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Anti-vascular endothelial growth factor combined with intravitreal steroids for diabetic macular oedema
(Review)

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[Intervention Review]

Anti-vascular endothelial growth factor combined with intravitreal steroids for diabetic macular oedema

Hemal Mehta^{1,2}, Charles Hennings¹, Mark C Gillies², Vuong Nguyen², Anna Campain², Samantha Fraser-Bell²

¹Royal Free London NHS Foundation Trust, London, UK. ²Macular Research Group, Save Sight Institute, University of Sydney, Sydney, Australia

Contact address: Hemal Mehta, Royal Free London NHS Foundation Trust, London, UK. hm@cantab.net.

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ABSTRACT

Background

The combination of steroid and anti-vascular endothelial growth factor (VEGF) intravitreal therapeutic agents could potentially have synergistic effects for treating diabetic macular oedema (DMO). On the one hand, if combined treatment is more effective than monotherapy, there would be significant implications for improving patient outcomes. Conversely, if there is no added benefit of combination therapy, then people could be potentially exposed to unnecessary local or systemic side effects.

Objectives

To assess the effects of intravitreal agents that block vascular endothelial growth factor activity (anti-VEGF agents) plus intravitreal steroids versus monotherapy with macular laser, intravitreal steroids or intravitreal anti-VEGF agents for managing DMO.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Trials Register) (2018, Issue 1); Ovid MEDLINE; Ovid Embase; LILACS; the ISRCTN registry; ClinicalTrials.gov and the ICTRP. The date of the search was 21 February 2018.

Selection criteria

We included randomised controlled trials (RCTs) of intravitreal anti-VEGF combined with intravitreal steroids versus intravitreal anti-VEGF alone, intravitreal steroids alone or macular laser alone for managing DMO. We included people with DMO of all ages and both sexes. We also included trials where both eyes from one participant received different treatments.

Data collection and analysis

We used standard methodological procedures recommended by Cochrane. Two authors independently reviewed all the titles and abstracts identified from the electronic and manual searches against the inclusion criteria. Our primary outcome was change in best corrected visual acuity (BCVA) between baseline and one year. Secondary outcomes included change in central macular thickness (CMT), economic data and quality of life. We considered adverse effects including intraocular inflammation, raised intraocular pressure (IOP) and development of cataract.

Main results

There were eight RCTs (703 participants, 817 eyes) that met our inclusion criteria with only three studies reporting outcomes at one year. The studies took place in Iran (3), USA (2), Brazil (1), Czech Republic (1) and South Korea (1). Seven studies used the unlicensed

anti-VEGF agent bevacizumab and one study used licensed ranibizumab. The study that used licensed ranibizumab had a unique design compared with the other studies in that included eyes had persisting DMO after anti-VEGF monotherapy and received three monthly doses of ranibizumab prior to allocation. The anti-VEGF agent was combined with intravitreal triamcinolone in six studies and with an intravitreal dexamethasone implant in two studies. The comparator group was anti-VEGF alone in all studies; two studies had an additional steroid monotherapy arm, another study had an additional macular laser photocoagulation arm. Whilst we judged these studies to be at low risk of bias for most domains, at least one domain was at unclear risk in all studies.

When comparing anti-VEGF/steroid with anti-VEGF monotherapy as primary therapy for DMO, we found no meaningful clinical difference in change in BCVA (mean difference (MD) -2.29 visual acuity (VA) letters, 95% confidence interval (CI) -6.03 to 1.45; 3 RCTs; 188 eyes; low-certainty evidence) or change in CMT (MD 0.20 μ m, 95% CI -37.14 to 37.53; 3 RCTs; 188 eyes; low-certainty evidence) at one year. There was very low-certainty evidence on intraocular inflammation from 8 studies, with one event in the anti-VEGF/steroid group (313 eyes) and two events in the anti-VEGF group (322 eyes). There was a greater risk of raised IOP (Peto odds ratio (OR) 8.13, 95% CI 4.67 to 14.16; 635 eyes; 8 RCTs; moderate-certainty evidence) and development of cataract (Peto OR 7.49, 95% CI 2.87 to 19.60; 635 eyes; 8 RCTs; moderate-certainty evidence) in eyes receiving anti-VEGF/steroid compared with anti-VEGF monotherapy. There was low-certainty evidence from one study of an increased risk of systemic adverse events in the anti-VEGF/steroid group compared with the anti-VEGF alone group (Peto OR 1.32, 95% CI 0.61 to 2.86; 103 eyes).

One study compared anti-VEGF/steroid versus macular laser therapy. At one year investigators did not report a meaningful difference between the groups in change in BCVA (MD 4.00 VA letters 95% CI -2.70 to 10.70; 80 eyes; low-certainty evidence) or change in CMT (MD -16.00 μ m, 95% CI -68.93 to 36.93; 80 eyes; low-certainty evidence). There was very low-certainty evidence suggesting an increased risk of cataract in the anti-VEGF/steroid group compared with the macular laser group (Peto OR 4.58, 95% CI 0.99 to 21.10, 100 eyes) and an increased risk of elevated IOP in the anti-VEGF/steroid group compared with the macular laser group (Peto OR 9.49, 95% CI 2.86 to 31.51; 100 eyes).

One study provided very low-certainty evidence comparing anti-VEGF/steroid versus steroid monotherapy at one year. There was no evidence of a meaningful difference in BCVA between treatments at one year (MD 0 VA letters, 95% CI -6.1 to 6.1, low-certainty evidence). Likewise, there was no meaningful difference in the mean CMT at one year (MD -9 μ m, 95% CI -39.87 μ m to 21.87 μ m between the anti-VEGF/steroid group and the steroid group. There was very low-certainty evidence on raised IOP at one year comparing the anti-VEGF/steroid versus steroid groups (Peto OR 0.75, 95% CI 0.16 to 3.55).

No included study reported impact of treatment on patients' quality of life or economic data. None of the studies reported any cases of endophthalmitis.

Authors' conclusions

Combination of intravitreal anti-VEGF plus intravitreal steroids does not appear to offer additional visual benefit compared with monotherapy for DMO; at present the evidence for this is of low-certainty. There was an increased rate of cataract development and raised intraocular pressure in eyes treated with anti-VEGF plus steroid versus anti-VEGF alone. Patients were exposed to potential side effects of both these agents without reported additional benefit. The majority of the evidence comes from studies of bevacizumab and triamcinolone used as primary therapy for DMO. There is limited evidence from studies using licensed intravitreal anti-VEGF agents plus licensed intravitreal steroid implants with at least one year follow-up. It is not known whether treatment response is different in eyes that are phakic and pseudophakic at baseline.

PLAIN LANGUAGE SUMMARY

Anti-vascular endothelial growth factor (anti-VEGF) plus intravitreal steroids for diabetic macular oedema

What is the aim of this review?

The aim of this Cochrane Review was to find out whether injecting two drugs in combination (inhibitors of VEGF and steroids) into the vitreous jelly of eyes with macular oedema (swelling at the centre of the retina) due to diabetes works better than treatment with one drug alone.

Key messages

There is insufficient evidence to suggest that the two drugs in combination are better than treatment with one drug alone.

What was studied in the review?

Diabetic macular oedema is swelling at the back of the eye (retina) in people with diabetes. It is the most common cause of acquired visual loss in the mainly working-age population.

Both steroids and anti-VEGF agents, injected into the vitreous jelly of the eye (intravitreal), improve vision and reduce the amount of fluid accumulating in the central retina. The drugs have different mechanisms of action and may work well in combination, with significant implications for improving patient outcomes. However, if there is no added benefit of combination therapy, then people could be potentially exposed to unnecessary side effects such as cataract, glaucoma, stroke and heart attack.

What are the main results of the review?

The Cochrane Review authors found eight relevant studies. Three studies were from Iran, two from USA and one each from Brazil, Czech Republic and South Korea. These studies compared an anti-VEGF (in most studies an unlicensed version called bevacizumab) plus intravitreal steroid agents versus anti-VEGF alone, an intravitreal steroid alone or macular laser alone.

We found insufficient evidence to suggest that the two drugs classes in combination are better than treatment with one drug class alone as the initial treatment for diabetic macula oedema. Moreover, there was a greater risk of raised intraocular pressure and cataract in people receiving anti-VEGF plus steroids compared with anti-VEGF alone.

How up-to-date is this review?

Cochrane Review authors searched for studies that had been published up to 21 February 2018.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Summary of findings: intravitreal anti-VEGF plus intravitreal steroid versus intravitreal anti-VEGF for diabetic macular oedema

Intravitreal anti-VEGF plus intravitreal steroid versus intravitreal anti-VEGF for diabetic macular oedema

Patient or population: adults with centre-involving diabetic macular oedema

Settings: eye care clinic

Intervention: intravitreal anti-VEGF plus intravitreal steroid (anti-VEGF/steroid)

Comparison: intravitreal anti-VEGF

Outcomes	Illustrative comparative risks*		Relative effect (95% CI)	No. of eyes (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Anti-VEGF alone	Anti-VEGF/steroid				
Mean change in visual acuity at 1 year (number of letters read on log-MAR chart)	The mean visual acuity gain at 1 year ranged from 4.9 to 10.5 letters in the anti-VEGF alone groups	The mean number of letters read was on average 2.29 fewer in the anti-VEGF/steroid group (95% CI -6.03 to 1.45)	—	188 (3)	Low ^a	—
Mean change in central macular thickness at 1 year	The mean reduction in central macular thickness at 1 year ranged from -30 µm to -179 µm in the anti-VEGF alone groups	The mean reduction in central macular thickness was on average 0.20 µm greater in the anti-VEGF/steroid groups (95% CI -37.14 to 37.53)	—	188 (3)	Low ^a	—
Significant intraocular inflammation at follow-up (from 6 months onwards)	6 per 1000	3 per 1000 (0 to 30 per 1000)	Peto OR 0.53 (0.05 to 5.08)	635 (8)	Very low ^b	Only 3 events
Development of cataract at follow-up (from 6 months onwards)	3 per 1000	22 per 1000 (9 to 56 per 1000)	Peto OR 7.49 (2.87 to 19.60)	635 (8)	Moderate ^c	NB: significant cataract progression may occur in the second year of intravitreal steroid use.

Raised intraocular pressure at follow-up (from 6 months onwards)	6 per 1000	47 per 1000 (27 to 79 per 1000)	Peto OR 8.13 (4.67 to 14.16)	635 (8)	Moderate ^c	1 participant needed glaucoma surgery in the anti-VEGF/steroid group. This outcome occurred only in 1 study. The threshold for glaucoma drainage surgery was not specified.
Systemic adverse events at follow-up (from 6 months onwards)	400 per 1000	468 per 1000 (289 to 1000)	Peto OR 1.32 (95% CI 0.61 to 2.86)	103 (1)	Low ^d	
Quality of life at follow-up (from 6 months onwards)	Not reported					

*The **assumed risk** is the control group risk across studies. The **corresponding risk** is based on the assumed risk in the comparison group and the **relative effect** of the intervention.

CI: confidence interval; RR: risk ratio; MD: mean difference; SD: standard deviation.

GRADE Working Group grades of evidence

High-certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate-certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low-certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low-certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

^aDowngraded one level because of risk of bias and by one level because of imprecision.

^bDowngraded one level because of risk of bias, and two levels for imprecision as there were very few events.

^cDowngraded one level because of risk of bias

^dDowngraded two levels for imprecision

Summary of findings 2. Summary of findings: intravitreal bevacizumab plus intravitreal steroid versus macular laser for diabetic macular oedema

Intravitreal bevacizumab plus intravitreal steroid versus macular laser for diabetic macular oedema

Patient or population: adults with centre-involving diabetic macular oedema

Setting: eye care clinic

Intervention: intravitreal bevacizumab plus intravitreal steroid (anti-VEGF/steroid)

Comparison: macular laser

Outcomes	Illustrative comparative risks*		Relative effect (95% CI)	No of eyes (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Macular laser	Anti-VEGF/steroid				
Mean change in visual acuity at 1 year (number of letters read on logMAR chart)	The mean visual acuity gain at 1 year was 1 letter with a standard deviation of 17 letters in the laser comparator group	The mean number of letters read was 4.00 more in the anti-VEGF/steroid group (95% CI -2.70 to 10.70)	—	80 (1)	Low ^a	
Gain or loss of 10 or more letters visual acuity at 1 year	Not reported					
Mean change in central macular thickness at 1 year	The mean change in central macular thickness at 1 year was an increase of 6 µm with a standard deviation of 36 microns in the laser comparator group	The mean reduction in central macular thickness was on average 16 µm greater in the anti-VEGF/steroid group (95% CI -68.93 to 36.93)	—	80 (1)	Low ^a	
Significant intraocular inflammation at follow-up (from 6 months onwards)	Not reported					
Development of cataract at follow-up (from 6 months onwards)	20 per 1000	85 per 1000 (20 to 301 per 1000)	Peto OR 4.58 (0.99 to 21.10)	100 (1)	Very low ^b	
Raised Intraocular Pressure at follow-up (from 6 months onwards)	1 per 1000	9 per 1000 (3 to 31 per 1000)	Peto OR 9.49 (2.86 to 31.51)	100 (1)	Very low ^b	There was 1 participant who needed glaucoma drainage surgery in the anti-VEGF/steroid group. Threshold for glaucoma drainage surgery not

specified in the included study.

Systemic adverse events at follow-up (from 6 months onwards)	Not reported
Quality of life at follow-up (from 6 months onwards)	Not reported

*The **assumed risk** is the control group risk across studies. The **corresponding risk** is based on the assumed risk in the comparison group and the **relative effect** of the intervention.

CI: confidence interval; **RR:** risk ratio; **MD:** mean difference; **SD:** standard deviation.

GRADE Working Group grades of evidence

High-certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate-certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low-certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low-certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

^aDowngraded one level because of risk of bias and by one level due to imprecision.

^bDowngraded one level because of risk of bias and by two levels due to imprecision (only 1 event in the comparator group).

