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Surgical implantation of steroids with antiangiogenic characteristics for treating neovascular age-related macular degeneration

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Abstract

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*Indicates the major publication for the study

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AT and SSV have no known conflicts of interest.

Background—Neovascular age-related macular degeneration (AMD) is associated with rapid vision loss due to choroidal neovascularization (CNV), leakage, and scarring. Steroids have gained attention in their role for the treatment of neovascular AMD for their antiangiogenic and anti-inflammatory properties.

Objectives—This review aims to examine effects of steroids with antiangiogenic properties in the treatment of neovascular AMD.

Search methods—We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (*The Cochrane Library* 2012, Issue 11), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to November 2012), EMBASE (January 1980 to November 2012), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to November 2012), the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictip/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 21 November 2012.

Selection criteria—We included randomized controlled clinical trials of intra- and peri-ocular antiangiogenic steroids in people diagnosed with neovascular AMD.

Data collection and analysis—Two authors independently screened abstracts and full-text articles, assessed risk of bias in the included trials, and extracted data. We did not conduct a meta-analysis.

Main results—We included three trials after screening a total of 1503 abstracts and 21 full-text articles. The three trials included a total of 809 participants. One trial compared different doses of acetate anecortave acetate with placebo, a second trial compared triamcinolone acetate versus placebo, and the third trial compared anecortave acetate against photodynamic therapy (PDT). We did not conduct a meta-analysis owing to heterogeneity of interventions and comparisons. The risk ratio for loss of 3 or more lines of vision at 12 months follow-up was 0.8 (95% confidence interval (CI) 0.45 to 1.45) with 3 mg anecortave acetate, 0.45 (95% CI = 0.21 to 0.97) with 15 mg anecortave acetate, 0.91 (0.52 to 1.58) with 30 mg anecortave acetate, 0.97 (95% CI 0.74 to 1.26) with triamcinolone acetate, all compared to placebo and 1.08 (95% CI 0.91 to 1.29) with anecortave acetate compared with PDT.

Authors' conclusions—Based on the included trials, we found no evidence that antiangiogenic steroids prevent visual loss in patients with neovascular AMD. With the emergence of antivascular endothelial growth factor modalities, based on evidence summarized in this review, it is unclear what role steroids have in treating patients with neovascular AMD.

Medical Subject Headings (MeSH)

Angiogenesis Inhibitors [*administration & dosage]; Choroidal Neovascularization [complications; *drug therapy]; Drug Implants; Macular Degeneration [*drug therapy; etiology]; Photochemotherapy; Pregnadienediols [*administration & dosage]; Randomized Controlled Trials as Topic; Triamcinolone Acetonide [*administration & dosage]

MeSH check wordsHumans

Background**Description of the condition**

Introduction—Age-related macular degeneration (AMD) continues to be among the leading causes of blindness in the developed world. It is a degenerative disorder involving the central portion of the retina that is responsible for high-resolution visual acuity. The two major types of AMD are classified based on specific abnormalities of the retinal pigment epithelium (RPE) and retina. The dry, or atrophic, form of AMD typically involves the RPE, choriocapillaris, and photoreceptors in the absence of serous or hemorrhagic leakage. The wet, or neovascular, form includes choroidal neovascularization (CNV), leakage of blood and serum, and fibrovascular scarring. Because of the severity of disease found in the neovascular form, it accounts for the majority of significant vision loss caused by AMD (Ferris 1984). Treatment options for this disease are limited and there are a variety of therapies currently being investigated for neovascular AMD. This review is concerned with the potential use of intravitreal antiangiogenic steroids for the treatment of neovascular AMD. Another Cochrane review is looking at agents that are specific to antivascular endothelial growth factors (anti-VEGF) (Vedula 2008).

Epidemiology—The World Health Organization estimates that at least eight million individuals worldwide are severely visually impaired due to AMD (WHO 1997). It is estimated that in the United States alone 1.6 million people aged 50 years and older have evidence of late AMD (Tielsch 2002). Large, population-based studies worldwide have found varying prevalence rates of AMD, though they have consistently shown increased risk with age (Evans 2001). Accordingly, the Beaver Dam Eye Study found an increased incidence of age-related maculopathy lesions with age (Klein 2002). With the growing aging population in the developed world, the number of people at risk of AMD is bound to increase further.

Presentation and diagnosis—Individuals with atrophic AMD typically present with a slow and gradual deterioration in fine discriminate visual acuity, which may eventually lead to central vision loss. Neovascular AMD is associated with a more rapid loss of vision. With CNV and leakage of fluid into the surrounding retina, central blurring or visual distortion occurs. Eventual scarring and extensive leakage can subsequently lead to more significant loss of vision.

Fundus examination of people with AMD reveals characteristic presentations that range from drusen and pigmentary changes in people with the atrophic form, to subretinal fluid or blood in the neovascular form. In neovascular AMD, fluorescein angiography is helpful in detecting subtle exudates associated with CNV. Based on fluorescein studies, CNV can be classified as classic or occult lesions. Classic lesions are characteristically well-defined and

have early hyperfluorescence, whereas occult lesions have late leakage or evidence of fibrovascular pigment epithelial detachment.

Description of the intervention

The Macular Photocoagulation Studies (MPSG 1994) demonstrated a delay in vision loss after laser photocoagulation treatment for extrafoveal and juxtafoveal classic CNV secondary to AMD. Argon thermal laser photocoagulation of CNV is not an option for subfoveal CNV as it causes immediate loss of central vision due to damage to the overlying retina. Recurrence of CNV following thermal laser has been shown to occur within three years (MPSG 1994). A Cochrane review summarizes the evidence on laser photocoagulation (Virgili 2007).

Photodynamic therapy (PDT) was developed as an alternative non-thermal treatment for subfoveal CNV. In PDT, a photoreactive drug is used and activated with light to induce release of free radicals as the drug fills the proliferative neovascularization. The Treatment of AMD with PDT (TAP) Study Group demonstrated a reduced risk of visual loss for eyes with predominantly classic CNV after PDT treatment (Bressler 2001; TAP 1999). However, most participants receiving PDT need multiple treatments within the first year. Recent fluorescein angiographic guidelines for the evaluation and treatment of subfoveal CNV describe patients who are most likely to benefit from PDT with verteporfin (TAP 1999; VIP 2003). A recently updated systematic review on PDT for AMD is also published in *The Cochrane Library* (Wormald 2007).

Cochrane reviews have also been published on other interventions such as antiangiogenic therapy with interferon alfa (Reddy 2006), radiotherapy (Evans 2010), antioxidants (Evans 2012) and ginkgo biloba (Evans 2013).

