRN **Placebo:** oral placebo twice daily over 24 months; monthly bevacizumab injection over 3 months, then PRN **Primary end point:** BCVA over 12 months **Other outcomes:** number of bevacizumab injections, CRT, safety **Outcome assessment:** 6, 12, 18, 24 months

Study	Participants and baseline values	Intervention / Outcomes
BEVACIZUMAB / TRIAMCINOLONE		
http://clinicaltrials.gov/show/NCT00566761 Mexico **Study aim:** to assess if treatment of macular oedema secondary to CRVO is more effective with combined therapy of bevacizumab and triamcinolone compared to bevacizumab alone **Design:** RCT, open-label, phase 4 **Follow-up:** 12 months	**N:** ~10 **Inclusion criteria:** macular oedema secondary to CRVO; BCVA <20/40; CRT >250 µm (OCT) **Exclusion criteria:** diabetic retinopathy or other retinopathy; media opacity that does not allow follow-up; steroid responder; diagnosed glaucoma or IOP > 21 mmHg	**Bev:** bevacizumab 2.5 mg for (3 applications, administered monthly) **Bev/Tria:** bevacizumab 2.5 mg + triamcinolone 4 mg first dose followed by two doses of bevacizumab alone **Primary end point:** BCVA over 12 months **Other outcomes:** treatment complications **Outcome assessment:** 3, 6 and 12 months
RANIBIZUMAB		

Study	Participants and baseline values	Intervention / Outcomes
http://clinicaltrials.gov/show/NCT01123564 Hungary **Study aim:** to assess if ranibizumab (Lucentis) injection applied into the eye is superior to conventional treatment concerning the prevention of visual loss in patients having clinically significant macular oedema secondary to retinal vein occlusion **Design:** RCT, open-label, phase 2 **Follow-up:** 12 months	**N:** ~40 **Inclusion criteria:**>18 years, macular oedema persisting for >3 months despite conventional medication; CRVO confirmed by slit-lamp biomicroscopy and fluorescein angiography (FLAG); patient in ranibizumab group do not receive macular laser treatment; CRT > 280 µm and/or retinal thickness is >330 µm at any region of the macula; baseline VA <64 ETDRS letters (or 0.4 decimal equivalent) **Exclusion criteria:** diabetes mellitus; additional vitreoretinal diseases; history of pars plana vitrectomy; previous macular grid laser treatment; intravitreal triamcinolone acetonide treatment; complicated cataract surgery; advanced glaucomatous damage of optic nerve head; cataract (except mild, defined as grade 1 nuclear sclerosis and/or grade 1 posterior subcapsular cataract); age-related macular degeneration; pregnancy and lactation; women in childbearing potential who are not using double safe contraception	**Rani:** intravitreal ranibizumab, applied monthly in the first 3 months, and after this only if visual acuity (VA) decreases with more than 5 letters at any monthly visits **Laser:** Argon laser treatment; conventional grid pattern argon laser treatment and panretinal argon laser photocoagulation in an as needed basis **Primary end point:** BCVA over 12 months **Other outcomes:** CRT **Outcome assessment:** monthly visits

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Appendix 1: Search strategy

CRVO: Clinical effectiveness search for RCTs and SRs

Ovid MEDLINE(R) 1946 to March Week 1 2013, searched on 20 March 2013

1 CRVO.mp.

2 Retinal Vein Occlusion/

3 retinal vein occlusion.mp.

4 retinal vein obstruction.mp.

5 retinal venous occlusion.mp.

6 retinal venous obstruction.mp.

7 retina*.mp.

8 ("central vein occlusion" or "central vein obstruction" or "central venous occlusion" or "central venous obstruction").mp.

9 7 and 8

10 1 or 2 or 3 or 4 or 5 or 6 or 9

11 randomized controlled trial.pt.

12 (random* or "controlled trial*" or "clinical trial*" or rct).tw.

13 11 or 12

14 (metaanalys* or "meta analys*" or "meta-analys*").tw.

15 "systematic review*".tw.

16 meta analysis.pt.

17 14 or 15 or 16

18 10 and 13

19 10 and 17

20 18 or 19

21 limit 20 to yr="2005 -Current"

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations March 19, 2013, searched on 20 March 2013

1 CRVO.mp.

2 retinal vein occlusion.mp.

