Current treatments in diabetic macular oedema: systematic review and meta-analysis

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ABSTRACT

Objectives: The aim of this systematic review is to appraise the evidence for the use of anti-VEGF drugs and steroids in diabetic macular oedema (DMO) as assessed by changes in best corrected visual acuity (BCVA), central macular thickness and adverse events.

Data source: MEDLINE, EMBASE, Web of Science with Conference Proceedings and the Cochrane Library (inception to July 2012). Certain conference abstracts and drug regulatory site web sites were also searched.

Study eligibility criteria, participants and interventions: Randomised controlled trials were used to assess clinical effectiveness and observational trials were used for safety. Trials which assessed triamcinolone, dexamethasone, fluocinolone, bevacizumab, ranibizumab, pegaptanib or aflibercept in patients with DMO were included.

Study appraisal and synthesis methods: Risk of bias was assessed using the Cochrane risk of bias tool. Study results are narratively described and, where appropriate, data were pooled using random effects meta-analysis.

Results: Anti-VEGF drugs are effective compared to both laser and placebo and seem to be more effective than steroids in improving BCVA. They have been shown to be safe in the short term but require frequent injections. Studies assessing steroids (triamcinolone, dexamethasone and fluocinolone) have reported mixed results when compared with laser or placebo. Steroids have been associated with increased incidence of cataracts and intraocular pressure rise but require fewer injections, especially when steroid implants are used.

Limitations: The quality of included studies varied considerably. Five of 14 meta-analyses had moderate or high statistical heterogeneity.

Conclusions and implications of key findings: The anti-VEGFs ranibizumab and bevacizumab have consistently shown good clinical effectiveness without major unwanted side effects. Steroid results have been mixed and are usually associated with cataract formation and IOP increase.

ARTICLE SUMMARY

Article focus

- To review the evidence for triamcinolone, dexamethasone, fluocinolone, bevacizumab, ranibizumab, pegaptanib and aflibercept in the treatment of diabetic macular oedema.

Key messages

- The anti-VEGFs ranibizumab and bevacizumab have consistently shown good clinical effectiveness in the short term without major unwanted side effects.
- Steroid results have been mixed and are usually associated with cataract formation and IOP increase.

Strengths and limitations of this study

- A robust, detailed review of the literature has been undertaken and, when appropriate, data have been combined in meta-analysis.
- The quality of studies included varied considerably.

INTRODUCTION

Diabetic macular oedema (DMO) is a complication of diabetic retinopathy and a leading cause of blindness. The prevalence of DMO is likely to increase with more people suffering from diabetes.1 Increasing DMO has significant implications for patients, healthcare providers and wider society. Laser has been the mainstay of treatment, but recently antivasular endothelial growth factor (anti-VEGF) drugs and steroids have been introduced as potential alternatives to laser photoocoagulation.

Burden of disease

Diabetic retinopathy is present at the time of diagnosis of diabetes mellitus in 0–30% of individuals.3 The incidence is estimated to be 2.3/100 person-years for the overall diabetic population and 4.5 for patients on insulin therapy.3 There is good evidence that progression to DMO is associated with...
duration of disease,6–7 poor glycaemic control8 and, in type 2 diabetes, the need for insulin,9 though the need for insulin therapy is more a marker for duration and poor control.

The number of people with DMO is likely to increase as diabetes becomes more common. Some reports have suggested a decrease in progression to severe visual loss between 1975–1985 and 1986–2008 in a combined population of types 1 and 2.10 Regular screening for retinopathy and better glycaemic control are thought to have reduced the progression to severe visual loss. Diabetic retinopathy is associated with a reduced quality of life. Compared with all diabetic complications, blindness was perceived to be the third worst health state after a major stroke and amputation.11

In the USA, the presence of DMO at diagnosis is associated with 29% additional costs within the first 3 years compared with individuals without retinopathy at diagnosis.12 In 2010, the estimated healthcare costs for DMO in England were £92 million, with £65.6 million being spent on hospital treatment and related costs.13

Visual impairment results in increased welfare costs, early retirement and costs of home help and carers.14 In England in 2010 (total population 52.23 million), the estimated population with diabetes was 2.34 million; the above social costs were estimated to be £11.6 million for DMO.15

Overview of pathophysiology
DMO is caused mainly by disruption of the blood-retinal barrier. The complex pathway that leads to this disruption has been previously described in this journal.15 Sustained hyperglycaemia causes a multifactorial cascade of physiological processes, involving increased permeability, cytokine activation, altered blood flow, hypoxia and inflammation. Vascular endothelial growth factor-A (VEGF-A) is a major contributor to the inflammatory process and, in particular, to angiogenesis and permeability.16 Hypoxia caused by microvascular disease stimulates the release of VEGF-A to aid perfusion. There are six major isoforms of VEGF-A: 121, 145, 165, 183, 189 and 206. In addition to causing widespread microvascular injury, there is now evidence that hyperglycaemia results in preceding neuronal dysfunction, which may contribute to visual loss.17

Overview of current treatments
Laser photocoagulation has been the mainstay of treatment for DMO. The landmark Diabetic Retinopathy Study18 and the Early Treatment Diabetic Retinopathy Study (ETDRS)19 20 demonstrated its clinical effectiveness. However, although laser photocoagulation was clearly effective in preserving vision, it was less successful in restoring it, once lost. Furthermore, patients with perifoveal ischaemia are not amenable to this form of therapy. In ETDRS, although laser was shown to reduce the risk of moderate visual loss (a loss of three ETDRS lines) by 50%, visual acuity improved in only 3% of patients.20 However, in some recent trials, laser has improved the proportion of patients with more than or equal to 10 letters by 7–31%.21–24 In addition, laser is not without side effects. Foveal burns, visual field defects, retinal fibrosis and laser scars have been reported.25 Over the following decade it became apparent that certain patients suffered severe visual loss despite aggressive treatment.26

Steroids and anti-VEGF drugs are newer treatments in DMO. Intravitreal corticosteroids have potent anti-inflammatory effects. Triamcinolone (Kenalog) is not licensed for eye use but has been used to treat DMO for over 10 years. Triamcinolone (Trivaris), recently, was licensed for eye use. The development of intravitreal implants has allowed sustained release formulations. Fluocinolone acetonide (Fluivien, Alimera Sciences) and dexamethasone (Ozudex, Allergan) are implants that have been introduced recently.

Anti-VEGF agents have shown efficacy compared with laser. Bevacizumab (Avastin, Genentech/Roche) is a monoclonal antibody that targets all VEGF isoforms. Although being developed for colorectal cancer, it is widely used off-label, as an intravitreal treatment for macular oedema of different aetiologies. Ranibizumab (Lucentis, Genentech/Roche) is a fragment of the bevacizumab antibody (molecular weight of ranibizumab 48.4 KDa compared with 149 KDa for bevacizumab). It was designed specifically for use in the eye. Ranibizumab is considerably more expensive than bevacizumab (the estimated cost of ranibizumab is $2000/dose compared with $50 for bevacizumab).27 Pegaptanib (Macugen, Eyetech Pharmaceuticals/Pfizer) is a PEGylated aptamer, with a high affinity to the VEGF isoform 165, and was approved for the treatment of exudative AMD in 2004. Affibercept (Regeneron/Bayer HealthCare) is a recent addition to the anti-VEGF class that targets all forms of VEGF-A and placental growth factor.

Aim of the review
The aim of this review is to provide clinicians with an up-to-date overview of current intraocular drug treatments for DMO. It is hoped that the information contained herein will assist clinicians to present their patients with the best evidence supporting each treatment, including possible complications. In addition, this review may be helpful to policy makers. The review focuses on the current evidence for the use of anti-VEGF drugs and steroids to treat DMO, as assessed by change in best corrected visual acuity (BCVA) (mean and proportion with more than two lines improvement), central macular thickness (CMT), as determined by optical coherence tomography (OCT), and their adverse events.

EVIDENCE ACQUISITION
A systematic literature search was performed. The databases searched included MEDLINE, EMBASE, Web of Science with Conference Proceedings and the Cochrane
Library. The dates searched were from the inception of each database until July 2012.

The search terms combined the following key words: ranibizumab or lucentis or bevacizumab or avastin or pegaptanib or macugen or aflibercept or vegf trap-eye or steroid* or corticosteroid* or dexamethasone or fluocinolone or triamcinolone or anti-VEGF* or anti-vascular endothelial growth factor*

AND

DMO or diabetic macular edema or diabetic retinopathy or diabetic maculopathy

AND

(masked or sham or placebo OR control group or random*) OR (systematic review or meta-analysis) OR (risk or safety or adverse or harm or pharmacovigilance or side-effect* or precaution* or warning* or contraindication* or contra-indication* or tolerability or toxic)

The meeting abstracts of the Association for Research in Vision and Ophthalmology, the American Diabetes Association (2002–2012) and the European Association for the Study of Diabetes were searched from 2002 to 2012.

In addition, the web sites of the European Medicines Agency and the US Food and Drug Association were searched for data on registration status and safety. Clinicaltrials.gov and the EU Clinical Trials Register were searched in July 2012 for data on ongoing research.

Full details of the searches are shown in appendix 1.

Randomised controlled trials (RCT) were used to evaluate clinical effectiveness. Safety was assessed through both RCTs and observational studies.

RCTs were included provided that they (1) addressed the use of triamcinolone, dexamethasone, fluocinolone, bevacizumab, ranibizumab, pegaptanib or aflibercept in patients with DMO, (2) had a minimum follow-up of 6 months and (3) had a minimum of 25 eyes per study arm. Studies were excluded if they (1) evaluated laser only, (2) assessed the effect of the aforementioned treatments in macular oedema due to other retinal diseases (instead of DMO), (3) used only a single dose, (4) were combined with a surgical intervention or (5) published studies in languages other than English. There were no exclusions based on drug dose. Trials were excluded if they evaluated combined drug treatment with surgery or systemic treatment.