How the intervention might work

Clinical and basic science research has directed attention to anti-angiogenesis as a key target for the medical treatment of CNV. Several antiangiogenic agents are being investigated in treating neovascular AMD and other pathologic neovascularization of ocular tissues (*see* Table 1). Intravitreal injection of pegaptanib sodium and ranibizumab have been approved by the US Food and Drugs Administration (FDA) for the treatment of CNV in patients with AMD. Inflammatory processes have also been shown to play a significant role in the pathogenesis of AMD and development of CNV (Penfold 2001). Given these potential pharmacologic targets for inducing regression of CNV, steroids have been investigated for their potential anti-inflammatory and antiangiogenic effects. Penfold et al reviewed laboratory evidence demonstrating that intravitreal corticosteroids mediate anti-inflammatory responses by inducing the resorption of exudates and down-regulating inflammatory stimuli (Penfold 2001). Angiostatic steroids are a separate class of steroids that mediate specific antiangiogenic activity independent of steroid hormone activity. Angiostatic steroids have been shown to inhibit neovascularization in intraocular tumors in animals (BenEzra 1997; Clark 1999; Penfold 2001). These steroids are believed to inhibit angiogenesis by increasing the synthesis of plasminogen activator inhibitor, which

subsequently inhibits plasmin generation, a process essential to the invasive growth of new vessels (Blei 1993).

Why it is important to do this review

With the support of laboratory evidence and advances in drug delivery systems, intravitreal steroids have been studied and used for the treatment of neovascular AMD in the clinical setting. However, the classes of steroids, dosages, and drug delivery systems being used vary between clinical studies. The diversity in methodology warrants a review of these trials to help draw meaningful conclusions about the effectiveness and relevance of steroids in the management of neovascular AMD.

Objectives

The primary aim of this review is to investigate the effects of intra- and periocular steroids with antiangiogenic properties in delaying visual loss in patients with neovascular macular degeneration. A secondary aim of this review is to compare the clinical outcomes and side effects of different antiangiogenic steroids. A third aim is to compare the intraocular drug delivery systems used for the administration of steroids in the treatment of neovascular AMD in different clinical trials.

Methods

Criteria for considering studies for this review

Types of studies—We included only randomized controlled trials (RCTs) in this review.

Types of participants—We included trials in which participants were diagnosed with neovascular age-related macular degeneration as defined by study investigators.

Types of interventions—We included trials in which implantation (injection, device, suspension, or micro-sphere) of a steroid with antiangiogenic characteristics was compared to another treatment, placebo, or no treatment.

Types of outcome measures

Primary outcomes: The primary outcome for this review is loss of visual acuity measured at 12 months or more, but no more than 24 months. Depending on the data presented in the trial reports, we also examined the proportion of people with loss of 3 or more lines of log-MAR visual acuity (equivalent to a doubling of the visual angle).

Secondary outcomes: The secondary outcomes for this review are as follows.

1. Contrast sensitivity measured at 12 months using standardized charts and analyzed using log contrast sensitivity values.
2. Size and characteristics of lesion as determined by fluorescein angiography.
3. Retinal thickness and parameters as measured by optical coherence tomography (OCT) at 12 months.

4. Quality of life measures assessed using any validated measurement scales.

Adverse effects—We categorized adverse effects reported in the included studies as ocular or systemic. We planned to report and describe all adverse effects observed including, but not limited to, those listed below. We enumerated adverse event data from each included trial, recognizing that reliable evidence of rare events was unlikely to emerge from RCTs alone. We did not attempt to summarize adverse events from observational studies.

Ocular: retinal detachment; hemorrhage; infection; cataract; steroid-induced rise in intraocular pressure (IOP) and steroid-induced glaucoma; pupillary abnormalities; rubeosis; pigment epithelial detachment; loss of vision; photopsia; ptosis; anterior chamber inflammation; corneal abrasion; pain; foreign body sensation; chemosis and subconjunctival hemorrhage; lid edema; dry eye; vitreous prolapse; vitreous floaters; intraocular air; tearing. Systemic: cardiovascular; neurological; respiratory; genitourinary; kidney; joint; fatigue; headache.

Search methods for identification of studies

Electronic searches—We searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2012, Issue 11, part of *The Cochrane Library*. www.thecochranelibrary.com (accessed 21 November 2012), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to November 2012), EMBASE (January 1980 to November 2012), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to November 2012), the metaRegister of Controlled Trials (mRCT) (www.controlledtrials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictip/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 21 November 2012.

See: Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), EMBASE (Appendix 3), LILACS (Appendix 4), mRCT (Appendix 5), ClinicalTrials.gov (Appendix 6), and the ICTRP (Appendix 7).

Searching other resources—The bibliographies of included trials were searched for details of further relevant trials. We did not conduct a manual search of any conference proceedings for the purpose of this review.

Data collection and analysis

Selection of studies—Two review authors independently scanned the titles and abstracts resulting from electronic searches. Full copies of all potentially or definitely relevant articles were further screened by the two review authors independently. Only those articles meeting the inclusion criteria were assessed for quality. We contacted the trial authors to clarify details as necessary for making a complete assessment of the relevance of each study.

Data extraction and management—Two review authors independently extracted data using a form developed by the Cochrane Eyes and Vision Group. Data were entered into RevMan 5 (RevMan 2011) by one review author, and verified by a second author.

Assessment of risk of bias in included studies—Two review authors independently assessed the risk of bias of the studies that met the inclusion criteria. The review authors were not masked to author or institution details of included trials during the assessment. We assessed the risk of bias according to the following domains: sequence generation and allocation concealment (selection bias), masking of patients and study personnel (performance bias), masking of outcome assessors (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other sources of bias. We judged each risk of bias domain to be at ‘high’, ‘low’, or ‘unclear’ risk of bias as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Disagreements between review authors were resolved by discussion. We contacted trial authors for clarification of any risk of bias domain.

Data synthesis—We planned to combine the data using a random-effects model if we found no substantial heterogeneity with a chi-square test and the I-square statistic. As more studies become available in the future, we will investigate any heterogeneity by examining study characteristics including: participant age, visual acuity, lesion size and composition, drug delivery system, type and dose of steroid used. We will use a fixed-effect model if there are fewer than three studies. Dichotomous outcome measures will be summarized as risk ratios. Continuous outcomes will be summarized as mean differences.

