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

Dina Gewaily[1] and **Paul B Greenberg**[1]

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

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Contact address: Paul B Greenberg, Division of Ophthalmology, Warren Alpert Medical School of Brown University, Providence, Rhode Island, 02908, USA. paul_greenberg@brown.edu..

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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
- Organizing retrieval of papers: DG
- Screening retrieved papers against inclusion criteria: DG, PBG
- Appraising quality of papers: DG, PBG
- Extracting data from papers: DG, PBG
- 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- Obtaining and screening data on unpublished studies: CEVG, DG, PBG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
- Analysis of data: DG, PBG
Interpretation of data
- Providing a methodological perspective: DG, PBG
- Providing a clinical perspective: PBG
- Providing a policy perspective: PBG
- Providing a consumer perspective: DG, PBG
Writing the review: DG, PBG
Providing general advice on the review: PBG
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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. There is no proven treatment; laser photocoagulation is not effective in treating cystoid macular edema secondary to CRVO. Intravitreal steroids, such as triamcinolone acetonide, have been utilized to treat macular edema stemming from a variety of etiologies and may represent a treatment option for CRVO-ME.

Objectives—The objective of this review was to explore the effectiveness and safety of intravitreal steroids in the treatment of CRVO-ME.

Search strategy—We searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library* Issue 4, 2008), MEDLINE (January 1950 to November 2008) and EMBASE (January 1980 to November 2008). There were no language or date restrictions in the search for trials. The electronic databases were last searched on 5 November 2008. For all included primary studies, we used The Science Citation Index and manually reviewed reference lists to identify other possible relevant trials. We contacted researchers in the field, currently working on a randomized controlled trial (RCT) on this topic (The Standard Care versus Corticosteroid for Retinal Vein Occlusion - SCORE study), for information on additional current, past, or unpublished trials.

Selection criteria—We considered RCTs that compared intravitreal steroids of any dosage/duration to observation in the treatment of CRVO-ME for inclusion in this review. We focused on studies that included individuals of any age or gender with unilateral or bilateral disease, with a minimum of six months follow up. Secondarily we considered non-randomized studies with the same criteria for description of evidence, however we did not conduct a separate electronic search for finding all non-randomized studies.

Data collection and analysis—We found no RCTs that met the inclusion criteria after independent and duplicate review of the search results.

Main results—We found no relevant RCTs and therefore performed no meta-analysis. Evidence from non-randomized studies is reported in this review.

Authors' conclusions—There is inadequate evidence for the use of intravitreal steroids for CRVO-ME due to a paucity of RCTs and well-designed observational studies on the topic; therefore, it is still an experimental procedure.

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 (AAO 2007). Patients are usually 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,

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and tortuosity of the retinal veins. A histopathological study of 29 eyes suggests 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. The mechanism of macular edema 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).

Despite these characteristic clinical and ophthalmic findings, there is no proven treatment. Laser photocoagulation is not effective in treating macular edema secondary to CRVO (CVOS 1995). The lack of effective treatment has prompted interest in other treatment modalities, including medical therapy with anticoagulants, fibrinolytics, acetazolamide, isovolemic hemodilution, anti-vascular endothelial growth factor (anti-VEGF), 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 has been proven effective in treating CRVO-induced cystoid macular edema.

Description of the intervention

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 2005). While 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 2005).

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 2005). The increased capillary permeability that occurs in macular edema may be partially mediated 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, a recent study 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 these improvements do not directly correlate with improvements in visual acuity (Moschos 2007).

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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 final visual acuity of 20/250 or worse three years after event onset (CVOS 1997). Macular edema remains the primary cause of decreased vision. With no current standard of care, the use of intravitreal steroids has been proposed in recent years. However, 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 intravit-real steroids in the treatment of CRVO-induced macular edema.

OBJECTIVES

To explore the effectiveness and safety of intravitreal steroids in the treatment of macular edema resulting from CRVO.

METHODS

Criteria for considering studies for this review

Types of studies

We intended to include all relevant randomized controlled trials (RCTs) in our review as well as in any applicable meta-analysis. Since relevant RCTs were lacking, 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 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 the current standard of care (in this case natural history) for CRVO-ME.

Intravitreal steroid administration can take the form of an injection or surgical implantation; although in the case of the latter, special notation was made. We included trials with any dosage and duration of treatment.

Types of outcome measures

Primary outcomes—The primary outcome of this review was the proportion of eyes with improved visual acuity at six months of follow up. We defined a significant improvement in visual acuity as a gain of greater than or equal to 0.1 logMAR (or standard equivalent) compared to visual acuity at the time of CRVO diagnosis. When available, we also reported improvements in visual acuity for subsequent follow-up dates.

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Secondary outcomes—When parameters were available, secondary outcomes of the review included:

1. mean change in visual acuity of treated eye at six months of follow up;
2. mean change in macular thickness using optical coherence tomography (OCT);
3. complications: all named complications were tabulated.

Adverse outcomes—We documented all adverse effects related to the use of intravitreal corticosteroids compared to the control group, for the treatment of retinal vein occlusion, that are mentioned in the primary studies. Specific adverse outcomes of interest included the development of sterile/nonsterile endophthalmitis, an increase in mean intraocular pressure or need for anti-glaucomatous therapy, and cataract formation and/or progression.

Economic data—There were no relevant economic data reported in the included primary studies.

Quality of life data—We did not find any relevant quality of life data in the included primary studies.