Search results were screened by two independent authors (JF and PR/DS). Data were extracted by one author (CC) and checked by a second (JF). Data extracted included inclusion/exclusion criteria, baseline demographics, BCVA expressed as a change in logMAR/ETDRS letters or proportion of participants with more than two or three lines BCVA improvement, CMT and adverse events. Risk of bias was assessed using the Cochrane risk of bias tool.

Studies were assessed for similarity in study population, interventions (dose and frequency), outcomes and time to follow-up, with a view to including similar studies in a meta-analysis. Conference abstracts were excluded from the meta-analysis because their quality and detailed methodology were not clear. A difference of 6 months was allowed between study follow-ups because of the potential heterogeneity from disease progression and differences in the number of doses prescribed. If salient data were not reported, such as SDs, data were sought by personal communication with authors. Data were analysed using Review Manager software. If data from multiple time-points were available, the primary end-point data were used. Data were entered by one author (JF) and double-checked by a second (DS). Mean differences were calculated for change in BCVA and CMT and ORs were calculated for proportion of participants with more than two lines improvement. The 95% CIs were calculated for all outcomes. Statistical heterogeneity was measured through $I^2$ scores. A score of less than 30% was considered as low heterogeneity, a score of more than 70% was considered as high heterogeneity and scores between 30% and 70% were considered as moderate. A random effects model was used throughout. The random effects model assumes variability between studies and therefore models uncertainty into the meta-analysis. Fixed assumes no variability. Generally speaking, the random effects model results in wider CIs.

RESULTS

The literature search identified 430 unique articles for possible inclusion, as shown in figure 1. In total, 328 articles were excluded on the basis of title and abstract, leaving 102 full papers to be read. Fifty-one of these articles were excluded; the reasons for their exclusion are summarised in table 1. Fifty-one articles from 29 studies met the inclusion criteria and were included in the review; these are described in tables 3–16. Seven studies were suitable for meta-analysis.

Study quality

The quality of the included studies was, in general, good as is shown in table 2. (Note that the meeting abstracts were not quality assessed, owing to the lack of details reported on the methods.) Most studies adequately described sequence generation, except in three studies where it was unclear.29–30 However, allocation concealment was poorly described throughout, with only eight reports addressing this issue appropriately.31–38 Reporting of masking also varied. A number of studies masked patients using sham injection or sham laser.21 24 29 31 33 36 38 39 40 Various studies reported that masking of patients was impossible. Assessors, where it was unclear.28
Intravitreal anti-VEGFs

The characteristics of all published studies including design, inclusion/exclusion criteria, intervention, outcomes and their timing are shown in tables 3–8. Safety data for each drug are shown in tables 9–16.

Ranibizumab

Nine RCTs have evaluated ranibizumab as a potential new treatment for patients with DMO (tables 3 and 8); seven were sponsored by industry, and two were led by independent investigators (table 7). READ-2 was the first large RCT (n=126). It compared ranibizumab (0.5 mg) alone, ranibizumab in combination with laser and laser alone. At 6 months, BCVA had improved significantly in the ranibizumab alone group compared with laser alone or ranibizumab plus laser. Addition of laser to ranibizumab did not provide additional BCVA gain. REVEAL (n=396) compared ranibizumab (0.5 mg) with ranibizumab plus laser and laser alone. At 12 months, both ranibizumab arms resulted in a statistically significantly better improvement in BCVA compared to laser alone. The addition of laser did not confer further benefit.

Within the past 2 years, the results of RESOLVE, RESTORE, and RISE and RIDE have been published in peer-reviewed journals. RESTORE (n=345) randomised similar groups as the READ-2 study (ranibizumab (0.5 mg) alone, laser alone and ranibizumab plus laser); outcomes were evaluated at 12 months. Ranibizumab improved mean BCVA, with laser providing no additional benefit. Two-year extended follow-up suggested that these results continued. RESOLVE (n=151) compared two doses of ranibizumab (0.5 and 0.5 mg) with sham injection. The greatest improvement in BCVA at 12 months was in the 0.5 mg group (11.8 letter gain) compared to the 0.5 mg group (8.8 letter gain) or sham injection (1.4 letter loss). In this study, rescue laser was

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**Figure 1** PRISMA flow diagram.
allowed after 3 months of treatment, if BCVA had decreased by 10 letters or more, or if the investigator considered the macula not to be flat as assessed by OCT. Only 4.9% of the ranibizumab group required rescue laser, compared with 34.7% in the sham injection group.

READ-2 and RESTORE were suitable for pooling through meta-analysis and, when doing so, it was found that ranibizumab statistically significantly improved mean BCVA compared with laser (figure 2). In regard to the proportion of patients gaining more than or equal to 15 letters, individual trials showed a statistically significant difference between laser and ranibizumab but when these two trials were pooled using a random effects model, the result was no longer statistically significant. When a fixed effects model was used, the result was statistically significant (figure not shown). Adding laser to ranibizumab did not add any significant benefit (figure 3). In fact, the mean change in BCVA and the proportion of patients with more than 15 letter gain favoured, although not statistically significantly so, ranibizumab alone compared with ranibizumab plus laser. This was probably a chance effect.

RISE (n=577) and RIDE (n=382) were identical in design. The study arms are similar to those in the RESOLVE study, 0.3 or 0.5 mg ranibizumab compared with sham. In the RISE study, the proportion of patients with 15 or more letter gain was greatest in the 0.3 mg group at 24 months, whereas in the RIDE study this was greatest in the 0.5 mg group. In the DRCRN trial (n=854), Elman and colleagues compared ranibizumab (0.5 mg) plus prompt (within 3–10 days post ranibizumab) or deferred (≥24 weeks) laser with sham injection plus prompt laser, or triamcinolone (4 mg, Trivaris) plus prompt laser (table 8). At 1 year, both ranibizumab groups reported greater gains in mean BCVA change than triamcinolone or laser alone. Interestingly, at 2 years (n=628), the proportion of patients with 10 or more letter gain was not statistically significantly different between ranibizumab plus prompt laser and laser alone groups, but was statistically significant in the ranibizumab plus deferred laser compared with laser alone comparison. The reason for this is not clear.

READ-3 (n=152) has been published in abstract form and compared monthly injections of intravitreal ranibizumab high dose (2.0 mg) and low dose (0.5 mg). At 6 months, there was no statistically significant difference in BCVA between groups.

One study (n=63), published in abstract form, was identified which directly compared monthly injections of ranibizumab (0.5 mg) with bevacizumab (1.5 mg). At 48 weeks, the authors found no statistically significant difference between bevacizumab and ranibizumab.

RESTORE, READ-2 and DRCRN (12 month data used) were suitable for pooling through meta-analysis to compare ranibizumab plus laser and laser alone (figure 4). Ranibizumab plus laser resulted in a statistically significantly greater change in mean BCVA, proportion of patients with more than 15 letter gain and CMT reduction versus laser alone.

**Table 1** List of excluded studies

| Study                | Reason                       | Study Reason                                      |
|----------------------|------------------------------|---------------------------------------------------|
| Active comparator trials | Single dose                 | et al[77] PDR, RVO, retinal vein occlusion.       |
| DRCRN 2010           | <6 months f/u                | Ischemic optic neuropathy, deferred treatment     |
| Faghihi et al[69]    | Single dose                  | bevacizumab, laser, compared with study           |
| Figueiroa 2004       | Single dose                  | DCRN—Scott et al[100]                             |
| Isaac et al[51]      | Single dose                  | Non-RTT                                          |
| Paccola et al[22]    | Single dose                  | Non-RCT                                          |
| Prager et al[63]     | <25 pts per arm              | Non-RCT                                          |
| Ozturk et al[44]     | Non-RCT                      | Non-RCT                                          |
| Shahin and El-Lakkany[96] | <6 months                  | Single dose                                      |
| Pegaptanib           | Quality of life data         |                                                   |
| Ferrone and Jonisch[98] | <25 pts per arm             |                                                   |
| Dexamethasone        | Study protocol               |                                                   |
| Avitable[104]        | Mixed RVO and DMO            |                                                   |
| Bandello et al[105]  | Case report-PDR              |                                                   |
| Bonini et al[106]    | Single dose injection technique |                                           |
| Cellini et al[107]   | Single injection PSTI        |                                                   |
| Cardillo et al[108]  | Single injection PSTI        |                                                   |
| Chung et al[109]     | Single injection PSTI        |                                                   |
| Dehghan et al[110]   | Single dose                  |                                                   |
| DRCRN—Chew et al[111]| <25 pts per arm              |                                                   |
| Gli et al[112]       | <25 pts per arm              |                                                   |
| Entezari et al[113]  | <6 months                    |                                                   |
| Hauser et al[114]    | Single dose                  |                                                   |
| Jonas et al[115]     | Single dose                  |                                                   |
| Joussen et al[116]   | Study protocol               |                                                   |
| Avci and Kaderli[117]| Anaesthetic technique        |                                                   |
| Kang et al[118]      | Single dose                  |                                                   |
| Kim et al[119]       | Single injection and CME     |                                                   |
| Lam et al[120]       | Single injection             |                                                   |
| Lee[121]             | Single injection             |                                                   |
| Maia et al[122]      | Single dose                  |                                                   |
| Massin et al[123]    | Single dose                  |                                                   |
| Mohamed et al[24]    | Post hoc analysis            |                                                   |
| Nakamura et al[25]   | Single dose                  |                                                   |
| Spandau et al[126]   | Single dose                  |                                                   |
| Tunc[127]            | <6 months                    |                                                   |
| Verma et al[128]     | Single dose                  |                                                   |
| Wickremasinghe et al[29]| Single dose         |                                                   |
| Yalcinbayir et al[30]| Single dose                  |                                                   |
| Dexamethasone        | <6 months                    |                                                   |
| Haller et al[31]     | <25 pts per arm              |                                                   |
| Kuppermann et al[133]| Mixture of macular oedema causes |                                             |
| Boyer et al[134]     | Non-randomised               |                                                   |
| Fluocinolone         | <35 pts per arm              |                                                   |
| Campochiaro and et al[36]| Single dose       |                                                   |
| Diclofenac           | <35 pts per arm              |                                                   |

