Intravitreal steroids versus observation for macular edema secondary to central retinal vein occlusion

Dina Gewaily[1,2], **Karthikeyan Muthuswamy**[3], and **Paul B Greenberg**[4,5]

[1]Deglin and Greene Retinal Center, Wynnewood, Pennsylvania, USA

[2]Department of Ophthalmology, Scheie Eye Institute, University of Pennsylvania, Philadelphia, Pennsylvania, USA

[3]Cooper University Hospital, Camden, New Jersey, USA

[4]Section of Ophthalmology, VA Medical Center, Providence, Rhode Island, USA

[5]Division of Ophthalmology, Warren Alpert Medical School of Brown University, Providence, Rhode Island, USA

Abstract

Background—Central retinal vein occlusion (CRVO) is a common retinal vascular abnormality associated with conditions such as hypertension, diabetes, glaucoma, and a wide variety of hematologic disorders. Macular edema (ME) represents an important vision-threatening complication of CRVO. Intravitreal steroids (IVS), such as triamcinolone acetonide, have been utilized to treat macular edema stemming from a variety of etiologies and may be a treatment option for CRVO-ME.

Objectives—To explore the effectiveness and safety of intravitreal steroids in the treatment of CRVO-ME.

Search methods—We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (2014 Issue 10), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to November 2014), EMBASE (January 1980 to November 2014), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 13 November 2014. For all included primary studies, we used The Science Citation Index (3 December 2014) and manually reviewed reference lists to identify other possible relevant trials.

Selection criteria—We included randomized controlled trials (RCTs) that compared intravitreal steroids, of any dosage and duration of treatment of at least six months, with observation for the treatment of CRVO-ME.

Contact address: Paul B Greenberg, Section of Ophthalmology, VA Medical Center, 830 Chalkstone Avenue, Providence, Rhode Island, 02908, USA. paul_greenberg@brown.edu.

Data collection and analysis—Two review authors independently screened titles and abstracts identified from the electronic searches and assessed full-text articles from potentially eligible trials. Two review authors independently assessed trial characteristics, risk of bias, and extracted data from included trials. We contacted investigators of included trials for desired data not provided in the trial reports.

Main results—We included two RCTs that enrolled a total of 708 participants with CRVO-ME. SCORE compared triamcinolone acetonide intravitreal injections (n = 165) with observation (n = 72); GENEVA compared dexamethasone intravitreal implants (n = 290) with sham injections (n = 147). We observed characteristics indicative of high risk of bias due to incomplete outcome data in SCORE and selective outcome reporting in GENEVA. Loss to follow-up was high with 10% in the steroid groups and almost twice as much (17%) in the observation group. GENEVA enrolled participants with both branch and central retinal vein occlusion, but did not present subgroup data for the CRVO-ME population. A qualitative assessment of the results from GENEVA indicated that the dexamethasone implant was not associated with improvement in visual acuity after six months among participants with CRVO-ME. Although the SCORE investigators reported that participants treated with 1 mg (n = 82) or 4 mg (n = 83) triamcinolone intravitreal injections were five times more likely to have gained 15 letters or more in visual acuity compared with participants in the observation group (1 mg; risk ratio (RR): 5.27; 95% confidence interval (CI) 1.62 to 17.15; 4 mg RR 4.92; 95% CI 1.50 to 16.10) by the eighth-month follow-up examination, the average visual acuity decreased in all three groups. However, eyes treated with triamcinolone lost fewer letters than participants in the observation group at 8 months (1 mg mean difference (MD): 8.70 letters, 95% CI 1.86 to 15.54; 4 mg MD: 9.80 letters, 95% CI 3.32 to 16.28). A higher incidence of adverse events was noted with IVS therapy when compared with observation alone. As many as 20% to 35% of participants experienced an adverse event in the IVS groups compared with 8% of participants in the observation group of the SCORE study. The GENEVA investigators reported 63% in the treatment arm versus 43% in the observation arm experienced an adverse event. The most commonly encountered adverse events were elevated intraocular pressure, progression of cataracts, and retinal neovascularization. We graded the quality of evidence as low due to study limitations, imprecision of treatment estimates, and selective outcome reporting.

Authors' conclusions—The two RCTs reviewed herein provide insufficient evidence to determine the benefits of IVS for individuals with CRVO-ME. The improvement in visual acuity noted in the SCORE trial should be interpreted with caution as outcome data were missing for a large proportion of the observation group. Adverse events were observed more often with IVS treatment compared with observation/no treatment.

INDEX TERMS: Medical Subject Headings (MeSH)

Macular Edema [*drug therapy; etiology]; Retinal Vein Occlusion [*complications]; Steroids [*administration & dosage]

MeSH check words

Humans

PLAIN LANGUAGE SUMMARY

Steroids inserted into the eye versus observation for macular edema secondary to central retinal vein occlusion

Review question—We aimed to examine the benefits and harms of inserting steroids into the eye for treating macular edema secondary to central retinal vein occlusion (CRVO-ME).

Background—Central retinal vein occlusion (CRVO) is a common abnormality of the blood vessels in the retina (back portion of the eye which receives visual images). CRVO usually presents as a painless loss of vision in one eye of people over the age of 40 who often have other health issues such as high blood pressure, diabetes, glaucoma, and blood diseases. Macular edema (ME) is the swelling of the macula (central area of the retina responsible for detailed vision, such as reading and seeing colors). ME is a complication of CRVO and is the primary reason for loss of vision in this condition. Steroids inserted into the eye, either by injection or an implanted device, have been used to treat ME caused by eye disorders other than CRVO. While steroids can lead to improvements in vision, the effect usually lasts only a few months and there is a risk of developing glaucoma, cataracts, and other complications.

Study characteristics—The review authors searched the medical literature up to 13 November 2014 and included two randomized controlled trials (GENEVA and SCORE) that had evaluated steroids in 708 participants with CRVO-ME. Both trials included participants with similar baseline characteristics with respect to age, gender, and co-morbidities. GENEVA was conducted in 24 countries across the world and SCORE was conducted in the US. Both trials compared two different doses of steroid, but the investigators of the two trials used different steroidal agents and different methods of delivery (implant versus injection). Both trials received full or partial sponsorship from the manufacturer of the drugs.

Key results—Neither trial provided sufficient evidence to determine whether steroids had improved visual acuity after six months of treatment. Due to the limited evidence, we are unable to determine reliably whether steroid implants improved vision in eyes with CRVO-ME. Although the SCORE trial showed that more eyes in the steroid injection groups had improvement in vision compared with eyes in the observation group, participants treated with steroids and those not treated with steroids both lost vision on average at eight months. The GENEVA investigators reported no difference in vision outcomes between participants treated with steroids and those not treated with steroids after six months of treatment; however the GENEVA study was not limited to participants with only CRVO-ME and included participants with other retinal disease. Both trials showed that patients treated with steroids were at increased risk for high eye pressure – requiring additional medications to lower the eye pressure – and developing cataracts.

Quality of the evidence—The overall quality of the evidence was low due to clinical differences between studies, incomplete information available to assess outcomes, and lack of masking which may lead to biased study results.

BACKGROUND

Description of the condition

Central retinal vein occlusion (CRVO) is a common retinal vascular abnormality associated with conditions such as hypertension, diabetes, glaucoma, and a wide variety of hematologic disorders (Eye Disease Case-Control Study 1996). Patients usually are aged 40 years or older and report sudden painless loss of vision in one eye upon waking. Funduscopic evaluation typically reveals intraretinal hemorrhages in all four quadrants ("blood and thunder appearance"), dilation, and tortuosity of the retinal veins. A histopathological study of 29 eyes suggested that central vein occlusion results from the formation of a thrombus at the lamina cribrosa (Green 1981).

Macular edema (ME) represents an important vision-threatening complication of CRVO. ME formation is presumed to occur from a hypoxic environment in the retina that leads to changes in retinal capillaries, including an increase in capillary permeability and plasma leakage (Ip 2004). Decreased visual acuity results from disruption of photoreceptor function by an edematous and hemorrhagic macula and, in some cases, ischemic retinal damage (Mandelcorn 2007).

Description of the intervention

At the time this review was originally prepared and published, there was no accepted treatment for CRVO-ME (Gewaily 2009). As of this update, the accepted treatments for CRVO are intravitreal administration of anti-vascular endothelial growth factor (anti-VEGF) inhibitors, such as ranibizumab, bevacizumab, and aflibercept (Braithwaite 2014); however, intravitreal steroids may still be used where anti-VEGF agents are not readily available. The CRUISE 2007 trial results showed significant improvements in vision for patients treated with intravitreal ranibizumab as early as one month after initiation of treatment. The GALILEO 2014 study showed a mean of 60% of patients treated with aflibercept (vs 32% in the control group) gained 15 letters or more in vision improvement at 52 weeks and the COPERNICUS 2013 trial results indicated that 56% of patients treated with aflibercept gained 15 letters from baseline (vs 12% in the control group). Bevacizumab is used off-label for CRVO therapy. Laser photocoagulation has not been shown to be effective in treating CRVO-ME (CVOS 1995). There continues to be interest in other treatment modalities, including medical therapy with anticoagulants, fibrinolytics, acetazolamide, isovolemic hemodilution, and angiostatic agents. Surgical options include vitrectomy, chorioretinal anastomosis, direct venous cannulation with injection of fibrinolytics, and radial optic neurotomy (Mohamed 2007). However, none of the aforementioned interventions (other than anti-VEGF therapy as noted above) has been proven effective in treating CRVO-induced cystoid macular edema.

Intravitreal steroids, such as triamcinolone acetonide, have been utilized to treat macular edema stemming from a variety of etiologies, including retinal vein occlusion, diabetic retinopathy, uveitis, pseudophakic cystoid macular edema, and exudative macular degeneration (Antcliff 2001; Bashshur 2004; Conway 2003; Jonas 2005b). Although past attempts using topical or systemic steroids failed to improve visual outcomes, intravitreal

administration, in the form of an injection or surgical implant, may serve as a method to increase local concentration of the drug while minimizing systemic side effects (Jonas 2005b). Promising results using intravitreal anti-VEGF therapy (CRUISE 2007; COPERNICUS 2013; GALILEO 2014) lend support to intravitreal injection as an alternative to systemic therapy.

How the intervention might work

Corticosteroids have been shown to reduce edema resulting from breaks in the blood-retina barrier by reducing both intraocular inflammation and capillary permeability (Jonas 2005b). The increased capillary permeability that occurs in macular edema may be mediated partially by vascular endothelial growth factor (VEGF). In cases in which macular ischemia has occurred due to CRVO, VEGF is further upregulated (Pe'er 1998). Corticosteroids have been demonstrated to decrease the induction of VEGF by pro-inflammatory mediators, such as platelet activating factor, in a dose-dependent manner (Nauck 1997; Nauck 1998). In addition, studies have found that intravitreal steroid injection led to significant improvements in retinal response density as measured by multi-focal electroretinography (mf-ERG) in both foveal and parafoveal regions in patients with CRVO-induced macular edema, although those improvements did not correlate directly with improvements in visual acuity (Moschos 2007).

Why it is important to do this review

The prognosis of CRVO can be very poor. Approximately half of non-ischemic eyes with an initial visual acuity of 20/50 or worse have a visual acuity of 20/250 or worse three years after event onset (CVOS 1997). Macular edema remains the primary cause of decreased vision. At the time of the original publication of this review (Gewaily 2009), there was no standard of care. The use of intravitreal steroids has been proposed over the last few years and multiple studies of this intervention are underway or have been completed. This review does not compare intravitreal steroid therapy with intravitreal anti-VEGF therapy as our goal is to evaluate whether intravitreal steroid injections are beneficial to patients with CRVO-ME. Further, the use of intravitreal steroids for CRVO-induced cystoid macular edema must be weighed against potential complications such as glaucoma, endophthalmitis, and cataracts. This review was designed to explore the benefits and medical risks of using intravitreal steroids in the treatment of CRVO-ME.

OBJECTIVES

To explore the effectiveness and safety of intravitreal steroids in the treatment of CRVO-ME.

METHODS

Criteria for considering studies for this review

Types of studies—We included all relevant randomized controlled trials (RCTs) in our review. We included relevant observational studies retrieved from electronic search results in our discussion of the topic, but not in statistical analyses.

Types of participants—We placed no restrictions with respect to the age or gender of participants enrolled in the primary studies. We included studies of individuals with either unilateral or bilateral macular edema secondary to CRVO.

Types of interventions—This review was limited to a comparison of intravitreal steroids with observation (in this case natural history, i.e., no treatment, sham treatment, or placebo) for CRVO-ME.

Intravitreal steroid administration could have taken the form of an injection or surgical implantation. We included trials with any dosage and duration of treatment of at least six months.

Types of outcome measures

<u>**Primary outcomes:**</u> The pre-specified primary outcome of this review was the proportion of eyes with improved best-corrected visual acuity at six months of follow-up compared with baseline visual acuity (Gewaily 2008). We defined a significant improvement in visual acuity as a gain of greater than or equal to 0.1 LogMAR unit (or standard equivalent) compared with visual acuity at the time of CRVO diagnosis. For this review we also reported other measures of improvement in best-corrected visual acuity as reported by the included studies (e.g., proportion of eyes with gain of 15 letters or more visual acuity). When available, we also reported improvements in visual acuity for longer follow-up intervals.