Search methods for identification of studies

Electronic searches—We searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library* Issue 4, 2008), MEDLINE (January 1950 to November 2008) and EMBASE (January 1980 to November 2008). There were no language or date restrictions in the search for trials. The electronic databases were last searched on 5 November 2008. We initially considered RCTs that compared intravitreal steroids of any dosage/duration to observation in the treatment of CRVO-ME for inclusion for meta-analysis. We focused on studies that included individuals of any age or gender with unilateral or bilateral disease, with a minimum of six months follow up. Secondarily we considered non-randomized studies with the same criteria for description of evidence, however we did not conduct a separate electronic search targeted towards finding non-randomized studies.

See Appendices for details of the search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2) and EMBASE (Appendix 3).

Searching other resources—We conducted manual searches by reviewing the reference lists of all non-randomized studies that compared intravitreal steroids to observation for CRVO-ME for additional relevant papers. We used the Science Citation Index to search for studies that had cited included primary trials. We contacted researchers in the field currently working on RCTs on the topic (i.e. The Standard Care versus Corticosteroid for Retinal Vein Occlusion study; SCORE 2009) and we also sought information on additional current, past, or unpublished trials.

Data collection and analysis

Selection of studies—Both authors independently reviewed all titles and abstracts retrieved from the electronic and manual searches and judged potential relevance based on

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the inclusion criteria described in the previous section. We only considered RCTs for inclusion in this review. We also reported evidence from observational studies. The authors retrieved the full reports from potentially relevant studies. We documented titles of excluded studies, along with primary reason(s) for exclusion. The authors discussed any discrepancies in listed included and excluded studies and made efforts to contact trial investigators when questions arose.

Data extraction and management—No trials were included in this review. If studies are found in the future, both authors will independently extract data using the data extraction form developed by the Cochrane Eyes and Vision Group for each included primary study. Data to be extracted will pertain to the study profile characteristics, participants (including the stated inclusion and exclusion criteria), intervention and control group descriptions, primary and secondary outcome data, and relevant corollary notes. We will make efforts to contact primary investigators in the event of missing data. One author will enter data into Review Manager (RevMan 5) (RevMan 2008) and the second author will verify data after it is entered. The authors will discuss discrepancies in data extraction or entry.

Assessment of risk of bias in included studies—Future work will also involve both authors independently assessing the quality of included RCTs using the quality assessment form developed by the Cochrane Eyes and Vision Group for each included primary study. We will evaluate five potential sources of bias, including selection bias, performance bias, attrition bias, detection bias, as well as reporting bias.

With respect to selection bias, we will review methods of allocation and allocation concealment up to the point of treatment assignment. Masking of participants and providers after treatment assignment (i.e. injection, laser, natural history) is not feasible, however. According to Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008a), examples of adequate concealment include the use of a centralized or pharmacy controlled randomization in which participant characteristics are unknown, serially-administered pre-numbered or coded identical containers, or sequentially numbered sealed and opaque envelopes. Inadequate allocation concealment methods include alternation, case record numbers, dates of birth or day of week, or another transparent method.

Performance bias exists if there are differences in the care of participants belonging to the intervention and control groups, other than the intervention in question. We will assess this source of bias, along with differences between the two groups in terms of outcome assessment (detection bias). When evaluating for the presence of attrition bias, we will appraise rates of follow up in each group, number of eyes included in final analyses, and the account of missing data from participants lost to follow up.

For each of the five parameters, an overall risk assessment will be recorded in table format corresponding to each included primary study using the assessments: low risk of bias, unclear risk of bias, or high risk of bias. We will discuss any discrepancies between authors and, in the case of unclear risk, attempts will be made to contact primary investigators for clarification.

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Measures of treatment effect—Using Chapter 9 of the Cochrane Handbook for Systematic Reviews of Interventions (Deeks 2008) as a guide, measures of treatment effect will depend on the types of data presented in the individual studies. The management of counts and rates data will depend on the relative occurrence of the event; we will summarize rare events as a rate ratio and express more common events in the same way as continuous outcome data. We will summarize ordinal data qualitatively.

Dichotomous data: We will analyze the primary outcome of interest, the proportion of patients achieving improved visual acuity at six months of follow up, as a dichotomous variable. We will present dichotomous data as a summary risk ratio with 95% confidence intervals.

Continuous data: We will measure the mean changes in visual acuity and macular thickness as continuous variables. We will express continuous data as a weighted mean difference with standard deviations if data are normally distributed for each group.

Ordinal data: We will measure the number of complications, number of interventions performed, number of adverse effects, and the economic and quality of life data as ordinal data or rates data.

Unit of analysis issues—The unit of analysis for visual acuity and adverse events will be an eye. However, for quality of life and specific types of intravitreal steroid data the unit of analysis will be by person.

Dealing with missing data—We will attempt to contact trial investigators for any missing data. If the investigators do not respond within four weeks, we will extract data as available from the published report. We will refer to guidelines in Chapter 16 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins2008b) for handling missing data.

Assessment of heterogeneity—We will assess heterogeneity in future updates when RCTs are found that meet the inclusion criteria. Both forest plots created using RevMan 5 software and results of Chi^2 tests will be used to judge heterogeneity between trials. The value of I^2 statistics will be used to evaluate any inconsistencies across studies.

Assessment of reporting biases—We will examine funnel plots to identify any evidence for publication bias if future trials are found and meta-analysis is performed.

Data synthesis—We will perform meta-analysis if RCTs are found that meet the inclusion criteria and substantial heterogeneity across studies does not exist. We will use a random-effects model for meta-analysis or a fixed-effect model if less than three trials are found. Given sufficient future data, we will perform meta-analysis for stratified data according to the type of CRVO (i.e. ischemic versus nonischemic), the delivery of the corticosteroid (i.e. injection versus surgical implant), the dosage of steroid used, and outcome measurement (i.e. mean change in visual acuity, mean change in macular thickness).

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Subgroup analysis and investigation of heterogeneity—We will investigate heterogeneity through quantitative subgroup analyses based on included primary studies.