Summary of findings 3. Summary of findings: intravitreal bevacizumab plus intravitreal steroid versus intravitreal steroid for diabetic macular oedema

Intravitreal bevacizumab plus intravitreal steroid compared with intravitreal steroid for diabetic macular oedema

Patient or population: adults with centre-involving diabetic macular oedema

Setting: eye care clinic

Intervention: intravitreal bevacizumab plus intravitreal steroid (anti-VEGF/steroid)

Comparison: intravitreal steroid (IVS)

Outcomes	Illustrative comparative risks*		Relative effect (95% CI)	No of eyes (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	IVS	Anti-VEGF/steroid				

Mean change in visual acuity at 1 year (number of letters read on logMAR chart)	The mean visual acuity at 1 year was 24.5 letters in the IVS comparator group	The mean number of letters read was on average 0 letters higher (i.e same) in the anti-VEGF/steroid group (95% CI -6.1 to 6.1)	-	73 (1)	Low ^a	SD not reported for change in visual acuity so difference in visual acuity at 1 year reported
Gain or loss of 10 or more letters visual acuity at 1 year	Not reported					
Mean change in central macular thickness at 1 year	The mean central macular thickness was 249 µm in the IVS comparator group at 1 year	The mean central macular thickness was 9 µm less in the anti-VEGF/steroid group (-39.87µm less to 21.87µm more)	Not estimable	73 (1)	Low ^a	SD not reported for change so difference in final value reported
Significant intraocular inflammation at follow-up (from 6 months onwards)	Not reported					
Development of cataract at follow-up (from 6 months onwards)	Not reported					
Raised intraocular pressure at 1 year at follow-up (from 6 months onwards)	108 per 1000	83 per 1000 (19 to 301 per 1000)	Peto OR 0.75 (0.16 to 3.55)	73 (1)	Very Low ^b	—
Systemic adverse events at follow-up (from 6 months onwards)	Not reported					
Quality of life at follow-up (from 6 months onwards)	Not reported					

The **assumed risk** is the control group risk across studies. The **corresponding risk** is based on the assumed risk in the comparison group and the **relative effect** of the intervention.

CI: confidence interval; **RR**: risk ratio; **MD**: mean difference; **SD**: standard deviation.

GRADE Working Group grades of evidence

High-certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate-certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low-certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low-certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

- ^aDowngraded one level because of risk of bias and by one level for imprecision.
- ^bDowngraded one level because of risk of bias and by two levels for imprecision (very few events).

BACKGROUND

Description of the condition

The worldwide prevalence of diabetes mellitus was estimated at 366 million in 2011, with projections that by 2030 the prevalence will reach 552 million people ([International Diabetes Federation 2011](#)). Diabetic macular oedema (DMO) is the most common cause of acquired visual loss in this population, affecting approximately 6.8% of all people with diabetes ([Antonetti 2012](#); [Bunce 2008](#); [Moss 1998](#); [Yau 2012](#)).

Description of the intervention

Systemic therapies aim to prevent or reduce DMO by targeting key modifiable risk factors. However, intensive control of glucose and blood pressure in clinical trials has achieved only limited success in preventing diabetic retinopathy ([Liew 2008](#)). There may also be a role for modification of the renin-angiotensin system and for lipid-lowering agents in the management of DMO ([Kiire 2013](#)). Fenofibrate may have a beneficial effect, although its mechanism of action appears to be independent of serum lipid concentration ([Keech 2007](#); [Liew 2008](#); [Scheen 2010](#)).

Up until the introduction of intravitreal pharmacotherapies, the standard of care for DMO was focal or grid laser photocoagulation. The Early Treatment Diabetic Retinopathy Study (ETDRS), which was undertaken in the 1980s, showed benefit of laser for DMO compared with no intervention ([ETDRS 1991](#)). In this trial the three-year risk of moderate visual loss, defined as a loss of 15 letters or 3 lines of LogMAR visual acuity, decreased by 50% in laser-treated eyes. Nonetheless, in most people with DMO, laser does not improve vision. Thus there was a major unmet need in terms of better treatments for DMO.

A systematic review found little evidence to support vitrectomy as an intervention for DMO in the absence of epiretinal membrane or vitreomacular traction ([Simunovic 2014](#)).

Some authors have proposed intravitreal steroid formulations such as triamcinolone acetate injections (IVTA), slow-release dexamethasone implants and sustained-release fluocinolone acetonide implants to treat clinically significant DMO ([Boyer 2011](#); [Campochiaro 2012](#); [Gillies 2009](#)). A Cochrane Review of intravitreal steroids in DMO concluded that steroids placed inside the eye by either intravitreal injection or surgical implantation may improve visual outcomes in eyes with persistent or refractory DMO; however, eyes treated with these formulations also frequently experience elevation of intraocular pressure and cataract progression ([Grover 2008](#)).

A Cochrane Review of antiangiogenic therapy in DMO identified strong evidence of a clinical benefit in maintaining and improving vision using anti-vascular endothelial growth factor (anti-VEGF) drugs versus laser photocoagulation ([Virgili 2014](#)). The systematic review reported that further data are needed to assess effectiveness under real-world monitoring and treatment conditions as well as safety (particularly regarding cardiovascular risk) in high-risk populations excluded from clinical trials ([Virgili 2014](#); [Virgili 2017](#); [Wong 2008](#)).

Combinations of the above intravitreal anti-VEGF and steroid formulations are the subject of this review.

How the intervention might work

Diabetic macular oedema is multifactorial, with significantly elevated levels of VEGF, interleukin-6, and intercellular adhesion molecule-1 in people with extensive DMO leakage versus those with minimal leakage ([Funatsu 2003](#); [Funatsu 2005](#)). Post hoc analyses of head-to-head clinical trial data have reported differences between the effects of intravitreal anti-VEGF and intravitreal steroids on surrogate endpoints of hard exudate resolution and vessel calibre diameter, suggesting different mechanisms of action in resolving DMO ([Mehta 2016](#); [Wickremasinghe 2017](#)). Steroid therapy has anti-inflammatory, anti-permeability and angiostatic effects in treating DMO ([Wang 2008](#)). Anti-VEGF agents, by inhibition of VEGF angiogenic activity on endothelial tight junctions, reduce retinal vascular permeability ([Aiello 2005](#)). The combination of steroid and anti-VEGF intravitreal therapeutic agents could potentially have synergistic effects for treating DMO ([Amoaku 2015](#)).

Why it is important to do this review

This systematic review will assess the effects of combining intravitreal anti-VEGF and steroid agents for managing DMO. We will assess the evidence base as to whether combining the intravitreal therapies has any advantage over monotherapy with macular laser, intravitreal steroids or intravitreal anti-VEGF agents in terms of functional (visual acuity) and anatomical (central macular thickness) outcomes. We will also address how the safety profile of the combined treatment compares to monotherapy. On the one hand, if combined treatment is more effective than monotherapy, there would be significant implications for improving patient outcomes worldwide. On the other hand, if there is no added benefit of combination therapy, then people could be potentially exposed to unnecessary local or systemic side effects.

OBJECTIVES

To assess the effects of intravitreal agents that block vascular endothelial growth factor activity (anti-VEGF agents) plus intravitreal steroids versus monotherapy with macular laser, intravitreal steroids or intravitreal anti-VEGF agents for managing diabetic macular oedema.

METHODS

Criteria for considering studies for this review

Types of studies

We included all relevant randomised controlled trials (RCTs).

Types of participants

We included people with diabetic macular oedema (DMO) of all ages and both sexes as diagnosed in the included studies. We included trials where the eyes from one participant had received different treatments.

Types of interventions

We included RCTs comparing intravitreal anti-VEGF plus intravitreal steroids versus intravitreal anti-VEGF alone, intravitreal steroids alone or macular laser alone for managing DMO.

Types of outcome measures

We excluded studies with follow-up of less than six months.

Primary outcomes

Visual acuity

The primary outcome for this review was mean change in best corrected visual acuity (BCVA) from baseline in the treated eye. We also assessed the proportion of eyes with at least 10 ETDRS letters' (equivalent to 2 ETDRS lines') change (Bailey 1976). Our primary analysis was at one year after randomisation.

Secondary outcomes

Visual acuity

We also assessed the above visual acuity outcomes at six months and at two years.

Anatomical outcomes

Mean change in central macular thickness (μm) as measured by optical coherence tomography (OCT) at six months, one year and two years.

Safety

We reported the frequency and severity of ocular or systemic adverse outcomes in the studies. In particular, we identified the following ocular adverse events reported in included randomised clinical trials: endophthalmitis, retinal tears or detachment, intraocular inflammation, development of cataract, raised intraocular pressure and need for glaucoma drainage surgery. We also recorded systemic side effects including thromboembolic events (as defined by the Antiplatelet Trialists' Collaboration), non-ocular haemorrhage and hypertension (APTC 1994; Boyer 2009).

Economic data

We reported any cost benefit data in the included studies.

Quality of life data

We reported any quality of life data in the included studies.

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist conducted systematic searches in the following databases for RCTs and controlled clinical trials. There were no language or publication year restrictions. The date of the search was 21 February 2018.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 1) (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (searched 21 February 2018) (Appendix 1);
- MEDLINE Ovid (1946 to 21 February 2018) (Appendix 2);
- Embase Ovid (1980 to 21 February 2018) (Appendix 3);
- LILACS (Latin American and Caribbean Health Science Information database (1982 to 21 February 2018) (Appendix 4);
- ISRCTN registry (www.isrctn.com/editAdvancedSearch; searched 21 February 2018) (Appendix 5);
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 21 February 2018) (Appendix 6);

- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictip; searched 21 February 2018) (Appendix 7).

Searching other resources

We handsearched the reference lists of the included trials to try to identify other relevant trials.

Data collection and analysis

We used standard methodological procedures expected by Cochrane.

Selection of studies

Two authors independently reviewed all the titles and abstracts identified from the electronic and manual searches against the inclusion criteria. We obtained full-text copies of all potentially or definitely relevant articles. We contacted trial investigators for further information if required. We resolved discrepancies between authors as to whether or not studies met inclusion criteria by discussion. We documented the excluded studies and reasons for exclusion in the [Characteristics of excluded studies](#) table.

Data extraction and management

We extracted the following participant and trial characteristics and reported them in a table format (Appendix 8).

1. Participant characteristics (age, sex, glycated haemoglobin (HbA1c), diagnostic criteria used for DMO, baseline visual acuity, OCT-determined central macular thickness, and fluorescein angiography assessment of macular ischaemia).
2. Intervention (agent, dose, timing of first dose in relation to diagnosis, delivery route, frequency, treatment length).
3. Methodology (group size, randomisation, masking).
4. Results (visual acuity, central macular thickness, and adverse events).
5. Additional data (economic data, quality-of-life data).
6. Treatment compliance and losses to follow-up.

We contacted trial investigators for key unpublished information that was missing from the reports of the included studies. Two review authors independently extracted the data and recorded it on paper data extraction forms developed by Cochrane Eyes and Vision. We resolved discrepancies by discussion. One review author entered all data into Review Manager 5 (RevMan 5) (Review Manager 2014), and a second author checked that the data entered were correct.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias of the selected trials according to Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We considered the following main criteria.

- Selection bias: random sequence generation, allocation concealment.
- Performance bias: masking of participants, researchers and outcome assessors.
- Attrition bias: loss to follow-up, rates of compliance.
- Reporting bias: selective outcome reporting.

We reported each parameter as being at high risk of bias, low risk of bias, or unclear risk of bias. We resolved discrepancies between the authors by discussion. We contacted study authors to clarify details for any studies at unclear risk of bias. If there was no response from the authors, we classified the trial based on available information.

For multi-arm studies, we analysed multiple intervention groups in an appropriate way that avoided arbitrary omission of relevant groups and prevented double counting of participants.

Measures of treatment effect

We measured treatment effects according to the data types described in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011).

Dichotomous data

Variables in this group include the primary outcome and the proportion of participants experiencing an adverse event during follow-up. We reported dichotomous variables as risk ratios (RRs) with 95% confidence intervals (CIs).

Continuous data

These variables include mean change in visual acuity and central macular thickness. We reported continuous variables as mean difference with 95% CI (if normally distributed) or median and interquartile range (if not normally distributed).

Unit of analysis issues

The unit of analysis for efficacy of treatment and ocular safety was the eye for which the data had been reported on.

Trials could randomise one or both eyes to the intervention or comparator. If people were randomly allocated to treatment but the trial included only one eye per person, then there was no unit of analysis issue. In these cases, we documented how investigators selected the included eye. If people were randomly allocated to treatment but trials included and reported on both eyes, we adjusted for within-person correlation by analysing as 'clustered data'. If the study was a within-person study, i.e. one eye was randomly allocated to intervention and the other eye received the comparator, then we analysed the results as paired data. If required, we contacted the trial investigators for further information to carry out these analyses.

The unit of analysis for systemic safety, economic and quality of life measures was the individual, with inferences as to effect of a treatment at the person level based on unpaired data only.

Dealing with missing data

We attempted to identify key unpublished information that was missing from reports of included studies by contacting study authors. If the authors did not respond within four weeks or were not able to provide additional data, we conducted a primary analysis based on participants with complete data (available case analysis). We made a judgement as to the risk of bias based on the amount and distribution of missing data in the study arms. Missing standard deviations were imputed using the largest reported standard deviation from the remaining included studies. We conducted a sensitivity analysis excluding studies with missing standard deviations.

Assessment of heterogeneity

We considered sources of heterogeneity related to study design (such as paired studies versus studies including only one eye of each participant) and baseline characteristics. We used I^2 value to determine the proportion of the variation that reflects variation in true effects (Higgins 2011). We considered I^2 values of greater than 50% to represent substantial heterogeneity not attributed to random error.

Data synthesis

If there was no substantial clinical or statistical heterogeneity between the trials, we combined the results in a meta-analysis using a random-effects model. We used a fixed-effect model if there were three or fewer trials. We also used this model if there were forest plots with few events, in which case we expressed effect measures as Peto odds ratios (ORs). In case of substantial clinical or statistical heterogeneity, we did not combine study results but presented a narrative or tabulated summary. An exception where pooling of data would still occur even in the presence of substantial statistical heterogeneity would be where examination of the forest plot indicated the individual trial results were all consistent in their direction of effect (i.e. the risk ratio and confidence intervals largely fall on one side of the line of null effect).

Sensitivity analysis

We conducted a sensitivity analyses on the primary review outcome to determine the impact of excluding studies with missing data such as standard deviations, lower methodological quality (defined as high risk of bias in one or more domains),.

Summary of findings table

A 'Summary of findings' table provides key information concerning the certainty of evidence, the magnitude of effect of the interventions examined, and the sum of available data on all specified review primary and secondary outcomes for a given comparison. Two review authors independently used the GRADE approach to assess the certainty of the evidence for each outcome as described in the standard methods of Chapters 11 and 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011a; Schünemann 2011b). We resolved discrepancies by discussion.

RESULTS

Description of studies

There was not sufficient data at participant level in the included studies to assess for clustered data in trials with a paired design. We considered paired versus studies with only one eye per participant as a source of heterogeneity but all included studies reporting the primary outcome at one year had the possibility of both eyes being enrolled.

Results of the search

The electronic searches yielded a total of 1057 records (Figure 1). After removing 282 duplicates, the Cochrane Information Specialist screened the remaining 775 records and removed 450 references that were not relevant to the review. We made additional searches of the ongoing trials registers and identified a further two studies for assessment. We screened 327 references and obtained 20 full-text reports for further assessment. We included 13 reports of eight

studies (see [Characteristics of included studies](#)), and excluded five studies (see [Characteristics of excluded studies](#)). We identified two ongoing studies ([NCT03126786](#); [UMIN000021630](#)) and will assess

these for potential inclusion in the review when data becomes available.