Sensitivity analysis—We planned to conduct a sensitivity analysis to examine the influence of any assumptions made during the review process on our conclusions and to examine the impact of exclusion of studies assessed as being at lower methodological quality (e.g., allocation concealment), unpublished data and industry funded studies.

Results

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search—The electronic searches for this review were dated November 21, 2012. We screened a total of 1503 abstracts retrieved from electronic searches of bibliographic databases and 23 references from ClinicalTrials.gov trials register. We identified 21 relevant full-text articles and excluded after further consideration, 11 full-text articles and 2 records retrieved from the National Research Register. See ‘Characteristics of excluded studies’ for reasons for excluding the articles. We included three trials, which were described in eight reports. Details of the included trials are summarized below and in the ‘Characteristics of included studies’ table.

Included studies

Types of participants: The Anecortave Acetate Clinical Study (AACS 2003) was a multicenter trial conducted in 18 clinical centers across Europe and the United States. The trial enrolled 128 participants and only one eye per participant was randomized. Participants had known AMD and subfoveal CNV with a classic component, were 50 years or older, and had a best-corrected visual acuity of 20/40 to 20/320. The Intravitreal Triamcinolone Study (IVTS 2003) conducted in a single tertiary care hospital in Sydney, Australia, enrolled 151 participants who were 60 years or older with known AMD and found to have classic or discrete CNV, best-corrected visual acuity of 20/200 or better, and symptoms lasting no longer than 12 months prior to enrollment. The trial included 139 participants of which 12 had both eyes randomized to different interventions. Slakter 2006 was conducted among 530 participants in 52 centers across Europe, USA, Canada, Israel and Australia. Participants in this trial were at least 50 years old and had been diagnosed with neovascular AMD, subfoveal CNV eligible for treatment with PDT and with no history of prior treatment with PDT. The best-corrected visual acuity range for eligibility was 20/240 to 20/400. The study randomized 130 participants.

Type of intervention: AACS 2003 investigated juxtascleral depot injection of an entirely different steroid, acetate anecortave acetate at three different doses, 3 mg, 15 mg, and 30 mg compared to placebo. A sterile posterior juxtascleral procedure, using a specially designed injecting cannula, was used to administer 0.5 ml of study medication or placebo (vehicle) onto the outer surface of the sclera near the macula.

IVTS 2003 examined the efficacy and safety of a single intravitreal injection of 4 mg triamcinolone acetonide (0.1 ml of Kenacort 40; Bristol-Myers Squibb Pharmaceuticals, Noble Park, Victoria, Australia). A placebo treatment consisting of a subconjunctival injection of isotonic sodium chloride solution was introduced after the 12th participant was enrolled, when it became apparent that participants allocated to no treatment were more likely to drop out of the study.

Slakter 2006 compared PDT with adjunct juxtascleral depot administration of 15 mg anecortave acetate versus PDT alone. Participants randomized to the anecortave acetate 15 mg group received a sham PDT treatment prior to the posterior juxtascleral depot, while the PDT group received a sham posterior juxtascleral depot procedure after the PDT treatment.

Types of outcome measures: AACS 2003 evaluated the mean change from baseline in best-corrected visual acuity as the primary outcome. Other vision outcomes included as percentage of participants with preservation or maintenance of vision (loss of < 3 logMAR lines vision), clinically significant worsening of vision (loss of at least 3 lines vision), and severe vision loss (at least 30 logMAR letters or 6 lines). The trial also commented on changes in CNV lesion characteristics. Participants were clinically evaluated at post-injection day one to two, week two and six, month three and six after each posterior juxtascleral administration of treatment. Visual acuity was measured at all study visits except on post-injection day one to two. Fluorescein angiography and fundus photography

was performed at week two and six, month three, prior to each additional retreatment and at the exit visit.

IVTS 2003 reported the proportion that developed severe visual loss (30 letters on a logMAR chart) at two years as their primary outcome. Other vision outcomes reported include the risk ratio of loss of 3 or more lines of vision, and loss of 6 or more lines of vision at 12 months. Participant data was reviewed before treatment, then at three, six, and 12 months when visual acuity was measured. Fluorescein angiography was performed at baseline, and at three and 12 months, while stereocolor photographs of the macula were taken at baseline, and then at six and 12 months. Other outcomes reported include changes in size of CNV and leakage of neovascular membranes.

Slakter 2006 assessed preservation of vision defined as loss of 3 or fewer logMAR lines of vision. The primary outcome measure was percentage of responders or participants losing fewer than 3 lines of vision at month 12. The follow up visits were scheduled for three, six, nine and 12 months. Digital fluorescein and indocyanine green angiography was done at all study visits and transmitted to a reading center for masked assessment.

Excluded studies—We excluded 11 full-text articles and two records retrieved from the National Research Register after full-text assessment (see the ‘Characteristics of excluded studies’ table).

Risk of bias in included studies

The risk of bias in the included studies is illustrated in Figure 1 and summarized below and in the ‘Characteristics of included studies’.

Allocation—Although the reports for AACS 2003 described that a randomization schedule was generated “by the biostatistics department at Alcon Research,” it is unclear how the sequence was actually generated. So we judged the risk of bias for allocation as unclear for this trial. For IVTS 2003, we judged risk of bias for this item to be low based on the description that the randomization schedule consisted of pseudo-random numbers generated using a computer. We judged both trials to be at low risk of selection bias based on the description of how allocation was concealed until randomization. Verbatim descriptions from the trial reports for allocation concealment are provided in the ‘Characteristics of included studies’ table.

We were unable to assess the risk of bias for Slakter 2006 because the report did not describe the details.

Blinding—Based on the description in the trial report, patients, investigators making a decision whether to retreat the patient during a follow-up visit, and investigators evaluating outcomes were masked and unaware of participants' treatment assignments during the trial in AACS 2003. Investigators administering study treatments to patients were unmasked to assignments. It is unclear from the trial report whether any pre-specified criteria were used by the masked ophthalmologist examining patients during follow-up and judging whether they would benefit from continued treatment or they should be excluded from the trial.

In IVTS 2003, the first 12 patients randomized into the trial were randomized to either the study treatment or no treatment. Placebo was introduced as an intervention for the control group after the 12th patient enrolled in the trial. Subsequent patients were masked to treatment assignment as were investigators evaluating photographs. Although the report for IVTS 2003 described that investigators measured visual acuity without considering the patient's medical history, it is possible that steroid-related side effects may have led to unmasking of the investigators.

Participants and outcome assessors were masked in Slakter 2006. Some of the study personnel, such as physicians administering the treatment, were aware of the treatment assignments. Masking of participants was achieved with a sham injection following the same procedure as anecortave acetate injection.