<u>**Secondary outcomes:**</u> Secondary outcomes for comparison of interventions included:

1. Mean change in best-corrected visual acuity at six months of follow-up;

2. Mean change in macular thickness using optical coherence tomography (OCT).

3. Mean change in macular edema grade by:

    i. Area of leakage using fluorescein angiography (FA):

    ii. Area of edema using FA and stereoscopic photography.

4. Mean change in electroretinogram recordings.

5. Complications: all named complications will be tabulated.

6. Number of interventions performed: frequency and time intervals will be tabulated.

<u>**Adverse outcomes:**</u> We compared all reported systemic and ocular complications and adverse events related to the use of intravitreal corticosteroids compared with the control group that were mentioned in the primary studies. Specific adverse outcomes of interest included the development of sterile/nonsterile endophthalmitis, an increase in mean intraocular pressure (IOP) or need for anti-glaucomatous therapy, and cataract formation and/or progression.

<u>**Economic outcomes:**</u> We planned to report cost-benefit analyses and other relevant economic data, but there were no relevant economic data reported in the included studies.

Quality-of-life outcomes: We planned to report quality-of-life outcomes, but did not find any relevant quality-of-life data in the included primary studies.

Search methods for identification of studies

Electronic searches—We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (2014 Issue 10), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to November 2014), EMBASE (January 1980 to November 2014), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 13 November 2014.

See Appendices for details of the search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), EMBASE (Appendix 3), *m*RCT (Appendix 4), ClinicalTrials.gov (Appendix 5) and the ICTRP (Appendix 6).

Searching other resources—For the previous version of this review, we conducted manual searches by reviewing the reference lists of all reviews and non-randomized studies that compared intravitreal steroids to observation for CRVO-ME for additional relevant papers. For this update, we also reviewed the reference lists from reports of included studies. We used the Science Citation Index to search for studies that had cited included primary trials (3 December 2014). We contacted researchers in the field currently working on RCTs on the topic to seek information on additional current, past, or unpublished trials.

Data collection and analysis

Selection of studies—Two authors independently reviewed all titles and abstracts retrieved from the electronic and manual searches and judged potential relevance based on the inclusion criteria for this review. The authors classified each abstract as: (a) definitely relevant, (b) possibly relevant, or (c) definitely not relevant. The authors retrieved the full reports from records assessed as (a) or (b). The authors reviewed the full reports and classified the studies as: (1) include, (2) awaiting assessment, or (3) exclude. A third review author resolved any discrepancies at each stage. We contacted the authors of studies classified as (2) for further information. Whenever the contacted authors did not respond within two weeks, we used the available data. We documented titles of excluded studies, along with primary reason(s) for exclusion. Reports identified in languages other than English were translated by colleagues for screening and classification.

Data extraction and management—Two review authors independently extracted data from each included primary study using data extraction forms developed by the Cochrane Eyes and Vision Group. We extracted data pertaining to study characteristics, participants (including the stated inclusion and exclusion criteria), intervention and control group descriptions, primary and secondary outcome data, and relevant corollary notes. We made efforts to contact primary investigators to obtain missing or unclearly reported data. The

authors discussed discrepancies in data extracted independently to reach a consensus. One author entered data into Review Manager 5.3 (RevMan 2014) and the second author verified the entered data.

Assessment of risk of bias in included studies—Two review authors independently evaluated the included trials for risks of bias following the guidelines in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We assessed the potential risk of bias in the included trials by examining selection bias (sequence generation and allocation concealment before randomization), performance bias (masking of participants and personnel), detection bias (masking of outcome assessors), attrition bias (incomplete outcome data), as well as reporting bias (selective outcome reporting). We also assessed whether other aspects of trial design or conduct could have biased the individual study results. We judged studies on each risk of bias domain to be at 'high risk,' 'low risk,' or 'unclear risk' of bias. We discussed discrepancies between authors regarding risk of bias assessments to come to a consensus and reported the rationale for each judgment in Characteristics of included studies tables. We contacted authors of trial reports for additional information when descriptions of study methods needed to judge risk of bias were unclear or not reported.

Measures of treatment effect

Dichotomous data: We analyzed the primary outcome of interest – the proportion of patients with a gain of visual acuity greater than or equal to 0.1 logMAR (or standard equivalent) at six months of follow-up – and the occurrence of adverse events as dichotomous variables. We presented dichotomous data as risk ratios (RR) with 95% confidence intervals (CIs).

Continuous data: We measured the mean changes in visual acuity and macular thickness as continuous variables, and calculated the mean differences with 95% CIs.

Ordinal data: We planned to analyze and report the number of complications and the economic and quality of life data as ordinal data.

Unit of analysis issues—The unit of analysis was the individual (one eye per person).

Dealing with missing data—The GENEVA study reports pooled data for CRVO and branch retinal vein occlusion (BRVO). Since the population of interest for our review was participants with CRVO, we needed subgroup analysis data for the CRVO cases from GENEVA. We contacted the GENEVA investigators and trial sponsor (Allergan, Inc.) for outcome data for the CRVO participants, a pre-specified subgroup analysis of the trial. Unfortunately, our request for the CRVO data from the GENEVA study was denied by the trial sponsor (email correspondence). We did not impute any data for either GENEVA or SCORE and used the data as available for all analyses.

Assessment of heterogeneity—We assessed both clinical and methodological heterogeneity among the included trials. Based on clinical and methodological heterogeneity, we did not conduct meta-analyses. In future updates, if additional RCTs are

found that meet the inclusion criteria and can be included in meta-analyses, we will assess statistical heterogeneity through inspection of forest plots and the results of Chi^2 tests and the I^2 statistic. We will consider I^2 values 60% to indicate substantial statistical heterogeneity.

Assessment of reporting biases—We could not assess publication bias through inspection of funnel plots because we had too few included studies. We will examine funnel plots to identify any evidence of publication bias if future trials are found and the same outcome is reported from 10 or more trials. We assessed selective outcome reporting by comparing trial protocols with published results of included studies.

Data synthesis—Due to heterogeneity in the types of intravitreal steroid evaluated, data reporting, and follow-up periods we were not able to perform meta-analyses. We will perform meta-analysis when RCTs are found that meet the inclusion criteria and substantial heterogeneity across studies is absent. We will use a random-effects model for meta-analysis, or a fixed-effect model whenever fewer than three trials report the same outcome.

Subgroup analysis and investigation of heterogeneity—We analyzed dosages of steroid used and delivery method of the corticosteroid (i.e., injection versus surgical implant) separately in this review. In future updates, we will investigate heterogeneity through quantitative subgroup analyses based on the type of CRVO (i.e., ischemic versus non-ischemic) and baseline measurements (i.e., visual acuity and macular thickness) when sufficient data are available.

Sensitivity analysis—We did not perform sensitivity analyses in this review. In future updates, we plan to assess the impact of excluding studies that have high risk of attrition bias using sensitivity analysis. We also plan to examine the impact of both unpublished studies and industry-funded trials on overall results.

Summary of findings—We did not prepare a summary of findings table as no meta-analysis was performed due to differences in intervention groups between the included studies. Two authors independently graded the overall quality of the evidence for each outcome using the GRADE classification (www.gradeworkinggroup.org/).

RESULTS

Description of studies

Results of the search—Electronic searches, inherently designed to include published and unpublished trials, conference proceedings, and papers written in languages other than English, originally yielded a total of 177 records as of November 2008. We screened the full-text reports corresponding to seven potentially relevant records. A preliminary review of the articles yielded no eligible RCTs.

In November 2014 the electronic searches were updated; we screened 286 additional titles and abstracts and 37 records from clinical trials registries (Figure 1). After screening titles and abstracts, we classified 19 records as 'definitely relevant' or 'possibly relevant.' After

review of the full-text, 15 reports from two RCTs met our inclusion criteria and were included in the review (GENEVA; SCORE); three studies were not RCTs and were excluded (Chuang 2010; Jain 2012; Muni 2010); and one study is ongoing (NCT01660802). We entered reports from the two included trials into the Science Citation Index which resulted in 355 unique citations. We identified and excluded one additional potentially relevant trial for this review (ROVO).

Included studies—We identified two RCTs that directly compared intravitreal steroids with observation for CRVO-ME (GENEVA; SCORE). Summary information regarding the two RCTs are included below with detailed information provided in the Characteristics of included studies table.

Types of participants: A total of 1538 participants, 708 with CRVO-ME, were enrolled in the two trials (GENEVA; SCORE). The baseline characteristics of participants in both trials were similar with respect to age, gender, and co-morbidities (e.g., diabetes mellitus, hypertension, and coronary artery disease). SCORE investigators enrolled 271 participants from the US with CRVO, best-corrected visual acuity ranging from 20/40 to 20/400 and retinal thickness 250 microns. GENEVA investigators at multiple study sites around the world enrolled participants with CRVO (n = 437) or BRVO (n = 930) and visual acuity between 20/50 and 20/200 with retinal thickness 300 microns. Both trials enrolled one study eye per participant; when both eyes of a participants were eligible, the eye with the shorter duration of macular edema was selected in the GENEVA study (the SCORE study did not report how the study eye was selected if both eyes were eligible).

Types of interventions: Both trials compared two different doses of intravitreal steroid with control, but different steroids and methods of intravitreal delivery were used between the two trials. 1 mg and 4 mg intravitreal injections of triamcinolone acetonide (with retreatment at four-month intervals) were compared to observation in the SCORE study while 0.35 mg and 0.70 mg dexamethasone intravitreal implants were compared to sham injection in the GENEVA study. After the first six months, participants in GENEVA were eligible for retreatment with either dose of the dexamethasone implant and followed for an additional 12 months in an open-label extension.

Types of outcomes: Both trials used the Early Treatment of Diabetic Retinopathy Scale (ETDRS) to measure visual acuity; investigators reported the proportion of participants who gained 15 letters or more of best-corrected visual acuity (BCVA) and the mean change in BCVA from baseline to a predetermined time point. The mean change in retinal thickness from baseline to a time point, based on optical coherence tomography of central subfield retinal thickness, was reported in both trials. Neither trial reported mean change in macular edema grade (assessed by area of leakage or area of edema), mean change in electroretinogram recordings, number of interventions performed, economic outcomes, or quality-of-life outcomes.

The greatest source of variation in terms of outcomes was the follow-up interval. There was no overlap in the time points at which any of the above outcome measures were reported in the two trials. SCORE investigators followed up participants at four-month intervals for 12

months, and then annually for 36 months. The GENEVA trial follow-up schedule was 1, 7, 30, 60, 90 and 180 days post-treatment.

Excluded studies—See the 'Characteristics of excluded studies' table for details of the 13 studies that were screened and excluded. Ten studies were not RCTs, one study was not eligible as intravitreal steroids were compared with laser treatment, one study was of participants with CRVO but not all had macular edema, and one study was excluded because follow-up was shorter than six months.

Risk of bias in included studies

Figure 2 provides a summary of our judgements for each risk of bias domain for the included studies.

Allocation—We judged both GENEVA and SCORE to be at low risk of selection bias because the investigators used appropriate methods to generate the randomization sequence and to conceal each allocation before assigning it.

Masking of study participants and personnel (performance bias)—Although participants in SCORE were masked to the doses of steroid injections (1 mg vs 4 mg), they were not masked to treatment assignment of observation versus steroid injection, suggesting a high risk of bias. A needle-less applicator was used to apply a sham injection in the control group in GENEVA. Thus, participants allocated to implants were masked to the dose (0.35 mg and 0.70 mg), but not to the treatment assignment (steroid implant versus no implant), resulting in high risk of bias. GENEVA and SCORE investigators were also unmasked to the treatment assignment (intravitreal steroid versus no steroid), although they were masked to the dosage assignment within the groups receiving steroids.

Masking of outcome assessors (detection bias)—Both SCORE and GENEVA used masked observers and technicians to assess OCT and visual acuity measurements. Thus, they both were at low risk of detection bias.

Incomplete outcome data—We observed a much higher proportion of missing data in the observation group (17%) compared to both steroid injection groups (10%) at the 12 month visit in the SCORE trial. Analysis was performed based on participants with available 12-month data assuming all missing data were missing at random, leading us to judge SCORE as having a high risk of bias for incomplete outcome data.

GENEVA investigators reported the combined number of BRVO and CRVO participants with missing data and reasons for the missing data at the end of six months which were consistent across treatment groups. We could not determine the amount of, or reasons for, missing data among the CRVO subgroup and therefore judged GENEVA to have an unclear risk of bias for incomplete outcome data.

Selective reporting—We judged SCORE to have a low risk of bias for selective outcome reporting as all primary and secondary outcomes were reported according to prespecified methods. Based on information provided in the GENEVA trial registry, a number of

secondary outcomes (e.g., contrast sensitivity, vessel leakage and quality of life assessments) were to be measured from one to 12 months, the results of which were not provided in the clinical trial registry results section, six month report or 12 month report (for either BRVO or CRVO). Macular thickness was a secondary outcome for only one of the trials, but the six month report used pooled data from both trials to analyze this outcome. Although GENEVA's six month report described key efficacy variables for a prespecified CRVO subgroup analysis, there was no information about central retinal thickness for just the CRVO subgroup. Thus we judged GENEVA to have a high risk of bias.