CME, cystoid macular edema; DMO, diabetic macular oedema; PDR, proliferative diabetic retinopathy; PSTI, posterior subtenon injection; RVO, retinal vein occlusion.
Table 2  Study quality

| Study (author and year) | Adequate sequence generation | Allocation concealment | Masking | Incomplete outcome data addressed | Free of selective reporting | Free of other bias (eg, similarity at baseline, power assessment) | Funder |
|-------------------------|------------------------------|------------------------|---------|----------------------------------|----------------------------|---------------------------------------------------------------|--------|
| Anti-VEGFs              |                              |                        |         |                                  |                            |                                                               |        |
| Ranibizumab             |                              |                        |         |                                  |                            |                                                               |        |
| READ-2 Study            | Unclear                      | Unclear                | Unclear | Yes (91.3% completion)           | Yes                        | Comparison groups similar at baseline; power analysis not mentioned | Juvenile Diabetes Research Foundation, Genentech Inc |
| RESOLVE Study (Massin et al) | Yes                  | Yes                    | Yes (patients and outcome assessors) | Yes (82% completion in sham arm, 90.2% with ranibizumab) | Yes                        | Comparison groups similar at baseline; power analysis unclear | Novartis Pharma, Switzerland |
| RESTORE Study (Mitchell et al) | Yes                  | Unclear                | Yes (patients, outcome assessors) | Yes (87.3–88.3% completion) | Yes                        | Comparison groups similar at baseline; power analysis carried out (power adequate for VA changes) | Novartis Pharma, Switzerland |
| RISE and RIDE (Nguyen et al) | Yes                  | Yes                    | Yes (patients, treating physician masked to assigned dose of ranibizumab) | Yes (2 year study completed by 83.3% of patients in RISE and by 84.6% in RIDE) | Yes                        | Comparison groups similar at baseline; ITT analysis; power analysis carried out (power adequate for primary endpoint) | Genentech Inc |
| Bevacizumab             |                              |                        |         |                                  |                            |                                                               |        |
| BOLT Study (Michaelides et al) | Yes                  | Unclear                | Partial (outcome assessors, not patients) | Yes (97.5% completion) | Yes                        | Comparison groups similar at baseline (except laser group had longer duration of clinically significant DMO); power analysis carried out (power adequate for VA changes) | Moorfields Special Trustees, National Institute for Health Research |
| Lam et al               | Yes                          | Unclear                | Yes (patient) | Yes (100% completion)         | Yes                        | Comparable groups at baseline                                | Not specified |
| Faghihi et al           | Yes                          | Unclear                | Yes (patients and technicians assessing BCVA, OCT and IOP) | Yes (92.3% follow-up at 6 months) | Yes                        | Comparison groups similar at baseline; power analysis carried out (power adequate for CMT changes) | Supported in part by the Action for Vision Eye Foundation Hong Kong (charity) |

Continued
| Study (author and year) | Adequate sequence generation | Allocation concealment | Masking | Incomplete outcome data addressed | Free of selective reporting | Free of other bias (eg, similarity at baseline, power assessment) | Funder |
|------------------------|-------------------------------|------------------------|---------|-----------------------------------|---------------------------|---------------------------------------------------------------|--------|
| Pegaptanib             | Yes                           | Unclear                | Yes (patients and outcome assessors) | Yes (95% completion)      | Yes                       | Comparison groups similar at baseline; acknowledge lack of power to detect differences between doses of pegaptanib | Pfizer Inc, New York |
| Cunningham et al       | Yes                           | Unclear                | Yes (patients and outcome assessors) | Yes (69.9–73.8% completion) | Yes                       | Comparison groups similar at baseline; power analysis carried out (power adequate for VA changes) | Eyetech Pharmaceuticals Inc, New York |
| Sultan et al           | Yes                           | Unclear                | Yes (patients and outcome assessors) | Yes (95% completion)      | Yes                       | Comparison groups similar at baseline, power calculation completed | Pfizer Inc, New York |
| Aflibercept            | UNCLEAR (predetermined randomisation scheme) | UNCLEAR | UNCLEAR | YES (PATIENTS) | YES | YES | Comparison groups similar at baseline; power calculation completed | Regeneron Pharmaceuticals, Inc, New York |
| Steroids               | Yes                           | Unclear                | Yes (patients) to dexamethasone dose, outcome assessors | Yes (92% completion)      | Yes                       | Comparison groups similar at baseline; power analysis carried out, but study not powered to detect differences in subgroups | Oculex Pharmaceuticals Inc |
| Fluocinolone           | UNCLEAR (masking of outcome assessment not mentioned) | UNCLEAR | UNCLEAR | YES (DROP-OUT RATE 19.0–22.7%) | YES | YES | Comparison groups similar at baseline; power analysis not mentioned | Alimera Sciences Inc, Atlanta, Georgia; Psivida Inc, Watertown, Massachusetts; Bausch & Lomb Inc, Rochester, New York |
| Pearson et al          | Yes                           | Unclear                | Third party masked design (patient and investigator not masked) | No losses to follow-up | Yes | YES | Demographic characteristics were similar between implant and SOC groups; power calculation done, study adequately powered | Alimera Sciences Inc, Atlanta, Georgia; Psivida Inc, Watertown, Massachusetts; Bausch & Lomb Inc, Rochester, New York |
| FAME Study (Campochiaro et al) | UNCLEAR | UNCLEAR | Partial (patients, masking of outcome assessment not mentioned) | YES | YES | YES | Comparison groups similar at baseline; power analysis not mentioned | Alimera Sciences Inc, Atlanta, Georgia; Psivida Inc, Watertown, Massachusetts; Bausch & Lomb Inc, Rochester, New York |
|                        |                               |                        |         |                                   |                           |                                                               |        |
| Study (author and year) | Adequate sequence generation | Allocation concealment | Masking | Incomplete outcome data addressed | Free of selective reporting | Free of other bias (eg, similarity at baseline, power assessment) | Funder |
|------------------------|-------------------------------|------------------------|---------|---------------------------------|--------------------------|------------------------------------------------------------------|---------|
| Triamcinolone DRCR Network 2008 | Yes | Unclear | Partial (patients to triamcinolone dose, outcome assessors not formally masked but generally not aware of participant’s study group) | Yes (81–86% completion) | Yes | Comparison groups similar at baseline; power analysis carried out (power adequate for VA changes) | Cooperative agreement from the National Eye Institute, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services |
| Gillies et al Sutter et al | Yes | Yes | Yes (patients, outcome assessors) | Yes (91% completion intervention, 83% control) | Yes | Comparison groups similar at baseline (but limited demographic data); power analysis carried out (power adequate for VA changes) | Sydney Eye Hospital Foundation and Juvenile Diabetes Research Foundation, New York |
| Gillies et al | Yes | Yes | Yes (patients, outcome assessors) | Yes (84.5% completion) | Yes | Power analysis carried out (power adequate for VA changes) | National Health and Medical Research Council, Canberra, Australia, and the Sydney Eye Hospital Foundation Sydney, Australia |
| Lam et al | Yes | Yes | Partial (outcome assessors) | No losses to follow-up | Yes | Comparison groups similar at baseline; power analysis carried out (power adequate for CMT changes) | Action for Vision Foundation, Hong Kong |
| Ockrim et al Sivaprasad et al | Yes | Unclear | Unclear | Yes (94% completion) | Yes | Comparison groups similar at baseline; power analysis carried out (power adequate for VA changes) | Special Trustees of Moorfields Eye Hospital |
| Study (author and year) | Adequate sequence generation | Allocation concealment | Masking | Incomplete outcome data addressed | Free of selective reporting | Free of other bias (eg, similarity at baseline, power assessment) | Funder |
|-------------------------|------------------------------|-----------------------|---------|----------------------------------|---------------------------|---------------------------------------------------------------|---------|
| **Active comparator trials** |                             |                       |         |                                  |                           |                                                              |         |
| Ahmadieh et al<sup>31</sup> | Yes                          | Yes                   | Yes (patients and outcome assessors) | Unclear                      | Yes                       | CMT lower in control group at baseline (p<0.05), other baseline values similar; power analysis carried out (power adequate for CMT changes) | Not reported |
| DRCR Network<sup>21 46</sup> | Yes                          | Unclear               | Yes (patients, except deferred laser group; outcome assessors); masking discontinued after the first year | Yes (1 year completion for 91–95% of eyes) | Yes                       | Comparison groups similar at baseline; power analysis carried out (power adequate for VA changes) | Cooperative agreement from the National Eye Institute, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health and Human Services; Ranibizumab provided by Genentech, triamcinolone provided by Allergan Inc; companies also provided funds to defray the study's clinical site costs |
| Lim et al<sup>55</sup> | Yes                          | Unclear               | Yes (investigators only) | Yes (7.5% drop out after enrolment) | Yes                       | Groups similar at baseline. The bevacizumab group received more injections | Not reported |
| Soheilian et al<sup>37 41</sup> | Yes                          | Yes                   | Yes (patients and outcome assessors) | Unclear (36 week completion for 76–88%) | Yes                       | CMT significantly lower and VA significantly better in MPC group at baseline, other baseline values similar; power analysis carried out (power adequate for VA changes) | Ophthalmic Research Centre, Labbafinejad Medical Center, Tehran |