Incomplete outcome data—For a large proportion of participants in AACS 2003, outcome data were unavailable at 12 months follow-up. It appears that for all such patients, outcome data were imputed with the last available observation. The trial report described finding no significant differences at baseline between patients with and without missing data at 12-months follow-up. But it is unclear whether such differences could have been detected if they did exist. It is also unclear whether the assumption made when carrying forward the last available observation, i.e., the visual acuity early during the follow-up remains unchanged until the end of follow-up, is reasonable. In addition, analyses based on such an assumption ignore any associated uncertainty (NRC 2010).

Incomplete data was less of a problem for analyses of the primary outcome in IVTS 2003. Few eyes were excluded from analyses in each group. It wasn't clear whether the criterion used by the authors to impute visual acuity data were pre-specified in the trial protocol or analysis plan.

Few patients in Slakter 2006 were excluded from the efficacy analysis. Although the analysis was described as intent to treat, all randomized participants were not included in the analysis. Missing values were imputed using the last observation but the analyses did not address the sensitivity of findings to assumptions made during imputation.

Selective reporting—The included trials reported primary and secondary outcomes according to how they were described in the study methods and were judged to have a low risk of bias for selective outcome reporting, although we didn't have access to the trial protocols.

Other potential sources of bias—AACS 2003 was sponsored by Alcon Research, a pharmaceutical company marketing the study intervention. An employee of the company sponsoring the trial was a member of the “Independent Safety Committee” for the trial. IVTS 2003 was sponsored by the National Research and Medical Research Council, Canberra, and the Sydney Eye Hospital Foundation. Some of the trial investigators and authors of the report are “listed as inventors on patents that cover the use of intraocular steroids to treat retinal neovascularization” (IVTS 2003).

Effects of interventions

We did not conduct a meta-analysis since the included studies evaluated different comparisons.

Anecortave acetate versus placebo

Visual acuity: AACS 2003 compared three different doses of anecortave acetate with placebo and reported visual acuity as both a dichotomous and continuous outcome. Data from this trial at 12 months included last observation carried forward for participants who were determined not to benefit with further treatment at six months by a masked investigator.

The risk ratio of loss of 3 or more lines at 12 months was 0.8 (95% confidence interval (CI) 0.45 to 1.45) in the 3 mg group, 0.45 (95% CI 0.21 to 0.97) in the 15 mg group and 0.91 (95% CI 0.52 to 1.58) in the 30 mg anecortave acetate group all compared with placebo. The risk ratio of loss of 6 or more lines at 12 months was 0.8 (95% CI 0.30 to 2.12) in the 3 mg group, 0.13 (95% CI 0.02 to 0.99) in the 15 mg group and 0.65 (95% CI 0.23 to 1.83) in the 30 mg anecortave acetate group all compared with placebo. Although the 95% confidence interval for the 15 mg group alone excludes the null value suggesting treatment benefit in decreasing the risk of moderate and severe vision loss, it is nearly half in magnitude compared with the other two doses. The inconsistent results may be a consequence of the large numbers of losses to follow-up in the 15 mg treatment group.

Triamcinolone acetonide versus placebo

Visual acuity: Analysis for visual acuity showed no evidence of beneficial effect with treatment. The risk ratio of loss of 3 or more lines at 12 months was 0.97 (95% CI 0.74 to 1.26) and the risk ratio of loss of six or more lines vision at 12 months was 1.03 (95% CI 0.64 to 1.64). Participants who were lost to follow-up, who died and who refused treatment in the placebo group were not included in the analysis (six of 70 or 8.5% of participants at baseline). In the treatment group, however, all participants randomized were analyzed despite loss of two participants to follow-up due to death, resulting in lack of clarity about the unit of analysis adopted in the trial.

Lesion characteristics: No change in lesion size or growth was observed at 12 months, but at three months there were more eyes in the treated group (35 out of 74) compared to the placebo group (26 out of 74) that had small and medium neovascular lesions. However, in about 30% of the participants in each group, lesion characteristics could not be assessed. Data on mean lesion size were not reported.

Anecortave acetate 15 mg versus PDT

Visual acuity: The risk ratio of loss of 3 or more lines of vision at 12 months follow-up (figure not shown) was 1.08 (95% CI 0.91 to 1.29) in an available case analysis and 1.08 (95% CI 0.91 to 1.27) in an intention-to-treat analysis conducted using the last observation carried forward method. However, Slakter 2006 was designed to be a non-inferiority trial. The investigators reported a primary outcome of preservation of visual acuity in terms of loss of fewer than 3 lines of vision at 12 months to compare anecortave acetate 15 mg versus

PDT. The risk ratio of loss of fewer than 3 lines at 12 months was 1.08 (95% CI 0.91 to 1.29) only slightly favoring PDT over anecortave acetate.

In the subgroup analysis performed within the anecortave acetate group, there was a higher proportion of responders in the group treated with anecortave acetate 15 mg within the six-month treatment window and for whom reflux was controlled. Overall however, there was no statistical difference between the two groups.

Adverse effects: In the AACS trial, the most common adverse events included vision loss defined as loss of 4 or more lines of vision and cataract progression. This occurred in all four treatment groups. The only ocular adverse events that occurred more frequently in the anecortave acetate groups were “vision abnormalities” and foreign body sensation. There is no mention of any dose-dependent response for any of these ocular events.

The IVTS analyzed adverse events in 142 eyes at 12 months, 100 eyes at two years and in 35 eyes at three years (IVTS 2003). Procedure related events such as transient discomfort or blurring were reported in both groups. Elevated IOP, however, was noted in 31 participants in the treatment group and only in three participants in the placebo group at 12 months. One additional participant in each group developed increased IOP over the three year follow-up period.

There was significant progression of posterior subcapsular cataracts in eyes treated with intravitreal triamcinolone. After 12 months, five participants had progression of cataract by two or more Age-related Eye Disease Study Grades in the treatment group and only one participant in the placebo group (IVTS 2003). In two years, eight participants in the treatment group compared to none in the placebo group developed progression of posterior subcapsular cataract. Other reported adverse events included arteritic anterior ischemic optic neuropathy in one participant in the treatment group and massive subretinal or break-through vitreous hemorrhage in three eyes in the placebo group.

Slakter 2006 evaluated safety data on participants who received at least one dose of anecortave acetate or PDT. The most frequently reported adverse event was vision loss as defined as a drop of 4 or more lines of vision. There was little difference between the participants treated with anecortave and PDT, with 31.9% and 30.4% having a decrease in vision respectively. Other adverse events were mostly unrelated to therapy except for one participant treated with anecortave acetate 15 mg who discontinued participation due to retinal artery occlusion, which is possibly related to the study drug.