Figure 1. Study flow diagram.

Included studies

We included 13 publications of eight RCTs in this review ([DRCRnet U 2018](#); [Lim 2012](#); [Maturi 2015](#); [Neto 2017](#); [Riazi-Esfahani 2017](#); [Shoeibi 2013](#); [Soheilian 2012](#); [Synek 2011](#)). Most studies used the unlicensed anti-VEGF agent bevacizumab and one study used ranibizumab ([DRCRnet U 2018](#)). Regarding the use of intravitreal steroid, six studies used intravitreal triamcinolone, whilst two studies used the intravitreal dexamethasone implant ([DRCRnet U 2018](#); [Maturi 2015](#)). Two of the RCTs ([Shoeibi 2013](#); [Soheilian 2012](#)) had used selected population subgroups referencing participants from previous trials ([Ahmadiieh 2008](#); [Soheilian 2009](#); [Yaseri 2014](#)). One study ([DRCRnet U 2018](#)) had a unique design compared with the other studies in that included eyes had persisting DMO after anti-VEGF monotherapy and received three monthly doses of ranibizumab prior to allocation. Three studies were from Iran

and one each from the Republic of Korea, the USA and the Czech Republic. We have documented the number of participants and eyes in each study and a summary of the characteristics of the study populations and settings, interventions, comparators and funding sources in the [Characteristics of included studies](#) tables.

Excluded studies

We excluded five studies because of insufficient length of follow-up ([Faghihi 2008](#); [Sheth 2011](#); [Soheilian 2007](#); [Wang 2011](#); [Yu 2018](#)). See the [Characteristics of excluded studies](#) table for further information.

Risk of bias in included studies

All included studies were at unclear risk of bias in one or more domains (see [Figure 2](#); [Figure 3](#)).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
DRCRnet U 2018	+	+	+	+	+	+	?
Lim 2012	+	+	?	+	?	+	?
Maturi 2015	?	?	?	?	?	+	?
Neto 2017	?	?	?	?	?	+	+
Riazi-Esfahani 2017	+	+	+	+	?	+	?
Shoeibi 2013	+	+	?	+	+	?	?
Soheilian 2012	+	+	?	+	-	?	?
Synek 2011	+	+	?	?	+	?	?

Allocation

We judged the risk of selection bias to be low in most studies.
In [Maturi 2015](#) and [Neto 2017](#) the methods of generating and

concealing the allocation sequence were not reported in enough detail to make a judgement.

Blinding

In five studies, authors stated that participants were masked to treatment allocation (Maturi 2015; Riazi-Esfahani 2017; Shoeibi 2013; Soheilian 2012; Synek 2011), but only two trials also masked the investigators delivering treatment (DRCRnet U 2018; Riazi-Esfahani 2017). Five trials specified that masked investigators assessed outcome measures (DRCRnet U 2018; Lim 2012; Riazi-Esfahani 2017; Shoeibi 2013; Soheilian 2012), but this was not reported in the other three studies (Maturi 2015; Neto 2017; Synek 2011).

Incomplete outcome data

Three studies were judged to be at low risk of attrition bias as follow-up was high (DRCRnet U 2018; Shoeibi 2013; Synek 2011). Soheilian 2012 was judged to be at high risk of attrition bias because of unequal loss to follow-up in the groups, possibly attributable to adverse events. For the other studies, follow-up was not reported in enough detail to make a judgement.

Selective reporting

Visual acuity and central macular thickness (CMT) data were in general well recorded. Authors did not always include safety data, particularly relating to systemic safety. The included RCTs were not powered to identify small increases in ocular or systemic harm.

Other potential sources of bias

Most studies enrolled a small proportion of participants with both eyes affected. Both eyes being eligible for allocation in a single individual poses the theoretical potential to influence outcomes in the fellow eye via systemic absorption.

Effects of interventions

See: [Summary of findings for the main comparison](#) Summary of findings: intravitreal anti-VEGF plus intravitreal steroid versus intravitreal anti-VEGF for diabetic macular oedema; [Summary of findings 2](#) Summary of findings: intravitreal bevacizumab plus intravitreal steroid versus macular laser for diabetic macular oedema; [Summary of findings 3](#) Summary of findings: intravitreal

bevacizumab plus intravitreal steroid versus intravitreal steroid for diabetic macular oedema

See: [Summary of findings for the main comparison](#) (anti-VEGF/steroid versus anti-VEGF alone); [Summary of findings 2](#) (anti-VEGF/steroid versus macular laser); [Summary of findings 3](#) (anti-VEGF/steroid versus steroid).

We could not perform meta-analyses when comparing anti-VEGF/steroid versus steroid monotherapy or macular laser monotherapy due to there only being one included studies reporting each comparison at 12 month. There was no evidence that BCVA and CMT data were skewed in included studies. There were no reported cases of endophthalmitis in included studies. Systemic side-effects were not fully reported. We did not identify any relevant studies reporting cost benefit or quality of life outcomes. Therefore, we were unable to comment on these secondary outcomes.

Intravitreal anti-VEGF plus steroid versus anti-VEGF alone

Visual outcome

Eyes that received intravitreal anti-VEGF plus steroid could read fewer average letters at one year compared with those receiving anti-VEGF alone. The difference was small, and the confidence intervals (CIs) corresponded to either fewer or more letters being read (mean difference (MD) -2.29 visual acuity (VA) letters, 95% confidence interval (CI) -6.03 to 1.45, $P = 0.23$; 188 eyes; 3 studies, [Figure 4](#)). The same pattern was apparent at six months (MD -0.88 VA letters, 95% CI -2.56 to 0.80; 618 eyes; 8 studies, [Analysis 1.1](#)) and at two years (MD -0.50 VA letters, 95% CI -8.42 to 7.42; 75 eyes, 1 study, [Analysis 1.3](#)). One study (DRCRnet U 2018) reported 10 letter gain and loss of vision at 6 months. An improvement of 10 letters or more was observed in 14 of the 63 eyes (22%) in the anti-VEGF plus steroid group and 9 of the 64 eyes (14%) in the anti-VEGF group (adjusted difference, 6%; 95% CI -6% to 18%; $P = 0.34$). In the anti-VEGF plus steroid group, 8 eyes (13%) lost 10 letters or more compared with 4 (6%) for anti-VEGF group (adjusted difference, 7%; 95% CI, -1% to 16%; $P = 0.09$); We judged the certainty of the visual acuity evidence described above to be low, downgrading for risk of bias in the included trials and imprecision (confidence intervals include both no effect and clinically important differences).

Figure 4. Forest plot of comparison: 1 Anti-VEGF and steroid versus anti-VEGF alone, outcome: 1.2 Mean change in visual acuity at 1 year [VA letters].

Central macular thickness

Eyes that received intravitreal anti-VEGF plus steroid had reduced CMT at one year compared with those receiving anti-VEGF alone. The difference was negligible, and the confidence intervals

corresponded to either increased or decreased CMT (MD -0.20 μm , 95% CI -37.14 to 37.53, $P = 0.99$; 188 eyes; 3 studies; [Figure 5](#)). There were similar results at six months (MD -19.73 μm , 95% CI -40.47 to 1.01; 617 eyes; 8 studies, [Analysis 1.4](#)) and at two years (MD 22.00 μm , 95% CI -45.93 to 89.93; 75 eyes, 1 study, [Analysis 1.6](#)).

Figure 5. Forest plot of comparison: 1 anti-VEGF/steroid versus anti-VEGF, outcome: 1.5 Mean change in central macular thickness at 1 year [μm].

Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Adverse effects

Table 1 and Figure 6 summarises the adverse events. There were 92 reported adverse events in eyes receiving intravitreal anti-VEGF plus steroids compared with 25 adverse events in those receiving intravitreal anti-VEGF alone (Peto OR 5.66, 95% CI 3.62 to 8.84; 635 eyes; 8 studies). There was less significant intraocular inflammation in the anti-VEGF/steroid group (Peto OR 0.53, 95% CI 0.05 to 5.08; 635 eyes; 8 studies) however, evidence was of very low-certainty with 1 event in the anti-VEGF/steroid group (313 eyes) and 2 events

in the anti-VEGF group (322 eyes). Development of cataract was more frequent in eyes receiving anti-VEGF/steroid compared with IVB (Peto OR 7.49, 95% CI 2.87 to 19.60; 635 eyes; 8 studies) however, evidence was of very low-certainty, with 18 events in the anti-VEGF/steroid group (313 eyes) and 1 event in the anti-VEGF group (322 eyes). Readers should note that cataract development due to intravitreal steroid often occurs after the first year of treatment. There was a substantially greater risk of raised intraocular pressure in eyes receiving anti-VEGF/steroid compared with anti-VEGF alone (Peto OR 8.13, 95% CI 4.67 to 14.16; 635 eyes; 8 studies).

Figure 6. Forest plot of comparison: 1 Anti-VEGF and steroid versus anti-VEGF alone, outcome: 1.7 Adverse events.

Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)

Figure 6. (Continued)

- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

One study ([DRCRnet U 2018](#)) with six month follow-up reported systemic adverse events. The study defined a systemic adverse event as: resulted in death, was life threatening, required hospitalisation or prolongation of an existing hospitalisation, resulted in persistent or significant disability /incapacity; was a congenital anomaly/birth defect. The difference was small, and the confidence intervals corresponded to either fewer or more events occurring. There were more systemic adverse events in the the anti-VEGF/steroid group (Peto OR 1.32, 95% CI 0.61 to 2.86; 103 eyes; 1 study) with 25 events in the anti-VEGF plus steroid group (52 eyes) and 21 events in the anti-VEGF group (51 eyes).

Sensitivity analyses

We conducted three sensitivity analyses on the one year data. One analysis excluded [Lim 2012](#) because the study did not report standard deviations for change in visual loss or CMT and had a high risk of selection bias. Another excluded [Maturi 2015](#) because the study received funding from industry and also had a high risk of selection bias. The third analysis excluded [Soheilian](#) because the study had a high risk of attrition bias. The results were reasonably robust.

Analysis	Change in visual acuity (VA) at one year Mean difference (95% CI)	Change in central macular thickness at one year Mean difference (95% CI)
All 3 studies (Lim 2012 ; Maturi 2015 ; Soheilian 2007)	-2.29 VA letters (-6.03 to 1.45)	0.20 µm (-37.14 to 37.53)
Excluding Lim 2012	-3.34 VA letters (-8.05 to 1.37)	10.86 µm (-35.29 to 57.01)
Excluding Maturi 2015	-3.11 VA letters (-7.36 to 1.15)	6.05 µm (-37.89 to 50.00)
Excluding Soheilian 2012	-0.12 VA letters (-4.96 to 4.72)	-17.77µm (-65.03 to 29.49)

Intravitreal anti-VEGF plus steroid compared to macular laser

Visual outcomes

See [Analysis 2.1](#).

Eyes that received intravitreal anti-VEGF plus steroid could, on average, read more letters at one year than those receiving macular laser. The difference was small, and the confidence interval corresponded to either fewer or more letters being read (MD 4.00 VA letters, 95% CI -2.70 to 10.70; 80 eyes; 1 study). The study reported the same pattern at 6 months (MD 6.00 VA letters, 95% CI -0.46 to 12.46; 86 eyes; 1 study) and at two years (MD 3.00 VA letters, 95% CI -4.52 to 10.52; 74 eyes; 1 study). However, participants in this trial received intravitreal anti-VEGF no more frequently than once every 12 weeks, which is considerably less than more recent trials.

Central macular thickness

See [Analysis 2.2](#)

Eyes that received intravitreal anti-VEGF plus steroids had more reduction in CMT at one year compared with those receiving macular laser. The difference was small, and the confidence interval corresponded to either increased or decreased CMT (MD 16.00 µm, 95% CI -68.93 to 36.93; 80 eyes; 1 study).

Adverse effects

See [Analysis 2.3](#)

There were 19 adverse events in eyes receiving intravitreal anti-VEGF plus steroids compared with 1 adverse event in eyes receiving macular laser (Peto OR 9.28, 95% CI 3.50 to 24.60; 100 eyes; 1 study). There was an increased risk of cataract in the anti-VEGF and steroids group compared with macular laser (Peto OR 4.58, 95% CI 0.99 to 21.10; 100 eyes; 1 study). Risk of raised intraocular pressure was higher in eyes receiving anti-VEGF plus steroids compared with macular laser (Peto OR 9.49, 95% CI 2.86 to 31.51; 100 eyes; 1 study).

Intravitreal anti-VEGF plus steroid compared with steroid alone

Two studies compared anti-VEGF/steroid versus IVS ([Lim 2012](#); [Neto 2017](#)) with only one study having 1 year outcomes ([Lim 2012](#)). The steroid used was intravitreal triamcinolone in both trials. [Lim 2012](#) did not report data on standard deviations for change in BCVA so we have included data on final value in the plot ([Analysis 3.1](#)). We judged the certainty of the VA and CMT evidence for this comparison to be low, downgrading for risk of bias in the included trials and imprecision (confidence intervals include both no effect and clinically important differences).

Visual outcomes

The mean change in BCVA at one year was 7.5 letters for eyes receiving anti-VEGF/steroid therapy (36 eyes) compared with 8 letters in the steroid alone arm (37 eyes). The trial authors reported the standard deviation for final value only, not change. The mean difference in final value was 4 letters (95% CI -2.6 to 10.6) at six months and 0 letters (95% CI -6.1 to 6.1) at one year ([Analysis 3.1](#)).

Central macular thickness

The mean change in CMT at one year was -199 µm for eyes receiving anti-VEGF/steroid therapy (36 eyes) compared with -200 µm in the steroid arm (37 eyes). The trial authors reported the standard deviation for final value only, not change. The mean difference in final value was 1.00 µm (95% CI -41.92 to 43.92) at six months and -9.00 µm (95% CI -39.87 to 21.87) at one year ([Analysis 3.1](#)).

Adverse effects

Raised intraocular pressure occurred at similar rates for eyes receiving intravitreal anti-VEGF plus steroids versus steroid alone (RR 0.77, 95% CI 0.19 to 3.20, 37 eyes; 1 study). There was a very low-certainty of evidence with 3 events in the anti-VEGF/steroid group (36 eyes) and 4 events in the steroid group (37 eyes).

DISCUSSION

Summary of main results

There were eight included studies, all at unclear risk of bias in at least one domain. Eyes treated with a combination of inhibitors of vascular endothelial growth factor (VEGF) and steroid therapy achieved similar visual acuity and central macular thickness outcomes as those receiving monotherapy at one year. There was a greater risk of raised intraocular pressure in people receiving intravitreal anti-VEGF plus steroids compared with anti-VEGF monotherapy.