MPC, macular photocoagulation.
### Table 3 Ranibizumab trials

| Study                | Participants and baseline values                                                                 | Intervention                                                                                       | Outcome (change from baseline at study end)                                                                 |
|---------------------|--------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|
| **READ-2 Study (Nguyen et al) USA** | **N: 126 eyes of 126 patients**<br>**Inclusion criteria:** ≥18 years, type 1 or 2 DM, DMO, BCVA 20/40-20/320, CMT ≥250 µm, HbA1c ≥6% within 12 months before randomisation; expectation that scatter laser photoagulation not required for 6 months<br>**Exclusion criteria:** contributing causes to reduced BCVA other than DMO, focal/grid laser within 3 months, intraocular steroid within 3 months, intraocular VEGF antagonist within 2 months<br>**Age:** 62 years<br>**Sex:** 52–69% female<br>**Diabetes type:** not reported<br>**HbA1c:** 7.39–7.77%<br>**Baseline VA:** ETDRS letter score 24.85–28.35<br>**Baseline CMT:** excess foveal thickness 198.75–262.52 µm<br>**Comorbidities:** not reported | **Group 1 (IVR, n=42 eyes): IV injections of 0.5 mg ranibizumab at baseline, 1, 3 and 5 months**<br>**Group 2 (L, n=42 eyes): focal/grid laser at baseline and 3 months if CMT ≥250 µm**<br>**Group 3 (IVRL, n=42 eyes): IV injections of 0.5 mg ranibizumab at baseline and 3 months, followed by focal/grid laser treatment 1 week later**<br>**Regimen for all groups:** after 6 months, patients could receive IV injections of ranibizumab no more than every 2 months or focal/grid laser no more than every 3 months if CMT ≥250 µm<br>**Laser Modified ETDRS protocol was used** | **At 6 months**<br>**BCVA (ETDRS): BCVA (letters) p Value**<br>**IVR** +7.24 0.0003 vs L<br>**L** −0.43 NS vs IVR or L<br>**IVRL** +3.80 0.0003 vs L<br>**Plus ≥3 lines**<br>**IVR** 22% <0.05 vs L<br>**L** 0 NS vs IVR or L<br>**IVRL** 8% <0.05 vs L | **At 6 months:**<br>**BCVA (mean BCVA letters gain) p Value**<br>**IVR2.0** +7.46 NR<br>**IVR0.5** +8.69 NR<br>**CST** −163.86 µm NR<br>**CST reduction** −169.27 µm NR<br>**Group 1 (IVR, n=42 eyes): monthly injections**<br>**Group 2 (IVR0.5, n=NR): monthly injections**<br>**After month 6, eyes evaluated and additional ranibizumab injections given on an as needed basis if DMO still present on OCT.**<br>**Baseline CST (central subfield thickness): 432 µm in the 2.0 mg group and 441 µm in the 0.5 mg group<br>**Comorbidities:** NR | **At 6 months:**<br>**BCVA (mean BCVA letters gain) p Value**<br>**IVR2.0** +7.46 NR<br>**IVR0.5** +8.69 NR<br>**CST** −163.86 µm NR<br>**CST reduction** −169.27 µm NR |

**READ-3 Study (Do et al) USA**<br>**Design:** phase 2, 2-arm RCT<br>**Follow-up:** 6 months
| Study                        | Participants and baseline values | Intervention                                                                 | Outcome (change from baseline at study end) |
|------------------------------|----------------------------------|-------------------------------------------------------------------------------|---------------------------------------------|
| RESOLVE Study (Massin et al)  | N: 151 eyes of 151 patients       | **Group 1 (IVR0.3, n=51 eyes):** 0.3 mg (0.05 ml) IV ranibizumab, 3 monthly injections (dose up to 0.6 mg, see below) | **At 12 months:** BCVA (ETDRS):              |
| Multicenter international    | Inclusion criteria: >18 years, type 1 or 2 DM, clinically significant DMO, BCVA 20/40–20/160, HbA1c <12%, decreased vision attributed to foveal thickening from DMO, laser photocoagulation could be safely withheld in the study eye for at least 3 months after randomisation | **Group 2 (IVR0.5, n=51 eyes):** 0.5 mg IV (0.05 ml) ranibizumab, 3 monthly injections (dose up to 1.0 mg, see below) | BCVA (letters)  p Value |
| **Design:** 3-arm placebo-controlled RCT | Exclusion criteria: unstable medical status, panretinal laser photocoagulation performed within 6 months before study entry, previous grid/laser photocoagulation except patients with only mild laser burns at least 1000 µm from the centre of the fovea performed >6 months previously | **Group 3 (C, n=49 eyes):** sham treatment, 3 monthly injections | **IVR0.3:** Gain 72.5% loss 0 <0.0001 vs C |
| **Follow-up:** 12 months     | Age: 63–65 (range 32–85) years   | **Regimen for all groups:** after month 1, the injection dose could be doubled if CMT remained >300 µm or was >225 µm and reduction in retinal oedema from previous assessment was <50 µm; once injection volume was 0.1 ml it remained that for subsequent injections; if treatment had been withheld for >45 days, subsequent injections restarted at 0.05 ml; 68.6% of dose doubling with ranibizumab, 91.8% with sham; 34.7% of rescue laser photocoagulation in sham group, 4.9% in ranibizumab group | **IVR0.5:** Gain 49% loss 9.8% 0.001 vs C |
|                             | Sex: 43.1–49% female             |                                                                              | **C:** Gain 18.4% loss 24.5%                 |
|                             | Diabetes type: 96.1–98% type 2 DM |                                                                              | **CMT (OCT):** CMT (µm) p Value               |
|                             | HbA1c: 7.3–7.6 (range 5.3–11.1) % |                                                                              | IVR0.3: −200.7 SD122.2 <0.0001 vs C          |
|                             | Baseline VA: ETDRS letter score   |                                                                              | IVR0.5: −187.6 SD147.8 <0.0001 vs C          |
|                             | 59.2–61.2 SD9.0–10.2              |                                                                              | **C:** −48.4 SD153.4                          |
|                             | Baseline CMT: 448.9–459.5         |                                                                              |                                             |
|                             | SD102.8–120.1 µm                  |                                                                              |                                             |
|                             | Comorbidities: not reported       |                                                                              |                                             |
| RESTORE Study (Mitchell et al) | N: 345 eyes of 345 patients       | **Group 1 (IVR, n=116 eyes):** 0.5 mg IV ranibizumab plus sham laser         | **At 12 months:** BCVA (ETDRS):              |
|                             | Inclusion criteria: ≥18 years, type 1 |                                                                              |                                               |
|                             |                                                                                  |                                               |                                               |

Continued
### Table 3: Study Participants and baseline values

| Study                                      | Participants and baseline values                                                                 | Intervention                                                                 | Outcome (change from baseline at study end)        |
|--------------------------------------------|--------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|---------------------------------------------------|
| **Multicenter international**              |                                                                                                  |                                                                              |                                                   |
| **Design:** 3-arm RCT                      |                                                                                                  | (median injections 7 (range 1–12), median sham laser treatments 2 (range 1–5)) |                                                   |
| **Follow-up:** 12 months                   |                                                                                                  | Group 2 (IVRL, n=118 eyes): 0.5 mg IV ranibizumab plus active laser (median injections 7 (range 2–12), median laser treatments 1 (range 1–5)) |                                                   |
| **Exclusion criteria:** concomitant eye conditions that could affect VA, active intraocular inflammation or infection, uncontrolled glaucoma in either eye, panretinal laser photocoagulation within 6 months or focal/grid laser photocoagulation within 3 months prior to study entry, history of stroke, hypertension |                                                                              | Group 3 (L, n=111 eyes): laser treatment plus sham injections (median sham injections 7 (range 1–12), median laser treatments 2 (range 1–4)) |                                                   |
| **Age:** 62.9–64.0 SD8.15–9.29 years       |                                                                              | Regimen for all groups: 3 initial monthly injections, followed by retreatment schedule; 1 injection per month if stable VA not reached; Laser retreatments in accordance with ETDRS guidelines at intervals no shorter than 3 months from previous treatment |                                                   |
| **Sex:** 37.1–47.7% female                 |                                                                              |                                                                              |                                                   |
| **Diabetes type:** 86.4–88.8% type 2 DM    |                                                                              |                                                                              |                                                   |
| **HbA1c:** not reported                     |                                                                              |                                                                              |                                                   |
| **Baseline VA:** ETDRS letter score 62.4–64.8 SD9.99–11.11 |                                                                              | **BCVA (letters)** p Value                                                   |                                                   |
| **Baseline CMT:** 412.4–426.6 µm            |                                                                              | IVR +6.1 SD6.43 <0.0001 vs L                                             |                                                   |
| **Comorbidities:** not reported             |                                                                              | IVRL +5.9 SD7.92 <0.0001 vs L                                             |                                                   |
| **REVEAL Study (Ohji and Ishibashi)**      |                                                                              | L +0.8 SD8.56 BCVA change categories                                       |                                                   |
| **Japan Multicenter**                      |                                                                              | **IVR** Plus ≥10: 37.4% <0.0001 vs L                                       |                                                   |
| **Design:** phase III double-masked RCT    |                                                                              | Loss ≥10: 3.5%                                                             |                                                   |
| **Follow-up:** 12 months                   |                                                                              | IVRL Plus ≥10: 43.2% <0.0001 vs L                                           |                                                   |
| **N:** 396 patients                        |                                                                              | L Plus ≥10: 15.5%                                                          |                                                   |
| **Inclusion criteria:** NR                  |                                                                              | Loss ≥10: 12.7%                                                             |                                                   |
| **Exclusion criteria:** NR                  |                                                                              |                                                                              |                                                   |
| **Age:** 61.1 years                        |                                                                              |                                                                              |                                                   |
| **Sex:** NR                                |                                                                              |                                                                              |                                                   |
| **Diabetes type:** 98.7% with type 2 diabetes |                                                                              |                                                                              |                                                   |
| **HbA1c:** 7.5%                            |                                                                              |                                                                              |                                                   |
| **Baseline VA:** 58.6 letters              |                                                                              |                                                                              |                                                   |
| **Baseline CMT:** 421.9 µm                  |                                                                              |                                                                              |                                                   |
| **Comorbidities:** NR                      |                                                                              |                                                                              |                                                   |