3 retinal vein obstruction.mp.

4 retinal venous occlusion.mp.

5 retinal venous obstruction.mp.

6 retina*.mp.

7 ("central vein occlusion" or "central vein obstruction" or "central venous occlusion" or "central venous obstruction").mp.

8 6 and 7

9 1 or 2 or 3 or 4 or 5 or 8

10 (random* or "controlled trial*" or "clinical trial*" or rct).tw.

11 (metaanalys* or "meta analys*" or "meta-analys*").tw.

12 "systematic review*".tw.

13 11 or 12

14 9 and 10

15 9 and 13

16 14 or 15

Embase 1980 to 2013 Week 11, searched on 20 March 2013

1 CRVO.mp.

2 Retina Vein Occlusion/

3 Central Retina Vein Occlusion/

4 retinal vein occlusion.mp.

5 retinal vein obstruction.mp.

6 retinal venous occlusion.mp.

7 retinal venous obstruction.mp.

8 retina*.mp.

9 ("central vein occlusion" or "central vein obstruction" or "central venous occlusion" or "central venous obstruction").mp.

10 8 and 9

11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 10

12 randomized controlled trial/

13 (random* or "controlled trial*" or "clinical trial*" or rct).tw.

14 12 or 13

15 systematic review/

16 meta analysis/

17 (metaanalys* or "meta analys*" or "meta-analys*").tw.

18 "systematic review*".tw.

19 15 or 16 or 17 or 18

20 11 and 14

21 11 and 19

22 20 or 21

23 limit 22 to yr="2005 -Current"

224

225 **Cochrane Library (including CDSR, CENTRAL, DARE, HTA, NHS EED), searched on 20 March 2013**

226 #1 CRVO

227 #2 MeSH descriptor: [Retinal Vein Occlusion] this term only

#3	"retinal vein occlusion"
#4	"retinal vein obstruction"
#5	"retinal venous occlusion"
#6	"retinal venous obstruction"
#7	retina*
#8	"central vein occlusion" or "central vein obstruction" or "central venous occlusion" or "central venous obstruction"
#9	#7 and #8
#10	#1 or #2 or #3 or #4 or #5 or #6 or #9
#11	#10 from 2005

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7-8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	68-71
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7-8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7-8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7-8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	23
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	25-35
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	56-59
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	N/A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16-20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16-20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	22

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

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CRVO: Clinical effectiveness search for RCTs and SRs

Ovid MEDLINE(R) 1946 to March Week 1 2013, searched on 20 March 2013

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8 6 and 7

9 1 or 2 or 3 or 4 or 5 or 8

10 (random* or "controlled trial*" or "clinical trial*" or rct).tw.

11 (metaanalys* or "meta analys*" or "meta-analys*").tw.

12 "systematic review*".tw.

13 11 or 12

14 9 and 10

15 9 and 13

16 14 or 15

Embase 1980 to 2013 Week 11, searched on 20 March 2013

1 CRVO.mp.

2 Retina Vein Occlusion/

3 Central Retina Vein Occlusion/

4 retinal vein occlusion.mp.

5 retinal vein obstruction.mp.

6 retinal venous occlusion.mp.

7 retinal venous obstruction.mp.

8 retina*.mp.

9 ("central vein occlusion" or "central vein obstruction" or "central venous occlusion" or "central venous obstruction").mp.

10 8 and 9

11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 10

12 randomized controlled trial/

13 (random* or "controlled trial*" or "clinical trial*" or rct).tw.

14 12 or 13

15 systematic review/

16 meta analysis/

17 (metaanalys* or "meta analys*" or "meta-analys*").tw.

18 "systematic review*".tw.