Overall completeness and applicability of evidence

The included studies assessed the combination of intravitreal bevacizumab (off-label) or ranibizumab and either intravitreal triamcinolone (off-label) or dexamethasone implants for the management of diabetic macular oedema (DMO). There were no published randomised clinical trial results on the combination of licensed VEGF inhibitors with intravitreal steroid agents. Intravitreal bevacizumab was often given at lower frequency in the included studies than is generally recommended. Additionally, in the BEVORDEX randomised clinical trial, intravitreal dexamethasone implants given more frequently, with a minimum interval of 16 weeks, may have better results than the studies included in this review ([BEVORDEX 2014](#), [BEVORDEX 2016](#)). Licensed intravitreal anti-VEGF agents (e.g. aflibercept) may have greater efficacy than the unlicensed intravitreal bevacizumab used in most of the included studies ([Virgili 2017](#)).

Quality of the evidence

Many studies did not have sufficient length of follow-up or were under-powered to identify significant local (e.g. cataract or glaucoma) or systemic adverse events (e.g. stroke or heart attack). Typically, cataract develops in the second year of treatment. Ideally, trials that involve intravitreal steroid therapy should run for three years to allow sufficient time for cataract to develop,

for cataract surgery to be undertaken, and for the study eye to stabilise following surgery. All included studies had unclear risk of bias in one or more domains and three studies ([Lim 2012](#); [Maturi 2015](#); [Riazi-Esfahani 2017](#)) had a high risk of selection bias. Many included studies had a paired design for treatments, which have a theoretical potential to influence outcomes in the fellow eye via systemic absorption. Additionally the disease may not be symmetrical and the paired design may preclude pragmatic trials with economic and quality of life outcomes. Clustering risks could potentially be addressed with statistical methods such as generalised estimated equations, however this was not possible in this review due to absence of available individual patient level data in included studies. The GRADE scores of certainty of evidence from the included studies ranged from very low to moderate.

Potential biases in the review process

We used standard methodological procedures as recommended by Cochrane. As we found fewer than 10 studies, we were unable to use a funnel plot to identify possible publication bias.

Agreements and disagreements with other studies or reviews

To our knowledge, this is the first systematic review of randomised clinical trials assessing inhibitors of VEGF plus intravitreal steroids for DMO.

AUTHORS' CONCLUSIONS

Implications for practice

Combination of intravitreal anti-VEGF plus intravitreal steroids does not appear to offer additional visual benefit compared with monotherapy for DMO; at present the evidence for this is of low-certainty. There was an increased rate of cataract development and raised intraocular pressure in eyes treated with anti-VEGF plus steroid versus anti-VEGF alone. Patients were exposed to potential side effects of both these agents without reported additional benefit. The majority of the evidence comes from studies of bevacizumab and triamcinolone used as primary therapy for DMO.

Implications for research

Agreed standardised ocular (e.g. intraocular pressure rise) and systemic (e.g. cardiovascular events) safety outcome measures would allow easier comparison of results. Quality of life and cost benefit indices should also be reported in future clinical trials. Evaluating differences in the relative effect of inhibitors of VEGF and intravitreal steroids on proliferative diabetic retinopathy and foveal threatening hard exudates would help clinicians understand whether these agents can be used in combination to target different aspects of diabetic retinopathy. There is limited evidence from studies using licensed intravitreal anti-VEGF agents plus licensed intravitreal steroid implants with at least one year follow-up. It is not known whether treatment response is different in eyes that are phakic and pseudophakic at baseline. The role of combined inhibitors of VEGF and steroid implants for DMO specifically at the time of cataract surgery has not been addressed in the included randomised clinical trials.

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REFERENCES

References to studies included in this review

DRCRnet U 2018 {published data only}

Maturi RK, Glassman AR, Liu D, Beck RW, Bhavsar AR, Bressler NM, et al. Effect of adding dexamethasone to continued ranibizumab treatment in patients with persistent diabetic macular edema: a DRCR network phase 2 randomized clinical trial. *JAMA Ophthalmology* 2018;**136**(1):29-38.

NCT01945866. Phase II combination steroid and anti-VEGF for persistent DME [Short-term evaluation of combination corticosteroid+anti-VEGF treatment for persistent central-involved diabetic macular edema following anti-VEGF therapy]. clinicaltrials.gov/ct2/show/NCT01945866 (first received 19 September 2013).

Lim 2012 {published data only}

Lim JW, Lee HK, Shin MC. Comparison of intravitreal bevacizumab alone or combined with triamcinolone versus triamcinolone in diabetic macular edema: a randomized clinical trial. *Ophthalmologica* 2012;**227**(2):100-6.

Maturi 2015 {published and unpublished data}

Maturi RK, Bleau L, Saunders J, Mubasher M, Stewart MW. A 12-month, single-masked, randomized controlled study of eyes with persistent diabetic macular edema after multiple anti-VEGF injections to assess the efficacy of the dexamethasone-delayed delivery system as an adjunct to bevacizumab compared with continued bevacizumab monotherapy. *Retina* 2015;**35**(8):1604-14.

Neto 2017 {published data only}

NCT00737971. Efficacy study of triamcinolone and bevacizumab intravitreal for treatment of diabetic macular edema (ATEMD) [Multicenter, randomized clinical trial to assess the effectiveness of intravitreal injections of bevacizumab, triamcinolone, or their combination in the treatment of diabetic macular edema]. clinicaltrials.gov/ct2/show/NCT00737971 (first received 20 August 2008).

Neto HO, Regatieri CV, Nobrega MJ, Muccioli C, Casella AM, Andrade RE, et al. Multicenter, randomized clinical trial to assess the effectiveness of intravitreal injections of bevacizumab, triamcinolone, or their combination in the treatment of diabetic macular edema. *Ophthalmic Surgery, Lasers and Imaging Retina* 2017;**48**(9):734-40.

Riazi-Esfahani 2017 {published data only}

Riazi-Esfahani M, Riazi-Esfahani H, Ahmadraji A, Karkhaneh R, Mahmoudi A, Rohipoor R, et al. Intravitreal bevacizumab alone or combined with 1 mg triamcinolone in diabetic macular edema: a randomized clinical trial. *International Ophthalmology* 2017;**37**:1-14.

Shoeibi 2013 {published data only}

Ahmadi H, Ramezani A, Shoeibi N, Bijanzadeh B, Tabatabaei A, Azarmina M, et al. Intravitreal bevacizumab with or without triamcinolone for refractory diabetic macular edema; a placebo-controlled, randomized clinical trial.

Graefe's Archive for Clinical and Experimental Ophthalmology 2008;**246**(4):483-9.

* Shoeibi N, Ahmadi H, Entezari M, Yaseri M. Intravitreal bevacizumab with or without triamcinolone for refractory diabetic macular edema: long-term results of a clinical trial. *Journal of Ophthalmic and Vision Research* 2013;**8**(2):99-106.

Soheilian 2012 {published data only}

Soheilian M, Garfami KH, Ramezani A, Yaseri M, Peyman GA. Two-year results of a randomized trial of intravitreal bevacizumab alone or combined with triamcinolone versus laser in diabetic macular edema. *Retina* 2012;**32**(2):314-21.

Soheilian M, Ramezani A, Obudi A, Bijanzadeh B, Salehipour M, Yaseri M, et al. Randomized trial of intravitreal bevacizumab alone or combined with triamcinolone versus macular photocoagulation in diabetic macular edema. *Ophthalmology* 2009;**116**(6):1142-50.

Yaseri M, Zeraati H, Mohammad K, Soheilian M, Ramezani A, Eslani M, et al. Intravitreal bevacizumab injection alone or combined with triamcinolone versus macular photocoagulation in bilateral diabetic macular edema; application of bivariate generalized linear mixed model with asymmetric random effects in a subgroup of a clinical trial. *Journal of Ophthalmic and Vision Research* 2014;**9**(4):453-60.

Synek 2011 {published data only}

Synek S, Vesely P. Intravitreal Bevacizumab with or without triamcinolone for refractory diabetic macular oedema. *Collegium Antropologicum* 2011;**35**(3):841-5.

References to studies excluded from this review

Faghihi 2008 {published data only}

Faghihi H, Rohipoor R, Mohammadi SF, Hojat-Jalali K, Mirshahi A, Lashay A, et al. Intravitreal bevacizumab versus combined bevacizumab-triamcinolone versus macular laser photocoagulation in diabetic macular edema. *European Journal of Ophthalmology* 2008;**18**(6):941-8.

Sheth 2011 {published data only}

Sheth S, Rush R, Natarajan S, Gillies M. Intravitreal triamcinolone acetate versus combined intravitreal bevacizumab and dexamethasone in diffuse diabetic macular oedema. *Clinical and Experimental Ophthalmology* 2011;**39**(7):673-81.

Soheilian 2007 {published data only}

Soheilian M, Ramezani A, Bijanzadeh B, Yaseri M, Ahmadi H, Dehghan MH, et al. Intravitreal bevacizumab (avastin) injection alone or combined with triamcinolone versus macular photocoagulation as primary treatment of diabetic macular edema. *Retina* 2007;**27**(9):1187-95.

Wang 2011 {published data only}

Wang YS, Li X, Wang HY, Zhang ZF, Li MH, Su XN. Intravitreal bevacizumab combined with/without triamcinolone acetate

in single injection for treatment of diabetic macular edema. *Chinese Medical Journal* 2011;**124**(3):352-8.

Yu 2018 {published data only}

Yu S Y, Nam D H, Lee D Y. Changes in aqueous concentrations of various cytokines after intravitreal bevacizumab and subtenon triamcinolone injection for diabetic macular edema. *Graefes Arch Clin Exp Ophthalmol* 2018;**256**:39-47.

References to ongoing studies

NCT03126786 {published data only}

NCT03126786. Suprachoroidal CLS-TA with intravitreal aflibercept versus aflibercept alone in subject with diabetic macular edema (TYBEE). clinicaltrials.gov/show/NCT03126786 (first posted 24 April 2017).

UMIN000021630 {unpublished data only}

UMIN000021630. Anti-VEGF and steroid combination therapy for diabetic macular edema. apps.who.int/trialsearch/Trial2.aspx?TrialID=JPRN-UMIN000021630 (date of registration 27 March 2016).

Additional references

Ahmadih 2008

Ahmadih H, Ramezani A, Shoeibi N, Bijanzadeh B, Tabatabaei A, Azarmina M, et al. Intravitreal bevacizumab with or without triamcinolone for refractory diabetic macular edema; a placebo-controlled, randomized clinical trial. *Graefes Archive for Clinical and Experimental Ophthalmology* 2008;**246**(4):483-9.

Aiello 2005

Aiello LP. Angiogenic pathways in diabetic retinopathy. *New England Journal of Medicine* 2005;**353**(8):839-41.

Amoaku 2015

Amoaku WM, Saker S, Stewart EA. A review of therapies for diabetic macular oedema and rationale for combination therapy. *Eye* 2015;**29**(9):1115-30.

Antonetti 2012

Antonetti DA, Klein R, Gardner TW. Diabetic retinopathy. *New England Journal of Medicine* 2012;**366**(13):1227-39.

APTC 1994

Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy-I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;**308**(6921):81-106.

Bailey 1976

Bailey IL, Lovie JE. New design principles for visual acuity letter charts. *American Journal of Optometry and Physiological Optics* 1976;**53**(11):740-5.

BEVORDEX 2014

Gillies MC, Lim LL, Campain A, Quin GJ, Salem W, Li J, et al. A randomized clinical trial of intravitreal bevacizumab versus intravitreal dexamethasone for diabetic macular edema: the BEVORDEX study. *Ophthalmology* 2014;**121**(12):2473-81.

BEVORDEX 2016

Fraser-Bell S, Lim LL, Campain A, Mehta H, Aroney C, Bryant J, et al. Bevacizumab or dexamethasone implants for DME: 2-year results (The BEVORDEX Study). *Ophthalmology* 2016;**123**(6):1399-01.

Boyer 2009

Boyer DS, Heier JS, Brown DM, Francom SF, Ianchulev T, Rubio RG. A phase IIIb study to evaluate the safety of ranibizumab in subjects with neovascular age-related macular degeneration. *Ophthalmology* 2009;**116**(9):1731-9.

Boyer 2011

Boyer DS, Faber D, Gupta S, Patel SS, Tabandeh H, Li XY, et al. Dexamethasone intravitreal implant for treatment of diabetic macular edema in vitrectomized patients. *Retina* 2011;**31**(5):915-23.

Bunce 2008

Bunce C, Wormald R. Causes of blind certifications in England and Wales: April 1999-March 2000. *Eye* 2008;**22**(7):905-11.

Campochiaro 2012

Campochiaro PA, Brown DM, Pearson A, Chen S, Boyer D, Ruiz-Moreno J, et al. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. *Ophthalmology* 2012;**119**(10):2125-32.

Deeks 2011

Deeks JJ, Higgins JP, Altman DG editor(s). Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JP, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

ETDRS 1991

Early Treatment Diabetic Retinopathy Study Research Group. Classification of diabetic retinopathy from fluorescein angiograms. ETDRS report number 11. *Ophthalmology* 1991;**98**(5 Suppl):807-22.

Funatsu 2003

Funatsu H, Yamashita H, Ikeda T, Mimura T, Eguchi S, Hori S. Vitreous levels of interleukin-6 and vascular endothelial growth factor are related to diabetic macular edema. *Ophthalmology* 2003;**110**(9):1690-6.

Funatsu 2005

Funatsu H, Yamashita H, Sakata K, Noma H, Mimura T, Suzuki M, et al. Vitreous levels of vascular endothelial growth factor and intercellular adhesion molecule 1 are related to diabetic macular edema. *Ophthalmology* 2005;**112**(5):806-16.

Gillies 2009

Gillies MC, Simpson JM, Gaston C, Hunt G, Ali H, Zhu M, et al. Five-year results of a randomized trial with open-label extension of triamcinolone acetonide for refractory diabetic macular edema. *Ophthalmology* 2009;**116**(11):2182-7.

Glanville 2006

Glanville JM, Lefebvre C, Miles JN, Camosso-Stepinovic J. How to identify randomized controlled trials in MEDLINE: ten years on. *Journal of the Medical Library Association* 2006;**94**(2):130-6.

Grover 2008

Grover D, Li TJ, Chong CCW. Intravitreal steroids for macular edema in diabetes. *Cochrane Database of Systematic Reviews* 2008, Issue 1. [DOI: [10.1002/14651858.CD005656.pub2](https://doi.org/10.1002/14651858.CD005656.pub2)]

Higgins 2011

Higgins JP, Altman DG, Sterne JAC editor(s). Chapter 8: Assessing risk of bias in included studies. In: Higgins JP, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

International Diabetes Federation 2011

International Diabetes Federation. *Diabetes Atlas*. 5th Edition. Brussels: International Diabetes Federation, 2011.

Keech 2007

Keech AC, Mitchell P, Summanen PA, O'Day J, Davis TM, Moffitt MS, et al. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. *Lancet* 2007;**370**(9600):1687-97.

Kiire 2013

Kiire CA, Porta M, Chong V. Medical management for the prevention and treatment of diabetic macular edema. *Survey of Ophthalmology* 2013;**58**(5):459-65.