Sensitivity analysis—We will assess the impact of excluding studies that have missing data or questionable methodological quality (high risk of bias) using sensitivity analysis. We also plan to examine the impact of both future unpublished studies and industry funded trials on overall results.

RESULTS

Description of studies

See: Characteristics of excluded studies.

Results of the search

Electronic searches, inherently designed to include unpublished trials, conference proceedings, and papers written in languages other than English, yielded a total of 177 potentially relevant titles with accompanying abstracts. We full text screened seven out of the 177 potentially relevant titles. A preliminary review of the articles yielded no RCTs. A second look for observational studies that directly compared IVS to observation for CRVO-ME resulted in four studies: Bashshur 2004; Cheng 2008; Gelston 2006; and Jonas 2005. These studies were entered into the Science Citation Index, yielding 40, 0, 1, and 8 citations, respectively. Additionally, we reviewed all references used in the studies. Of these citations, we performed two additional full text screens. No further trials were found that met the inclusion criteria after reviewing a total of 313 references; however relevant studies that did not meet the inclusion criteria were included in the results and discussion sections.

We contacted two principle investigators for the SCORE trial, one citing that the ISIS trial may be relevant; however this trial was never completed according to the former principle investigator.

Excluded studies

See the 'Characteristics of excluded studies' table for details of the nine studies that were screened and excluded.

Risk of bias in included studies

No RCTs met the inclusion criteria and we only identified four relevant observational studies that directly compared intravitreal steroids to observation for CRVO-ME: Bashshur 2004; Cheng 2008; Gelston 2006; and Jonas 2005. We retrieved the title and abstract of two RCTs but they were excluded on the basis of short follow up (Manaviat 2008; Ramezani 2006). We assessed the quality of the observational studies by examining the existence of attrition bias, detection bias, performance bias, selection bias, and reporting bias. None of the studies used randomization or masking as techniques to limit the degree of bias. Overall, the observational studies were of average methodological quality. Given the limitation in quantity and quality of evidence, we did not deem a meta-analysis appropriate. However, we

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report data from the observational studies and outline major points in Table 1; Table 2; Table 3; and Table 4.

Effects of interventions

The primary outcome was related to the effect of intravitreal steroids on visual acuity in eyes with CRVO-ME. The relatively well-designed Bashshur 2004 study found a statistically signifi-cant improvement in visual acuity in individuals treated with 4 mg of triamcinolone acetonide after a 10 to 12-month follow-up period, with a greater proportion of treated individuals presenting with a final visual acuity of > or = 20/40 compared to controls. Alternatively, 40% of non-treated eyes in the study had a final visual acuity of < 20/200, while none of the intravitreal steroid-treated individuals fell into this category. These somewhat promising results only apply to non-ischemic CRVO cases since individuals with ischemic CRVO were excluded from the study. The Cheng 2008 study, which included both ischemic and non-ischemic CRVO cases, also found a statistically significant improvement in visual acuity amongst treated patients, with 12 treated eyes (54.5%) showing an improvement of at least two Snellen lines. There was no statistically significant improvement in visual acuity in control cases. However, subgroup analysis in the Cheng study revealed that only non-ischemic CRVO eyes (86.36% of treated eyes) showed improvement in visual acuity and that the three ischemic CRVO eyes showed no improvement. The trend of visual acuity improvement in non-ischemic CRVO cases was also observed in subgroup analyses performed in the Gelston 2006 and Jonas 2005 studies. While the Gelston 2006 study was only powered to detect a four-line Snellen difference between groups, the study indicated that “non-statistically significant trends suggested that intravitreal steroids may have some benefit to non-ischemic CRVO patients.” The Jonas 2005 study found that while visual acuity returned to baseline approximately five months after intravitreal triamcinolone acetonide treatment in all CRVO patients, there was a significant improvement of visual acuity from baseline to best postoperative visual acuity in non-ischemic cases, although it is unclear at which follow-up date this gain was observed.

Less emphasis was placed on macular edema as an outcome in the observational studies. The only quantitative results related to macular edema came from the Bashshur 2004 and Cheng 2008 studies. The Bashshur 2004 study found a 75% rate of macular edema resolution in the treated group compared to only a 20% rate of macular edema resolution in controls. This finding was statistically significant ($P < 0.001$). The course of macular edema in this study was monitored both clinically and angiographically. However, 2/20 treated eyes developed a macular edema recurrence at six-month follow up; one individual was re-treated with intravitreal steroids, improved, and remained stable until study completion. Optical coherence tomography results in the Cheng 2008 study revealed a statistically significant decrease in macular edema of 46.95% in study cases, while control cases experienced a non-statistically significant decrease of 8.33%. It is important to note that 28.47% of control cases in this study were not strictly treated via observation only since panretinal photocoagulation (PRP) was performed prophylactically in ischemic CRVO eyes to prevent neovascular sequelae; panretinal photocoagulation treatment has the potential to lead to secondary macular edema in these eyes (Hendrikse 2000). In the same study, macular edema recurrence occurred in 6/22 study eyes, however re-injection resulted in improvement in

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four eyes with resultant improvement in visual acuity. Gelston 2006 noted that at each follow-up visit the amount of macular edema in both ischemic and non-ischemic CRVO groups was less clinically apparent compared to the observation group. However, they note that despite this anatomical improvement, a certain degree of macular ischemia in both ischemic and non-ischemic CRVO is likely to limit functional improvement in visual acuity following intravitreal triamcinolone acetonide treatment. The Jonas 2005 study did not comment on macular edema outcomes.