19 15 or 16 or 17 or 18

20 11 and 14

21 11 and 19

22 20 or 21

23 limit 22 to yr="2005 -Current"

Cochrane Library (including CDSR, CENTRAL, DARE, HTA, NHS EED), searched on 20 March 2013

#1 CRVO

#2 MeSH descriptor: [Retinal Vein Occlusion] this term only

#3 "retinal vein occlusion"

#4 "retinal vein obstruction"

#5 "retinal venous occlusion"

#6 "retinal venous obstruction"

#7 retina*

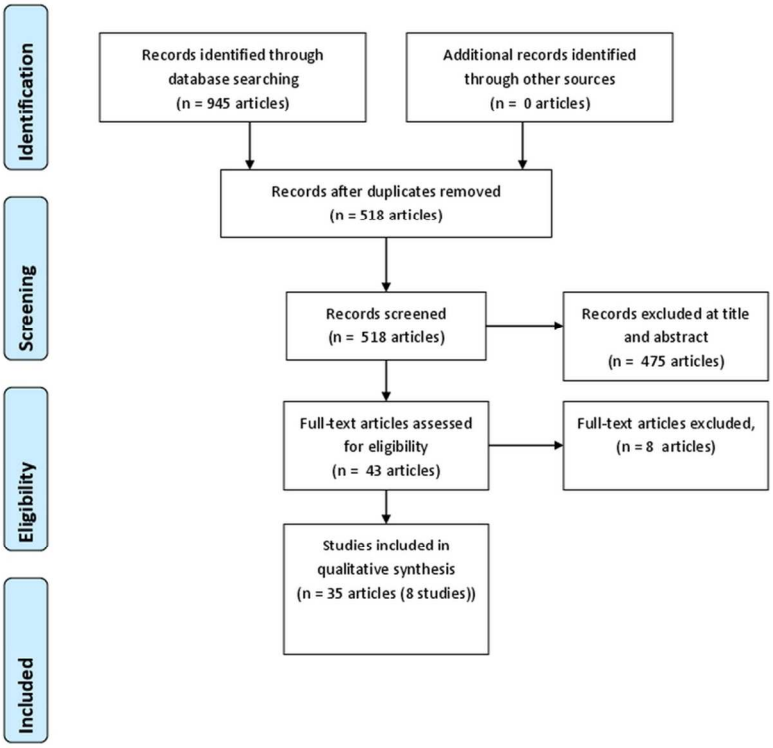
#8 "central vein occlusion" or "central vein obstruction" or "central venous occlusion" or "central venous obstruction"

#9 #7 and #8

#10 #1 or #2 or #3 or #4 or #5 or #6 or #9

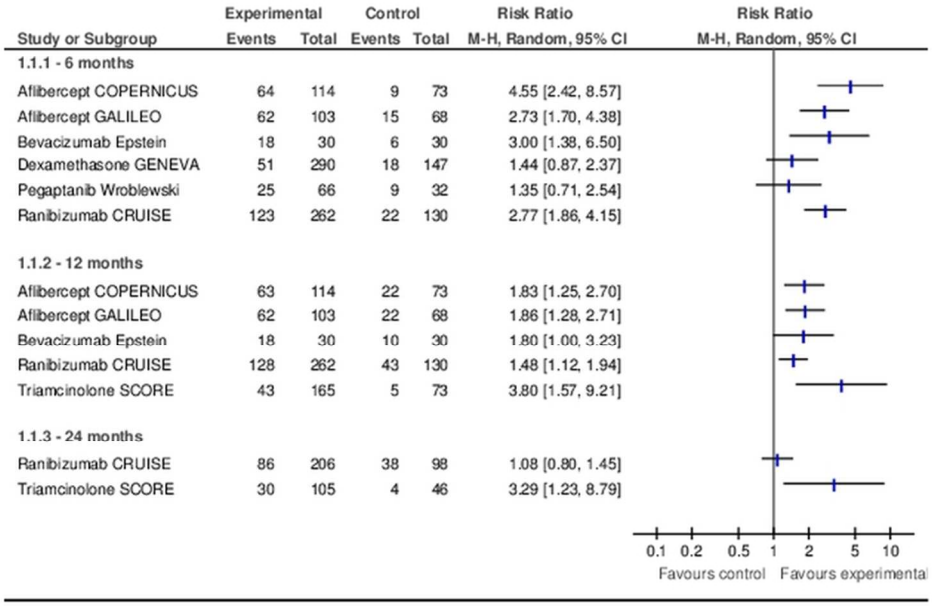
#11 #10 from 2005

Figure 1: PRISMA statement



90x116mm (300 x 300 DPI)

Figure 2. Study results for the primary outcome (≥15 ETDRS letter gain).



74x57mm (300 x 300 DPI)