Liew 2008

Liew G, Gillies MC, Wang JJ. Fenofibrate and diabetic retinopathy. *Lancet* 2008;**371**(9614):721.

Mehta 2016

Mehta H, Fraser-Bell S, Yeung A, Campain A, Lim LL, Quin GJ, et al. Efficacy of dexamethasone versus bevacizumab on regression of hard exudates in diabetic maculopathy: data from the BEVORDEX randomised clinical trial. *British Journal of Ophthalmology* 2016;**100**(7):1000-4.

Moss 1998

Moss SE, Klein R, Klein BE. The 14-year incidence of visual loss in a diabetic population. *Ophthalmology* 1998;**105**(6):998-1003.

Review Manager 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Scheen 2010

Scheen AJ, Van Gaal LF. Accord-lipid and accord-eye: towards a new positioning of fenofibrate in the management of type 2 diabetes. *Revue Medicale de Liege* 2010;**65**(9):533-9.

Schünemann 2011a

Schünemann HJ, Oxman AD, Higgins JP, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JP, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Schünemann 2011b

Schünemann HJ, Oxman AD, Vist GE, Higgins JPT, Deeks JJ, Glasziou P, et al. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JP, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Simunovic 2014

Simunovic MP, Hunyor AP, Ho IV. Vitrectomy for diabetic macular edema: a systematic review and meta-analysis. *Canadian Journal of Ophthalmology* 2014;**49**(2):188-95.

Soheilian 2009

Soheilian M, Ramezani A, Obudi A, Bijanzadeh B, Salehipour M, Yaseri M, et al. Randomized trial of intravitreal bevacizumab alone or combined with triamcinolone versus macular photocoagulation in diabetic macular edema. *Ophthalmology* 2009;**116**(6):1142-50.

Virgili 2014

Virgili G, Parravano M, Menchini F, Evans JR. Anti-vascular endothelial growth factor for diabetic macular oedema. *Cochrane Database of Systematic Reviews* 2014, Issue 10. [DOI: [10.1002/14651858.CD007419.pub4](https://doi.org/10.1002/14651858.CD007419.pub4)]

Virgili 2017

Virgili G, Parravano M, Menchini F, Evans JR, Gordon I, Lucenteforte E. Anti-vascular endothelial growth factor for diabetic macular oedema: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2017, Issue 6. [DOI: [10.1002/14651858.CD007419.pub5](https://doi.org/10.1002/14651858.CD007419.pub5)]

Wang 2008

Wang K, Wang Y, Gao L, Li X, Li M, Guo J. Dexamethasone inhibits leukocyte accumulation and vascular permeability in retina of streptozotocin-induced diabetic rats via reducing vascular endothelial growth factor and intercellular adhesion molecule-1 expression. *Biological and Pharmaceutical Bulletin* 2008;**31**(8):1541-6.

Wickremasinghe 2017

Wickremasinghe SS, Fraser-Bell S, Alessandrello E, Mehta H, Gillies MC, Lim LL. Retinal vascular calibre changes after intravitreal bevacizumab or dexamethasone implant treatment for diabetic macular oedema. *British Journal of Ophthalmology* 2017;**101**(10):1329-33.

Wong 2008

Wong LJ, Desai RU, Jain A, Feliciano D, Moshfeghi DM, Sanislo SR, et al. Surveillance for potential adverse events associated with the use of intravitreal bevacizumab for retinal and choroidal vascular disease. *Retina* 2008;**28**(8):1151-8.

Yaseri 2014

Yaseri M, Zeraati H, Mohammad K, Soheilian M, Ramezani A, Eslani M, et al. Intravitreal bevacizumab injection alone or combined with triamcinolone versus macular photocoagulation in bilateral diabetic macular edema; application of bivariate generalized linear mixed model with asymmetric random effects in a subgroup of a clinical trial. *Journal of Ophthalmic and Vision Research* 2014;**9**(4):453-60.

Yau 2012

Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, et al. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care* 2012;**35**(3):556-64.

References to other published versions of this review

Mehta 2015

Mehta H, Fraser-Bell S, Campain A, Gillies MC. Anti-vascular endothelial growth factor combined with intravitreal steroids for diabetic macular oedema. *Cochrane Database of Systematic Reviews* 2015, Issue 3. [DOI: [10.1002/14651858.CD011599](https://doi.org/10.1002/14651858.CD011599)]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

DRCRnet U 2018

Methods	<p>Study design: parallel group RCT/within-person study (40 clinical centres)</p> <p>Unit of randomisation: people and eyes if both eyes eligible</p> <p>Number randomised:</p> <p>116 people, 129 eyes</p> <p>Unit of analysis: individual eyes</p> <p>Sample size: For a sample size of 70 study eyes per group (increased to 75 to account for approximately 5% loss to follow-up), a 2-sided 95% CI for the difference in the 2 means of visual acuity change from randomisation to 24 week visit will extend 2.3 visual acuity letter score in either direction from the observed difference in means, assuming that the common standard deviation is a letter score of 7, not adjusting for correlation between eyes in participants with 2 study eyes.</p>
Participants	<p>Country: USA</p> <p>Mean age: 65 years</p> <p>Sex: 67 women; 62 men</p> <p>Underlying condition: persistent DMO</p> <p>Inclusion criteria: age ≥ 18 years; diagnosis of diabetes mellitus (type 1 or type 2); meets all of the following ocular criteria in at least the one eye: at least 3 injections of anti-VEGF drug (ranibizumab, bevacizumab, or aflibercept) within the prior 20 weeks, visual acuity letter score in study eye ≤ 78 and ≥ 24 LogMAR letters (approximate Snellen equivalent 20/32 to 20/320), on clinical exam, definite retinal thickening due to DMO involving the centre of the macula, OCT CMT thickness greater than 300 μm before adjusting for sex and machine-specific factors</p> <p>Exclusion criteria: chronic kidney disease, renal transplant; unstable medical status including blood pressure, cardiovascular disease, and glycaemic control; participation in an investigational trial within 30 days of enrolment; systolic blood pressure > 180 mmHg; acute cardiovascular event within 1 month prior to enrolment; systemic steroid, anti-VEGF or pro-VEGF treatment within prior 4 months; pregnant; macular oedema is considered to be due to a cause other than DMO; an ocular condition is present (other than DMO) that, in the opinion of the investigator, might affect macular oedema or alter visual acuity during the course of the study; substantial posterior capsule opacity; history of intravitreal anti-VEGF drug within 21 days prior to enrolment; history of intravitreal or peribulbar corticosteroids</p>

DRCRnet U 2018 (Continued)

within 3 months prior to enrolment; history of macular laser photocoagulation within 4 months prior to enrolment; laser therapy within 4 previous months; any history of vitrectomy.

Interventions	<p>Intervention: intravitreal ranibizumab (0.3 mg) and dexamethasone implant (0.7g)</p> <p>Comparator: intravitreal ranibizumab (0.3 mg) and sham injection</p> <p>Dexamethasone: sustained dexamethasone drug delivery system. Retreatment: ranibizumab was administered if the visual acuity letter score was less than 84 (approximate Snellen equivalent of 20/25 or worse) or the OCT CST was at or above the pre-defined cut-points. At the 4-week and 8-week visits, only ranibizumab injections were permitted. At 12 weeks and continuing through 20 weeks, retreatment was according to allocation group. A maximum of 2 injections of either dexamethasone or sham treatment were given in each eye.</p>
Outcomes	<p>Primary outcome measure:</p> <ul style="list-style-type: none"> mean change in visual acuity letter score <p>Secondary outcome measures:</p> <ul style="list-style-type: none"> percentage of eyes with at least 10 and at least 15 ETDRS letter gain (increase) or loss (decrease) in visual acuity. visual acuity area under the curve (AUC) mean change in OCT central macular thickness percentage of eyes with worsening or improvement of diabetic retinopathy on clinical exam <p>Length of follow-up: 6 months (24 weeks)</p>
Notes	<p>Trial registration: NCT01945866</p> <p>Source of funding: EY14231 (other grant/funding number: National Eye Institute), EY23207 (other grant/funding number: National Eye Institute), EY18817 (other grant/funding number: National Eye Institute)</p> <p>Declaration of interest: Several of the authors report receiving consultancy fees from the manufacturer of the implant, for example, quote "Dr Maturi reported receiving consultancy fees, research grants, payment for manuscript preparation, and travel, accommodations, and meeting expenses from Allergan, Inc"</p> <p>Date study conducted: February 2014 to December 2016</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote "Randomization was performed on the study website (http://www.dr-cr.net) using a permuted-block design."
Allocation concealment (selection bias)	Low risk	Quote "Randomization was performed on the study website (http://www.dr-cr.net) using a permuted-block design."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote "Study participants and the medical monitor, who reviewed all adverse events, were masked to treatment group assignments. Refractionists, visual acuity testers, and OCT technicians were masked at the 24-week primary outcome visit. Investigators and study coordinators were not masked."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote "Study participants and the medical monitor, who reviewed all adverse events, were masked to treatment group assignments. Refractionists, visual acuity testers, and OCT technicians were masked at the 24-week primary outcome visit. Investigators and study coordinators were not masked."

DRCRnet U 2018 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	High follow-up (127/129, 98%)
Selective reporting (reporting bias)	Low risk	Almost all outcomes on clinical trials registry were reported. The exception "Percent of eyes with worsening or improvement of diabetic retinopathy on clinical exam [Time Frame: 24 weeks after randomization]" was not an outcome of this review.
Other bias	Unclear risk	Both eyes being eligible to allocation in a single individual poses the theoretical potential to influence outcomes in the fellow eye via systemic absorption.

Lim 2012

Methods	<p>Study design: parallel group RCT</p> <p>Unit of randomisation: participants were randomly allocated to treatment. For participants with both eyes eligible on entry, the allocated randomised treatment was applied to the right eye, whereas the left eye received the other treatment.</p> <p>Number randomised:</p> <p>Total: 120 eyes, 110 participants, 10 people had both eyes enrolled</p> <p>Unit of analysis: individual eyes</p> <p>Number analysed:</p> <p>Total: 111 eyes</p> <p>There were 6 study eyes lost to follow-up and 3 eyes declined to continue intervention</p> <p>Intervention arms: 36 eyes anti-VEGF/steroid, 38 eyes anti-VEGF, 37 eyes IVS</p> <p>There were 36 eyes per group required for an 80% power to detect a significance level of 5% in a two-sided test of the outcome measures.</p>
Participants	<p>Country: South Korea</p> <p>Mean age: 60 years</p> <p>Sex: 55 women; 50 men</p> <p>Underlying condition: DMO</p> <p>Inclusion criteria: eyes with clinically significant DMO based on ETDRS criteria. Macular oedema with CMT of at least 300 µm by optical coherence tomography</p> <p>Exclusion criteria: unstable medical status, previous treatment for DMO, history of vitreoretinal surgery, uncontrolled glaucoma; proliferative diabetic retinopathy with active neovascularisation, previous panretinal photocoagulation, presence of vitreomacular traction, history of systemic corticosteroids use in last 6 months</p>
Interventions	<p>Intervention: Intravitreal bevacizumab (1.25mg/0.05ml) and intravitreal triamcinolone acetonide (2mg/0.05ml)</p> <p>Comparator 1: Intravitreal bevacizumab (1.25mg/0.05ml)</p> <p>Comparator 2: intravitreal triamcinolone acetonide (2mg/0.05ml)</p>

Lim 2012 (Continued)

Bevacizumab was given as 2 injections at 6-week intervals. During follow-up, all three groups received repeated bevacizumab injections when CMT was greater than 300 μ m on OCT at 6 week intervals.

Outcomes	Primary outcome: <ul style="list-style-type: none">Change in BCVA at 1 year (LogMAR chart) Secondary outcome <ul style="list-style-type: none">Change in CMT at 1 year (Stratus OCT 3; Carl Zeiss Meditec) Length of follow-up: 1 year	
Notes	Trial registration: NCT01342159 Source of funding: not reported Declaration of interest: Quote "No conflicting relationship exists for any author." Date study conducted: March 2008 to February 2010 (start date was March 2009 on clinical trials.gov)	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote "Randomization was performed using a random block permutation method according to a computer-generated randomization list. Block lengths varied randomly"
Allocation concealment (selection bias)	Low risk	Quote "The random allocation sequence was performed by a biostatistician. Details of the series were unknown to the investigators."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors do not state whether investigators or participants were masked to treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote "Visual acuity assessment and OCT were performed by an optometrist who was blinded to the group status of the patients."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Nine study eyes did not complete the study. In the case of 3 eyes, it was because the person refused the intervention, reasons for the other 6 eyes lost to follow-up was not stated. It was not reported which group these eyes were randomly allocated to.
Selective reporting (reporting bias)	Low risk	VA and CMT outcomes reported at 6 weeks and at 3, 6 and 12 months. Rates of cataract progression, ocular hypertension, vitreous haemorrhage, retinal detachment, endophthalmitis, increase in blood pressure and thromboembolic events were also recorded.
Other bias	Unclear risk	Both eyes being eligible to allocation in a single individual poses the theoretical potential to influence outcomes in the fellow eye via systemic absorption.

Maturi 2015

Methods	Study design: parallel group RCT
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Maturi 2015 (Continued)

Unit of randomisation: participants were randomly allocated to treatment. For participants in whom both eyes were eligible, the right eye was randomised to combination therapy and the left eye was assigned to monotherapy.

Number randomised:

Total: 40 eyes, 30 participants. 10 people had both eyes enrolled

Intervention arms: 21 combination therapy (anti-VEGF/steroid), 19 monotherapy (anti-VEGF)

Unit of analysis: individual eyes

Number analysed:

Total: 35 eyes

1 year follow-up on 18/21 eyes in anti-VEGF/steroid group (2 withdrew, 1 lost to follow-up) and 17/19 of anti-VEGF group (1 withdrew, 1 lost to follow-up).