Other potential sources of bias—For the SCORE trial, study drugs were provided by the pharmaceutical company Allergan which also provided funding for study site visits and conducted secondary analyses. It is unclear whether this support could have introduced bias. Furthermore, the intravitreal triamcinolone group (both 1 mg and 4 mg) had additional safety visits at 4 days and 4 weeks to make visual acuity and IOP measurements and to perform a dilated fundus examination. Thus, participants in the steroid groups may have perceived that they were getting superior care which may have introduced additional performance bias. GENEVA had a similar source of bias: personnel from Allergan – the study sponsor – participated in the design of the study and in data analysis and interpretation, and also supervised the preparation of the final manuscript. This involvement of the sponsor was judged to result in a high risk of bias. Furthermore, GENEVA conducted two separate trials for regulatory purposes with slightly different primary end points. The final 6 month results from the two GENEVA trials were pooled, possibly introducing external sources of bias.

Effects of interventions

Due to differences in comparisons and outcome measurements between the two included trials, we did not combine trial results in meta-analysis. Rather, we discuss the relevant trial results for each study. Neither trial reported mean change in macular edema grade (assessed by area of leakage or area of edema), mean change in electroretinogram recordings, number of interventions performed, economic outcomes, or quality-of-life outcomes. We assessed the overall quality of evidence as low due to study limitations, imprecision, and selective outcome reporting.

Dexamethasone implant versus sham injection—One trial compared dexamethasone implants (two doses: 0.35 mg and 0.70 mg) with sham injections in 437 participants with CRVO-ME (GENEVA). Outcome data for both primary and secondary outcomes at six months were described for participants with CRVO-ME in a difficult to read figure without sufficient information to estimate steroid effects (i.e., risk ratios or mean differences) or corresponding variances (i.e., confidence intervals, standard deviations, or standard errors). The insufficient reporting of outcomes among the participants with CRVO-ME prevented us from analyzing results regarding the effectiveness of individual or combined doses of the dexamethasone implant compared with sham injection. Based on a qualitative assessment of the published figures and narrative description of the effects of the two doses of the dexamethasone implant in the subgroup of participants with CRVO, there did not appear to be a difference between either dose group and the sham group at six

months with respect to gaining 15 letters or more BCVA or mean change in BCVA from baseline. Change in macular thickness was not reported in the figures or in the text for the CRVO subgroup. We assessed the quality of evidence comparing dexamethasone implants with sham injections as low due to limitations of the trial and lack of quantitative results for eyes with CRVO-ME for any outcome.

Triamcinolone acetonide versus observation—One trial compared triamcinolone acetonide (two doses: 1 mg and 4 mg) with observation in 271 participants with CRVO-ME (SCORE). SCORE investigators did not designate a six-month evaluation for primary or secondary outcomes specified for this review. We therefore evaluated each of the primary and secondary outcomes at time points beyond six months as reported. At the 12-month primary follow-up time for the trial, visual acuity data were available for 238 (88%) of 271 total participants. At 24 months, the longest follow-up in the study, visual acuity data were available for 151 (56%) of 271 total participants.

Improvement in visual acuity: Both doses of triamcinolone acetonide (1 mg and 4 mg) were associated with a greater proportion of participants who experienced a gain of 15 letters or more of BCVA when compared with observation at 8 months (1 mg RR: 5.27, 95% CI 1.62 to 17.15; 4 mg RR: 4.92, 95% CI 1.50 to 16.10), 12 months (1 mg RR: 3.87, 95% CI 1.54 to 9.70; 4 mg RR: 3.74, 95% CI 1.49 to 9.41), 16 months (1 mg RR: 2.63, 95% CI 1.11 to 6.28; 4 mg RR: 2.87, 95% CI 1.21 to 6.78), 20 months (1 mg RR: 2.52, 95% CI 0.98 to 6.46; 4 mg RR: 2.08, 95% CI 0.78 to 5.51), and 24 months (1 mg RR: 3.55, 95% CI 1.29 to 9.82; 4 mg RR: 2.99, 95% CI 1.05 to 8.52) follow-up (Analysis 1.1; Analysis 2.1). Results were similar when results from the two triamcinolone acetonide groups were combined and compared with the observation group (RR: 5.09, 95% CI 1.62 to 16.02 at 8 months; RR: 3.80, 95% CI 1.57 to 9.21 at 12 months; RR: 2.75, 95% CI 1.22 to 6.21 at 16 months; RR: 2.30, 95% CI 0.94 to 5.65 at 20 months; and RR: 3.29, 95% CI 1.23 to 8.79 at 24 months) (Analysis 3.1).

The large relative effects seen in both doses compared with observation across each time point suggest that eyes treated with triamcinolone acetonide may be up to five times more likely to experience improvement in BCVA than those not treated. However, none of the differences between groups (each dose separately or the two dose groups combined compared to control) were statistically significant at 20 months follow-up, and the amount of missing data throughout the 24 months of follow-up adds uncertainty to the size and precision of these estimates. For these reasons, we graded the quality of evidence for this outcome as low.

Change in visual acuity: Overall there was a decrease in the average BCVA from baseline through 24 months of follow-up in all three groups. Participants treated with either dose of triamcinolone acetonide lost approximately six to 11 fewer letters than participants in the observation group at 8 months (1 mg MD: 8.70 letters, 95% CI 1.86 to 15.54; 4 mg MD: 9.80 letters, 95% CI 3.32 to 16.28), 12 months (1 mg MD: 10.90 letters, 95% CI 3.80 to 18.00; 4 mg MD: 10.90 letters, 95% CI 3.80 to 18.00), 16 months (1 mg MD: 9.90 letters, 95% CI 2.47 to 17.33; 4 mg MD: 7.80 letters, 95% CI 0.02 to 15.58), 20 months (1 mg MD: 7.30 letters, 95% CI −1.23 to 15.83; 4 mg MD: 4.30 letters, 95% CI −4.23 to 12.83), and 24

months (1 mg MD: 6.30 letters, 95% CI −3.22 to 15.82; 4 mg MD: −0.93 letters, 95% CI −0.93 to 17.53) (Analysis 1.2; Analysis 2.2). Results were similar when doses were combined and compared with the observation group (MD: 9.25 letters, 95% CI 3.61 to 14.90 at 8 months; MD: 10.90 letters, 95% CI 4.80 to 17.00 at 12 months; MD: 8.87 letters, 95% CI 2.28 to 15.45 at 16 months; MD: 5.82 letters, 95% CI −1.54 to 13.19 at 20 months; and MD: 7.30 letters, 95% CI −0.72 to 15.32 at 24 months) (Analysis 3.2). The smaller reductions in loss of BCVA in the 1 mg and 4 mg triamcinolone groups, or the two groups combined, compared with the observation group were not statistically significant at 20 and 24 months follow-up. Again, the imprecision of these estimates and the amount of missing data adds further uncertainty to these estimates across all follow-up periods. Therefore, we graded the quality of evidence for this outcome as low.

Change in macula thickness: Participants in all three groups had a decrease in the median center point thickness throughout the 24 months of follow-up (Table 1). Given the way these data were reported (median and interquartile range) we were not able to estimate a treatment effect for this outcome. Qualitatively, no clinically meaningful difference in the decrease in center point thickness between groups throughout 24 months follow-up was observed. We assessed the quality of evidence for this outcome as low due to lack of quantitative data and missing data at 24 months follow-up.

Adverse events—Overall, more adverse events occurred in both the 4 mg triamcinolone acetonide group (35%) and 1 mg group (20%) compared with the observation group (8%) in the SCORE study through 12 months of follow-up. Almost twice as many participants were reported to have experienced an ocular adverse event in the GENEVA trial steroid groups compared to the control group, with 63% of participants in the 0.7 mg and 62% of participants in the 0.35 mg dexamethasone implant groups experiencing an ocular adverse event compared with 43% of participants in the sham injection group. The most common adverse events were related to elevated IOP and cataract in both trials (Table 2; Table 3). Although less common, vitreous hemorrhage and retina hemorrhage and detachment also were reported from both trials. Ocular adverse events that required additional medical treatment were reported from SCORE.

DISCUSSION

Summary of main results

When the original version of this review was published in 2009, no RCTs had yet been completed (Gewaily 2009). With the recent completion and publication of results from two RCTs – SCORE and GENEVA – we have more information regarding the effects of two different methods of administration of intravitreal steroids for CRVO-ME. Based on the available published evidence from GENEVA, neither dose of the dexamethasone implant appeared to provide clinically meaningful improvements in BCVA at six months compared with the sham injection group. Throughout longer follow-up periods, results from SCORE suggested that intravitreal injections of triamcinolone acetonide may provide benefits in terms of a greater proportion of participants experiencing an improvement in BCVA as well as an overall smaller decrease in BCVA compared with observation alone. However, the

imprecision of the effect estimates and considerable amount of missing data through follow-up in SCORE warrants caution in interpreting these results. Furthermore, although the differences between treatment and observation groups with respect to the mean changes in BCVA reported by SCORE are striking, the modest improvements in BCVA are overshadowed by an overall loss of BCVA from baseline. As much as 25% of study eyes in the treatment group continued to experience moderate losses of BCVA.

Adverse events were noted in at least a quarter of the participants in SCORE given intravitreal steroids. GENEVA reported a higher incidence of adverse events: over 60% in dexamethasone implant groups and over 40% in the control group. Although the control groups in both trials experienced adverse events, the treatment groups had noticeably more. The most common adverse events were elevations of IOP and progression of cataracts. Additional side effects, such as retinal neovascularization, were also reported but were rare. In both SCORE and GENEVA, retinal neovascularization was seen more often in observation groups than in steroid groups, which may suggest that intravitreal steroids help to reduce neovascularization, a known complication of untreated CRVO-ME.

Overall completeness and applicability of evidence

Athough both RCTs included in the update of this review addressed the primary objective of the review, neither trial provided complete data for the primary or secondary outcomes of interest at six months as pre-specified for this review. We also observed significant heterogeneity in terms of the actual steroids used, retreatment schedules, and follow-up intervals which limited our ability to draw conclusions. In the SCORE study, retreatment was common, making it difficult to assess a specific treatment schedule. Adding to the insufficient reporting of outcome data, one trial included participants with both CRVO- and BRVO-ME, and did not clearly report outcomes for the CRVO-ME participants separately (GENEVA). At the time this review was originally conceived, observation was considered standard practice for treating CRVO-ME based on results from CVOS 1995. In the time since the initial publication of this review, standard of care has evolved with evidence for intravitreal steroids and the introduction of newer treatment options including anti-vascular growth factor (anti-VEGF) agents. Thus, observation may no longer be the most appropriate method of managing CRVO against which to compare the efficacy of steroids.

Quality of the evidence

Neither RCT was free of potential biases which may call into question the validity and reliability of study results. Of note, in neither SCORE nor GENEVA were participants masked to the assigned group (steroid vs observation) which could have resulted in performance bias affecting the observed outcomes. In SCORE, there was a differential proportion of missing data between the two steroid groups and the observation group. Incomplete documentation of the reasons for loss of follow-up data makes it difficult to determine whether the reasons for missing data were treatment-related. When comparing the published reports and trial registrations for GENEVA, we noticed potential selective outcome reporting as not all pre-specified outcomes and subgroup analyses (CRVO participants) had been published. Furthermore, GENEVA pooled results from two independent trials, which limits our ability to comment on any potential variability in the

participants, methods, or results from each trial independently. Due to these study limitations, imprecision in effect estimates, and inconsistency in results, we graded the overall quality of the evidence as low.

Potential biases in the review process

A potential bias in the review process is that the level of visual acuity improvement specified for this review was not reported completely by the included studies; we relied on the way that the authors of the GENEVA and SCORE trials reported this outcome (15 letters or more improvement). We also included the GENEVA trial which enrolled participants who did not meet the eligibility criteria specified for this review (participants with branch retinal vein occlusion were included in addition to participants with CRVO). However, given that randomization was stratified by branch and central retinal vein occlusion and the trial investigators pre-specified subgroup analyses by type of retinal vein occlusion, it was appropriate to include this trial. We also judged the control group in the GENEVA trial, which received a sham injection, to be comparable to observation. We were not able to evaluate the presence of publication bias through inspection of funnel plots.

Agreements and disagreements with other studies or reviews

Based on unpublished data related to participants with CRVO in GENEVA, a report from the Aberdeen Health Technology Assessment Group sponsored by the National Institute for Health Research Health Technology Assessment Programme (UK) showed no difference between the 0.70 mg dexamethasone implant and sham group in the proportion of participants who gained 15 letters or more BCVA at six months or in the mean change in BCVA from baseline to six-month follow-up (Shyangdan 2010). The conclusions based on the unpublished data for the CRVO participants in GENEVA are consistent with our qualitative assessment of the limited information in this subgroup of participants provided in the published reports. In terms of adverse events, the 0.70 mg dexamethasone implant was also shown to be associated with an increase in the frequency of adverse events (i.e., increased IOP and ocular hypertension, retinal neovascularization and retinal detachment).