Discussion

Summary of main results

The available evidence scarcely supports the use of anti-angiogenic steroids for neovascular AMD. The effect estimates comparing steroids to placebo and steroids to PDT are small in magnitude and have large variances. We observed consistency across the three trials, which used different doses of two drugs, in the lack of a significant clinical or statistical effect of treatment. The interventions tested in the included trials comprised both a steroid with

glucocorticoid activity (triamcinolone acetonide) and a steroid without glucocorticoid activity (anecortave acetate). Adverse effects anticipated with corticosteroids, such as cataract, occurred frequently.

Overall completeness and applicability of evidence

Although we included three relatively small trials, descriptions in the individual studies indicate that they were adequately powered to detect meaningful effects of the interventions. The trials excluded individuals with other ocular pathologies in addition to AMD. However, because the eligibility criteria for the three trials were broad, we believe that our conclusions are applicable to most patients presenting with neovascular AMD.

Quality of the evidence

Overall, the risk of bias for the three trials was moderate. Potential for selection bias was an important concern for AACS 2003 and Slakter 2006. The potential for unmasking of participants and investigators and differential care of participants in the comparison groups was adequately addressed only in AACS 2003.

Agreements and disagreements with other studies or reviews

Findings from numerous uncontrolled clinical trials in the past have suggested that there may be some benefit with intravitreal triamcinolone. A study by Challa et al showed that 18 months after triamcinolone treatment (4 mg) only 30% (6/20) of eyes with an initial visual acuity of 6/60 or better developed severe vision loss (Challa 1998). In another case series by Ranson et al only one out of 11 (9%) eyes treated with intravitreal triamcinolone (4 mg) developed severe vision loss after one year (Ranson 2002). However, given the lack of prospective controls and the small size of the previous trials, it is difficult to draw meaningful conclusions regarding the relative benefit of treatment versus observation alone. The absence of evidence of benefit from a single dose of 4 mg intravitreal triamcinolone as reported by IVTS investigators (IVTS 2003), suggests that the effects of intraocular steroid treatment is transient. Jonas 2004 reported an increase in visual acuity in three out of six participants after a second injection of triamcinolone. Although findings from another case series suggested a potential benefit with using 25 mg triamcinolone (Jonas 2003), such high doses raise concerns about increased incidence of adverse effects. Prior randomized clinical trials provide evidence that participants with subfoveal CNV, such as those included in AACS 2003, may benefit from PDT. Although trials evaluating combination interventions with steroids for neovascular AMD do not meet eligibility criteria for this review, we tabulate details from three relevant trials in Table 2 (Arias 2008; Maberley 2009; Tsuchiya 2008).

Authors' Conclusions

Implications for practice

There is little evidence from the three RCTs included in this review to suggest that anti-angiogenic steroids are effective for neovascular AMD. Although the RCTs included in our review provide limited evidence of safety with surgical implantation of the intervention, they have demonstrated the utility of the route of administration.

Implications for research

Considering recent advances in treating AMD with other anti-angiogenic drugs, the relevance of future research on the effects of steroids is questionable. Future research on steroids should carefully evaluate the potential risk and lack of evidence of any benefit in the study design and while obtaining informed consent. Although some recent research has focused on comparing combination interventions of steroids and PDT with other interventions, the relevance of using steroids in such studies should be re-examined. Since the evidence suggests that steroids alone are not effective for neovascular AMD, it is unclear how a combination intervention with PDT can be superior. Studies evaluating combined interventions of steroids with other treatments such as PDT should be substantiated by adequate pharmacological and physiological rationale.

The consistent evidence from three trials included in our review also raise the question of why anti-angiogenic steroids did not result in clinically meaningful and statistically significant beneficial effects. Future research may examine reasons for discrepancies in the clinical effects between anti-angiogenic corticosteroids studied in trials included in this review and antivascular endothelial growth factor modalities.

We included one trial comparing steroids with PDT but we excluded trials evaluating combination interventions or staged treatment of exudative AMD with PDT forming a component of therapy. Combination interventions (anti-VEGF combined with photodynamic therapy and/or intravitreal steroids) are the subject of another planned Cochrane review.

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Characteristics of Studies

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

AACS 2003

Methods

Number randomized: Treatment arms: 3 mg (n = 32), 15 mg (n = 33), and 30 mg (n = 33), and control arm: n = 30.

	<p>Losses to follow-up: At 6 months, 6.25%, 24.2%, 3% and 13.3% participants were lost to follow-up in the 3 mg, 15 mg, 30 mg anecortave acetate and placebo groups respectively. At 1 year, however, 37.5%, 48.5%, 36.4% and 40% participants were not analyzed in the 3 mg, 15 mg, 30 mg anecortave acetate and placebo groups respectively.</p> <p>Intention-to-treat analysis: The last observation was carried forward to impute missing values for analyses at 6 months and 12 months.</p> <p>Reported sample size calculation: Assuming a standard deviation of 0.285 logMAR lines in visual acuity, the study reported a 80% power to detect an average difference of 2 logMAR lines in a 2-tailed t-test at a 0.05 level of significance with 30 patients per group.</p> <p>Unusual study design: The patients were examined by a masked ophthalmologist at 6 months who determined whether the patient was likely to benefit with further treatment. Patients judged as unlikely to benefit from continued treatment were excluded from further follow-up</p>
Participants	<p>Inclusion criteria: Individuals older than 50 years with exudative AMD and subfoveal choroidal neovascularization (CNV); the neovascularization should have comprised of classical CNV occupying at least 50% of the total lesion area; and best corrected visual acuity between 20/40 and 20/320 at baseline</p> <p>Exclusion criteria: History of pre-existing disease, surgery, or use of any investigational drug within 30 days before enrolment in the study eye</p> <p>Age: Mean age was 78.1, 75.8, 75.7 and 78.3 years in 3 mg, 15 mg, 30 mg anecortave acetate and placebo groups, respectively</p> <p>Gender: 46.9%, 54.5%, 54.5% and 60% were females in 3 mg, 15 mg, 30 mg anecortave acetate and placebo groups, respectively</p> <p>Equivalence of baseline characteristics: All groups were similar at baseline with respect to age, race, composition of lesions, logMAR visual acuity, sizes of choroidal neovascularization and classic component of the lesions</p>
Interventions	<p>Treatment: Juxtascleral depot injection of three doses of anecortave acetate: 30 mg, 15 mg, and 3 mg. After every 6 months, an ophthalmologist masked to treatment assignment determined whether the patient might benefit with another injection of the drug. The study drug was injected by a different ophthalmologist, unmasked to treatment assignment.</p> <p>Control: Placebo injection in the same fashion as the treatment.</p>
Outcomes	<p>Primary outcome: Mean change in logMAR visual acuity from baseline.</p> <p>Secondary outcomes: Percentage of all participants exhibiting stabilized vision (< 3 lines lost). Percentage of participants with clinically significant worsening of vision defined as loss of at least 3 lines vision.</p> <p>Percentage of participants with severe vision loss (at least 6 logMAR lines lost).</p> <p>Percentage of participants that demonstrated reduced lesion growth (percent change from baseline)</p>
Notes	<p>Country: 18 centres across United States and Europe.</p> <p>Time period of study: April 1999 to May 2001.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>"Sequential patient numbers were randomly assigned to treatment groups according to a randomization schedule generated by the biostatistics department of Alcon Research."</p> <p>"The randomization was built into the sequential numbering of the treatment kits and blocked within each site to maintain equal distribution across treatment assignments."</p>
Allocation concealment (selection bias)	Low risk	Sequentially numbered, opaque, sealed boxes were used.
Masking of study participants (performance bias)	Low risk	Participants were masked to their treatment assignment.
Masking study personnel (performance bias)	Unclear risk	Study personnel were not masked: "Masking of treatment is also being maintained at each site by having an unmasked injecting investigator perform the treatments and the day 1-2 visit."
Masking outcome assessors (detection bias)	Low risk	The investigator performing the other evaluations was masked to treatment assignment
Incomplete outcome data	High risk	<p>"Fifteen of the 128 patients in this study exited before their month 6 visit."</p> <p>"Of the 128 patients enrolled and treated, 76 patients (59.4%) completed their month 12 visit."</p>