Continued
Table 3 Continued

| Study                                      | Participants and baseline values                                      | Intervention                                                                 | Outcome (change from baseline at study end) |
|--------------------------------------------|----------------------------------------------------------------------|------------------------------------------------------------------------------|---------------------------------------------|
| RISE Study (Brown et al/Nguyen et al)      | N. 377 eyes of 377 patients                                          | Group 1 (IVR0.3, n=125 eyes): 0.3 mg IV ranibizumab                          | At 24 months                                |
| USA Multicenter Design: 3-arm double-blind | Inclusion criteria: ≥18 years, type 1 or 2 diabetes, BCVA 20/40–20/320, DMO CMT ≥275 µm | Group 2 (IVR0.5, n=125 eyes): 0.5 mg IV ranibizumab                          | BCVA:                                       |
| sham-controlled RCT Follow-up: 24 months    | Exclusion criteria: prior vitreoretinal surgery, recent history (within 3 months of screening) of panretinal or macular laser in the study eye, intraocular corticosteroids or antiangiogenic drugs, those with uncontrolled hypertension, uncontrolled diabetes (HbA1c >12%), recent (within 3 months) cerebrovascular accident or myocardial infarction | Group 3 (C, n=127 eyes): sham injection Regimen for all groups: monthly injections; need for macular rescue laser assessed monthly starting at month 3 | Plus ≥15 letters p Value                    |
|                                           | Age: 61.7–62.8 SD8.9–10.0 (range 21–87) years                       |                                                                             | IVR0.3 44.8% <0.0001 vs C                  |
|                                           | Sex: 41.6–48% female                                                 |                                                                             | IVR0.5 39.2% =0.0002 vs C                  |
|                                           | Diabetes type: type 1 or 2                                          |                                                                             | C 18.1%                                     |
|                                           | HbA1c: 7.7% SD 1.4–1.5; ≤8% (65–68.3%); >8% (31.7%–35%)            | Loss of <15 letters                                                         | IVR0.3 97.6% =0.0086 vs C                  |
|                                           | Baseline VA: Mean ETDRS letter score 54.7–57.2; ≤20/200             | Mean BCVA gain (letters)                                                    | IVR0.5 97.6% =0.0126 vs C                  |
|                                           | (7.9–13.6%); >20/200 but <20/40 (72.4–72.8%); ≥20/40 (13.6–19.7%)  |                                                                             | C 37.8%                                     |
|                                           | Baseline CMT: 463.8–474.5 µm                                        | Mean change from baseline p Value                                            |                                             |
|                                           | Comorbidities: History of smoking                                   |                                                                             | CFT:                                       |
|                                           | 46.4–51.2%                                                         | −250.6 SD212.2 <0.0001 vs C                                                 | IVR0.3                                      |
| RIDE study (Boyer et al/Nguyen et al)      | N. 382 eyes                                                         | At 24 months                                | −253.1 SD183.7 <0.0001 vs C                |
| USA Multicentre Design: 3-arm double-blind | Inclusion criteria: ≥18 years, type 1 or 2 diabetes, BCVA 20/40–20/320, and DMO CMT ≥275 µm | Group 2 (IVR0.5, n=127 eyes): 0.5 mg IV ranibizumab                          | −133.4 SD209.0                             |
| sham-controlled RCT Follow-up: 24 months    | Exclusion criteria: prior vitreoretinal surgery, recent history (within 3 months of screening) of panretinal or macular laser in the study eye, intraocular corticosteroids or antiangiogenic drugs, those with uncontrolled hypertension, uncontrolled diabetes (HbA1c >12%), recent (within 3 months) cerebrovascular accident or myocardial infarction | Group 3 (C, n=130 eyes): sham injection Regimen for all groups: Patients | p Value                                     |
|                                           | Age: 56.2–74.5 SD12.4–12.0 (range 21–87) years                     |                                                                             | IVR0.3 33.6% <0.0001 vs C                  |
|                                           | Sex: 40.8% female                                                   |                                                                             | IVR0.5 45.7% <0.0001 vs C                  |
|                                           | Diabetes type: type 1 or 2                                          |                                                                             | C 12.3%                                     |
|                                           | HbA1c: 7.5% SD 1.4–1.5; ≤8% (66.7%); >8% (31.7%–35%)              |                                                                             |                                             |
|                                           | Baseline VA: Mean ETDRS letter score 53.4–56.2; ≤20/200             |                                                                             |                                             |
|                                           | (7.1–12.7%); >20/200 but <20/40 (72.4–72.8%); ≥20/40 (13.6–19.7%)  |                                                                             |                                             |
|                                           | Baseline CMT: 467.2–479.7 µm                                        |                                                                             |                                             |
|                                           | Comorbidities: History of smoking                                   |                                                                             |                                             |
| Study | Participants and baseline values | Intervention | Outcome (change from baseline at study end) |
|-------|---------------------------------|--------------|------------------------------------------|
| panretinal or macular laser in the study eye, intraocular corticosteroids or antiangiogenic drugs, those with uncontrolled hypertension, uncontrolled diabetes (HbA1c >12%), recent (within 3 months) cerebrovascular accident or myocardial infarction | were eligible for rescue macular laser starting at month 3 | IVR0.3 | 1.6% | >0.05 vs C |
| | | IVR0.5 | 3.9% | <0.05 vs C |
| | | C | 8.5% | Snellen equivalent of 20/40 or better |
| Age: 61.8–63.5 (range 22–91) years | | IVR0.3 | 54.4% | =0.0002 vs C |
| Sex: 37–49.1% female | | IVR0.5 | 62.2% | <0.0001 vs C |
| Diabetes type: type 1 or 2 | | C | 34.6% | Mean BCVA gain (letters) |
| HbA1c: 7.6 SD1.3–1.5; ≤8% (65.8–67.5%); >8% (32.5–34.2%) | | IVR0.3 | +10.9 SD10.4 | <0.0001 vs C |
| Baseline VA: Mean ETDRS letter score 56.9–57.5 | | IVR0.5 | +12.0 SD14.9 | <0.0001 vs C |
| Baseline CMT: 447.4–482.6 µm | | C | +2.3 SD14.2 | Mean change from baseline p Value |
| Comorbidities: history of smoking 33.6–51.6% | | IVR0.3 | −259.8 SD169.3 | <0.0001 vs C |
| | | IVR0.5 | −270.7 SD201.6 | <0.0001 vs C |
| | | C | −125.8 SD198.3 | |

Injections are intravitreal unless otherwise noted. BCVA, best corrected visual acuity; C, control; CMT, central macular thickness; CSME, clinically significant macular oedema; DDS, dexamethasone; DIL, dexamethasone followed by laser; DM, diabetes mellitus; DMO, diabetic macular oedema; DP, diastolic pressure; DR, diabetic retinopathy; HR Qol, health-related quality of life; IOP, intraocular pressure; IV, intravitreal; IVB, intravitreal bevacizumab; IVP, intravitreal pegaptanib; IVR, intravitreal ranibizumab; IVT, intravitreal triamcinolone; IVTL, intravitreal triamcinolone plus laser; IVTETE, intravitreal VEGF Trap Eye; L, laser; MLT/MPC, macular laser therapy/macular photoagulation; NEI VFQ-25, National Eye Institute Visual Function Questionnaire-25; NPDR, non-proliferative diabetic retinopathy; NR, not reported; OCT, optical coherence tomography; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation; RCT, randomised controlled trial; SOC, standard of care; SP, systolic pressure; SRFA, fluocinolone; VA, visual acuity; VEGF, vascular endothelial growth factor.
### Table 4  Bevacizumab studies

| Study         | Participants and baseline values | Intervention                                                                 | Outcome (change from baseline at study end) |
|---------------|----------------------------------|-------------------------------------------------------------------------------|---------------------------------------------|
| BOLT Study (Michaelides et al/Rajendram et al)\(^{23}\) | N: 80 eyes of 80 patients        | Group 1 (MLT, n=38 eyes): modified ETDRS macular laser therapy; reviewed every 4 months up to 52 weeks; retreatment performed if clinically indicated by ETDRS guidelines (median 4 laser treatments) | At 24 months BCVA (ETDRS): BCVA, p Value mean (SD) −0.5 (10.6) 0.005 vs MLT +8.6 (9.1) 0.001 vs MLT |
| UK            |                                  | Group 2 (IVB, n=42 eyes): 1.25 mg (0.05 ml) IV bevacizumab at baseline, 6 and 12 weeks; subsequent IVB injections (up to 52 weeks) guided by an OCT-based retreatment protocol (median 13 injections) | BCVA gain categories (letters) gaining ≥10: 7% losing >15: 4% 0.001 vs MLT ≥10: 49% MLT losing >15: 0.004 vs 32% MLT |
| Design: 2-arm RCT | Follow-up: 12 months           | Laser modified ETDRS protocol, retreatment by ETDRS guidelines                | CMT (µm, quartiles) −118 SD171 −146 SD122 MLT |
| Lam et al\(^{95}\) | N: 52 eyes of 52 patients        | Group 1 (IVB1.25, n=26 eyes): 1.25 mg bevacizumab (0.05 ml)                  | At 6 months BCVA (ETDRS chart): |
| Hong Kong     |                                  | Group 2 (IVB2.5, n=26 eyes): 2.5 mg bevacizumab (0.1 ml)                     | BCVA (ETDRS chart): |
| Design: 2-arm RCT |                                |                                                                             | BCVA gain categories (letters) gaining ≥10: 88% phakic ≤10: 5% phakic 0.62 vs MLT |