The primary complication amongst eyes treated with intravitreal steroids in the observational studies was an increase in intraocular pressure. In all four studies, immediate paracentesis of the anterior chamber was performed alongside the intravitreal steroid injection, either conditionally or routinely. Bashshur 2004 performed anterior chamber paracentesis if the intraocular pressure was greater than 25 mm Hg after injection (18/20 treated eyes), Cheng 2008 performed it in all cases before the intravitreal steroid treatment, Gelston 2006 performed it if the patient's visual acuity was worse or light perception only at five minutes, and Jonas 2005 performed it routinely. In the Bashshur 2004 study, 3/20 treated eyes experienced an increase in intraocular pressure at one-month follow up that was no greater than 25 mm Hg. All cases responded to 0.5% timolol maleate and treatment was discontinued well before the six-month follow-up date. Seven treated eyes (31.82%) experienced ocular hypertension with an absence of neovascular changes in the Cheng 2008 study (intraocular pressure > or = 22 mm Hg), with one eye requiring a trabeculotomy for intraocular pressure control. In addition to intraocular pressure increase, one treated eye developed a mature cataract during follow up in this study as well. In the Gelston 2006 study, 6/9 treated eyes had a rise in intraocular pressure that was statistically significant at one and two-month follow ups, however measurements returned to baseline by the six-month visit. While 3/6 of the individuals responded well to a single topical anti-glaucomatous medication, the remainder required multiple topical medications and eventual panretinal photocoagulation for neovascular glaucoma. Glaucoma in this study was defined as an intraocular pressure > 24 mm Hg. Baseline intraocular pressure measurements were not included in either study and it is unclear why a greater proportion of treated individuals experienced intraocular pressure rises and increased severity in the latter study. A similar trend was also observed in the Jonas 2005 study, in which a transient increase in intraocular pressure occurred but returned to baseline by the six-month follow up. In the Jonas 2005 study, intraocular pressure rise occurred in both treated and control groups, with 23% of treated eyes and 20% of control group eyes developing intraocular pressure measurements greater than 21 mm Hg; however, intraocular pressure was significantly higher in the treated group versus the observation group (P = 0.007). In all eyes, intraocular pressure was controlled by using topical medication and neither group varied significantly in intraocular pressure at the end of follow up, relative to baseline measurements.

It is worth mentioning that individuals who were managed via observation alone also experienced complications. As mentioned, intraocular pressure rise was not specific to the treatment group, although it was observed at a higher frequency. In the Bashshur 2004 study, 2/20 of control eyes required panretinal photocoagulation for rubeosis iridis, while none of the treated eyes had this complication.

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DISCUSSION

There is currently no standard of care for the treatment of macular edema secondary to CRVO. The 1995 Central Vein Occlusion Study, a RCT evaluating the use of macular grid photocoagulation for the treatment of CRVO-ME, found that while laser reduced angiographic evidence of macular edema, visual acuity was not improved compared to observation alone (CVOS 1995). Intravitreal steroids have been used recently as a treatment modality for persistent macular edema stemming from a variety of etiologies, however systematic documentation of the safety and efficacy of this procedure for CRVO-ME was lacking. The objective of this review was to evaluate both the medical benefits and risks of using intravitreal steroids for the treatment of CRVO-ME. This review is limited because conclusions are primarily drawn from case series and case reports of relatively short follow up, small sample size, no randomization, and no masking. However, we noted several consistent trends in the use of intravitreal steroids for CRVO-ME and compiled a list of potential complications found in the literature to date.

Functional outcomes reported in various observational studies include the proportion of eyes with improved visual acuity, mean change in visual acuity, best corrected visual acuity, and multifocal electroretinography recordings after a trial of intravitreal steroids for CRVO-ME. Similarly, anatomical outcomes reported in studies involve cystoid macular edema status, mean foveal or macular thickness, collateral formation, and venous tortuosity after treatment. In general, beneficial results of intravitreal triamcinolone acetonide treatment appear to be transient. Studies that report good outcomes without a decline in parameters tended to be studies with shorter follow-up periods. Usually a correlation between anatomical and functional outcomes was observed (i.e. a decrease in macular edema correlated with an improvement in visual acuity); however this direct relationship did not always exist. The dichotomy in functional and anatomical results was sometimes more pronounced amongst the non-perfused CRVO cases, in which pre-existing ischemic injury may limit the amount of functional recovery possible (Gelston 2006; Ozdek 2005). Tables 2 to 4 summarize the main features and key outcomes of one RCT (Table 5), 10 case series studies (Table 6), and nine case reports (Table 7) involving the use of intravitreal steroids for CRVO-ME.

The only reported complication of intravitreal steroids in the primary observational studies was a rise in intraocular pressure. While intraocular pressure was controlled by using topical anti-glaucomatous medications and panretinal photocoagulation for neovascular glaucoma in the most severe cases in the included studies, the risk of glaucoma should not be underestimated. Kaushik 2004 reports a case of intractable glaucoma requiring removal of depot steroid via pars plana vitrectomy in combination with a trabeculectomy in a patient treated with 4.0 mg of intravitreal triamcinolone acetonide for CRVO-ME. While ocular hypertension may be unpredictable, the complication has been statistically associated with high baseline intraocular pressure, younger age, and diabetes mellitus status (Wang 2007). A peak in intraocular pressure is observed approximately two months following intravitreal triamcinolone acetonide treatment (Bashshur 2004; Gelston 2006; Wang 2007; Yang 2005), however there is a need to monitor for intraocular pressure rise beyond six months post-injection (Wang 2007). Transient hypertony is also a concern, occurring in over half of eyes

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receiving intravitreal triamcinolone acetonide (Table 8). This complication appears to have been avoided in the included primary studies by performing immediate anterior chamber paracentesis after the steroid injection, although the necessity of this maneuver is unclear. Overall the risk of ocular hypertension is approximately 40% and the need for anti-glaucomatous surgery is at a rate of 1% to 2% after an intravitreal steroid injection (Jonas 2006).