Results from the observational studies cited in the previous publication of this review are consistent with the findings from SCORE with regards to improvements in visual acuity (Gewaily 2009). Bashshur 2004 found improvements in visual acuity in individuals treated with 4 mg of triamcinolone acetonide after 10 to 12 months of follow-up, although this study excluded ischemic CRVOs. The Cheng 2009 study, which included both ischemic and non-ischemic CRVO cases, also found improvement in visual acuity amongst treated patients. In general, visual acuity improvements were more noticeable in non-ischemic CRVO as reported by subgroup analyses performed in the Gelston 2006 and Jonas 2005a studies. The results from the Jonas 2005a study seem to agree with those from GENEVA in that visual acuity returned to baseline approximately five months after intravitreal triamcinolone acetonide treatment in all CRVO participants after an initial significant improvement of visual acuity from baseline. This change was more pronounced in non-ischemic CRVO.

Macular edema resolution was not emphasized in the observational studies. The only quantitative results related to macular edema came from the Bashshur 2004 and Cheng 2009 studies. The Bashshur 2004 study found noticeable improvements in macular edema with treatment but 2 of 20 treated eyes re-developed macular edema during the study. OCT results in the Cheng 2009 study revealed a significant decrease in macular edema among treated eyes, although edema reoccurred in 6 of 22 study eyes.

Adverse events were consistent across observational studies and agree with the included trials. The most common complication was an increase in IOP. In all four observational studies, immediate paracentesis of the anterior chamber was performed alongside the intravitreal steroid injection, either conditionally or routinely. The Gelston 2006 and Jonas 2005a studies showed transient increases in IOP which eventually returned to baseline at later follow-up visits. Retinal toxicity reported in rabbit models (Lang 2007; Ruiz-Morena 2007) and some human cases (Kivilcim 2000) was not observed in SCORE or GENEVA.

Two other interesting (but rare) potential complications to note include the unmasking of ocular syphilis and cytomegalovirus retinitis after intravitreal steroid treatment. These were reported in small case reports by Mushtaq 2009 and Sekiryu 2008 respectively. It is worth noting that in both case series' some of the affected individuals had complicating histories including preexisting immunosuppression or infection (Appendix 7).

Similar to GENEVA and SCORE, a number of case series' reported sustained improvements in BCVA and some reported relapses or only transient improvements in BCVA (Batioglu 2007; Goff 2006; Gregori 2006; Ip 2003; Ip 2004; Krepler 2005; Moschos 2007; Ozdek 2005; Park 2003; Williamson 2005). They also agree that improvements in macular edema are transient. On the other hand, individual case reports indicated that patients were more likely to have improved BCVA (Al-Dhibi 2007; Ip 2002; Jonas 2002; Karacorlu 2004; Paques 2005).

AUTHORS' CONCLUSIONS

Implications for practice

In the original version of this review, it was not possible to draw reliable conclusions about the benefits and harms from intravitreal steroids in people with CRVO-ME. Despite the completion of two RCTs (GENEVA; SCORE) uncertainty remains regarding the overall benefits of intravitreal steroids in terms of reducing vision loss associated with CRVO or improving vision compared with no treatment. Furthermore, there is a clear increase in adverse events when using intravitreal steroids including increased IOP, cataract progression, and retinal detachment.

Implications for research

In this review we evaluated two different agents and methods of administering intravitreal steroids (triamcinolone acetonide injection and dexamethasone implant). We did not plan to make a head-to-head comparison of these two methods for corticosteroid delivery, but it is possible that the type of delivery (injection versus implant) and the length of time over which the steroid is delivered, as well as the type of steroid itself, could affect outcomes.

Results from both GENEVA and SCORE suggest that retreatments may be necessary in order to maintain the benefits. The need for dexamethasone retreatment is further supported by a recent case study (Joshi 2013) and the unpublished data from GENEVA (Shyangdan 2010) which suggest that the effects of dexamethasone implants may not last for six months and may begin to wane after 60 days. In SCORE, participants in the 1 mg and 4 mg triamcinolone treatment groups were eligible for retreatment every four months, with participants in both groups having an average of two injections in the first 12 months. Therefore, the number and frequency of treatments and retreatments remains unclear.

Results from the SCORE study indicate sustained visual improvements when compared with observation up to 24 months after steroid injection, however about 25% of treated participants had significant visual loss. Thus, there is room for improvement in therapy. Results from CVOS 1995 indicated that visual acuity improvements may not be linked to ME changes, as also observed in SCORE. The failure of anatomical improvements to correlate with functional outcomes associated with the use of intravitreal steroids underscores the need to identify a possible alternative mechanism for the salvage of visual acuity. Research into alternate agents with other mechanisms of action, such as neuroprotective factors, may prove fruitful. As multiple randomized controlled trials have shown success with anti-VEGF treatments for CRVO-ME (Braithwaite 2014), further research will need to incorporate these agents as a standard treatment for CRVO-ME.

Acknowledgments

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Macular Edema, Cystoid

#2 MeSH descriptor Edema

#3 MeSH descriptor Macula Lutea

#4 macula* near/3 oedema

#5 macula* near/3 edema

#6 CME or CMO

#7 (#1 OR #2 OR #3 OR #4 OR #5 OR #6)

#8 MeSH descriptor Retinal Vein Occlusion

#9 MeSH descriptor Retinal Vein

#10 retina* near/3 (vein* or occlu* or obstruct* or clos* or stricture* or steno* or block* or embolism*)

#11 CRVO or CVO or RVO

#12 (#8 OR #9 OR #10 OR #11)

#13 MeSH descriptor Steroids

#14 MeSH descriptor Triamcinolone

#15 MeSH descriptor Triamcinolone Acetonide

#16 triamcin* or acetonide or kenalog*

#17 steroid* or glucorticoid*

#18 (#13 OR #14 OR #15 OR #16 OR #17)

#19 (#6 AND #12 AND #18)

Appendix 2. MEDLINE (OvidSP) search strategy

1. randomized controlled trial.pt.

2. (randomized or randomised).ab,ti.

3. placebo.ab,ti.

4. dt.fs.

5. randomly.ab,ti.

6. trial.ab,ti.

7. groups.ab,ti.

8. or/1–7

9. exp animals/

10. exp humans/

11. 9 not (9 and 10)

12. 8 not 11

13. exp macular edema cystoid/

14. exp edema/

15. exp macula lutea/

16. (macula$ adj3 oedema).tw.

17. (macula$ adj3 edema).tw.

18. (CME or CMO).tw.

19. or/13–18

20. exp retinal vein occlusion/

21. exp retinal vein/

22. ((vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$) adj3 retina$).tw.

23. (CRVO or CVO or RVO).tw.

24. or/20–23

25. exp steroids/

26. exp triamcinolone/

27. exp triamcinolone acetonide/

28. (triamcin$ or acetonide$ or kenalog$).tw.

29. (steroid$ or glucocorticoid$).tw.

30. or/25–29

31. 19 and 24 and 30

32. 12 and 31

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville (Glanville 2006).

Appendix 3. EMBASE (OvidSP) search strategy

1. exp randomized controlled trial/

2. exp randomization/

3. exp double blind procedure/

4. exp single blind procedure/

5. random$.tw.

6. or/1–5

7. (animal or animal experiment).sh.

8. human.sh.

9. 7and 8

10. 7 not 9

11. 6 not 10

12. exp clinical trial/

13. (clin$ adj3 trial$).tw.

14. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.

15. exp placebo/

16. placebo$.tw.

17. random$.tw.

18. exp experimental design/

19. exp crossover procedure/

20. exp control group/

21. exp latin square design/

22. or/12–21

23. 22 not 10

24. 23 not 11

25. exp comparative study/

26. exp evaluation/

27. exp prospective study/

28. (control$ or prospectiv$ or volunteer$).tw.

29. or/25–28

30. 29 not 10

31. 30 not (11 or 23)

32. 11 or 24 or 31

33. exp retina macula cystoid edema/

34. exp eye edema/

35. exp retina macula lutea/

36. (macula$ adj3 oedema).tw.

37. (macula$ adj3 edema).tw.

38. (CME or CMO).tw.

39. or/33–38

40. exp retinal vein occlusion/

41. exp retina vein/

42. ((vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$) adj3 retina$).tw.

43. (CRVO or CVO or RVO).tw.

44. or/40–43

45. exp steroids/

46. exp triamcinolone/

47. exp triamcinolone acetonide/

48. (triamcin$ or acetonide$ or kenalog$).tw.

49. (steroid$ or glucocorticoid$).tw.

50. or/45–49

51. 39 and 44 and 50

52. 51 and 32

Appendix 4. metaRegister of Controlled Trials search strategy

(Central Retinal Vein Occlusion) AND (Macular Edema)

Appendix 5. ClinicalTrials.gov search strategy

Interventional Studies | macular edema AND retinal vein occlusion | (steroid OR glucocorticoid OR triamcinolone)

Appendix 6. ICTRP search strategy

Macular Edema = Title AND Central Retinal Vein Occlusion = Condition.

Appendix 7. Other complications for intravitreal steroids: select studies

Study (in chronological order)	Complication	Corollary notes
Clemens 2013	Onset and formation of macular hole	–
Turaka 2013	Anterior migration of implant	Patient had history of pars plana vitrectomy and scleral buckle retinal detachment surgery; prior treatment for CRVO-ME with multiple intravitreal bevacizumab and dexamethasone injections

Study (in chronological order)	Complication	Corollary notes
Bakri 2012	Worsening of vitreomacular traction	Patient had diabetes, hypertension, anemia and rheumatoid arthritis
Pardo-Lopez 2012	Diffuse corneal edema and anterior migration of implant	Patient treated for BRVO-ME; patient had prior cataract surgery with intraoperative violation of the lens posterior capsula; implant removed and treated with corneal transplantation
Hirasawa 2009	Secondary macular hole	Patient had mild ROP that resolved spontaneously
Mushtaq 2009	Syphilitic infection of the eye	May have had previous syphilis infection that reactivated locally
Sekiryu 2008	CMV retinitis	Patient was immunocompetent
Roth 2008	Corneal epithelial defect	Thought to be related to pretreatment with povidone-iodine solution
Lattanzio 2007	Macular hole progression	Occurred despite improvement in CME and VA
Konstantopoulos 2007	Phacoanaphylactic glaucoma	Required vitrectomy with cataract surgery
	Retinal detachment	In 2 patients with previous retinal tears
Nkeme 2006	Pseudo-endophthalmitis	–
	Transient hypertony	Occurred in 53% eyes
	Full-thickness macular hole	–
Jain 2006	Pseudocataract	Result of adherence of triamcinolone particles to posterior lens
Aggermann 2006	Endophthalmitis with retinal necrosis	Clinically resembles herpetic retinopathies
Yang 2005	Refractory ocular hypertension	–
Srinivasan 2005	Conjunctival necrosis overlaying sclera entry site	Patient treated for BRVO-ME
Kaushik 2004	Intractable glaucoma	–
Benz 2003	Mycobacterium chelonae abscess	Patient treated for diabetic macular edema Eventual enucleation of eye

DATA AND ANALYSES

Comparison 1. 1 mg triamcinolone versus observation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Gain of 15 letters or more (ETDRS)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 8 months follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 12 months follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 16 months follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 20 months follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.5 24 months follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Change in visual acuity (ETDRS) from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 8 months follow-up	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 12 months follow-up	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 16 months follow-up	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 20 months follow-up	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.5 24 months follow-up	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 2. 4 mg triamcinolone versus observation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Gain of 15 letters or more (ETDRS)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 8 months follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 12 months follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 16 months follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 20 months follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.5 24 months follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Change in visual acuity (ETDRS) from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 8 months follow-up	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 12 months follow-up	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 16 months follow-up	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 20 months follow-up	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.5 24 months follow-up	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 3. Combined doses of triamcinolone versus observation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Gain of 15 letters or more (ETDRS)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 8 months follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 12 months follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 16 months follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 20 months follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.5 24 months follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Change in visual acuity (ETDRS) from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 8 months follow-up	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 12 months follow-up	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 16 months follow-up	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 20 months follow-up	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.5 24 months follow-up	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Review: Intravitreal steroids versus observation for macular edema secondary to central retinal vein occlusion

Comparison: 1 1 mg triamcinolone versus observation

Outcome: 1 Gain of 15 letters or more (ETDRS)

Study or subgroup	1 mg triamcinolone n/N	Observation n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 8 months follow-up				
SCORE	18/82	3/72		5.27 [1.62, 17.15]
2 12 months follow-up				
SCORE	22/83	5/73		3.87 [1.54, 9.70]
3 16 months follow-up				
SCORE	17/71	6/66		2.63 [1.11, 6.28]
4 20 months follow-up				
SCORE	15/62	5/52		2.52 [0.98, 6.46]
5 24 months follow-up				
SCORE	17/55	4/46		3.55 [1.29, 9.82]