Participants	<p>Country: USA</p> <p>Mean age: 61 years</p> <p>Sex: 13 women; 17 men</p> <p>Underlying conditions: DMO</p> <p>Inclusion criteria: aged 18 years or older, BCVA scores between 24 and 78, early treatment of Diabetic Retinopathy Study letters (20/32–20/320 Snellen equivalent), and the presence of DMO (because of type 1 or 2 diabetes mellitus) with a CMT of greater than 250 µm measured by time-domain OCT</p> <p>Exclusion criteria: intravitreal anti-VEGF injection within the previous 4 weeks, IVS injection within the previous 8 weeks, and macular laser within the previous 16 weeks, iris neovascularisation, poorly controlled diabetes mellitus (HbA1c > 10 mg/dL), a known history of intraocular pressure increase because of corticosteroids that would not be adequately controlled with 2 topical glaucoma medications, and any condition that in the opinion of the investigator might compromise the results of the trial or preclude the participant from completing all study visits. Female participants needed a negative pregnancy test and the use of a contraceptive.</p>
Interventions	<p>Intervention: intravitreal bevacizumab (1.25mg) and dexamethasone implant (0.7mg)</p> <p>Comparator: intravitreal bevacizumab (1.25mg)</p> <p>Bevacizumab was given at baseline and 1 month, dexamethasone implant was given at 1 month. Bevacizumab injections were repeated at months 2, 3, 4, 6, 7, 8, 10, and 11 when the CMT > 250 µm, and the ETDRS VA score was < 80 letters (20/25); dexamethasone implants were re-injected at months 5 and 9 according to the same criteria.</p>
Outcomes	<ul style="list-style-type: none"> Visual acuity (ETDRS letters) at 12 months Central subfield thickness (OCT) at 12 months Speed of visual improvement: time until gain 15 letters Number of injections required <p>Length of follow-up: 1 year</p>
Notes	<p>Trial registration: not stated</p> <p>Source of funding: supported by an investigator-initiated trial grant from Allergan, Inc. The Leona M and Harry B Helmsley Charitable Trust provided funding for the statistical centre at the Jaeb Center for Health Research to conduct the statistical analyses.</p> <p>Declaration of interest: Quote "R. K. Maturi, Allergan, Regeneron: Advisory Board; Ely Lilly, Jaeb Center for Health Research: consultant; Alcon, Alimera, Quark: subinvestigator; Allergan, Sanofi, Eyegate,</p>

Maturi 2015 (Continued)

Glaxosmithkline, Jaeb Center, Parexel, Santen: principal investigator and M. W. Stewart, Allergan, Regeneron: Advisory Board, Boehringer-Ingelheim: consultant. The remaining authors have no conflicting interests to disclose."

Date study conducted: May 2011 to January 2012

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Generation of the allocation sequence not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants were masked to the treatment modality; investigators performing interventions were not.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not specified in publication.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The 12-month evaluation was performed on 18 of 21 eyes in the combination group (2 withdrew and 1 was lost to follow-up) and 17 of 19 eyes in the bevacizumab monotherapy group (1 withdrew and 1 was lost to follow-up). The exact reasons for participants exiting the study early were not published.
Selective reporting (reporting bias)	Low risk	VA, central subfield thickness, injection load and safety outcomes were reported.
Other bias	Unclear risk	Both eyes being eligible to allocation in a single individual poses the theoretical potential to influence outcomes in the fellow eye via systemic absorption.

Neto 2017

Methods	Study design: parallel group RCT (8 clinical sites) Unit of randomisation: people, one eye per person Number randomised: 142 (on trials registry entry) 111 reported in analyses Unit of analysis: Individual eyes
Participants	Country: Brazil Mean age: not reported Sex: 50 women; 61 men Underlying conditions: diabetic macular oedema Inclusion criteria: 18 years of age at least

Neto 2017 (Continued)

Diagnosis of diabetes mellitus (type 1 or type 2. any one of the following will be considered to be sufficient evidence that diabetes is present:

Current regular use of insulin for the treatment of diabetes

Current regular use of oral hypoglycaemic agents for the treatment of diabetes

Diabetes as defined by American Diabetes Association (ADA)

Symptoms of diabetes (polyuria, polydipsia, and unexplained weight loss) or eighth-hour fasting plasma glucose > 126 mg/dl

Diabetic macular edema clinically observable associated with diabetic retinopathy:

Without prior foveal treatment with laser therapy

If photocoagulation or peripheral or macular laser, at least 3 months

Absence of macular ischaemia by fluorescein angiography on baseline visit

BCVA score between 20 letters (20/400 ETDRS) and 70 letters (20/40 ETDRS) in the study eye measured by the ETDRS method at qualification/baseline visit

Retinal thickness > 275 µm by OCT

One eye per participant will be chosen for the study. In case of both eye eligible, one eye will be randomised to be treated with study medication. The second eye can receive macular laser therapy at baseline or intravitreal injection after the protocol has finished.

Taught hyaloid syndrome

Exclusion criteria:

Uncontrolled systemic disease

Initiation of medical therapy for diabetes or a change from oral hypoglycaemic agents to insulin therapy within 4 months prior to the qualification visit

Renal failure requiring haemodialysis or peritoneal dialysis within 6 months prior to the qualification visit

Any ocular condition in the study eye that in the opinion of the investigator would prevent a 2 lines improvement of visual acuity (e.g. severe macular ischaemia)

Presence of branch retinal vein occlusion, central retinal vein occlusion, uveitis, pseudophakic cystoid oedema or any other condition in the study eye which could be contributing to macular oedema

Presence of an epiretinal membrane in the study eye

History of IOP elevation in response to steroid treatment in either eye

History of glaucoma or optic nerve head change consistent with glaucoma damage

Ocular hypertension requiring more than 1 anti-glaucoma medication to maintain IOP < 11mmHg at qualification visit

Presence of anterior chamber intraocular lens in the study eye

Active optic disc or retinal neovascularisation in the study eye at qualification visit

Active or history of choroidal neovascularisation in the study eye

Interventions

Intervention: intravitreal bevacizumab (1.25mg/0.05ml) and intravitreal triamcinolone acetate (4mg/0.1ml)

Comparator 1: Intravitreal bevacizumab (1.25mg/0.05ml)

Neto 2017 (Continued)

Comparator 2: intravitreal triamcinolone acetate (4mg/0.1ml)

Pro re nata regimen: participants treated monthly unless BCVA was 20/30 and foveal thickness of 275 microns or less.

Outcomes	<p>Primary outcome:</p> <ul style="list-style-type: none"> BCVA (ETDRS) <p>Secondary outcomes:</p> <ul style="list-style-type: none"> IOP measured by tonometry Retinal thickness measured by OCT <p>Length of follow-up: 6 months (24 weeks)</p>
Notes	<p>Trial registration: NCT00737971</p> <p>Source of funding: This work was supported in part by Sao Paulo Research Foundation.</p> <p>Declaration of interest: Reported no relevant disclosures</p> <p>Date study conducted: December 2012 to December 2013</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote "the study participants were randomly assigned into groups of 30 subjects followed by a process of simple randomization with cards with equal probability (1:1:1)"
Allocation concealment (selection bias)	Unclear risk	Study was described as "masked" but not enough information to judge how this was done
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study was described as "masked" but not enough information to judge how this was done
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study was described as "masked" but not enough information to judge how this was done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Clinical trials registry entry suggested 142 people enrolled but only 111 (87%) reported.
Selective reporting (reporting bias)	Low risk	All outcomes on clinical trials registry entry reported.
Other bias	Low risk	

Riazi-Esfahani 2017

Methods	<p>Study design: within-person RCT</p> <p>Unit of randomisation: one eye was randomised to monotherapy and the other eye assigned to combined therapy.</p>
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Riazi-Esfahani 2017 (Continued)

Number randomised:

Total: 92 eyes of 46 participants

46 eyes anti-VEGF, 46 eyes anti-VEGF/steroid

Unit of analysis: individual eyes

Number analysed:

Total: 92 eyes at week 2, falling to 82 eyes at week 24

Two participants lost to follow-up. 3 progressed to proliferative retinopathy

At 6 months:

41 eyes in anti-VEGF group

41 eyes in anti-VEGF/steroid group

Participants	<p>Country: Iran</p> <p>Mean age: 62 years</p> <p>Sex: 25 women; 21 men</p> <p>Underlying conditions: diabetic macular oedema</p> <p>Inclusion criteria: bilateral clinically significant DMO based on ETDRS criteria and central macular thickness of (CMT) > 320 µm.</p> <p>Exclusion criteria: proliferative diabetic retinopathy, a history of any treatment for DMO (panretinal or focal laser photocoagulation and anti-VEGF or IVS), ocular surgery, glaucoma or ocular hypertension, monocularly, pregnancy, VA ≤ 20/320, significant media opacity, CMT ≤ 320 µm, and a serum creatinine level > 3mg/dL.</p>
Interventions	<p>Intervention: intravitreal bevacizumab (1.25mg/0.05ml) and intravitreal triamcinolone acetonide (1mg/0.025ml)</p> <p>Comparator: intravitreal bevacizumab (1.25mg/0.05ml)</p> <p>Retreatments were performed at a 6-week interval after reevaluation of the participants. Retreatment indications consisted of centrally involved macular oedema (more than 320 µm) based on OCT findings if VA was worse than 20/40. Retreatment was not performed if little or no oedema involving the centre of the macula or VA was ≥ 20/40 or any clinically significant adverse effect from prior treatment was reported.</p>
Outcomes	<ul style="list-style-type: none"> • Mean change in BCVA at 24 weeks: Snellen chart • CMT change at weeks 2, 4, 6, 12 and 24: SD-OCT • Injection - related complications • Number of injections <p>Length of follow-up: 6 months (24 weeks)</p>
Notes	<p>Trial registration: clinical trial registration IRCT ID: IRCT2014080818733N1 (retrospectively registered)</p> <p>Source of funding: not reported</p> <p>Declaration of interest: Quote "The authors declare that they have no conflict of interest."</p> <p>Date study conducted: October 2014 to May 2015 (from clinical trials registry entry)</p>

Risk of bias

Riazi-Esfahani 2017 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed by a random block permutation method according to a computer-generated randomisation list.
Allocation concealment (selection bias)	Low risk	Details of the series were unknown by the study investigators. A biostatistician performed random allocation sequencing.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Single surgeon other than the study investigators ran all the procedures to maintain investigator masking
Blinding of outcome assessment (detection bias) All outcomes	Low risk	At each visit, certified examiners masked to both the randomisation and previous measurements determined visual acuity and performed OCT.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Five participants lost to follow-up: 3 excluded due to progressing to high risk proliferative retinopathy before intervention; reasons for other 2 dropouts were unclear.
Selective reporting (reporting bias)	Low risk	VA and CMT outcomes reported at 6 weeks and at 3, 6 and 12 months. Rates of cataract progression, ocular hypertension, vitreous haemorrhage, retinal detachment, endophthalmitis, increase in blood pressure and thromboembolic events were also recorded.
Other bias	Unclear risk	Both eyes being eligible to allocation in a single individual poses the theoretical potential to influence outcomes in the fellow eye via systemic absorption.

Shoeibi 2013

Methods	<p>Study design: parallel group RCT</p> <p>Unit of randomisation: participants were randomly allocated to treatment. In bilateral cases, each eye was randomised individually</p> <p>Number randomised:</p> <p>Total: 115 eyes, 101 participants</p> <p>Intervention arms: 41 anti-VEGF, 37 anti-VEGF/steroid, 37 control eyes</p> <p>Unit of analysis: individual eyes</p> <p>Number analysed:</p> <p>Total: 115 eyes</p> <p>No study eyes lost to follow-up</p>
Participants	<p>Country: Iran</p> <p>Mean age: 60 years</p> <p>Sex: 44 women, 34 men</p> <p>Underlying conditions: DMO refractory to laser treatment</p>

Shoeibi 2013 (Continued)

Inclusion criteria: participants were from an earlier trial. These participants had refractory DMO that had not responded to macular laser treatment and had been previously allocated to 1 of the 3 treatment arms (anti-VEGF, anti-VEGF/steroid or sham injection). They had received 3 doses of anti-VEGF (alone in the anti-VEGF group or combined at the time of first injection with IVS in the anti-VEGF/steroid group) at 6-week intervals. As the beneficial effect of anti-VEGF at 6 months was established, participants in the sham group also received anti-VEGF according to the protocol but were not included in the current study.

Exclusion criteria: cataract surgery likely during the study period, significant media opacity precluding retinal view, presence of traction on the macula evidenced by OCT, monocularly and pregnancy.

Interventions	<p>Intervention: Intravitreal bevacizumab (1.25mg/0.05ml) and triamcinolone acetonide (2mg/0.05ml)</p> <p>Comparator: Intravitreal bevacizumab (1.25mg/0.05ml) and sham injection</p> <p>Bevacizumab 3 loading doses at 6-week intervals. After week 24, all study eyes could receive further bevacizumab on an as required basis.</p> <p>Triamcinolone acetonide was given in the first dose only.</p>
Outcomes	<ul style="list-style-type: none"> • Change in CMT: OCT (Stratus OCT 3; Carl Zeiss Meditec) • BCVA: Snellen chart converted into LogMAR • Adverse events <p>Length of follow-up: 6 months (24 weeks)</p>
Notes	<p>Trial registration: not stated</p> <p>Source of funding: not reported</p> <p>Declaration of interest: Quote "Conflicts of interest: none"</p> <p>Date study conducted: November 2005 to September 2006</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed using a random block permutation method according to a computer-generated randomisation list. The block lengths varied randomly. In bilateral cases, each eye was randomised individually.
Allocation concealment (selection bias)	Low risk	A biostatistician performed the random allocation sequence and details of the series were unknown to the investigators
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants only were masked to the treatment modality.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	VA assessment and OCT were performed by optometrists who were masked to the groups.
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant in the combined anti-VEGF/steroid group developed vitreous haemorrhage after the third injection and was excluded from the study according to the 24-week report. One participant in the control group died during the first 24 weeks of the study. The flow diagram of the study, where long-term results are presented, does not make reference to these exclusions.

Shoeibi 2013 (Continued)

Selective reporting (reporting bias)	Unclear risk	Primary outcome measure was change in CMT measured on OCT. However, VA change was included as a secondary outcome
Other bias	Unclear risk	Snellen chart was used for measurement of BCVA. However, inherent shortcomings of this chart, such as non-geometric progression of letter size, variable number of letters per line and lack of a standardised scaling system, should be kept in mind. Both eyes being eligible to allocation in a single individual poses the theoretical potential to influence outcomes in the fellow eye via systemic absorption.