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*Note: ETDRS = Early Treatment Diabetic Retinopathy Study, DMO = diabetic macular oedema, BCVA = best-corrected visual acuity, OCT = optical coherence tomography, MLT = macular laser therapy, IVB = intravitreal bevacizumab.*
Table 4

| Study | Participants and baseline values | Intervention | Outcome (change from baseline at study end) |
|-------|---------------------------------|--------------|---------------------------------------------|
| Follow-up: 6 months | angiography, CMT ≥250 µm on OCT), BCVA ≥1.3 ETDRS logMAR units; only patients with diffuse DMO recruited | Regimen for all groups: 3 monthly IV injections, topical 0.5% levofloxacin 4×/day for up to 2 weeks after each injection | BCVA (logMAR) |
| | Exclusion criteria: macular oedema due to reasons other than diabetes, significant media opacities, macular ischemia of ≥1 disk area, vitreomacular traction, PDR, aphakia, glaucoma or ocular hypertension, previous anti-VEGF treatment, intraocular surgery except uncomplicated cataract extraction (but > 6 months prior), focal DMO, any laser procedure within previous 4 months, subtenon or intravitreal triamcinolone injection within 6 months, pregnancy | IVB1.25 | 0.11 SD0.31 (+5.5 letters) |
| | Age: 65.3 SD8.9 years | IBV2.5 | 0.13 SD0.26 (+6.5 letters) |
| | Sex: 46.2% female | | baseline |
| | Baseline HbA1c: 7.5 SD1% | | baseline |
| | Baseline VA: 0.61 SD0.29 logMAR | | baseline |
| | Baseline CMT: 466 SD127 µm | | baseline |
| | Comorbidities: not reported | | baseline |
| | Subgroups: | | baseline |
| | ▶ For patients with previous DMO treatment (mainly laser): no significant reduction in CMT at 6 months (452 µm at baseline to 416 µm at 6 months, p=0.22); no significant improvement in BCVA (0.66 logMAR at baseline to 0.56 logMAR at 6 months (+5 letters), p=0.074) | |

Ford JA, Lois N, Royle P, et al. BMJ Open 2013;3:e002269. doi:10.1136/bmjopen-2012-002269

Continued
| Study | Participants and baseline values | Intervention | Outcome (change from baseline at study end) |
|-------|----------------------------------|--------------|--------------------------------------------|
| Faghihi et al | | Group 1 (IVB, n=40 eyes): 1.25 mg bevacizumab | At 6 months Mean change in BCVA (ETDRS chart): |
| Iran | | Group 2 (IVB+MPC, n=40 eyes): 1.25 mg bevacizumab | BCVA (logMAR) p Value |
| Design: 2-arm RCT | |Regimen for all groups: Eyes examined every 2 months and if evidence of CSME IVB was injected. Mean of the number of IVB injections in IVB group and IVB+MPC group were 2.23±1.24 and 2.49±1.09, respectively | IVB 0.138 <0.05 vs baseline |
| Follow-up: 6 months | | | IVB+MPC 0.179 <0.05 vs baseline |
| | | | ▶ no statistically significant difference between the two groups |
| | | | CMT (OCT): |
| | | | IVB −39 <0.05 vs baseline |
| | | | IVB+MPC −39 <0.05 vs baseline |
| | | | ▶ No statistically significant difference between the two groups |

BCVA, best corrected visual acuity; C, control; CMT, central macular thickness; CSME, clinically significant macular oedema; DDS, dexamethasone; DIL, dexamethasone followed by laser; DM, diabetes mellitus; DMO, diabetic macular oedema; DP, diastolic pressure; DR, diabetic retinopathy; HR QoL, health-related quality of life; IOP, intraocular pressure; IV, intravitreal; IVB, intravitreal bevacizumab; IVP, intravitreal pegaptanib; IVR, intravitreal ranibizumab; IVT, intravitreal triamcinolone; IVTL, intravitreal triamcinolone plus laser; IVVTE, intravitreal VEGF Trap Eye; L, laser; MLT/MPC, macular laser therapy/macular photocoagulation; NEI VFQ-25, National Eye Institute Visual Function Questionnaire-25; NPDR, non-proliferative diabetic retinopathy; NR, not reported; OCT, optical coherence tomography; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation; RCT, randomised controlled trial; SOC, standard of care; SP, systolic pressure; SRFA, fluocinolone; VA, visual acuity; VEGF, vascular endothelia growth factor.
### Table 5 Pegaptanib and aflibercept studies

| Study                  | Participants and baseline values                                                                 | Intervention                                                                 | Outcome (change from baseline at study end)       |
|------------------------|---------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|---------------------------------------------------|
| **Pegaptanib**          |                                                                                                  |                                                                              |                                                   |
| Cunningham et al       | N: 172 eyes of 172 patients<br>**Inclusion criteria:** ≥ 18 years, type 1 or 2 DM, DMO involving the center of the macula with corresponding leakage from microaneurysms, retinal telangiectasis, or both; clear ocular media, BCVA letter scores between 68 and 25 in the study eye and at least 35 in the fellow eye; IOP ≤ 23 mm Hg, focal photocoagulation could be safely deferred for 16 weeks; no ECG abnormalities, no major serological abnormalities<br>**Exclusion criteria:** history of panretinal or focal photocoagulation; neodymium:yttrium–aluminum–garnet laser or peripheral retinal cryoablation in previous 6 months; any ocular abnormality interfering with VA assessment or fundus photography; vitreoretinal traction; vitreous incarceration; retinal vein occlusion involving the macula; history of intraocular surgery within previous 12 months, myopia of ≥ 8 diopters, axial length of ≥ 25 mm, likelihood of requiring panretinal photocoagulation following within 9 months; cataract surgery within 12 months; active ocular or periorbital infection; previous therapeutic radiation to the eye, head, or neck; known serious disorders to fluorescein dye; HbA1c ≥ 13%, pregnancy<br>**Age:** 61.3–64.0 SD 9.3–10.1 years<br>**Sex:** 45–55% female<br>**Diabetes type:** 5–10% IDDM<br>**HbA1c:** 7.1–7.7 SD 1.2–1.6<br>**Baseline VA:** letter score 55.0–57.1 SD 9.1–11.5<br>**Baseline CMT:** 423.2–476.0 μm<br>**Comorbidities:** not reported | Group 1 (IVP0.3, n=44 eyes): 0.3 mg IV pegaptanib (90 µl) (median 5 injections (range 1–6))<br>**Group 2 (IVP1, n=44 eyes):** 1 mg IV pegaptanib (90 µl) (median 6 injections (range 1–6))<br>**Group 3 (IVP3, n=42 eyes):** 3 mg IV pegaptanib (90 µl) (median 6 injections (range 1–6))<br>**Group 4 (C, n=42 eyes):** sham injection (median 5 injections (range 1–6))<br>**Regimen for all groups:** injections at baseline, week 6 and week 12; thereafter, additional injections administered every 6 weeks at the discretion of the investigators if judged indicated (maximum of 6 injections up to week 30); laser photocoagulation allowed after week 13 if judged indicated by the study-masked ophthalmologist (25% for IVP0.3, 30% for IVP1, 40% for IVP3, 48% for C)<br>**Subgroups:** of 16 participants with retinal neovascularisation at baseline, 8 of 13 (62%) in the pegaptanib groups and 0 of 3 in the sham group had regression of neovascularisation at 36 weeks | BCVA:<br>**BCVA (letters) p Value**<br>IVP0.3: +4.7 0.04 vs C<br>IVP1: +4.7 0.05 vs C<br>IVP3: +1.1 NS vs C<br>C: −0.4<br>**Plus ≥ 10 letters**<br>**CMT (OCT): p Value**<br>IVP0.3: −68.0 (−118.9 to −9.88) 0.02 vs C<br>IVP1: −22.7 (−76.9 to +33.8) NS vs C<br>IVP3: −5.3 (−63.0 to +49.5) NS vs C<br>C: +3.7 |
| USA Design: 4-arm phase II RCT Follow-up: 36 weeks |                                                                                                  |                                                                              |                                                   |
| Adamis et al           |                                                                                                  |                                                                              |                                                   |
| Age: 61.3–64.0 SD 9.3–10.1 years<br>Sex: 45–55% female<br>Diabetes type: 5–10% IDDM<br>HbA1c: 7.1–7.7 SD 1.2–1.6<br>Baseline VA: letter score 55.0–57.1 SD 9.1–11.5<br>Baseline CMT: 423.2–476.0 μm<br>Comorbidities: not reported | Group 1 (IVP0.3, n=44 eyes): 0.3 mg IV pegaptanib (90 µl) (median 5 injections (range 1–6))<br>**Group 2 (IVP1, n=44 eyes):** 1 mg IV pegaptanib (90 µl) (median 6 injections (range 1–6))<br>**Group 3 (IVP3, n=42 eyes):** 3 mg IV pegaptanib (90 µl) (median 6 injections (range 1–6))<br>**Group 4 (C, n=42 eyes):** sham injection (median 5 injections (range 1–6))<br>**Regimen for all groups:** injections at baseline, week 6 and week 12; thereafter, additional injections administered every 6 weeks at the discretion of the investigators if judged indicated (maximum of 6 injections up to week 30); laser photocoagulation allowed after week 13 if judged indicated by the study-masked ophthalmologist (25% for IVP0.3, 30% for IVP1, 40% for IVP3, 48% for C)<br>**Subgroups:** of 16 participants with retinal neovascularisation at baseline, 8 of 13 (62%) in the pegaptanib groups and 0 of 3 in the sham group had regression of neovascularisation at 36 weeks | BCVA:<br>**BCVA (letters) p Value**<br>IVP0.3: +4.7 0.04 vs C<br>IVP1: +4.7 0.05 vs C<br>IVP3: +1.1 NS vs C<br>C: −0.4<br>**Plus ≥ 10 letters**<br>**CMT (OCT): p Value**<br>IVP0.3: −68.0 (−118.9 to −9.88) 0.02 vs C<br>IVP1: −22.7 (−76.9 to +33.8) NS vs C<br>IVP3: −5.3 (−63.0 to +49.5) NS vs C<br>C: +3.7 |