0.01 0.1 1 10 100

Favors observation   Favors triamcinolone
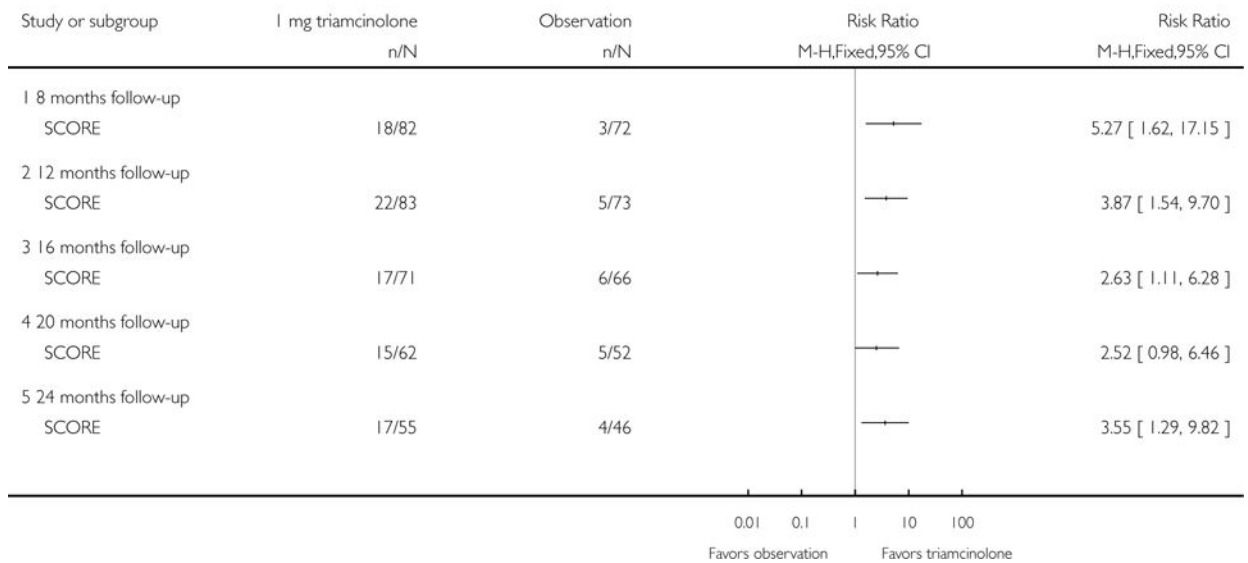
Analysis 1.1.

Comparison 11 mg triamcinolone versus observation, Outcome 1 Gain of 15 letters or more (ETDRS).

Review: Intravitreal steroids versus observation for macular edema secondary to central retinal vein occlusion

Comparison: 1 1 mg triamcinolone versus observation

Outcome: 2 Change in visual acuity (ETDRS) from baseline

Study or subgroup	1 mg triamcinolone		Observation		Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
	N	Mean(SD)	N	Mean(SD)		
1 8 months follow-up						
SCORE	82	-3 (24.1212)	72	-11.7 (19.1499)		8.70 [1.86, 15.54]
2 12 months follow-up						
SCORE	83	-1.2 (23.8143)	73	-12.1 (21.43)		10.90 [3.80, 18.00]
3 16 months follow-up						
SCORE	71	-1.5 (21.9691)	66	-11.4 (22.3731)		9.90 [2.47, 17.33]
4 20 months follow-up						
SCORE	62	-2.5 (24.414)	66	-9.8 (24.8138)		7.30 [-1.23, 15.83]
5 24 months follow-up						
SCORE	50	-4.4 (25.3346)	46	-10.7 (22.225)		6.30 [-3.22, 15.82]

-20 -10 0 10 20

Favors observation   Favors triamcinolone

Analysis 1.2.

Comparison 11 mg triamcinolone versus observation, Outcome 2 Change in visual acuity (ETDRS) from baseline.

Review: Intravitreal steroids versus observation for macular edema secondary to central retinal vein occlusion

Comparison: 2 4 mg triamcinolone versus observation
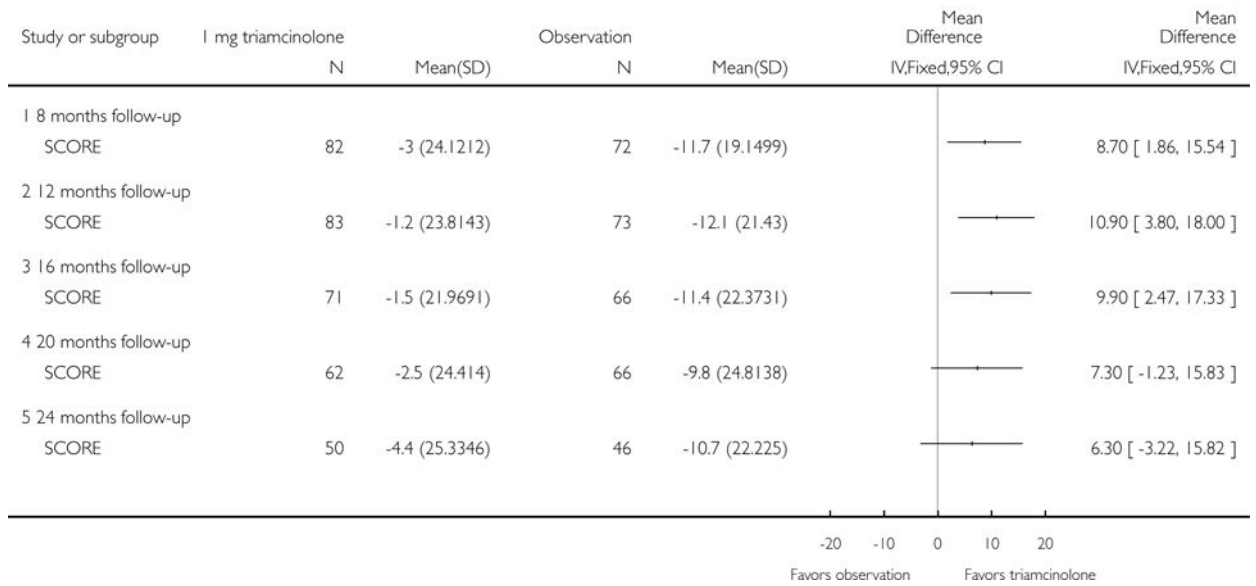
Outcome: 1 Gain of 15 letters or more (ETDRS)

Study or subgroup	4 mg triamcinolone n/N	Observation n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 8 months follow-up				
SCORE	17/83	3/72		4.92 [1.50, 16.10]
2 12 months follow-up				
SCORE	21/82	5/73		3.74 [1.49, 9.41]
3 16 months follow-up				
SCORE	18/69	6/66		2.87 [1.21, 6.78]
4 20 months follow-up				
SCORE	12/60	5/52		2.08 [0.78, 5.51]
5 24 months follow-up				
SCORE	13/50	4/46		2.99 [1.05, 8.52]

0.01 0.1 1 10 100
Favors observation   Favors triamcinolone

Analysis 2.1.
Comparison 24 mg triamcinolone versus observation, Outcome 1 Gain of 15 letters or more (ETDRS).

Review: Intravitreal steroids versus observation for macular edema secondary to central retinal vein occlusion

Comparison: 2 4 mg triamcinolone versus observation

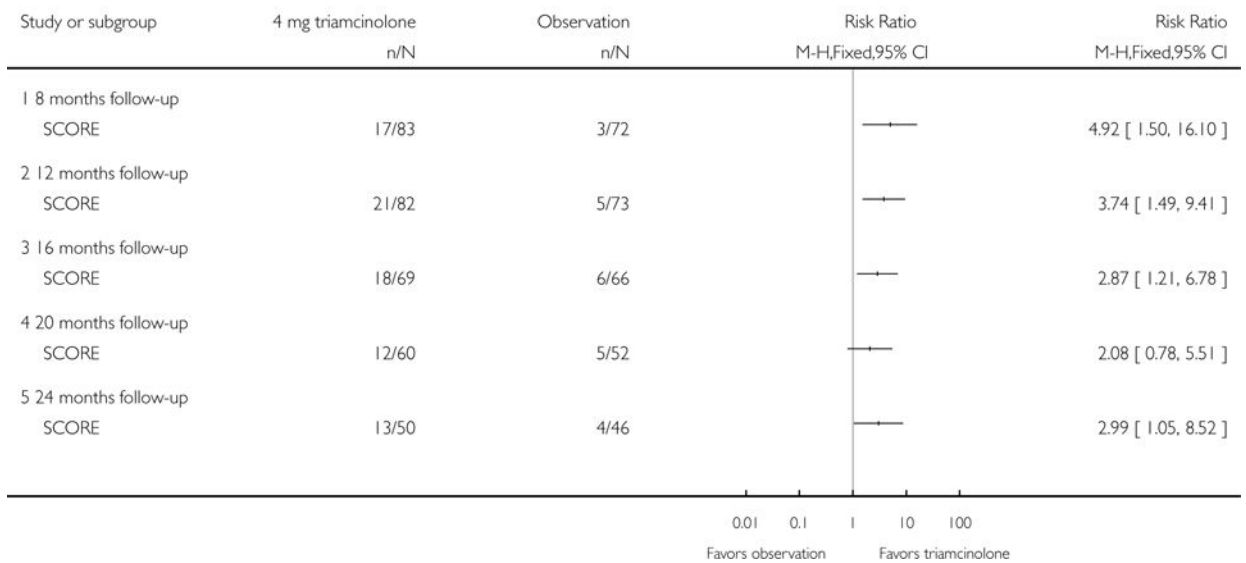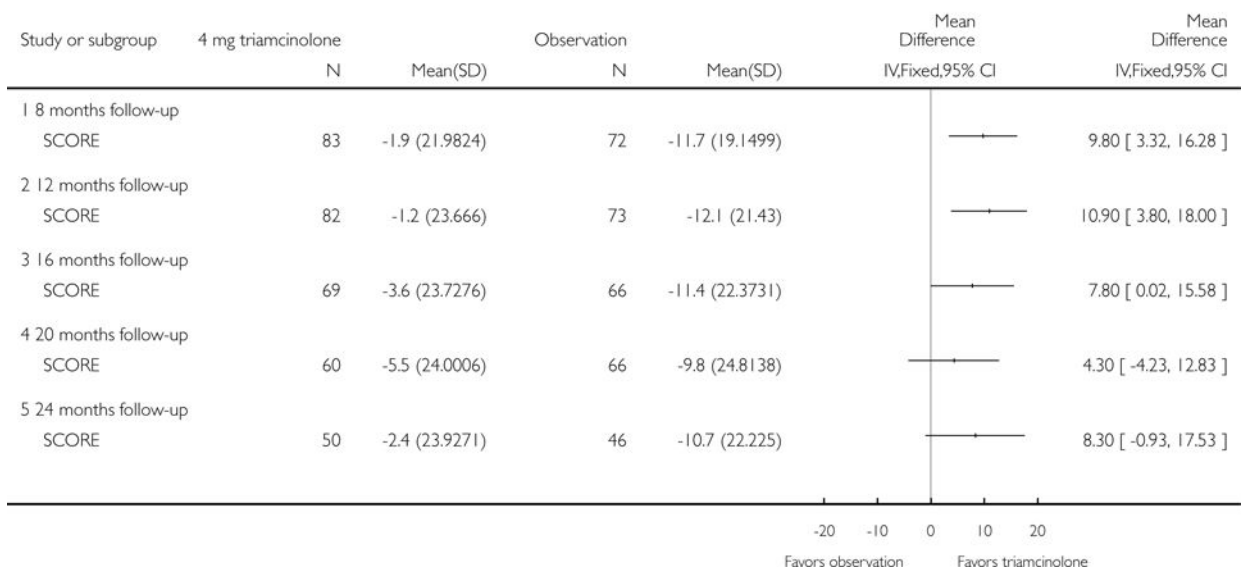Outcome: 2 Change in visual acuity (ETDRS) from baseline

Study or subgroup	4 mg triamcinolone N	Mean(SD)	Observation N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 8 months follow-up						
SCORE	83	-1.9 (21.9824)	72	-11.7 (19.1499)		9.80 [3.32, 16.28]
2 12 months follow-up						
SCORE	82	-1.2 (23.666)	73	-12.1 (21.43)		10.90 [3.80, 18.00]
3 16 months follow-up						
SCORE	69	-3.6 (23.7276)	66	-11.4 (22.3731)		7.80 [0.02, 15.58]
4 20 months follow-up						
SCORE	60	-5.5 (24.0006)	66	-9.8 (24.8138)		4.30 [-4.23, 12.83]
5 24 months follow-up						
SCORE	50	-2.4 (23.9271)	46	-10.7 (22.225)		8.30 [-0.93, 17.53]

-20 -10 0 10 20
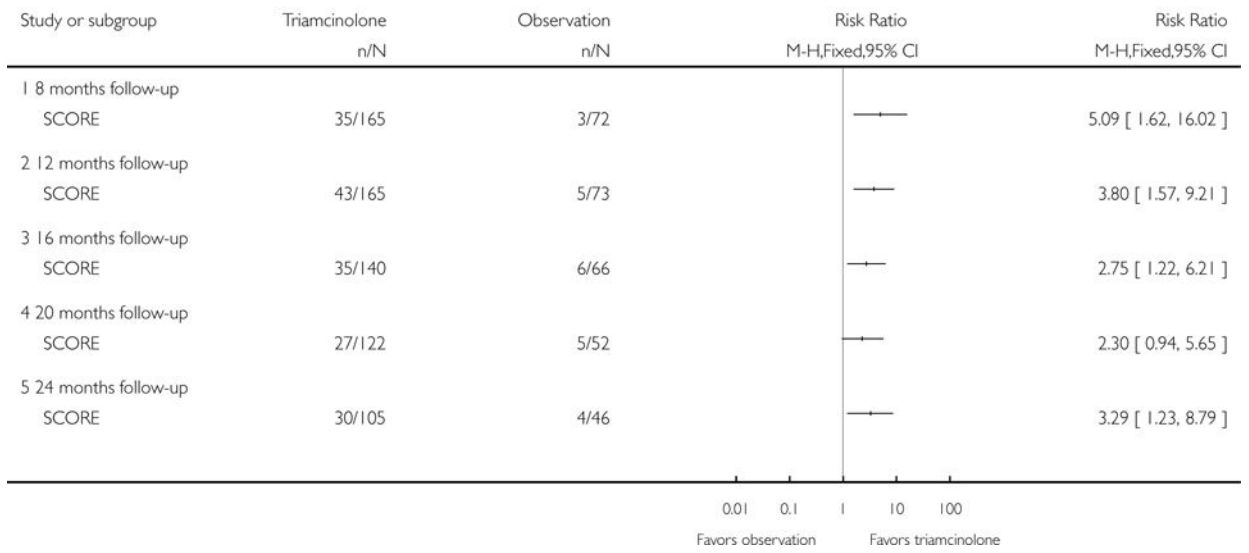Favors observation   Favors triamcinolone

Analysis 2.2.