(attrition bias) All outcomes		"Last observation carried forward was used in the analysis to impute missing data."
Selective reporting (reporting bias)	Low risk	Reported 6 and 12 month results for both primary and secondary outcomes as described in the study methods, although the protocol was not available
Other bias	Unclear risk	-Funded by industry (Alcon Research Ltd.) -Intervention design: "At each month 6 visit, a masked examining ophthalmologist made the decision as to whether the patient might benefit from re-treatment. Re-treatment was performed by an unmasked injecting ophthalmologist (using the assigned study medication or the placebo as originally randomized), and the same study visits were repeated during the 6-month post-treatment phase that followed. If the masked examining ophthalmologist judged that the patient would not benefit from continued participation in the clinical trial, the patient exited the study."

IVTS 2003

Methods	<p>Number randomized: Treatment arm: n = 75, and control arm: n = 76</p> <p>Losses to follow-up: Two participants in the triamcinolone group and six participants in the placebo group were lost to follow-up at the end of 1 year.</p> <p>Intention-to-treat analysis: The trial report described that the analysis was by intention-to-treat but participants lost to follow-up (due to death or withdrawal from the study) were not included in the analyses.</p> <p>Reported sample size calculation: A sample size of 130 participants was calculated to be required for detecting a reduction in risk of severe visual loss (less than or equal to 30 letters on a logMAR chart) from 55% to 25% over 2 years with 90% power at a 0.05 level of significance.</p> <p>Unusual study design: Both eyes were randomized in the case of 12 participants but the correlation between eyes was not addressed in the analyses</p>	
Participants	<p>Inclusion criteria: Individuals 60 years or older with neovascular AMD and subfoveal CNV with any classic component, visual acuity of at least 20/200 at baseline, symptomatic for at least one year, and declined laser treatment</p> <p>Exclusion criteria: History of ocular pathology such as diabetic retinopathy, myopia, hypertensive retinopathy, use of corticosteroids or other drugs affecting the macula, for example, chloroquine, inability to provide regular follow-up data.</p> <p>Age: Mean age was 76 years in triamcinolone group and 77 years in the placebo group.</p> <p>Gender: 57% in triamcinolone and 64% in placebo group were females.</p> <p>Equivalence of baseline characteristics: Participants were similar at baseline with respect to age, gender, smoking history and number of letters read</p>	
Interventions	<p>Treatment: Triamcinolone acetonide, 4 mg (40 mg/mL; 0.1 mL of Kenacort40; Bristol-Myers Squibb Pharmaceuticals) injected into the vitreous 5 minutes after subconjunctival injection of 2% lidocaine and digital massage to reduce intraocular pressure. A small amount of 1% chloramphenicol ointment was administered after the procedure.</p> <p>Control: Placebo was not administered to the first 12 participants enrolled in the trial. Placebo consisted of a subconjunctival injection of isotonic sodium chloride solution</p>	
Outcomes	<p>Primary outcome: Rate of development of severe visual loss (greater than or equal to 30 letters on a logMAR chart).</p> <p>Secondary outcomes:</p> <div><div>1</div>Changes in size of lesion.</div> <div><div>2</div>Leakage of neovascular membranes on fluorescein angiography.</div> <div><div>3</div>Adverse events including elevated intraocular pressure and cataract</div>	
Notes	<p>Country: Sydney, Australia.</p> <p>Time period of study: Not explicitly reported.</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	"A randomization schedule with variable block sizes was produced using a list of computer-generated pseudo-random numbers."
Allocation concealment (selection bias)	Low risk	Treatment assignments were printed on cards "folded in half and inserted into sealed, opaque, numbered envelopes."
Masking of study participants (performance bias)	Unclear risk	Patients were masked: "To mask patients to their treatment assignment, they were advised that floaters, which are prominent after an injection of triamcinolone, might occur after an injection of placebo and the active study medication." Masking could have been broken: "...some patients may well have suspected that they have received treatment..."
Masking study personnel (performance bias)	Unclear risk	The surgeon administering the treatment "was given the next in the series of envelopes by a designated member of the clinical staff. Neither the surgeon nor the designated member of staff was otherwise involved in the study."
Masking outcome assessors (detection bias)	Unclear risk	Outcome assessor was masked: "Photographic outcomes were analyzed by a grader... who was masked to treatment assignment." "All angiograms were reviewed by 2 masked independent graders..." Masking could have been broken: "It was recognized that the development of corticosteroid-related adverse events might unmask the clinical observers. To reduce the impact of this, the measurement of best-corrected VA, the main outcome measure, was performed when the patients arrived at the clinic, without reference to their previous notes and before a medical history was taken."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two patients died in the treatment group and did not provide follow-up data. In the placebo group, two patients died, four withdrew, and one discontinued the intervention. The last observation was carried forward for participants with no outcome data at 12 months In 32.5% of eyes in the corticosteroid group and 28.5% of eyes in the placebo group, angiograms could not be evaluated because patients died or dropped out, angiograms were not of sufficient quality, or the patient declined the angiogram at 3-months follow-up
Selective reporting (reporting bias)	Low risk	Primary outcome was reported: the rate of development of severe visual loss Secondary outcomes were reported: <ol style="list-style-type: none">1 changes in size;2 changes in leakage of neovascular membranes on fluorescein angiography.
Other bias	Unclear risk	-Three authors are listed as inventors on patents related to the intraocular steroids use for the treatment of retinal neovascularization -Deviation from protocol: Because two patients assigned to a no treatment control group did not continue in the study, placebo was administered to the control group only after 12 patients were enrolled