Soheilian 2012

Methods	<p>Study design: parallel group RCT</p> <p>Unit of randomisation: participants were randomly allocated to intervention. In bilateral cases each eye was randomised individually</p> <p>Number randomised:</p> <p>Total: 150 eyes, 129 participants</p> <p>Intervention arms: 50 anti-VEGF, 50 anti-VEGF/steroid, 50 MPC</p> <p>Unit of analysis: Individual eyes</p> <p>Number analysed:</p> <p>Total: 113 eyes</p> <p>There were 21 bilateral cases: 2 bilateral MPC, 2 bilateral anti-VEGF, 2 bilateral anti-VEGF/steroid. 4 received anti-VEGF for one eye and anti-VEGF/steroid for the other, 4 participants had anti-VEGF for one eye and MPC for the fellow eye, and the remaining 7 participants treated by anti-VEGF/steroid for one eye and MPC for the other.</p> <p>Individual eyes:</p> <p>39 anti-VEGF, 36 anti-VEGF/steroid, 38 MPC</p> <p>Lost to follow-up:</p> <p>12 anti-VEGF, 13 anti-VEGF/steroid, 12 MPC</p> <p>There were 25% of study eyes lost to follow-up at 2 years, 12% at 1 year. Investigators reported that visual acuity outcomes between those eyes that exited early were similar to those that completed follow up. However the methods of this analysis were not reported.</p>
Participants	<p>Country: Iran</p> <p>Mean age: 61 years</p> <p>Sex: 74 women, 76 men</p> <p>Underlying conditions: DMO</p> <p>Inclusion criteria: clinically significant DMO based on ETDRS criteria</p> <p>Exclusion criteria: panretinal or focal laser photocoagulation, previous intraocular surgery or injection, history of glaucoma or ocular hypertension, VA between 20/40 and 20/300, presence of iris neovascularisation, high-risk proliferative diabetic retinopathy, and significant media opacity, monocularly, pregnancy, raised serum creatinine, and uncontrolled diabetes mellitus</p>

Soheilian 2012 (Continued)

Interventions	Intervention: intravitreal bevacizumab (1.25mg/0.05ml) and triamcinolone acetonide (2mg/ 0.05ml) Comparator 1: intravitreal bevacizumab (1.25mg/0.05ml) Comparator 2: focal or modified grid laser The study eyes received re-treatment with the initial intervention at 12 week intervals if there was persistent clinically significant macula oedema and BCVA was worse than 20/40. Bevacizumab re-treatment was at a maximum frequency of 12 weeks, which is significantly less than the treatment interval in more recent trials.	
Outcomes	<ul style="list-style-type: none">• BCVA: Snellen chart converted into LogMAR letters• CMT OCT (Zeiss, Dublin, CA)• Injection related complications <p>The primary outcome was change in BCVA at 6 months but change at 1 year and 2 years was also recorded.</p> <p>Length of follow-up: 2 years with review every 3 months</p>	
Notes	<p>Trial registration: clinicaltrials.gov identifier: NCT00370669.</p> <p>Source of funding: supported in part by Ophthalmic Research Center of Shahid Beheshti, University of Medical Sciences, Tehran, Iran</p> <p>Declaration of interest: Quote: "Conflicts of interest: none"</p> <p>Date study conducted: September 2005 to May 2007</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed using a random block permutation method according to a computer-generated randomisation list. The block lengths varied randomly. In bilateral cases each eye was randomised individually
Allocation concealment (selection bias)	Low risk	A biostatistician performed random allocation sequence, and details of series were unknown to the study investigators.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Sham injections and laser were performed to ensure participants remained masked. Procedures were carried out by team members other than those assessing outcomes. However, those delivering treatment were not masked to treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Certified masked examiners performed BCVA and OCT measurements.
Incomplete outcome data (attrition bias) All outcomes	High risk	38/50 (76%) of anti-VEGF/steroid group followed up to 36 weeks. 44/50 (88%) of anti-VEGF group followed up to 36 weeks. 43/50 (86%) of MPC group followed up to 36 weeks. Higher loss to follow-up in anti-VEGF/steroid group appeared to be related to adverse effects (cataract, neovascular glaucoma)
Selective reporting (reporting bias)	Unclear risk	VA and CMT outcomes were recorded. Not all safety outcomes were presented.

Soheilian 2012 (Continued)

Other bias	Unclear risk	<p>Snellen chart was used for measurement of BCVA. However, inherent shortcomings of this chart, such as non-geometric progression of letter size, variable number of letters per line and lack of a standardised scaling system, should be kept in mind.</p> <p>Both eyes being eligible to allocation in a single individual poses the theoretical potential to influence outcomes in the fellow eye via systemic absorption.</p>
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Synek 2011

Methods	<p>Study design: parallel group RCT using block permutation</p> <p>Unit of randomisation: 1 eye included in the study, unclear how selection was carried out in cases of bilateral DMO</p> <p>Number randomised:</p> <p>Total: 60 eyes, 60 participants</p> <p>Intervention arms: 30 anti-VEGF, 30 anti-VEGF/steroid</p> <p>Unit of analysis: individual eyes</p> <p>Number analysed:</p> <p>Total: 60 eyes, 60 participants</p> <p>Intervention arms: 30 anti-VEGF, 30 anti-VEGF/steroid</p> <p>To have a power of 90%, a level of significance equal to 0.05 and an assumed standard deviation of 50 microns, a minimum sample size of 30 eyes for each arm was calculated to detect a 30% difference in CMT changes between the two treatment groups.</p>
Participants	<p>Country: Czech Republic</p> <p>Mean age: 60 years</p> <p>Sex: 31 women, 29 men</p> <p>Underlying conditions: DMO</p> <p>Inclusion criteria: eyes with clinically significant macular oedema unresponsive to previous macular laser photocoagulation, with the last session being more than 3 months prior</p> <p>Exclusion criteria: VA > 20/40, history of cataract surgery within the past 6 months, prior intraocular injection or vitrectomy, glaucoma or ocular hypertension, proliferative diabetic retinopathy with high-risk characteristics, vitreous haemorrhage, significant media opacity, and presence of traction on the macula. Monocular participants excluded. Pregnancy and raised serum creatinine level were also contraindications.</p>
Interventions	<p>Intervention: intravitreal bevacizumab (1.25mg/0.05ml) and triamcinolone acetonide (2mg/0.05ml)</p> <p>Comparator: intravitreal bevacizumab (1.25mg/0.05ml)</p> <p>3 injections of bevacizumab at 6-week intervals. One injection of triamcinolone acetonide on first dose only</p>
Outcomes	<ul style="list-style-type: none"> Change in CMT at 6 months: OCT Change in BCVA at 6 months: Snellen chart converted to LogMAR Ocular adverse events: IOP rise, cataract progression, intraocular inflammation

Synek 2011 (Continued)

Length of follow-up: 6 months (24 weeks)

Notes
Trial registration: not stated

Source of funding: not stated

Declaration of interest: Quote "The author has no proprietary interest in this study."

Date study conducted: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed using a random block permutation method according to a computer-generated randomisation list. The block lengths varied randomly.
Allocation concealment (selection bias)	Low risk	A biostatistician performed the random allocation sequence. Details of the series were unknown to the investigators.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants were masked to the treatment modality. Investigators performing interventions were not.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated whether outcome measures were assessed by masked investigators.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reported no cases lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	Primary outcome measure was change in CMT measured on OCT. However, VA change was included as a secondary outcome.
Other bias	Unclear risk	Snellen chart was used for measurement of BCVA. However, inherent shortcomings of this chart, such as non-geometric progression of letter size, variable number of letters per line and lack of a standardised scaling system should be kept in mind.

BCVA: best corrected visual acuity; **CMT:** central macular thickness; **DMO:** diabetic macular oedema; **ETDRS:** Early Treatment Diabetic Retinopathy Study; **IOP:** intraocular pressure; **IVB:** intravitreal bevacizumab; **IVS:** intravitreal steroid; **LogMAR:** Logarithm of the Minimum Angle of Resolution; **MPC:** macular photocoagulation; **OCT:** optical coherence tomography; **RCT:** randomised controlled trial; **VA:** visual acuity; **VEGF:** vascular endothelial growth factor.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Faghihi 2008	Insufficient length of follow-up (16 weeks)
Sheth 2011	Insufficient length of follow-up (6 weeks)
Soheilian 2007	Insufficient length of follow-up (12 weeks)

Study	Reason for exclusion
Wang 2011	Insufficient length of follow-up (12 weeks)
Yu 2018	Insufficient length of follow-up (4 weeks)

Characteristics of ongoing studies [ordered by study ID]

NCT03126786

Trial name or title	Suprachoroidal CLS-TA With Intravitreal Aflibercept Versus Aflibercept Alone in Subject With Diabetic Macular Edema (TYBEE)
Methods	Study design: parallel group RCT
Participants	<p>71 people with DMO</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> Clinical diagnosis of type 1 or type 2 DM DME with central involvement ($> 300 \mu\text{m}$ in the central subfield on spectral-domain optical coherence tomography (SD-OCT)), in the study eye ETDRS BCVA score of ≥ 20 letters read and ≤ 70 letters read in the study eye Naïve to local pharmacologic treatment for DMO in the study eye <p>Exclusion criteria:</p> <ul style="list-style-type: none"> IOP > 21 mmHg in the study eye at Visit 1 (Day -30 to -1); participants are not excluded if IOP is < 22 mmHg in the study eye with no more than 1 IOP lowering medication Any previous treatment in the study eye with an ocular corticosteroid implant Has significant media opacity precluding evaluation of retina and vitreous in the study eye. History of glaucoma or optic nerve head change consistent with glaucoma damage History of glaucoma surgery History of clinically significant IOP elevation in response to corticosteroid treatment ("steroid responder")
Interventions	<p>Intervention: intravitreal aflibercept (2mg/0.05mL) plus suprachoroidal injection of triamcinolone acetate (40mg/mL)</p> <p>Comparator: intravitreal aflibercept (2mg/0.05mL) plus sham injection</p>
Outcomes	<p>Primary outcome:</p> <p>Mean change from baseline in BCVA at 6 months</p> <p>Secondary outcome:</p> <p>Mean change from baseline in central subfield thickness at 6 months (measured by OCT)</p>
Starting date	<p>July 2017</p> <p>End date: April 2018</p>
Contact information	https://clinicaltrials.gov/show/NCT03126786
Notes	Suprachoroidal rather than intravitreal delivery of triamcinolone

UMIN000021630

Trial name or title	Anti-VEGF and steroid combination therapy for diabetic macular oedema
Methods	Study design: parallel non-masked prospective randomised controlled trial Unit of randomisation: not specified
Participants	Country: Japan Underlying conditions: diabetic macular oedema Inclusion criteria: > 20 years of age, clinically significant DMO refractory to laser treatment, Japanese LogMAR visual acuity 1.52-1.22, CMT > 300 µm Exclusion criteria: treated with macular laser within 3 months, ischaemic maculopathy, vitreo-macular traction, proliferative diabetic retinopathy, glaucoma, optic neuropathy, vitrectomy, phakic eye, previous intravitreal or subtenon steroid injection, steroid responder, heart failure, cerebral vascular disease, hematological disease, tumour, concurrent systemic steroids, renal failure (> CKD S3), grade III hypertension, HbA1c NGSP over 10%.
Interventions	Intervention 1: 2 months after loading doses of intravitreal ranibizumab injections, intravitreal ranibizumab is continued Intervention 2: 2 months after loading doses of intravitreal ranibizumab injections, an intravitreal triamcinolone injection is delivered The exact treatment schedule and retreatment criteria are not specified. Length of follow-up: not specified
Outcomes	The primary outcome is the number of ranibizumab injections required over duration of trial. The length of the trial is not specified.
Starting date	27 March 2016
Contact information	upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000024947
Notes	Trial registration: UMIN000021630 Source of funding: Self funded

CKD: chronic kidney disease; **DMO:** diabetic macular oedema; **ETDRS:** Early Treatment Diabetic Retinopathy Study; **Hb1Ac:** glycated haemoglobin; **LogMAR:** Logarithm of the Minimum Angle of Resolution; **NGSP:** National Glycohemoglobin Standardization Program; **OCT:** optical coherence tomography; **VEGF:** vascular endothelial growth factor.

DATA AND ANALYSES

Comparison 1. Anti-VEGF and steroid versus anti-VEGF alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean change in visual acuity at 6 months	8	618	Mean Difference (IV, Random, 95% CI)	-0.88 [-2.56, 0.80]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Mean change in visual acuity at 1 year	3	188	Mean Difference (IV, Fixed, 95% CI)	-2.29 [-6.03, 1.45]
3 Mean change in visual acuity at 2 years	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Mean change in central macular thickness at 6 months	8	617	Mean Difference (IV, Random, 95% CI)	-19.73 [-40.47, 1.01]
5 Mean change in central macular thickness at 1 year	3	188	Mean Difference (IV, Fixed, 95% CI)	0.20 [-37.14, 37.53]
6 Mean change in central macular thickness at 2 years	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7 Adverse events	8		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
7.1 All	8	635	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.66 [3.62, 8.84]
7.2 Significant intraocular inflammation	8	635	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.53 [0.05, 5.08]
7.3 Development of cataract	8	635	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.49 [2.87, 19.60]
7.4 Raised intraocular pressure	8	635	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.13 [4.67, 14.16]
7.5 Systemic adverse events	1	103	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.32 [0.61, 2.86]
8 Need for glaucoma drainage surgery	8		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Anti-VEGF and steroid versus anti-VEGF alone, Outcome 1 Mean change in visual acuity at 6 months.

Analysis 1.2. Comparison 1 Anti-VEGF and steroid versus anti-VEGF alone, Outcome 2 Mean change in visual acuity at 1 year.

Analysis 1.3. Comparison 1 Anti-VEGF and steroid versus anti-VEGF alone, Outcome 3 Mean change in visual acuity at 2 years.

Analysis 1.4. Comparison 1 Anti-VEGF and steroid versus anti-VEGF alone, Outcome 4 Mean change in central macular thickness at 6 months.

Analysis 1.5. Comparison 1 Anti-VEGF and steroid versus anti-VEGF alone, Outcome 5 Mean change in central macular thickness at 1 year.

Analysis 1.6. Comparison 1 Anti-VEGF and steroid versus anti-VEGF alone, Outcome 6 Mean change in central macular thickness at 2 years.

Analysis 1.7. Comparison 1 Anti-VEGF and steroid versus anti-VEGF alone, Outcome 7 Adverse events.

Analysis 1.8. Comparison 1 Anti-VEGF and steroid versus anti-VEGF alone, Outcome 8 Need for glaucoma drainage surgery.

Comparison 2. Anti-VEGF and steroid versus macular laser

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean change in visual acuity	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 1 year	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 2 years	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Mean change in central macular thickness	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 1 year	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 2 years	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Adverse events	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
3.1 All	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Development of cataract	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Raised intraocular pressure	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 Anti-VEGF and steroid versus macular laser, Outcome 1 Mean change in visual acuity.

Analysis 2.2. Comparison 2 Anti-VEGF and steroid versus macular laser, Outcome 2 Mean change in central macular thickness.

Analysis 2.3. Comparison 2 Anti-VEGF and steroid versus macular laser, Outcome 3 Adverse events.

Comparison 3. Anti-VEGF and steroid versus steroid alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean change in visual acuity	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 6 months	2		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 1 year	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Mean change in central macular thickness	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 6 months	2		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 1 year	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Raised intraocular pressure	2	145	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.33 [0.11, 1.04]

Analysis 3.1. Comparison 3 Anti-VEGF and steroid versus steroid alone, Outcome 1 Mean change in visual acuity.

Study or subgroup	Anti-VEGF/steroid		Steroid		Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)		
3.1.1 6 months						
Lim 2012	36	26 (14.5)	37	22 (14.5)		4[-2.65,10.65]
Neto 2017	34	10 (15)	38	16 (15)		-6[-12.94,0.94]
3.1.2 1 year						
Lim 2012	36	24.5 (16)	37	24.5 (9.5)		0[-6.06,6.06]

Favours steroid -20 -10 0 10 20 Favours anti-VEGF/steroid

Analysis 3.2. Comparison 3 Anti-VEGF and steroid versus steroid alone, Outcome 2 Mean change in central macular thickness.