Continued
| Study                     | Participants and baseline values                                                                                                                                                                                                                                                                                                                                                      | Intervention                                                                                                                                                                                                                                                                                                                                                                       | Outcome (change from baseline at study end)                                                                                                                                                                                                                                                                                                                                 |
|--------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sultan et al<sup>10</sup> Multicenter international Design: 2-arm placebo-controlled RCT Follow-up: 2 years (primary efficacy endpoint at 1 year)                                                                 | **N**: 260 eyes of 260 patients  
**Inclusion criteria**: ≥18 years, type 1 or 2 DM, DMO involving the center of the macula not associated with ischemia, CMT ≥250 µm, BCVA letter score 65–35, IOP ≤21 mm Hg, clear ocular media  
**Exclusion criteria**: any abnormality other than DMO affecting VA assessment, vitreomacular traction; yttrium–aluminum–garnet laser, peripheral retinal cryoablation, laser retinopathy for retinal tears, focal or grid photoaquagulation within prior 16 weeks; panretinal photoaquagulation <6 months before baseline or likely to be needed within 9 months; significant media opacities; intraocular surgery in prior 6 months; pathological high myopia; prior radiation in region of study eye; history of severe cardiac or peripheral vascular disease, stroke in prior 12 months, major surgery in prior 1 month, treatment in prior 90 days with any investigational agent or with bevacizumab for any nonocular condition, HbA1c ≥10% or signs of uncontrolled diabetes, hypertension, known relevant allergies; pregnant or lactating  
**Age**: 62.3–62.5 SD9.3–10.2 years  
**Sex**: 39–46% female  
**Diabetes type**: 6.3–7.5% type 1 DM, 92.5–93.7% type 2 DM  
**HbA1c**: 42.5–45.9% <7.6%, 54.1–57.5% >7.6%  
**Baseline VA**: letter score 57.0–57.5 SD8.1–8.9  
**Baseline CMT**: 441.6–464.6 SD135.5–148.5 µm  
**Comorbidities**: not reported                                                                                                                                                                                                                                           | Group 1 (IVP, n=133 eyes):  
0.3 mg IV pegaptanib sodium (mean number of injections 12.7 SD4.6)  
**Group 2 (C, n=127 eyes)**:  
sham injection (mean number of injections 12.9 SD4.4)  
**Regimen for all groups**: injections every 6 weeks up to week 48 (9 injections); at investigator determination (ETDRS criteria), laser photocoagulation could be performed at week 18, with possible repeat treatment at a minimum of 17 weeks later (maximum 3 treatments per year) (laser treatments in 25.2% of IVP group and 45% of C group); in year 2, injections as judged necessary  
**At 1 year**:  
BCVA (ETDRS):  
IVP +5.2  
C +1.2  
**Plus ≥10 letters**:  
IVP 36.8%  
C 19.7%  
Retinopathy:  
Increase in degree by ≥2 steps  
IVP 4.1%  
C 12.4%  
Decrease in degree by ≥2 steps  
IVP 10.2%  
C 3.1%  
**CMT (OCT)**:  
Decrease in CMT  
IVP ≥25%: 31.7%  
>50%: 14.6%  
≥25%: 23.7%  
>50%: 11.9%  
**At 2 years**:  
BCVA (ETDRS):  
IVP +6.1  
C +1.3  
**Plus ≥10 letters**:  
IVP 38.3%  
C 30%  
Retinopathy:  
Increase in degree by ≥2 steps  
IVP 6.3%  
C 13.8%  
Decrease in degree by ≥2 steps  
IVP 16.3%  
C 0.3%  
**CMT (OCT)**:  
Decrease in CMT  
IVP ≥25%: 40.4%  
>50%: 19.2%  
≥25%: 44.6%  
>50%: 26.1%  
Continued |
**Table 5**

| Study | Participants and baseline values | Intervention | Outcome (change from baseline at study end) |
|-------|----------------------------------|--------------|---------------------------------------------|
| DA VINCI 2010 (Do et al) | Multicenter, 5-arm phase II RCT | Aflibercept | **NEI VFQ-25:** between group differences not significant at 54 weeks; at 102 weeks, significantly greater improvement in composite score and subscales distance vision, activities, social functioning, and mental health with pegaptanib. |
| | | EQ-5D | No significant differences between groups in EQ-5D scores at weeks 54 or 102. |
| **Trial of VEGF Trap-Eye (VTE), randomised on a 1:1:1:1:1 basis** | | | **BCVA (letters) p Value** |
| | | | **IVVTE1** | +8.6 | 0.005 vs L |
| | | | **IVVTE2** | +11.4 | ≤0.0001 vs L |
| | | | **IVVTE3** | +10.3 | 0.0001 vs L |
| | | | **IVVTE4** | +8.5 | 0.0001 vs L |
| | | | **L** | +2.5 | 0.0001 vs L |
| | | | | **≥10 letters** |
| | | | **IVVTE1** | NR | NR |
| | | | **IVVTE2** | NR | NR |
| | | | **IVVTE3** | 58% | NR |
| | | | **IVVTE4** | 58% | NR |
| | | | **L** | 58% | NR |
| | | | | **CMT(um)** |
| | | | | **IVVTE1** | −144.6 | 0.0001 vs L |
| | | | | **IVVTE2** | −194.5 | <0.0001 vs L |
| | | | | **IVVTE3** | −127.3 | 0.0001 vs L |
| | | | | **IVVTE4** | −153.3 | <0.0001 vs L |
| | | | | **L** | −67.9 |

**Note:** BCVA = best-corrected visual acuity; CRT = central retinal thickness; DMO = diabetic macular oedema; ETDRS = Early Treatment Diabetic Retinopathy Study; IVT = intravitreal; L = laser photocoagulation; NR = not reported; VTE = VEGF Trap-Eye; VFQ = Visual Function Questionnaire; WMV = white matter volume.
Table 5 Continued

| Study | Participants and baseline values | Intervention | Outcome (change from baseline at study end) |
|-------|----------------------------------|--------------|--------------------------------------------|
|       | Membrane evident biomicroscopically or on OCT; history of idiopathic autoimmune uveitis; structural damage to the center of the macula that is likely to preclude improvement in visual acuity after the resolution of macular oedema; uncontrolled glaucoma or previous filtration surgery; infectious blepharitis, keratitis, scleritis, or conjunctivitis; or current treatment for serious systemic infection: uncontrolled diabetes mellitus; uncontrolled hypertension; history of cerebral vascular accident or myocardial infarction within 6 months; renal failure requiring dialysis or renal transplant; pregnancy or lactation; history of allergy to fluorescein or povidone iodine; only 1 functional eye (even if the eye met all other entry criteria); or an ocular condition in the fellow eye with a poorer prognosis than the study eye | L | –1.3 +15 letters |
|       | Age: 60.7–64.0 years (SD 8.1–11.5) | IVVTE1 | 40.9% 0.0031 vs L |
|       | Sex: % female 35.6–47.6% | IVVTE2 | 45.5% 0.0007 vs L |
|       | Diabetes type: percentage of type 2, 88.6–97.7% | IVVTE3 | 23.8% 0.1608 vs L |
|       | HbA1c: 7.85–8.10 (SD 1.71–1.94) | IVVTE3 | 42.2% 0.0016 vs L |
|       | Baseline VA: 57.6–59.9 (SD 10.1–12.5) | L | 11.4% +10 letters |
|       | Baseline CMT: 426.1–456.6 µm (SD 111.8–152.4) | IVVTE1 | 57% 0.0031 vs L |
|       | Comorbidities: history of any cardiac disease was twice as common in the VEGF Trap-Eye groups compared with the laser group | IVVTE2 | 71% 0.0007 vs L |
|       | | IVVTE3 | 45% 0.1608 vs L |
|       | | L | 62% 0.0016 vs L |
|       | | | | CMT(µm) |
|       | | IVVTE1 | −165.4 <0.0001 vs L |
|       | | IVVTE2 | −227.4 <0.0001 vs L |
|       | | IVVTE3 | −187.8 <0.0001 vs L |
|       | | L | −180.3 <0.0001 vs L |
|       | | | −58.4 |