Slakter 2006

Methods	<p>Number randomized: Treatment arm: n = 263, and control arm: n = 267</p> <p>Losses to follow-up: Only 3 participants in the PDT group and none in the anecortave acetate group were lost to follow-up. Data from 18.6% in anecortave acetate group and 17.6% in PDT group were not available for 12-month analyses.</p> <p>Intention-to-treat analysis: The trial was designed as a non-inferiority study and the authors reported a per-protocol analysis as well as an intention-to-treat with the last observation carried forward.</p> <p>Reported sample size calculation: Yes, an a priori sample size calculation was reported. 261 per group to provide 90% coverage probability to achieve non-inferiority margin of 7% points.</p> <p>Unusual study design: None.</p>
Participants	<p>Inclusion criteria: Individuals at least 50 years of age with exudative AMD and subfoveal CNV comprising at least 50% of the total lesion area, best corrected visual acuity of 20/40 to 20/400</p>

	<p>Exclusion criteria: History of systemic, ocular disease, ocular surgery, and prior treatment with PDT or any experimental treatment for AMD within 30 days of enrolment.</p> <p>Age: Mean age was 76.6 years (51-96 years), group-wise data not provided.</p> <p>Gender: Overall, 52% were females; no group-wise data available.</p> <p>Equivalence of baseline characteristics: Age, gender, mean baseline visual acuity were similar in the two groups at baseline</p>
Interventions	<p>Treatment: Posterior juxtascleral depot administration of 15 mg anecortave acetate every 6 months, a sham PDT every 3 months if there was leakage on fluorescein angiogram.</p> <p>Control: PDT administered every 3 months and influenced by investigator's decision based on fluorescein angiographic evidence of leakage, and sham anecortave acetate at baseline and at 6 months</p>
Outcomes	<p>Primary outcome: Visual acuity, measured as loss of fewer than 3 lines of vision at month 12. Visual acuity was measured at 2 meters using the ETDRS and TAP study methodology. Visual acuity was also reported as logMAR scores</p> <p>Secondary outcomes: Safety outcomes/adverse events.</p>
Notes	<p>Country: USA, Canada, Europe, Israel, Australia.</p> <p>Time of study: Not reported.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Five hundred thirty patients were randomized in a 1:1 ratio to receive either anecortave acetate 15 mg (n = 263) or PDT with verteporfin (n = 267) within 7 days after completing all screening procedures."
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described in the report.
Masking of study participants (performance bias)	Low risk	"The examining physician, patient, visual acuity (VA) technician, photographer, study coordinator, and the sponsor (Alcon Research) were masked."
Masking study personnel (performance bias)	High risk	"The physician administering the drug and the assistant were unmasked."
Masking outcome assessors (detection bias)	Low risk	"The examining physician, patient, visual acuity (VA) technician, photographer, study coordinator, and the sponsor (Alcon Research) were masked."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Of the 530 patients, 527 were analyzed for safety, 522 were analyzed for intent to treat, and 511 were analyzed for per protocol analysis." "The withdrawal rates by treatment group were 11 % (30/263) for anecortave acetate 15 mg and 9% (23/267) for PDT"
Selective reporting (reporting bias)	Low risk	The Results section described findings for all outcomes specified in the Methods section
Other bias	Low risk	No other sources of bias were identified.

AMD: age-related macular degeneration

BCVA: best corrected visual acuity

CNV: choroidal neovascularization

ETDRS: early treatment diabetic retinopathy study

PDT: photodynamic therapy

TAP: treatment of age-related macular degeneration with photodynamic therapy

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Arevalo 2005	Non-randomized study
Argurto 2005	Only 6-month follow-up
Bakri 2006	Review
Challa 1998	Case series
Danis 2000	Primary outcome not at 12-months follow-up
EudraCT 2004-004857-24	Not an anti-angiogenic steroid
Jonas 2003	Case series
Jonas 2004	Case series
Penfold 1995	Case series
Ranson 2002	Case series
Spaide 2003	Case series
TPDT	Trial stopped
Van De Moere 2005	Historical controls

Data and Analyses

Comparison 1. Triamcinolone acetonide versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Visual acuity	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Loss of 3 or more lines vision at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Loss of 6 or more lines vision at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 2. Anecortave acetate versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Visual acuity - loss of 3 or more lines at 12 months	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 3 mg Anecortave acetate versus placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 15 mg Anecortave acetate versus placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 30 mg Anecortave acetate versus placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Anecortave acetate versus PDT	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Visual acuity - loss of 6 or more lines at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 3 mg Anecortave acetate versus placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 15 mg Anecortave acetate versus placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 30 mg Anecortave acetate versus placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Triamcinolone acetonide versus placebo, Outcome 1 Visual acuity

Review: Surgical implantation of steroids with antiangiogenic characteristics for treating neovascular age-related macular degeneration

Comparison: 1 Triamcinolone acetonide versus placebo

Outcome: 1 Visual acuity

Analysis 2.1. Comparison 2 Anecortave acetate versus control, Outcome 1 Visual acuity - loss of 3 or more lines at 12 months

Review: Surgical implantation of steroids with antiangiogenic characteristics for treating neovascular age-related macular degeneration

Comparison: 2 Anecortave acetate versus control

Outcome: 1 Visual acuity - loss of 3 or more lines at 12 months

Analysis 2.2. Comparison 2 Anecortave acetate versus control, Outcome 2 Visual acuity - loss of 6 or more lines at 12 months