In the same review, Jonas reported the risk of infectious endophthalmitis after intravitreal steroids to be 0.1% (Jonas 2006). A study reporting the incidence of endophthalmitis following intravitreal steroids in the Diabetic Retinopathy Clinical Research network (DRCRnet) and SCORE clinical trials found the rate to be 0.05% with a 95% confidence interval ranging from 0.001% to 0.277% (SCORE 2009). This low rate of endophthalmitis was achievable despite a lack of antibiotic prophylaxis (Bhavsar 2007). Sterile, or pseudo-endophthalmitis has also been reported after intravitreal steroid administration and is likely secondary to a reaction with a solvent in the triamcinolone acetonide preparation. A decreased rate of endophthalmitis is attained when triamcinolone is filtered to remove the solvent agent (Jonas 2006).

Concerns have arisen regarding the potential retinal toxicity of intravitreal steroids. Aggermann 2006 reported a case of endophthalmitis with retinal necrosis that clinically resembled the herpetic retinopathies (Table 8). A study designed to evaluate the potential retinotoxicity of commercially prepared triamcinolone acetonide, or Kenalog®, found an approximately 50% reduction in electroretinogram b-wave amplitude in albino rabbits. Pure triamcinolone acetonide resulted in a milder 14% reduction in electroretinography b-wave amplitude, leading the researchers to believe that the vehicle of Kenalog® is the likely cause of retinal toxicity (Lang 2007). However, the same group evaluated the effects of intravitreal Kenalog® in human eyes and found no statistical difference in electroretinography parameters before or three months after injection (Lang 2007). Ruiz-Morena et al. examined the effect of 30 mg/0.1 ml triamcinolone acetonide on the retina of albino rabbits and found no signs of retinal damage via microscopy or electroretinography parameters 28 days post-injection (Ruiz-Morena 2007). Similar results were obtained in vitrectomized silicone-filled rabbit eyes receiving doses of intravitreal triamcinolone acetonide up to 4 mg/0.1 ml (Kivilcim 2000).

AUTHORS' CONCLUSIONS

Implications for practice

Currently, there is insufficient evidence to draw reliable conclusions regarding the use of intravitreal steroids for macular edema secondary to CRVO. This limitation is secondary to a paucity of RCTs on the topic as well as a small number of observational studies that directly compare the use of intravitreal steroids to the current standard of care (observation). Therefore, the use of intravit-real steroids for CRVO-ME is still an experimental procedure.

Implications for research

Based on the results of non-randomized studies and case reports, the beneficial anatomical and functional outcomes derived from the use of intravitreal steroids appear to be transient

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and in the order of months. This phenomenon may be related in part to the method of intravitreal steroid administration and further experiments examining the effects of different dosages, delivery systems, and injection protocols are in order. A Phase II RCT showed that a 700 ug dose using the "Dexamethasone posterior segment drug delivery system" (DEX PS DDS) aka Posurdex®, had promising results for persistent macular edema stemming from a variety of etiologies at a six-month follow up (Kuppermann 2007).

The SCORE (Standard Care versus COrticosteroid for REtinal Vein Occlusion) study is a multi-centre National Institute of Health-sponsored RCT with 682 enrollees, specifically designed to evaluate the benefits and risks of intravitreal steroids for both central and branch retinal vein occlusions (SCORE 2009). Both 1 mg and 4 mg dosages of intravitreal triamcinolone acetonide in the form of injection will be compared to observation. This three-year study is expected to be completed by February 2009, at which time more definitive conclusions on the use of intravitreal steroids for CRVO-induced cystoid macular edema may be determined.

CHARACTERISTICS OF STUDIES

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

Bashshur 2004	Mixed prospective and retrospective comparative case series
Batioglu 2007	Case series
Cheng 2008	Prospective comparative non-randomized clinical interventional study
Gelston 2006	Retrospective comparative case series
Georgopoulos 2006	Dexamethasone as intervention, not limited to CRVO
Jiang 2006	BRVO also, no control
Jonas 2005	Prospective non-randomized clinical interventional study
Manaviat 2008	Did not meet inclusion criteria: Included patients with ME and retinal vein occlusion, either CRVO or BRVO; 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
Ramezani 2006	Did not meet inclusion criteria: 4-month follow up, sham injection as control group (not observation)

BRVO: branch retinal vein occlusion

CRVO: central retinal vein occlusion

DR: diabetic retinopathy

IVS: intravitreal steroid

IVTA: intravitreal triamcinolone

NVG: neovascular glaucoma

PRP: panretinal photocoagulation

RCT: randomized controlled trial

SCORE: Standard Care vs. COrticosteroid for REtinal Vein Occlusion

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External sources

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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)

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

Appendix 2. MEDLINE 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.y
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.

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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 search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin$ 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

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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

WHAT'S NEW

Last assessed as up-to-date: 9 February 2009.

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16 June 2010	Amended	External source of support added.
10 February 2009	Amended	A reference has been added for the SCORE study.

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PLAIN LANGUAGE SUMMARY

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

Central retinal vein occlusion (CRVO) is the most common retinal vascular abnormality second to diabetic retinopathy. It classically presents as a unilateral painless loss of vision in individuals over the age of 40 and is associated with conditions such as high blood pressure, diabetes, glaucoma, and hematologic diseases. Macular edema (ME) is a complication of CRVO and is the primary reason for loss of vision in this condition. Currently there is no treatment for this disorder and laser treatment is not effective for CRVO-induced macular edema. Steroid injections in the eye have been used to treat macular edema caused by other eye disorders. This review aimed to examine the risks and benefits of using intravitreal steroids in treating CRVO-ME. While intravitreal 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. Due to an inadequate number of well-designed studies on the topic, we cannot make definitive conclusions and therefore the use of intravitreal steroids is still experimental. More definitive answers may appear when the results of a new randomized controlled trial (the SCORE trial) are published.