Comparison 24 mg triamcinolone versus observation, Outcome 2 Change in visual acuity (ETDRS) from baseline.

Review: Intravitreal steroids versus observation for macular edema secondary to central retinal vein occlusion

Comparison: 3 Combined doses of triamcinolone versus observation

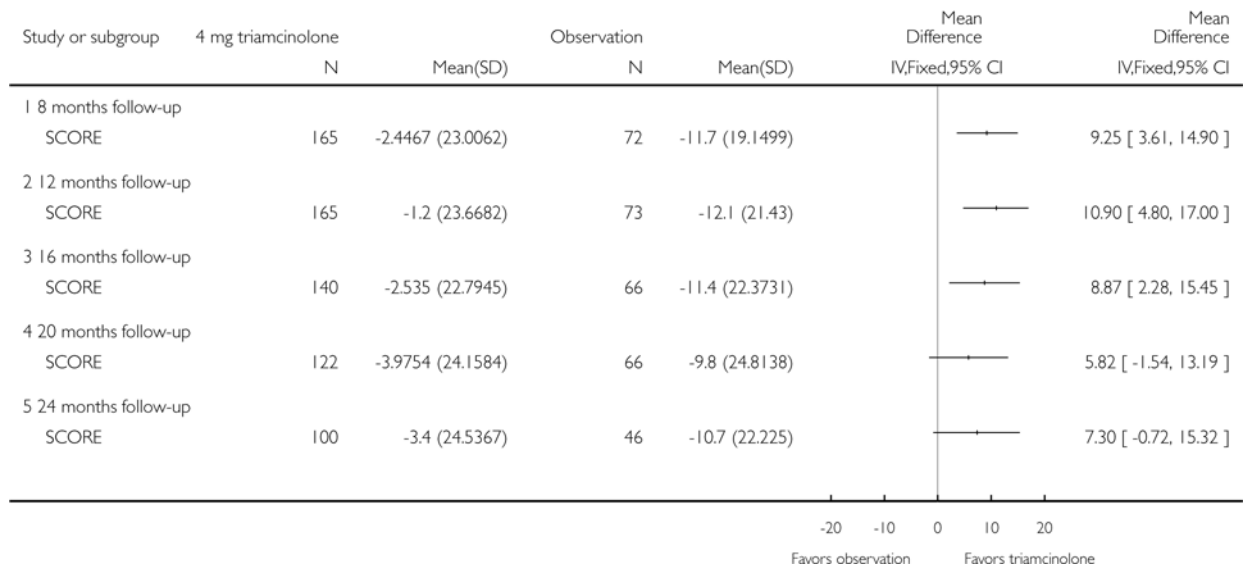Outcome: 1 Gain of 15 letters or more (ETDRS)

Study or subgroup	Triamcinolone n/N	Observation n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 8 months follow-up				
SCORE	35/165	3/72		5.09 [1.62, 16.02]
2 12 months follow-up				
SCORE	43/165	5/73		3.80 [1.57, 9.21]
3 16 months follow-up				
SCORE	35/140	6/66		2.75 [1.22, 6.21]
4 20 months follow-up				
SCORE	27/122	5/52		2.30 [0.94, 5.65]
5 24 months follow-up				
SCORE	30/105	4/46		3.29 [1.23, 8.79]

0.01   0.1   1   10   100

Favors observation   Favors triamcinolone

Analysis 3.1.

Comparison 3 Combined doses of triamcinolone versus observation, Outcome 1 Gain of 15 letters or more (ETDRS).

Review: Intravitreal steroids versus observation for macular edema secondary to central retinal vein occlusion