Appendix 1. CENTRAL search strategy

- #1 MeSH descriptor: [Retinal Degeneration] explode all trees
- #2 MeSH descriptor: [Retinal Neovascularization] explode all trees
- #3 MeSH descriptor: [Choroidal Neovascularization] explode all trees
- #4 MeSH descriptor: [Macula Lutea] explode all trees
- #5 macula* near lutea*
- #6 maculopath*
- #7 ((macul* or retina* or choroid*) and (degener* or neovasc*))
- #8 (AMD or ARMD or CNV)
- #9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
- #10 MeSH descriptor: [Triamcinolone] explode all trees
- #11 triamcin?lone*
- #12 kenalog or kenacort
- #13 MeSH descriptor: [Glucocorticoids] explode all trees
- #14 MeSH descriptor: [Pregnadienediols] explode all trees
- #15 anecortave* or retaane
- #16 MeSH descriptor: [Dexamethasone] explode all trees
- #17 dexamethasone*

#18 #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17

#19 #9 and #18

#20 implant* or inject* or depot

#21 #19 and #20

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 retinal degeneration/
14. retinal neovascularization/
15. choroidal neovascularization/
16. exp macula lutea/
17. maculopath\$.tw.
18. ((macul\$ or retina\$ or choroid\$) adj3 degener\$).tw.
19. ((macul\$ or retina\$ or choroid\$) adj3 neovasc\$).tw.
20. (macula\$ adj2 lutea).tw.
21. (AMD or ARMD or CNV).tw.
22. or/13-21
23. exp triamcinolone/
24. triamcin?lone\$.tw.
25. (kenalog or kenacort).tw.
26. exp glucocorticoids/

27. exp pregnadienediols/
28. anecortave\$.tw.
29. retaane.tw.
30. exp Dexamethasone/
31. dexamethasone\$.tw.
32. or/23-31
33. 22 and 32
34. 12 and 33
35. (implant\$ or inject\$ or depot).tw.
36. 34 and 35

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. 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
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 degeneration/
34. exp retinal degeneration/
35. exp subretinal neovascularization/
36. maculopath\$.tw.
37. ((macul\$ or retina\$ or choroid\$) adj3 degener\$).tw.
38. (((macul\$ or retina\$ or choroid\$) adj3 neovasc\$).tw.
39. (macula\$ adj2 lutea).tw.
40. (AMD or ARMD or CNV).tw.
41. or/33-40
42. exp triamcinolone/
43. exp triamcinolone acetone/
44. triamcin?lone\$.tw.
45. (kenalog or kenacort).tw.
46. exp glucocorticoid/
47. exp pregnane derivative/
48. anecortave\$.tw.
49. retane\$.tw.
50. exp Dexamethasone/

51. exp Dexamethasone Isonicotinate/
52. dexamethasone\$.tw.
53. or/42-52
54. 41 and 53
55. 32 and 54
56. (implant\$ or inject\$ or depot).tw.
57. 55 and 56

Appendix 4. LILACS search strategy

macul\$ or retina\$ or choroid\$ and degener\$ or neovasc\$ and triamcinolone or kenalog or kenacort or glucocorticoid\$ or anecortave\$ or retane or dexamethasone

Appendix 5. metaRegister of Controlled Trials search strategy

Macular Degeneration AND Steroid AND injection

Appendix 6. ClinicalTrials.gov search strategy

Macular Degeneration AND Steroid AND Injection

Appendix 7. ICTRP search strategy

Macular Degeneration = Condition AND Steroid AND Injection = Intervention

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Plain Language Summary

Steroids with antiangiogenic properties for treating neovascular age-related macular degeneration

Neovascular age-related macular degeneration (AMD) is associated with rapid loss of vision due to abnormal growth of blood vessels in the macula. Corticosteroids that reduce this growth of blood vessels have been tested for treatment of such vision loss. This review included three trials evaluating two different types of steroids, triamcinolone acetonide and anecortave acetate, for the treatment of neovascular AMD. The findings across the three trials, which included a total of 809 participants, were consistent with no evidence of benefit, in terms of preventing vision loss, with antiangiogenic steroids compared with placebo or photodynamic therapy. Based on available evidence, there is little benefit of steroids with anti-angiogenic properties in the treatment of neovascular age-related macular degeneration.”.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Masking of study participants (performance bias)	Masking study personnel (performance bias)	Masking outcome assessors (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
AACS 2003	?	+	+	?	+	-	+	?
IVTS 2003	+	+	?	?	?	+	+	?
Slakter 2006	?	?	+	-	+	+	+	+

Figure 1.

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

Table 1
Antiangiogenic agents investigated for potential benefit in exudative AMD

Agent	Putative mechanism
VEGF antagonists i.e. Rhu-fab	Binds and neutralizes/inactivates VEGF
Dexamethasone	Down-regulates VEGF expression
Triamcinolone acetonide	Effects vascular endothelial cell matrix turnover and down-regulates inflammation
Anecortave acetate	Suppression of Plasminogen Activator
Interferon-alpha	Blocks angiogenic basic fibroblast growth factor and endothelial cell functions
Thalidomide	Inhibits cell migration
Growth hormone antagonists	Inhibits endothelial cell proliferation and VEGF release

Table 2
2 Summary of trials evaluating combination interventions with anti-angiogenic steroids

Characteristics	Arias 2008	Maberley 2009	Tsuchiya 2008
Interventions compared	PDT plus intravitreal triamcinolone acetonide versus PDT alone	PDT plus intravitreal triamcinolone versus PDT plus sham injection	PDT plus juxtascleral triamcinolone acetonide versus PDT alone
Summary of patient characteristics	Patients aged 50 years or older, with neovascular, sub-foveal AMD, with classic neovascularization for at least 50% of the total lesion, visual acuity of 20/40 to 20/400 and intraocular pressure of 21 mm Hg or lower at baseline	Patients aged 50 years or older with neovascular sub-foveal AMD with classic lesion occupying at least 50% of the total area, visual acuity of at least 20/320, without a history of elevated intraocular pressure, previous photocoagulation, PDT, or retinal/vitreous surgery, or myopia greater than 6 Diopters, or systemic diseases such as stroke, myocardial infarction, or hepatitis	Patients aged 68 to 83 years with exudative AMD and sub-foveal choroidal neovascularization
Duration of follow-up	12 months	2 years	12 months
Outcomes reported	Visual acuity, angiographic area of the lesion, neuroretinal foveal thickness, outer high reflectivity band thickness, and safety outcomes	Visual acuity and safety outcomes.	Visual acuity, number of treatments, angiography, and OCT measurements, occlusion due to neovascularization, safety outcomes