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Table 1

Table 1a: *Bashshur 2004*

Methods	**Study type**	**Mixed prospective and retrospective comparative case series**
	Enrollment method	Consecutive patients who met inclusion criteria in clinic (treatment) and databases (control)
	Inclusion criteria	CRVO of 3 to 4 months duration from day of symptoms with no improvement in vision, BCVA between 20/50 and 20/200, ME confirmed clinically and angiographically, phakic with clear media, IOP < 22 mm Hg, willingness to consent form
	Exclusion criteria	Prior laser treatment, other ocular conditions that may affect VA, DM, history of uveitis, APD > 0.3 log unit, 10 disc areas or more of capillary nonperfusion on FA, presence of neovessels on iris or in angle, use of topical medications containing prostaglandin derivatives, rubeosis iridis
	Follow up	10 to 12 months
	Funding source	“No relevant financial interest”
Participants	Country	Beirut, Lebanon
	Study period	September 2001 to March 2002
	No. of eyes	40 (20 treatment, 20 control)
	Baseline characteristics	Equivalent
Interventions	Treatment	4 mg in 0.1 ml of triamcinolone acetonide
	Control	Observation
	Notes	Anterior chamber paracentesis was performed if IOP > 25 mm Hg s/p IVTA (done on 18/20 patients)
Outcomes	Final mean VA	Baseline VA: intervention = 20/132; control = 20/123; P = 0.570 10 to 12 months: intervention = 20/37; control = 20/110; P = 0.001
	Distribution of VA	Final VA > or = 20/40: intervention = 12 (60%); control = 4 (20%); P = 0.01 Final VA 20/50 to 20/100: intervention = 8 (40%); control = 8 (40%) Final VA 20/200: intervention = 0; control = 0 Final VA < 20/200: intervention = 0; control = 8 (40%); P < 0.001
	ME: 2/20 treated eyes had ME recurrence at 6 months	Resolution of ME at 10 to 12 months: intervention = 75%; control = 20%; P < 0.001
	Complications	3/20 treated eyes had elevated IOP that was treated by 6-month follow up; 2/20 control eyes required PRP for rubeosis iridis
	Subgroup analysis	None, ischemic CRVO excluded from study
	Notes	Patients in treatment group were seen 24 hours s/p IVTA, 1 week later, and monthly

APD: afferent pupillary defect

BCVA: best corrected visual acuity

CRVO: central retinal vein occlusion

DM: diabetes mellitus

FA: fluorescein angiography

IOP: intraocular pressure

ME: macular edema

PRP: panretinal photocoagulation

s/p IVTA: post intravitreal triamcinolone

VA: visual acuity

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Table 2

Table 1b: *Cheng 2008*

Methods	**Study type**	**Prospective non-randomized clinical interventional study**
	Enrollment method	Consecutive patients with CRVO; patients who agreed to IVS were assigned to the intervention group, while those refusing were assigned to the control group
	Inclusion criteria	Clinical evidence of CRVO with intraretinal hemorrhage and dilated, tortuous veins in all 4 quadrants in addition to ME
	Exclusion criteria	Not stated
	Follow up	Intervention group: 283 ± 70.62 days Control group: 354.05 ± 173.18 days
	Funding source	Not stated
Participants	Country	Kaohsiung, Taiwan
	Study period	Not stated
	No. of eyes	43 (22 treatment; 21 control)
	Baseline characteristics	Not equivalent
	Notes	Higher male:female ratio in control group (10:11 versus 9:13); over twice as many ischemic CRVO cases in control group (28.57% of cases versus 13.64% of cases); older age in control group (64.57 ± 8.77 versus 56.45 ± 14.67), and longer follow-up period for control group
Interventions	Treatment	4 mg (0.1 ml) of triamcinolone acetonide (Kenacort-A; Bristol Myers Squibb, Taipei, Taiwan)
	Control	Observation (+ PRP for ischemic CRVO cases)
	Notes	6 eyes in the control group were ischemic CRVO cases and received prophylactic PRP to prevent neovascular complications at start of study (3 eyes in study group received prophylactic PRP during follow-up periods); anterior chamber paracentesis performed before all IVS injections; Tobramycin-Tobrex used after all IVS injections
Outcomes	Final mean VA	Intervention: statistically significant increase in VA from 1.00 ± 0.45 logMAR pre-operative to best postoperative VA of 0.67 ± 0.65 logMAR (P = 0.007); 12 eyes (54.5%) improved ≥ 2 Snellen lines during follow-up period Control: no significant increase in VA from 1.04 +/− 0.57 logMAR to 1.11 +/− 0.53 logMAR (P = 0.457)
	Clinical appearance	Intervention: decline in cotton wool spots, retinal hemorrhage, and ME in all eyes Control: not stated
	ME	Intervention: average decrease of 46.95% in foveal thickness at end of follow up as measured by OCT (P< 0.001) Control: average decrease of 8.33% in foveal thickness at end of follow up as measured by OCT (P = 0.062)
	Complications	Intervention: ME recurrence in 6/22 eyes; 7 eyes (31.82%) had IOP > or = 22 mm Hg (1 trabeculotomy); 1 mature cataract
	Subgroup analysis	Intervention: ischemic CRVO cases showed no improvement in VA
	Notes	Unclear if measured BCVA in both groups occurred after the 6-month end-point