Study or subgroup	Anti-VEGF/steroid		Steroid		Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)		
3.2.1 6 months						
Lim 2012	36	358 (89)	37	357 (98)		1[-41.92,43.92]
Neto 2017	34	-125.4 (125)	38	-160.2 (125)		34.8[-23.04,92.64]
3.2.2 1 year						
Lim 2012	36	259 (60)	37	268 (74)		-9[-39.87,21.87]

Favours IVB/IVS -100 -50 0 50 100 Favours IVB

Analysis 3.3. Comparison 3 Anti-VEGF and steroid versus steroid alone, Outcome 3 Raised intraocular pressure.

ADDITIONAL TABLES

Table 1. Adverse events

	Significant ocular in- flammation	Development of cataract	Raised in- traocular Pressure	Need for glaucoma drainage surgery	Sample size
Intravitreal anti-VEGF + steroid					
Lim 2012	—	0	3	0	36
Maturi 2015	—	9	6	0	20
DRCRnet U 2018	1	3	19	0	65
Neto 2017	0	0	6	0	34
Riazi-Esfahani 2017	—	—	3	—	41
Shoeibi 2013	0	0	3	0	37
Soheilian 2012	—	6	12	1	50
Synek 2011	—	0	2	0	30
Total	1	18	54	1	313
Intravitreal anti-VEGF					
Lim 2012	—	0	0	0	38
Maturi 2015	—	0	1	0	19
DRCRnet U 2018	0	0	0	0	64
Neto 2017	0	0	1	0	39
Riazi-Esfahani 2017	—	0	—	—	41

Table 1. Adverse events *(Continued)*

Shoeibi 2013	1	0	0	0	41
Soheilian 2012	—	1	0	0	50
Synek 2011	1	0	0	0	30
Total	2	1	2	0	322
Intravitreal steroid					
Lim 2012	—	0	4	0	37
Maturi 2015	—	—	—	—	0
DRCRnet U 2018	—	—	—	—	—
Neto 2017	0	0	6	0	38
Riazi-Esfahani 2017	—	—	—	—	—
Shoeibi 2013	—	—	—	—	0
Soheilian 2012	—	—	—	—	0
Synek 2011	—	—	—	—	0
Total	—	0	10	0	75
Macular laser					
Lim 2012	—	—	—	—	0
Maturi 2015	—	—	—	—	0
DRCRnet U 2018	—	—	—	—	—
Neto 2017	—	—	—	—	—
Riazi-Esfahani 2017	—	—	—	—	—
Shoeibi 2013	—	—	—	—	0
Soheilian 2012	—	1	0	0	50
Synek 2011	—	—	—	—	0
Total	—	1	0	0	50

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Macular Edema] explode all trees

#2 macula* near/3 oedema

#3 macula* near/3 edema
 #4 maculopath*
 #5 CME or CSME or CMO or CSMO
 #6 DMO or DME
 #7 #1 or #2 or #3 or #4 or #5 or #6
 #8 MeSH descriptor: [Diabetes Mellitus] explode all trees
 #9 MeSH descriptor: [Diabetic Retinopathy] this term only
 #10 MeSH descriptor: [Diabetes Complications] this term only
 #11 diabet*
 #12 retinopath*
 #13 #8 or #9 or #10 or #11 or #12
 #14 #7 and #13
 #15 MeSH descriptor: [Steroids] explode all trees
 #16 triamcin*
 #17 dexamethasone*
 #18 fluocinolone*
 #19 steroid* or glucocorticoid*
 #20 #15 or #16 or #17 or #18 or #19
 #21 MeSH descriptor: [Angiogenesis Inhibitors] explode all trees
 #22 MeSH descriptor: [Angiogenesis Inducing Agents] explode all trees
 #23 MeSH descriptor: [Endothelial Growth Factors] explode all trees
 #24 anti near/2 VEGF*
 #25 endothelial near/2 growth near/2 factor*
 #26 anti next angiogen*
 #27 macugen* or pegaptanib* or lucentis* or rhufab* or ranibizumab* or bevacizumab* or avastin* or aflibercept*
 #28 VEGF TRAP*
 #29 #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28
 #30 #14 and #20 and #29

Appendix 2. MEDLINE Ovid search strategy

1. randomized controlled trial.pt.
2. (randomized or randomized).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/
14. (macula\$ adj3 oedema).tw.
15. (macula\$ adj3 edema).tw.
16. maculopath\$.tw.
17. (CME or CSME or CMO or CSMO).tw.
18. (DMO or DME).tw.
19. or/13-18
20. exp diabetes mellitus/
21. diabetic retinopathy/
22. diabetes complications/
23. diabet\$.tw.
24. retinopath\$.tw.
25. or/20-24
26. 19 and 25
27. exp steroids/
28. triamcin\$.tw.
29. dexamethasone\$.tw.
30. fluocinolone.tw.
31. (steroid\$ or glucocorticoid\$).tw.

32. or/27-31
33. exp angiogenesis inhibitors/
34. exp angiogenesis inducing agents/
35. exp endothelial growth factors/
36. (anti adj2 VEGF\$.tw.
37. (endothelial adj2 growth adj2 factor\$.tw.
38. (anti adj1 angiogen\$.tw.
39. (macugen\$ or pegaptanib\$ or lucentis\$ or rhufab\$ or ranibizumab\$ or bevacizumab\$ or avastin or aflibercept\$.tw.
40. VEGF TRAP\$.tw.
41. or/33-40
42. 26 and 32 and 41
43. 12 and 42

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

Appendix 3. Embase Ovid 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 edema/
34. (macula\$ adj3 oedema).tw.
35. (macula\$ adj3 edema).tw.
36. maculopath\$.tw.
37. (CME or CSME or CMO or CSMO).tw.
38. (DMO or DME).tw.
39. or/33-38
40. exp diabetes mellitus/
41. diabetic retinopathy/
42. diabet\$.tw.
43. retinopath\$.tw.
44. or/40-43
45. 39 and 44

46. exp steroid/
47. triamcin\$.tw.
48. dexamethasone\$.tw.
49. fluocinolone.tw.
50. (steroid\$ or glucocorticoid\$).tw.
51. or/46-50
52. angiogenesis/
53. angiogenesis inhibitors/
54. angiogenesis factor/
55. monoclonal antibody/
56. exp endothelial cell growth factor/
57. vasculotropin/
58. (anti adj2 VEGF\$).tw.
59. (endothelial adj2 growth adj2 factor\$).tw.
60. (anti adj1 angiogen\$).tw.
61. (macugen\$ or pegaptanib\$ or lucentis\$ or rhufab\$ or ranibizumab\$ or bevacizumab\$ or avastin or aflibercept\$).tw.
62. VEGF TRAP\$.tw.
63. or/52-62
64. 45 and 51 and 63
65. 32 and 64

Appendix 4. LILACS search strategy

macula\$ edema or macula\$ oedema or DMO or DME or CMO or CME or CSMO and steroid\$ or triamcin\$ or dexamethasone\$ or fluocinolone \$ and angiogenesis or endothelial growth factor or macugen\$ or pegaptanib\$ or lucentis\$ or rhufab\$ or ranibizumab\$ or bevacizumab\$ or avastin\$ or aflibercept\$

Appendix 5. ISRCTN search strategy

"(diabetic macular edema OR DMO OR DME) AND (endothelial growth factor OR anti VEGF OR macugen OR pegaptanib OR lucentis OR rhufab OR ranibizumab OR bevacizumab OR avastin OR aflibercept) AND (steroid OR triamcinolone OR dexamethasone OR fluocinolone)"

Appendix 6. ClinicalTrials.gov search strategy

(diabetic macular edema OR DMO OR DME) AND (endothelial growth factor OR anti VEGF OR macugen OR pegaptanib OR lucentis OR rhufab OR ranibizumab OR bevacizumab OR avastin OR aflibercept) AND (steroid OR triamcinolone OR dexamethasone OR fluocinolone)

Appendix 7. WHO ICTRP search strategy

steroid OR triamcinolone OR dexamethasone OR fluocinolone = Title AND diabetic macular edema OR DMO OR DME = Condition AND endothelial growth factor OR anti VEGF OR macugen OR pegaptanib OR lucentis OR rhufab OR ranibizumab OR bevacizumab OR avastin OR aflibercept = Intervention

Appendix 8. Data on study characteristics

Mandatory items		Optional items
Methods		
Study design	<ul style="list-style-type: none"> • Parallel group RCT<i>i.e. people randomized to treatment</i> • Within-person RCT<i>i.e. eyes randomized to treatment</i> • Cluster RCT<i>i.e. communities randomized to treatment</i> • Cross-over RCT • Other, specify 	Exclusions after randomization Losses to follow up Number randomized/analysed
Eyes or Unit of randomization/unit of analysis	<ul style="list-style-type: none"> • One eye included in study, specify how eye selected • Two eyes included in study, both eyes received same treatment, briefly specify how analysed (best/worst/average/both and adjusted for within person correlation/both and not adjusted for within person correlation) and specify if mixture one eye and two eye 	How were missing data handled? <i>e.g. available case analysis, imputation methods</i>

(Continued)

- **Two eyes included in study, eyes received different treatments, specify if correct pair-matched analysis done**
- Reported power calculation (Y/N), if yes, sample size and power
- Unusual study design/issues

Participants

Country(s)		Setting
Total number of participants	<i>This information should be collected for total study population recruited into the study. If these data are only reported for the people who were followed up only, please indicate.</i>	Ethnic group
Number (%) of men and women		Equivalence of baseline characteristics (Y/N)
Average age and age range		
Inclusion criteria		
Exclusion criteria		

Interventions

Intervention (n)	• Number of people randomized to this group	—
Comparator (n)	• Drug (or intervention) name	
See MECIR 65 and 70	• Dose	
	• Frequency	
	• Route of administration	

Outcomes

Primary and secondary outcomes as defined in study reports	<ul style="list-style-type: none"> • List outcomes • Adverse events reported (Y/N) • Length of follow up and intervals at which outcomes assessed 	Planned/actual length of follow-up
See MECIR R70		

Notes

Date conducted	Specify dates of recruitment of participants month/year to month/year	Full study name: (if applicable)
Sources of funding		Reported subgroup analyses (Y/N)
Declaration of interest		Were trial investigators contacted?
See MECIR 69		

CONTRIBUTIONS OF AUTHORS

Conceiving the review: HM

Designing the review: HM, AC, SFB, MG

Co-ordinating the review: HM

Anti-vascular endothelial growth factor combined with intravitreal steroids for diabetic macular oedema (Review)

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Data collection for the review

- Designing electronic search strategies: IG*, HM
- Undertaking manual searches: HM, SFB,
- Screening search results: HM, SFB
- Organizing retrieval of papers: HM, SFB
- Screening retrieved papers against inclusion criteria: HM, SFB
- Appraising quality of papers: HM, SFB, CH, VN
- Extracting data from papers: HM, SFB, CH, VN
- Writing to authors of papers for additional information: HM
- Providing additional data about papers: HM, SFB
- Obtaining and screening data on unpublished studies: HM, SFB

Data management for the review

- Entering data into RevMan: HM, SFB, CH, VN
- Analysis of data: HM, VN, SFB, CH, MG

Interpretation of data

- Providing a methodological perspective: VN, AC, HM, SFB, MG
- Providing a clinical perspective: HM, SFB, MG
- Providing a policy perspective: HM, SFB, MG
- Providing a consumer perspective: HM, SFB, MG

Writing the review: HM, CH

Providing general advice on the review: SFB, MG

*Iris Gordon - Cochrane Eyes and Vision Information Specialist

DECLARATIONS OF INTEREST

Professor Mark Gillies is a member of National and International Ophthalmic (Retinal) Advisory Boards for Allergan, Inc, Pfizer, Inc, Novartis Pharmaceuticals, and Bayer HealthCare Pharmaceuticals. Associate Professor Samantha Fraser-Bell and Dr Hemal Mehta have received research grants and honoraria from Allergan, Bayer HealthCare Pharmaceuticals and Novartis Pharmaceuticals. The other authors have no financial or proprietary interest in any product mentioned.

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The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Clarification of the inclusion criteria

We identified a number of studies with follow-up less than 6 months. We excluded these studies.

Additional methods

We imputed standard deviations by using the largest reported standard deviation from the other included studies.

We conducted a sensitivity analyses on the primary outcome (mean change in best corrected visual acuity) at one year to determine the impact of excluding studies with missing data and high risk of bias.

Methods not used

We planned to conduct sensitivity analyses to determine the impact of excluding studies with unlicensed medications to identify whether newer licensed drugs are more efficacious. This was not possible as only one study used licensed anti-vascular endothelial growth factors (VEGF) drugs. Similarly planned sensitivity analyses excluding industry funded studies were not possible.

It was not possible to fully evaluate reporting bias due to having only six included studies where 10 is considered a minimum to produce informative funnel plots (see *Cochrane Handbook for Systematic Reviews of Interventions*, 10.4.3.1; Higgins 2011).

There was not sufficient data at participant level in the included studies to assess for clustered data in trials with a paired design. We considered paired versus studies with only one eye per participant as a source of heterogeneity but all included studies reporting the primary outcome at one year had the possibility of both eyes being enrolled.

We planned to measure adverse events as counts and rates but due to the limited number of adverse events and the way in which they were reported, we instead analysed them as dichotomous data.

We planned subgroup analyses to investigate for clinical heterogeneity. We considered clinical sources of heterogeneity including the type of diabetes, baseline visual acuity, baseline central macular thickness (CMT), and duration of diabetic macular oedema (DMO). When parameters were available, we planned to stratify data according to baseline visual acuity worse than 6/24 Snellen equivalent (55 LogMAR letters), baseline CMT as measured by optical coherence tomography (OCT) greater than 400 µm, type 1 or 2 diabetes, and duration of DMO greater than three years at study entry. We planned these subgroup analyses only for the primary review outcome. There were insufficient data in included studies to perform the planned subgroup analyses.

INDEX TERMS

Medical Subject Headings (MeSH)

Bevacizumab [*therapeutic use]; Dexamethasone [*therapeutic use]; Diabetic Retinopathy [*drug therapy] [etiology] [surgery]; Drug Therapy, Combination [methods]; Glucocorticoids [*therapeutic use]; Intraocular Pressure; Intravitreal Injections; Macula Lutea [drug effects]; Macular Edema [*drug therapy] [etiology] [surgery]; Randomized Controlled Trials as Topic; Ranibizumab [*therapeutic use]; Receptors, Vascular Endothelial Growth Factor [antagonists & inhibitors]; Triamcinolone [*therapeutic use]; Vascular Endothelial Growth Factor A [*antagonists & inhibitors]; Visual Acuity [drug effects]

MeSH check words

Humans