Comparison: 3 Combined doses of triamcinolone versus observation

Outcome: 2 Change in visual acuity (ETDRS) from baseline

Study or subgroup	4 mg triamcinolone		Observation		Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
	N	Mean(SD)	N	Mean(SD)		
1 8 months follow-up						
SCORE	165	-2.4467 (23.0062)	72	-11.7 (19.1499)		9.25 [3.61, 14.90]
2 12 months follow-up						
SCORE	165	-1.2 (23.6682)	73	-12.1 (21.43)		10.90 [4.80, 17.00]
3 16 months follow-up						
SCORE	140	-2.535 (22.7945)	66	-11.4 (22.3731)		8.87 [2.28, 15.45]
4 20 months follow-up						
SCORE	122	-3.9754 (24.1584)	66	-9.8 (24.8138)		5.82 [-1.54, 13.19]
5 24 months follow-up						
SCORE	100	-3.4 (24.5367)	46	-10.7 (22.225)		7.30 [-0.72, 15.32]

```
        -20   -10    0    10   20
     Favors observation   Favors triamcinolone
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Analysis 3.2.

Comparison 3 Combined doses of triamcinolone versus observation, Outcome 2 Change in visual acuity (ETDRS) from baseline.

CONTRIBUTIONS OF AUTHORS

Conceiving the review: CEVG, PBG

Designing the review: PBG

Coordinating the review: PBG

Data collection for the review

- Designing search strategies: DG, PBG, CEVG

- Undertaking searches: CEVG, DG, PBG

- Screening search results: DG, PBG, KM

- Organizing retrieval of papers: DG

- Screening retrieved papers against inclusion criteria: DG, PBG, KM

- Appraising quality of papers: DG, PBG, KM

- Extracting data from papers: DG, PBG, KM

- Writing to authors of papers for additional information: DG, PBG

- Providing additional data about papers: DG, PBG

- Obtaining and screening data on unpublished studies: CEVG, DG, PBG

Data management for the review

- Entering data into RevMan: DG, KM

- Analysis of data: DG, PBG, KM

Interpretation of data

- Providing a methodological perspective: DG, PBG, KM

- Providing a clinical perspective: PBG

- Providing a policy perspective: PBG

- Providing a consumer perspective: DG, PBG

Writing the review: DG, PBG, KM

Providing general advice on the review: PBG

Securing funding for the review: PBG

Performing previous work that was the foundation of the current study: PBG

Updating the review: DG, PBG, KM

DECLARATIONS OF INTEREST

DG, PBG, KM: none known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Our review protocol stated that we would include trials with any dosage and duration of treatment (Gewaily 2008); however, after further reflection, we felt that duration of treatment less than six months may not be appropriate to compare steroid and observation groups. Intravitreal steroid treatment regimens generally consist of multiple injections administered every few months, in which case trials with less than six months duration may only measure the effects of a single injection, such as with SCORE in which injections were administered every four months. Thus, we modified the eligibility criteria to include trials with any dosage and duration of treatment of at least six months.

Due to the lack of comparability between treatment interventions between included studies, we did not conduct methods specified in the protocol for this review in regards to meta-synthesis, subgroup analysis, and sensitivity analysis. We performed GRADE assessments of the quality of the evidence, which was not specified in the protocol for this review, but has become standard procedure for Cochrane reviews of treatment interventions.

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* Indicates the major publication for the study

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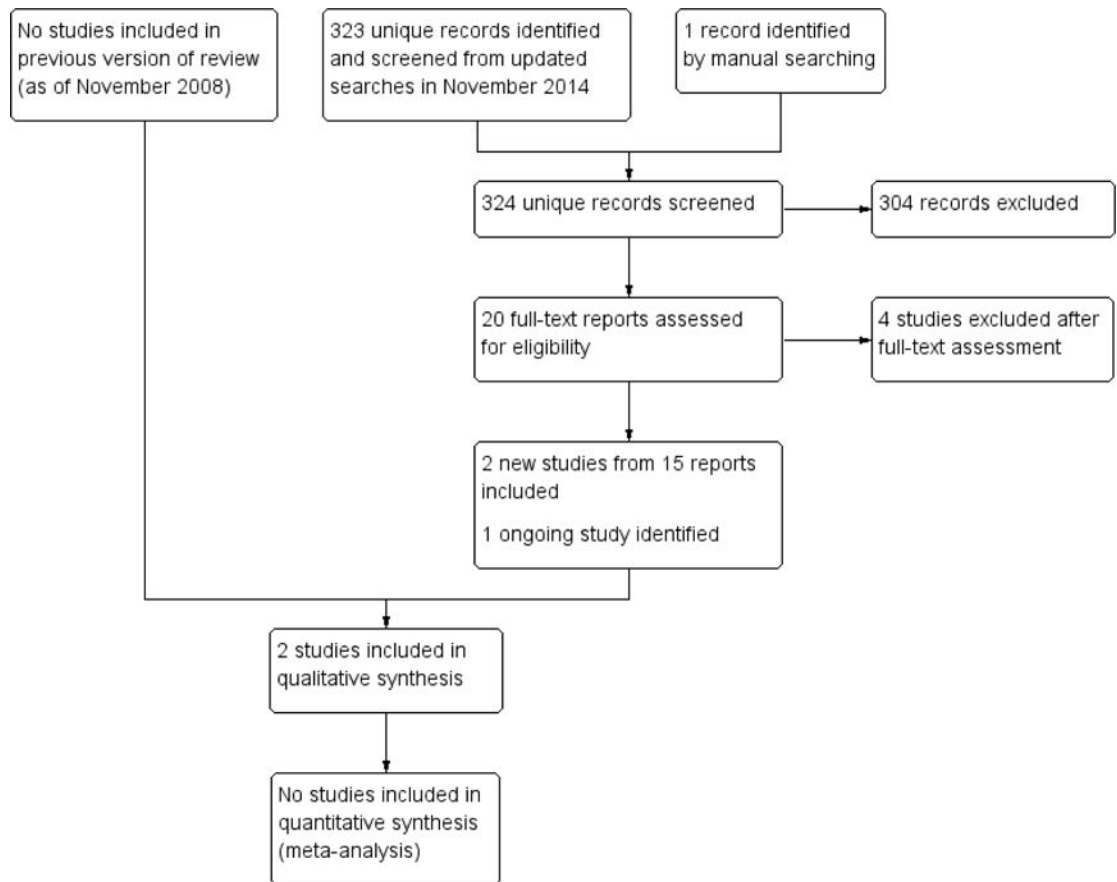
No studies included in previous version of review (as of November 2008)

323 unique records identified and screened from updated searches in November 2014

1 record identified by manual searching

324 unique records screened → 304 records excluded

20 full-text reports assessed for eligibility → 4 studies excluded after full-text assessment

2 new studies from 15 reports included

1 ongoing study identified

2 studies included in qualitative synthesis

No studies included in quantitative synthesis (meta-analysis)

Figure 1.
Study flow diagram.

Figure 2.
Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Table 1

Change in macular thickness[*] from baseline in SCORE study

Follow-up time	1 mg triamcinolone		4 mg triamcinolone		Observation	
	No. of participants	Median change from baseline (IQR)	No. of participants	Median change from baseline (IQR)	No. of participants	Median change from baseline (IQR)
8 months	73	−173 (−306 to −17)	80	−219 (−351 to −63)	70	−198 (−326 to −102)
12 months	72	−196 (−390 to −62)	78	−261 (−407 to −79)	68	−277 (−418 to −40)
16 months	61	−242 (−426 to −108)	59	−259 (−396 to −91)	61	−315 (−427 to −145)
20 months	55	−296 (−450 to −60)	47	−249 (−362 to −102)	44	−343 (−458 to −102)
24 months	48	−286 (−458 to −119)	45	−236 (−421 to −63)	43	−304 (−465 to −108)

[*]
change reported in micrometers

IQR: interquartile
range mg: milligram

Table 2

Adverse events in GENEVA

	Total number of adverse events in GENEVA			Comparison of dexamethasone with sham	
	0.35 mg dexamethasone	0.70 mg dexamethasone	sham injection	0.35 mg vs sham group (RR, CI)	0.70 mg vs sham group (RR, CI)
Elevated IOP:					
10 mm Hg	NR	NR	NR	–	–
35 mm Hg	NR	NR	NR	–	–
Ocular hypertension:	16/414 (3.9%)	17/427 (4.0%)	3/426 (0.7%)	5.49 (1.61, 18.69)	5.65 (1.67, 19.15)
Eye pain:	17/414 (4.1%)	31/427 (7.3%)	16/426 (3.8%)	5.49 (1.61, 18.69)	5.65 (1.67, 19.15)
Conjunctiva:					
Hemmorrhage	72/414 (17.4%)	85/427 (19.9%)	63/426 (14.8%)	1.18 (0.86, 1.60)	1.35 (1.00, 1.81)
Hyperemia	27/414 (6.5%)	28/427 (6.6%)	20/426 (4.7%)	1.39 (0.79, 2.44)	1.40 (0.80, 2.44)
Cornea/lens:					
Infection/endophthalmitis	NR	NR	NR	–	–
Cataract/lens opacity	17/414 (4.1%)	31/427 (7.3%)	19/426 (4.5%)	0.92 (0.49, 1.75)	1.63 (0.93, 2.84)
Iris neovascularization:	NR	NR	NR	–	–
Vitrious:					
Hemorrhage	NR	NR	NR	–	–
Detachment	12/414 (2.9%)	12/427 (2.8%)	8/426 (1.9%)	1.54 (0.64, 3.74)	1.50 (0.62, 3.62)
Retina:					
Neovascularization	4/414 (1.0%)	3/427 (0.7%)	11/426 (2.6%)	0.37 (0.12, 1.17)	0.27 (0.08, 0.97)
Detachment	NR	NR	NR	–	–
Hemorrhage	8/414 (1.9%)	12/427 (2.8%)	10/426 (2.3%)	0.82 (0.33, 2.07)	1.20 (0.52, 2.74)
Maculopathy	22/414 (5.3%)	19/427 (4.4%)	23/426 (5.4%)	0.98 (0.56, 1.74)	0.82 (0.46, 1.49)
Required additional therapy:					
IOP lowering medications	NR	NR	NR	–	–
Cataract surgery	NR	NR	NR	–	–
Photocoagulation	NR	NR	NR	–	–
Pars plana vitrectomy	NR	NR	NR	–	–

CI: 95% confidence interval

IOP: intraocular pressure
mg: milligram
mm Hg: millimeter of mercury
NR: not reported
RR: risk ratio

Table 3

Adverse events in SCORE

	Total number of adverse events in SCORE			Comparison of triamcinolone with observation	
	1 mg triamcinolone	4 mg triamcinolone	observation	1 mg vs observation group (RR, CI)	4 mg vs observation group (RR, CI)
Elevated IOP:					
10 mm Hg	15/92 (16.3%)	24/91 (26.4%)	2/88 (2.3%)	7.17 (1.69, 30.47)	11.60 (2.83, 47.65)
35 mm Hg	5/92 (5.4%)	8/91 (8.8%)	1/88 (1.1%)	4.78 (0.57, 40.13)	7.74 (0.99, 60.59)
Ocular hypertension:	NR	NR	NR	–	–
Eye pain:	NR	NR	NR	–	–
Conjunctiva:					
Hemmorhage	NR	NR	NR	–	–
Hyperemia	NR	NR	NR	–	–
Cornea/lens:					
Infection/endophthalmitis	0/92 (0%)	0/91 (0%)	0/88 (0%)	N/A	N/A
Cataract/lens opacity	20/92 (21.7%)	25/91 (27.5%)	12/88 (13.6%)	1.59 (0.83, 3.06)	2.01 (1.08, 3.76)
Iris neovascularization:	9/92 (9.8%)	4/91 (4.4%)	2/88 (2.3%)	4.30 (0.96, 19.37)	1.93 (0.36, 10.29)
Vitrious:					
Hemorrhage	4/92 (4.3%)	0/91 (0%)	4/88 (4.5%)	4.30 (0.96, 19.37)	1.93 (0.36, 10.29)
Detachment	NR	NR	NR	–	–
Retina:					
Neovascularization	2/92 (2.2%)	2/91 (2.2%)	4/88 (4.5%)	0.48 (0.09, 2.55)	0.48 (0.09, 2.57)
Detachment	0/92 (0%)	0/91 (0%)	0/88 (0%)	N/A	N/A
Hemorrhage	NR	NR	NR	–	–
Maculopathy	NR	NR	NR	–	–
Required additional therapy:					
IOP lowering medications	18/92 (19.6%)	32/91 (35.2%)	7/88 (8.0%)	2.46 (1.08, 5.60)	4.42 (2.06, 9.49)
Cataract surgery	0/92 (0%)	4/91 (4.4%)	0/88 (0%)	N/A	N/A
Photocoagulation	9/92 (9.8%)	3/91 (3.3%)	5/88 (5.7%)	1.72 (0.60, 4.94)	0.58 (0.14, 2.36)
Pars plana vitrectomy	2/92 (2.2%)	0/91 (0%)	1/88 (1.1%)	1.91 (0.18, 20.72)	N/A

CI: 95% confidence interval

IOP: intraocular pressure
mg: milligram
mm Hg: millimeter of mercury
NR: not reported
RR: risk ratio

Characteristics of included studies *[ordered by study ID]*

GENEVA

Methods	**Study design:** 2 parallel-group, randomized controlled trials **Number randomized:** Total: 1267 (CRVO: 437): trial 1–599; trial 2–668 Per group: 427 DEX 0.70 mg; 414 DEX 0.35 mg; 426 sham (CRVO: 136 DEX 0.70 mg; 154 DEX 0.35 mg; 147 sham) **Unit of randomization:** one eye per participant (when both eyes eligible the eye with the shorter duration of macular edema was selected) **Exclusions after randomization:** Total: 71 (BRVO and CRVO) Per group: 24 DEX 0.70 mg; 19 DEX 0.35 mg; 28 sham **Losses to follow-up:** Total: 5 (BRVO and CRVO) prior to day 180 Per group: 2 DEX 0.70 mg; 0 DEX 0.35 mg; 3 sham **Number analyzed:** Total: 1267 (CRVO: 437): trial 1–599; trial 2–668 Per group: 427 DEX 0.70 mg; 414 DEX 0.35 mg; 426 sham (CRVO: 136 DEX 0.70 mg; 154 DEX 0.35 mg; 147 sham) **Unit of analysis:** one eye per participant **Analysis of outcomes:** intention-to-treat analysis including all randomized participants for the primary and secondary efficacy variables; missing data were replaced by last-observation-carried-forward method for all BCVA analyses, except Kaplan-Meier analysis **Sample size calculation:** 495 eyes (165 per group) was estimated to provide 81% power for detecting an 11 % difference between the DEX implant groups and sham in the proportion of eyes that achieved at least a 15 letter improvement in BCVA at day 180
Participants	**Country:** 167 clinical sites in 24 countries across the world **Study period:** recruitment November 2004 and March 2008 **Age (mean):** BRVO and CRVO combined: 65 years (range 33 to 90) DEX 0.70 mg; 65 years (range 31 to 96) DEX 0.35 mg; 64 years (range 31 to 91) sham **Gender (% male):** BRVO and CRVO combined: 50.8% DEX 0.70 mg; 53.1% DEX 0.35 mg; 56.3% sham **Underlying conditions:** diabetes mellitus, hypertension, coronary artery disease **Inclusion criteria:** • at least 18 years of age • decreased visual acuity as a result of clinically detectable macular edema associated with either central or branch retinal vein occlusion • duration of macular edema (time since initial diagnosis of macular edema between 6 weeks and 9 months for CRVO and between 6 weeks and 12 months for BRVO) • BCVA between 34 letters (20/200) and 68 letters (20/50) in the study eye, and better than 34 letters in the nonstudy eye • retinal thickness greater than or equal to 300 μm in the study eye **Exclusion criteria:** • presence of clinically significant epiretinal membrane, active retinal or optic disc neovascularization • active or history of choroidal neovascularization • presence of rubeosis iridis • any active infection • aphakia or anterior-chamber intraocular lens • clinically significant media opacity • glaucoma or current ocular hypertension requiring more than one medication to control IOP in the study eye • diabetic retinopathy in either eye • uncontrolled systemic disease, using or anticipating using systemic steroids or anticoagulants • any ocular condition in the study eye that would prevent a 15 letter improvement in visual acuity **Equivalence of baseline characteristics?** yes
Interventions	**Intervention 1:** dexamethasone intravitreal implant (DEX) 0.35 mg **Intervention 2:** dexamethasone intravitreal implant (DEX) 0.70 mg **Control:** sham needleless intravitreal injection **Length of follow up:** Planned: 6 months Actual: 6 months, with additional 12 month open-label extension

	Notes: approximately half of the participants (BRVO and CRVO) had their 6-month follow-up evaluation after 6-months of treatment
Outcomes	**Primary outcome, as defined in the study:** time to reach a 15 letter improvement in BCVA **Secondary outcomes, as defined in the study:** • proportion of eyes with 10, 11, 12, 13, 14, or 15 letters improvement from baseline BCVA • proportion of eyes with 15 letters of worsening from baseline BCVA • mean change from baseline BCVA • central subfield retinal thickness **Measurement of outcomes in the study:** BCVA was measured using the ETDRS chart at 4 meters under standardized lighting conditions; retinal thickness was measured by collecting two OCT images at the screening visit and six images during the 90 and 180 day follow-up visits; central retinal thickness was determined from the central 1-mm macular subfield **Other outcomes:** safety parameters including IOP, slit-lamp biomicroscopy, ophthalmoscopy, and adverse events. Presence of nuclear, cortical, and posterior subcapsular lens opacities was measured during the slit-lamp examination **Intervals at which outcomes were assessed:** Participants were evaluated at baseline and days 1, 7, 30, 60, 90, and 180 post-treatment. BCVA, IOP, biomicroscopy, ophthalmoscopy, and adverse events were evaluated at each study visit. Fluorescein angiography and vital signs were assessed at baseline and day 180. Central retinal thickness was assessed at baseline, day 90, and day 180 **Outcomes related to cost of interventions:** not reported **Outcomes related to quality of life:** not reported
Notes	**Full study name:** Global Evaluation of implaNtable dExamethasone in retinal Vein occlusion with macular edemA **Publication types:** all types (journal articles, conference abstracts, regulatory documents, and trial registry information) **Trial registration number:** NCT00168298; NCT00168324 **Source of funding:** sponsored by Allergan, Inc., which participated in the design of the study, data analysis, and interpretation, and supervised the preparation of the manuscript and approved the final version **Declarations of interest:** trial authors made several disclosures including serving as a consultant, equity owner, lecturer, or patent holder in pharmaceutical companies, including Allergan (manufacturer of the DEX implant) **Subgroup analyses:** prospectively planned subgroup analyses based on type of retinal vein occlusion (BRVO vs CRVO) and a post hoc analysis based on duration of macular edema at baseline (but not reported or available)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomized to either a sham procedure or treatment with 0.35 mg or 0.70 mg DEX implant using a 1:1:1 allocation ratio. Randomization was performed centrally (using an interactive voice response system) and stratified by the underlying cause of RVO (BRVO or CRVO)
Allocation concealment (selection bias)	Low risk	Randomization was performed centrally (using an interactive voice response system) and stratified by the underlying cause of RVO (BRVO or CRVO)
Masking of participants and personnel of the allocated intervention during the study (performance bias)	High risk	Personnel administering treatments were not masked – sham had a needleless applicator. Participants were masked to dose of implant, but not to treatment (steroid implant versus no implant)
Masking of outcome assessors during follow-up examination (detection bias)	Low risk	"…key efficacy variables were collected and evaluated by follow-up investigators who were also masked with regard to study treatment." A central reading center with masked graders was used to evaluate OCT measurements of central retinal thickness
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Combined incomplete outcome data from both trials including BRVO and CRVO participants were reported for the 6-month analyses. The number of participants with missing data and reasons for exclusion were consistent across treatment arms. Incomplete outcome data for CRVO participants only were not reported and the risk of bias in this subgroup could not be determined for the 6-month analyses