BCVA: best corrected visual acuity

CRVO: central retinal vein occlusion

IVS: intravitreal steroids

ME: macular edema

OCT: optical coherence tomography

PRP: panretinal photocoagulation

VA: visual acuity

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Table 3

Table 1c: *Gelston 2006*

Methods	**Study type**	**Retrospective comparative case series**
	Enrollment method	Records of all patients were reviewed
	Inclusion criteria	CRVO of 1 to 24 weeks duration prior to treatment or presentation, ischemic CRVO defined as APD or > 10 disc areas ofnon-perfusion, both types ofCRVO included
	Exclusion criteria	Pre-existing DR, prior photocoagulation, uveitis, or ME
	Follow up	Minimum of 6 months
	Funding source	Not stated
Participants	Country	Colorado, USA
	Study period	Records reviewed October 2002 to July 2004; observation group chosen over 7-year period
	No. of eyes	19 eyes (9 treatment, 10 control)
	Baseline characteristics	Not equivalent
	Notes	Initial VA of observation group higher than initial VA of treatment group (20/75 versus 20/161, P = 0.15); average duration of CRVO prior to treatment in treatment group was 10.8 weeks and prior to presentation for observation group was 6.7 weeks (P = 0.26); greater proportion of males in the treatment group compared to observation (8/9 versus 7/10)
Interventions	Treatment	4 mg (0.1 ml) of triamcinolone acetonide (Kenalog®; Bristol Meyers Squibb, NJ)
	Control	Observation
	Notes	Anterior chamber paracentesis performed iflight perception only or worse VA at 5 minutes
Outcomes	Final mean VA	Baseline VA: intervention = 20/161; control = 20/75; P = 0.15 6 months follow up: intervention = 20/99; control = 20/282; P = 0.33
	ME	“Appeared to be less clinically apparent ME in both ischemic and non-ischemic CRVO treatment groups vs. observation group.”
	Complications	3/6 treated eyes who developed IOP rise required PRP for NVG; IOP returned to baseline by 6-month visit (P = 0.11)
	Subgroup analysis: non-ischemic CRVO - VA	Baseline VA: intervention = 20/86; control = 20/57; P = 0.10 6-month follow up: intervention = 20/59; control = 20/100; P = 0.20
	Subgroup analysis: gain/loss of Snellen lines after 6 months	Final VA > or = 20/40: intervention = 1; control = 0 Final VA 20/50 to 20/100: intervention = 4; control = 5 Final VA 20/100 to 20/200: intervention = 1; control = 1 Final VA < 20/200: intervention = 0; control = 0
	Notes	More frequent follow-up examinations for treatment group compared to observation group prior to 6-month end-point; data of specific follow-up exams beyond 6 months not shown; this study was only powered to detect a 4-line Snellen difference

APD: afferent pupillary defect

CRVO: central retinal vein occlusion

DR: diabetic retinopathy

IOP: intraocular pressure

ME: macular edema

NVG: neovasular glaucoma

PRP: panretinal photocoagulation

VA: visual acuity

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Table 4

Table 1d: *Jonas 2005*

Methods	**Study type**	**Prospective non-randomized clinical interventional study**
	Enrollment method	Not stated
	Inclusion criteria	Not stated
	Exclusion criteria	Not stated
	Follow up	10.1 +/− 8.6 months in intervention group 6.0 +/− 5.2 months in control group
	Funding source	“No proprietary interest”
	Notes	Unclear as to why follow-up rates differed between intervention and control group; decision to offer patients IVTA depended on examining ophthalmologist, time of recruitment, and patient preference
Participants	Country	Heidelberg, Germany
	Study period	Not stated
	No. of eyes	33 eyes of 32 Patients (13 eyes treatment, 20 eyes control)
	Baseline characteristics	Equivalent
	Notes	Exclusion criteria not stated in study; while treatment group had symptoms at least 3 months prior to IVTA, unclear how long symptoms present in observation group; initial VA of observation group higher than initial VA of treatment group (0.64 0.38 logMAR versus 1.20 0.55 logMAR); according to FA, 46% of treatment group had ischemic CRVO versus 20% of observation group
Interventions	Treatment	20 to 25 mg (0.2 ml) of triamcinolone acetonide
	Control	Observation
	Notes	Routine paracentesis
Outcomes	VA compared to baseline	Treatment: VA returned to baseline approximately 5 months s/p IVTA Control: VA did not differ significantly at end of follow up compared to baseline, P = 0.42
	Complications	Although IOP rise was significantly higher in treatment group versus observation group (P = 0.007) during study, neither group varied significantly at end of follow up (P = 0.65)
	Subgroup analysis: ischemic treatment versus non-ischemic treatment	Ischemic (n = 4): VA did not vary significantly (P = 0.10) from baseline to best postoperative VA (1.57 0.64 logMAR) Non-ischemic (n = 9): VA increased significantly (P = 0.04) from baseline to best postoperative VA (0.69 0.25 logMAR)
	Notes	Throughout study, VA results are not compared between treatment and observation groups; rather, P values represent VA changes compared to baseline within a group; FA not performed regularly for all patients in study; for subgroup analysis, pre-operative VA was significantly higher (P = 0.003) in non-ischemic CRVO (0.93 0.32 logMAR versus 1.79 0.51 logMAR)

CRVO: central retinal vein occlusion

FA: fluorescein angiography

IOP: intraocular pressure

IVTA: intravitreal triamcinolone

s/p: status post

VA: visual acuity

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Table 5

Table 2: Randomized controlled trial on IVTA for CRVO-ME

Study	# Eyes	Intervention	Control	Follow up	Key outcomes
Ramezani 2006	27 eyes	4 mg	Natural history	4 months	Compared to natural history, VA and central macular thickness of treated CRVO was significantly improved at 1 and 2 months respectively No significant difference in occurrence of neovascularisation of iris in both groups