Selective reporting (reporting bias)	High risk	Based on the information provided in the trial registry for both trials, contrast sensitivity, vessel leakage and quality of life assessment were described as secondary outcomes to be measured from 1 to 12 months. Results were not provided for these outcomes in the clinical trial registry results section, 6-month report, or 12-month report for either BRVO or CRVO participants. Macular thickness was described as a secondary outcome in the trial registry

		for one trial only (NCT00168298), but the 6-month reported results used the pooled data from both trials to analyze this outcome at 6 months The 6-month report only described "key efficacy variables" for the prespecified CRVO subgroup analysis (time to achieve 15 letters improvement, proportion with 15 letters improvement, and mean change in BCVA from baseline to day 180). The secondary outcome for central retinal thickness was not reported for the CRVO subgroup
Other bias	High risk	Two separate trials were conducted for regulatory purposes with different primary endpoints determined by the regulatory agency. For the first trial the proportion of participants with at least 15 letters improvement at 180 days was the primary outcome while the time to reach a 15-letter improvement from baseline was the primary outcome for the second trial. Results from both trials were pooled in the 6-month report to analyze both primary outcomes Allergan, Inc. participated in the design, data analysis, and interpretation, and supervised the preparation of the manuscript

SCORE

Methods	**Study design:** parallel-group, randomized controlled trial **Number randomized:** Total: 271 Per group: 92 IVTA 1 mg; 91 IVTA 4 mg; 88 observation **Unit of randomization:** one eye per participant **Exclusions after randomization:** Total: none reported Per group: none reported **Losses to follow-up:** Total: 33 Per group: 9 IVTA 1 mg; 9 IVTA 4 mg; 15 observation **Number analyzed:** Total: 238 at 12 months Per group: 83 IVTA 1 mg; 82 IVTA 4 mg; 73 observation **Unit of analysis:** one eye per participant **Analysis of outcomes:** "The primary analysis of the SCORE-CRVO trial is based on an observed case analysis that analyzed participants based on the arm to which they were randomized (consistent with the intention-to-treat principle) and treated missing 12-month observations as missing completely at random. To be included in the primary analysis, a study participant must have had 12-month visual acuity within a window ranging from 2 months before the target date to 3 months after the target date, with the target date defined as 12 months after the date of randomization." **Sample size calculation**: "target sample size of 630 participants to be divided equally across three treatment arms. Due to slow recruitment, adjust to 486 participants. When it was determined about only half of the sample size was enrolled, a series of conditional power calculations were presented to the DSMB which determined the trial should continue."
Participants	**Country:** 66 clinical sites in the USA **Study period:** recruitment November 2004 to February 2008 with follow-up and study close-out through February 2009 **Age (mean):** 68 years (range 27 to 93 years) **Gender (% male):** 55% **Underlying conditions:** 62 (23%) participants had diabetes mellitus; 197 (73%) had hypertension; 56 (21%) had coronary artery disease; and 58 (21%) had a history of cancer **Inclusion criteria:** • best-corrected ETDRS visual acuity letter score 73 (approximate Snellen equivalent, 20/40 or worse) and 19 (20/400 or better) • center-involved macular edema secondary to CRVO present on clinical examination • mean central subfield retinal thickness of 2 OCT fast macular scans, 250 μm • media clarity, pupillary dilation, and participant cooperation sufficient for adequate fundus photographs **Exclusion criteria:** • macular edema due to a cause other than CRVO • any ocular condition such that visual acuity would not improve from resolution of the edema (e.g., foveal atrophy) • substantial cataract estimated to have reduced visual acuity by 3 lines or more • prior treatment with intravitreal corticosteroids at any time or peribulbar steroid injection within 6 months prior to randomization • history of focal or grid macular photocoagulation within 15 weeks (3.5 months), panretinal photocoagulation within 4 months prior to randomization, or anticipated need for panretinal photocoagulation within the 4 months following randomization • prior pars plana vitrectomy • major ocular surgery (including cataract extraction) within prior 6 months or anticipated within the next 6 months following randomization

- yttrium aluminum garnet capsulotomy performed within 2 months prior to randomization

- IOP 25 mm Hg, open-angle glaucoma (either primary open-angle glaucoma or other cause of open-angle glaucoma), steroid-induced IOP elevation that required IOP-lowering treatment, or pseudoexfoliation

- aphakia

Equivalence of baseline characteristics? yes

Interventions	**Intervention 1:** intravitreal triamcinolone acetonide 1 mg; preservative-free, single-use, 0.05 mL dose injected into the vitreous cavity via the pars plana 3 to 4 mm posterior to the limbus **Intervention 2:** intravitreal triamcinolone acetonide 4 mg; preservative-free, single-use, 0.05 mL dose injected into the vitreous cavity via the pars plana 3 to 4 mm posterior to the limbus **Control:** observation Eyes assigned to observation could receive intravitreal triamcinolone when there was a loss from baseline in BCVA letter score of 15 or more that was present at 2 consecutive 4-month-interval visits. The decrease in visual acuity had to be a result of persistent or recurrent macular edema (not because of cataract or other abnormality) that was documented on OCT. If the above criteria were met, eyes assigned to observation could receive (but were not required to receive) intravitreal triamcinolone (4 mg dose, study formulation) **Length of follow up:** Planned: the prespecified primary efficacy evaluation was performed at month 12 Actual: 4-month intervals through 12 months, then annually through 36 months
Outcomes	**Primary outcome, as defined in the study:** the proportion of participants who experienced a gain in visual acuity of 15 letters or more from baseline to month 12, as assessed by electronic-ETDRS **Secondary outcomes, as defined in the study:** mean change in visual acuity from baseline to 12 months. Additional secondary analyses were conducted to determine the consistency of the primary results which included a last-observation-carried-forward analysis and a per protocol analysis that included only study eyes with 12-month visual acuity data and excluded participants who, before 12 months, received an alternative treatment (i.e., treatment crossovers) or a non-protocol treatment, who did not meet the eligibility criteria, or who did not receive the treatment assigned at randomization **Measurement of outcomes in the study:** BCVA was measured using the electronic-ETDRS method at 3 meters by a masked certified tester **Other outcomes:** other visual acuity measures included loss in visual acuity of 15 letters or more; imaging outcomes included OCT-measured center point thickness (study eye only) and disc areas of fluorescein leakages **Intervals at which outcomes were assessed:** Participants were evaluated every 4 months through first 12 months and annually through 36 months. Additional safety visits were scheduled 4 days and 4 weeks after intravitreal triamcinolone injections. Stereoscopic color fundus photographs (7 fields) were taken of the study eye at baseline and at the annual visits. Three-field photographs were taken of the study eye at the month 4, 8, 16, 20, 28, and 32 visits, and of the fellow eye at the baseline and annual visits. Fluorescein angiograms were performed at baseline and at the month 4, 12, and 24 visits. All images were sent to the reading center and graded by a masked observer **Outcomes related to cost of interventions:** not reported **Outcomes related to quality of life:** not reported
Notes	**Full study name:** Standard Care vs COrticosteroid for REtinal Vein Occlusion **Publication types:** all types (journal articles, conference abstracts, regulatory documents, and trial registry information) **Trial registration number:** NCT00106132 **Source of funding:** National Eye Institute (USA) grants 5U10EY014351, 5U10EY014352, and 5U10EY014404. Allergan, Inc. donated investigational drug, partially funded site monitoring visits, and performed secondary data analyses **Declarations of interest:** "The authors have no proprietary or commercial interest in any of the materials discussed in this article" **Subgroup analyses:** according to eyes with the following baseline characteristics: pseudophakic, duration of macular edema, visual acuity letter score, and OCT-measured center point thickness

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"participants were randomly assigned centrally through a Web-based data entry system maintained at the data coordinating center (EMMES Corporation, Rockville, Maryland), with equal probability to receive standard care (observation group), 1 mg of intravitreal triamcinolone, or 4 mg of intravitreal triamcinolone using a permuted blocks design with random block sizes"
Allocation concealment (selection bias)	Low risk	"participants were randomly assigned centrally through a Web-based data entry system"
Masking of participants and personnel of the allocated intervention during the study (performance bias)	High risk	"Participants and physicians were masked to the intravitreal triamcinolone dose (1 mg vs 4 mg) but not to the treatment assignment of observation vs intravitreal triamcinolone."

Masking of outcome assessors during follow-up examination (detection bias)	Low risk	Fluorescein angiograms and OCT results were assessed by a masked observer at the reading center. Visual acuity was measured at each visit by a masked technician
Incomplete outcome data (attrition bias) All outcomes	High risk	Proportion of participants with missing data at the 12-month visit (which was the basis of the primary outcome analysis) was identical in both 1 mg and 4 mg triamcinolone intravitreal injection arms (10%). In the observation arm, 17% of participants had missing data compared with the 6.8% observed risk for the primary outcome. Reasons for missing data were not reported. Data were analyzed assuming all missing data were missing at random
Selective reporting (reporting bias)	Low risk	Primary analysis reported as described in methods paper. All secondary analyses were reported according to prespecified methods as well
Other bias	Unclear risk	Study drugs provided by pharmaceutical company (Allergan, Inc.) which also provided funding for study site visits, and conducted the secondary analyses

BCVA: best-corrected visual acuity

BRVO: branch retinal vein occlusion

CRVO: central retinal vein occlusion

DEX: dexamethasone

ETDRS: Early Treatment Diabetic Retinopathy Study

IOP: intraocular pressure

IVTA: intravitreal triamcinolone acetonide

OCT: optical coherence tomography

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bashshur 2004	Not an RCT: prospective case series of 20 patients treated with an intravitreal injection of 4 mg of triamcinolone acetonide compared with a retrospective matched observation group
Batioglu 2007	Not an RCT: case series of 20 patients treated with intravitreal injections of triamcinolone acetonide
Cheng 2009	Not an RCT: prospective comparative non-randomized interventional study of 22 patients who accepted an intravitreal injection of 4 mg of triamcinolone acetonide compared with 21 patients who refused intravitreal injection
Chuang 2010	Not an RCT: retrospective cohort of 68 patients (39 with CRVO and 29 with BRVO); 36 patients who received an intravitreal injection of 2 mg of triamcinolone acetonide compared with 32 patients who received an intravitreal injection of 4 mg of triamcinolone acetonide
Gelston 2006	Not an RCT: retrospective comparative case series of 9 patients treated with an intravitreal injection of 4 mg of triamcinolone acetonide compared with 10 patients managed by observation
Georgopoulos 2006	Not an RCT: review of dexamethasone implants for macular edema, not limited to CRVO
Jain 2012	Not an RCT: prospective case series of 23 patients treated with fluocinolone acetonide intravitreal implant
Jiang 2006	Not an RCT: case series of 39 patients with CRVO or BRVO treated with intravitreal injections of triamcinolone acetonide
Jonas 2005a	Not an RCT: prospective comparative non-randomized clinical interventional study of 12 patients who received an intravitreal injection of 20 to 25 mg of triamcinolone acetonide compared with 20 patients managed by observation
Manaviat 2008	Did not meet inclusion criteria: "randomized case-control trial" of 21 patients with macular edema and retinal vein occlusion (16 with CRVO and 5 with BRVO); 9 patients treated with an intravitreal injection of 4 mg of triamcinolone acetonide compared with 12 patients treated with aspirin and laser treatment; length of follow-up was not consistent for all patients, range was 1 to 16 months and only three patients were followed up after 4 months
Muni 2010	Not an RCT: commentary on SCORE study
Ramezani 2006	Did not meet inclusion criteria: RCT of 13 participants treated with an intravitreal injection of 4 mg of triamcinolone acetonide compared with 14 patients receiving sham injection as control group; follow-up was less than six months (4-month follow-up)
ROVO	Did not meet inclusion criteria: RCT of 90 participants with CRVO treated with radial optic neurotomy, intravitreal injection of 4 mg of triamcinolone acetonide, or sham injection; not all participants had macular edema (about 75% in the sham group) and no results are presented separately for the participants who had macular edema at baseline

BRVO: branch retinal vein occlusion
CRVO: central retinal vein occlusion
RCT: randomized controlled trial
SCORE: Standard Care vs COrticosteroid for REtinal Vein Occlusion study

Characteristics of ongoing studies *[ordered by study ID]*

NCT01660802

Trial name or title	Safety and Efficacy Study of Dexamethasone in the Treatment of Patients With Macular Edema Following Retinal Vein Occlusion (RVO)
Methods	Randomized controlled trial
Participants	**Location:** China **Inclusion criteria:** 18 years of age or older Presence of macular edema due to branch or central retinal vein occlusion**Exclusion criteria:** History of glaucoma, ocular hypertension or optic nerve head change Any active bacterial, viral, parasitic, or fungal infections in either eye History of use of intravitreal steroids or any intravitreal injectable drug in the study eye within three months prior to study start Use of oral, intravenous, intramuscular, antimetabolites, and/or alkylating agents within three months prior to study start Use of topical ophthalmic corticosteroids within two weeks of study start
Interventions	**Intervention 1:** 700 μg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) intravitreal injection in the study eye on day one and month six **Intervention 2:** sham PS DDS intravitreal injection in the study eye on day one and 700 μg DEX PS DDS intravitreal injection month six
Outcomes	**Primary outcome:** best-corrected visual acuity at six months **Secondary outcomes:** central retinal thickness measured with optical computed tomography and fluorescein leakage on fluorescein angiography at six months
Starting date	August 2012
Contact information	Allergan, Inc. (clinicaltrials@allergan.com)
Notes	Estimated enrollment: 260 Estimated study completion date: August 2014 Estimated primary completion date: June 2014 (final data collection date for primary outcome measure) Responsible party: Allergan ClinicalTrials.gov identifier: NCT01660802 Other study ID numbers: 206207-020 Last updated: March 20, 2013 Health Authority: China: Food and Drug Administration