CRVO: central retinal vein occlusion

VA: visual acuity

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Table 6

Table 3: Case series on IVTA for CRVO-ME

Study (in chronological order)	# Eyes	IVTA dose (mg)	Follow up	Key outcomes
Batioglu 2007	20 Pts	4 mg	24 months	Mean CMT 49.2% of baseline value at 1-year follow up No change in VA IVTA improves short-term anatomy but recurrences and complications occur in long-term in non-ischemic CRVO
Moschos 2007	15 eyes	4 mg	12 months	Significant improvement in VA in non-ischemic CRVO lasted 6 months Decrease in macular thickness but with less significance at 12 months Significant improvements in foveal mfERG lasted 6 months Improvement in parafoveal mfERG but with less significance at 12 months Increase in IOP up to 6 months but returned to baseline at 1 year Effects of IVTA last maximum of 3 to 6 months
Goff 2006	29 eyes	2 or 4 mg	11.6 months	Improvement in VA 3 months post IVTA but final VA was same as baseline Elevated IOP in 5/22 patients Multiple injections resulted in better outcomes
Gregori 2006	40 eyes	4 mg	12 months	IVTA can improve VA in some but most return to baseline VA at 1 year despite repeated injections 50% received > 1 injection by 1 year IOP increased > or = 10 mmHg in 24% at 1 year with 2/12 requiring trabeculectomy
Williamson 2005	18 eyes	2 mg	12 months	10patients required repeat injections Significant improvement in VA lasted for 6 months Significant decline in retinal thickness lasted for 3 months 11patients had rise in IOP 10 patients developed collateral circulation formation Beneficial effects of IVTA in non-ischemic CRVO transient
Ozdek 2005	22 eyes	4 mg	Mean 11.5 2.4	At least 3 lines of VA increase occurred in 81.8% of non-ischemic CRVO and 18.2% of ischemic CRVO Significant decrease in mean foveal thickness in both ischemic and non-ischemic CRVO at 9 months Although anatomical results similar in 2 groups, functional results are better in non-ischemic cases
Krepler 2005	13 eyes	4 mg	9 months	Significant improvement in VA in non-ischemic CRVO lasted for a maximum of 6 months Mean macular thickness significantly reduced until 9 months
Ip 2004	13 eyes	4 mg	6 months	Patients with non-ischemic CRVO had significant improvement in VA at 6 months while ischemic CRVO patients had non-statistically significant increase Decrease in mean foveal thickness 75% of patients with recurrence responded to retreatment No significant adverse effects
Park 2003	10 eyes	4 mg	Mean 4.8 months	All non-ischemic CRVO cases showed significant improvement in CME by volumetric OCT Statistically significant increase in BCVA at end of study and 60% had VA of 20/50 or better 30% with history of glaucoma required treatment and 1 case with history of open angle glaucoma required trabeculectomy
Ip 2003	8 eyes	4 mg	3 months	Average gain in VA of 3.3 lines with 4/8 improving and 4/8 no change from baseline 7/8 had clinical resolution of ME No adverse effects

BCVA: best corrected visual acuity

CME: cystoid macular edema

CMT: central macular thickness

CRVO: central retinal vein occlusion

IOP: intraocular pressure

IVTA: intravitreal triamcinolone

ME: macular edema

mfERG: multifocal electroretinography

OCT: optical coherence tomography

Pts: patients

VA: visual acuity

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Table 7

Table 4: Case reports on IVTA for CRVO-ME

Study	Patient demographics	Diagnoses	IVTA dose	Outcomes
Al-Dhibi 2007	24F	Non-ischemic CRVO OS post anti-androgen treatment for hirsutism	4 mg X 1	Improvement of CME VA improved 20/200 changed to 20/50 OS Sustained over 3-year follow up
Paques 2005	23F	CRVO OD	4 mg X 1	VA improved CF changed to 20/50, along with decrease in CME and venous tortuosity 3 months s/p IVTA, 20/100 OD, venous tortuosity returned and no triamcinolone particles found in vitreous
	34M	CRVO and serous RD OD	4 mg X 1	VA 20/200 changed to 20/60 s/p IVTA changed to 20/60 after 3 months 1044 um (RD) changed to 310 um s/p IVTA changed to 828 um after 3 months Decrease in venous tortuosity s/p IVTA but no improvement in perfusion Tortuosity worsened after 3 months
Karacorlu 2004	28F	Non-ischemic CRVO OD	4 mg X 1	VA 20/200 changed to 20/32 at 6-month follow up Mild venous tortuosity and venous calibre Resolution of CME
	27M	Non-ischemic CRVO OD	4 mg X 1	VA 20/80 changed to 20/32 at 6-month follow up Mild venous tortuosity and venous calibre Resolution of CME
Jonas 2002	70M	Bilateral long-standing CRVO-ME	25 mg X 1	VA increased bilaterally and FA showed decrease in macular leakage IVTA as option in chronic cases ofCME
Ip 2002	57M	Non-ischemic CRVO OD	4 mg X 1	Improvement in CME with VA 20/200 changed to 20/25 Sustained at 6-month follow up

CF: counting fingers

CME: cystoid macular edema

CRVO: central retinal vein occlusion

FA: fluorescein angiography

F: female

IVTA: intravitreal triamcinolone

M: male

ME: macular edema

OD: ocular dexter (right eye)

OS: ocular sinister (left eye)

RD: retinal detachment

s/p: status post

VA: visual acuity

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Table 8

Table 5: Other complications of IVS: select studies

Study (in chronological order)	Complication	Corollary notes
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
Srinivasan 2005	Conjunctival necrosis overlaying sclera entry site	Patient treated for BRVO-ME
Benz 2003	Mycobacterium chelonae abscess	Patient treated for diabetic macular edema Eventual enucleation of eye

BRVO-ME: macular edema secondary to branch retinal vein occlusion

CME: cystoid macular edema

VA: visual acuity