BCVA, best corrected visual acuity; C, control; CMT, central macular thickness; CSME, clinically significant macular oedema; DDS, dexamethasone; DIL, dexamethasone followed by laser; DM, diabetes mellitus; DMO, diabetic macular oedema; DP, diastolic pressure; DR, diabetic retinopathy; HR QoL, health-related quality of life; IOP, intraocular pressure; IV, intravitreal; IVB, intravitreal bevacizumab; IVP, intravitreal pegaptanib; IVR, intravitreal ranibizumab; IVT, intravitreal triamcinolone; IVTL, intravitreal triamcinolone plus laser; IVVTE, intravitreal VEGF Trap Eye; L, laser; MLT/MPC, macular laser therapy/macular photocoagulation; NEI VFQ-25, National Eye Institute Visual Function Questionnaire-25; NPDR, non-proliferative diabetic retinopathy; NR, not reported; OCT, optical coherence tomography; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation; RCT, randomised controlled trial; SOC, standard of care; SP, systolic pressure; SRFA, fluocinolone; VA, visual acuity; VEGF, vascular endothelia growth factor.
| Study                          | Participants and baseline values                                                                                                                                                                                                 | Intervention                                                                                                                                                                                                 | Outcome (change from baseline at study end)                                                                                                                                                                                                                                                                                                                                 |
|-------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| **Dexamethasone**              |                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                     |
| Callanan et al USA⁴⁴           | N: 253 eyes of 253 patients                                                                                                                                                                                                          | Group 1 (DIL, n=126 eyes): dexamethasone IV implant followed by laser photoagulation after 1 month (mean 1.6 implants; 78.6% completion) Group 2 (L, n=127 eyes): laser alone (79.5% completion) Regimen for all groups: if needed, patients were retreated with the dexamethasone implant at months 6 or 9, and with laser at months 4, 7 and 10; mean 2.2 laser treatments per patient Laser protocol not reported | At 12 months BCVA: Plus ≥ 10 letters (%) DIL: 28 L: 24 ▶ Patients in DIL group had significantly greater increases in BCVA from baseline than patients in the laser group (p<0.05) at months 1–9 only CMT (OCT): ▶ Patients in DIL group had significantly greater mean reductions from baseline in CMT at months 1 and 6 only (p<0.001) |
| Design: 2-arm RCT Follow-up: 12 months | Inclusion criteria: diffuse DMO, CMT ≥275 µm, BCVA ≥34 and ≤70 letters Exclusion criteria: not reported Age: not reported Sex: not reported Diabetes type: not reported HbA1c: not reported Baseline VA: not reported Baseline CMT: not reported Comorbidities: not reported |                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                     |
| Haller et al⁵⁹                 | N: 171 eyes of 171 patients                                                                                                                                                                                                          | Group 1 (DDS350, n=57 eyes): 350 µg dexamethasone IV drug delivery system, implanted into the vitreous cavity Group 2 (DDS700, n=57 eyes): 700 µg dexamethasone IV drug delivery system, implanted into the vitreous cavity Group 3 (C, n=57 eyes): no treatment Regimen for all groups: eyes demonstrating a VA loss of ≥5 letters could be treated with any other therapy (including laser photoagulation and IV triamcinolone) (n=4 with photoagulation or IV triamcinolone in the C group, n=2 in the DDS350 group, none in the DDS700 group) | At 90 days BCVA (ETDRS): Plus ≥10 letters CMT (µm) p Value DDS350: −42.57 SD95.96 NS (p=0.07) vs C DDS700: −132.27 SD160.86 <0.001 vs C C: +30.21 SD82.12 At 180 days BCVA (ETDRS): Plus ≥10 letters DDS350: 20% (graph) DDS700: 33% (graph) C: 23% (graph) |
| USA Multicenter Design: 3-arm RCT Follow-up: 6 months (180 days), primary outcome 3 months (90 days) | Inclusion criteria: ≥12 years, DMO persisting for ≥90 days after laser treatment or medical therapy, BCVA by ETDRS between 20/40 (67 letters) and 20/200 (35 letters) due to clinically detectable DMO; analysis includes only eyes with DMO associated with DR Exclusion criteria: history of vitrectomy in the study eye; use of systemic, periocular, or intraocular steroids within 30 days of enrolment; moderate or severe glaucoma in the study eye; poorly controlled hypertension (SP >160 mm Hg or DP >90 mm Hg); poorly controlled diabetes (HbA1c >13%) Age: 62.9–63.8 years SD10.2–12.0 Sex: 45.6–49.1% female Diabetes type: not reported HbA1c: 7.3–7.6% Baseline VA: letter score 54.4–54.7 SD9.96–11.88 Baseline CMT: 417.5–446.5 µm SD123.7–155.9 Comorbidities: 19–21% prior cataract extraction |                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                     |
Table 6
Continued

| Study | Participants and baseline values | Intervention | Outcome (change from baseline at study end) |
|-------|---------------------------------|--------------|---------------------------------------------|
| **Fluocinolone** | | | |
| **FAME Study (Campochiaro et al)** | N: 956 eyes of 956 patients | Group 1 (0.5, n=375 eyes): intravitreal insert releasing 0.2 µg/day fluocinolone acetamide (FA) (2, 3, or 4 treatments received by 21.3, 1.9 and 0.3%) | **At 24 months** |
| **Multicenter international placebo-controlled RCT** Design: 3-arm Follow-up: 24 months; abstract with 36 month outcomes | Inclusion criteria: DMO, CMT ≥250 µm despite at least 1 prior focal/grid macular laser photocoagulation treatment, BCVA ETDRS letter score between 19 and 68 (20/50–20/400) | **BCVA (ETDRS):** | **BCVA (letters) p Value** |
| | Exclusion criteria: glaucoma, ocular hypertension, IOP >21 mm Hg, taking IOP lowering drops; laser treatment for DMO within 12 weeks of screening, any ocular surgery in the study eye within 12 weeks of screening; ocular or systemic steroid therapy; active ocular infection; pregnancy | **SRFA0.2** +4.4 0.02 vs C | |
| | Age: 62.5 SD9.4 years | **SRFA0.5** +5.4 0.017 vs C | |
| | Sex: 40.6% | **C** +1.7 | |
| | Diabetes type: 6.6% type 1 DM, 92% type 2 DM, 1.4% uncertain | **Plus ≥15 letters (%) p Value** | |
| | HbA1c: 7.8 SD1.59% | **SRFA0.2** 29 0.002 | |
| | Baseline VA: ETDRS letter score 53.4 SD12.23 | **SRFA0.5** 29 | |
| | Baseline CMT: 469.0 SD164.78 µm | **C** 16 | |
| | Comorbidities: 47.1% cataract at baseline, 62.7–67.4% phakic | | |
| | | Subgroups: | |
| | | BCVA benefits only in pseudophakic eyes (cataract surgery before or during the study), in phakic eyes, BCVA letter score was reduced by 5 (high dose) and 9 (low dose) from baseline at 24 months | |
| | | **Regimen for all groups:** patients could receive rescue focal/grid laser therapy any time after the first 6 weeks for persistent oedema (35.2–36.7% in FA groups, 58.9% control group, p<0.001); treatments were allowed every 3 months for persistent or recurrent oedema; patients eligible for another FA insert at 1 year if ≥5 letter reduction in BCVA or ≥50 µm CMT increase from best status | |
| | | **CMT (optical coherence tomography):** | **CMT (µm) p Value** |
| | | **SRFA0.2** −167.8 0.005 vs C | |
| | | **SRFA0.5** −177.1 <0.001 vs C | |
| | | **C** −111.3 | |
| | | **effect maintained at 36 months** | |
| | | **At 36 months** | |
| | | **Plus ≥15 letters (%) p Value** | |
| | | **SRFA0.2/0.5** 28.7% 0.018 | |
| | | **C** 18.9% | |

Continued
| Study | Participants and baseline values | Intervention | Outcome (change from baseline at study end) |
|-------|---------------------------------|--------------|-------------------------------------------|
| Pearson et al²³ USA Multicenter | N: 196 patients | Group 1 (SRFA, n=127): 0.5 mg sustained release fluocinolone acetone implant | At 3 years BCVA: |
| Design: 2-arm RCT Follow-up: 36 months | Inclusion criteria: persistent or recurrent unilateral or bilateral DMO with retinal thickening involving fixation of ≥1 disc area in size, ETDRS visual acuity of ≥20 letters (20/400) to ≤68 letters (20/50) and ≥1 macular laser treatment in the study eye more than 12 weeks prior to enrolment | Group 2 (SOC, n=69): standard of care—either repeat laser or observation Laser ETDRS protocol | Gain ≥15 letters p Value 31% NS |
| | Exclusion criteria: Ocular surgery within 3 months prior to enrolment, uncontrolled IOP within the past 12 months while on ≥1 antiglaucoma medication, IOP of ≥22 mm Hg at screening while on ≥1 antiglaucoma medication, peripheral retinal detachment in the area of implantation or media opacity precluding diagnosis of status in the study eye | | SRFA SOC |
| | Age: 61.4–62.7 years | SRFA | 17% NS |
| | Sex: 41.7–42% female | SOC | 14% NS |
| | Diabetes type: 62.3–70% on insulin | CMT: | Mean change in baseline CMT |
| | HbA1c: not reported | SRFA | –86 NS |
| | Baseline VA: not reported | SOC | –110 NS |
| | Baseline CMT: not reported | | |
| | Comorbidities: not reported | | |

BCVA, best corrected visual acuity; C, control; CMT, central macular thickness; CSME, clinically significant macular oedema; DDS, dexamethasone; DIL, dexamethasone followed by laser; DM, diabetes mellitus; DMO, diabetic macular oedema; DP, diastolic pressure; DR, diabetic retinopathy; HR QoL, health-related quality of life; IOP, intraocular pressure; IV, intravitreal; IVB, intravitreal bevacizumab; IVP, intravitreal pegaptanib; IVR, intravitreal ranibizumab; IVT, intravitreal triamcinolone; IVTL, intravitreal triamcinolone plus laser; IVT-E, intravitreal VEGF Trap Eye; L, laser; MLT/MPC, macular laser therapy/macular photocoagulation; NEI VFO-25, National Eye Institute Visual Function Questionnaire-25; NPDR, non-proliferative diabetic retinopathy; NR, not reported; OCT, optical coherence tomography; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation; RCT, randomised controlled trial; SOC, standard of care; SP, systolic pressure; SRFA, fluocinolone; VA, visual acuity; VEGF, vascular endothelia growth factor.
| Study                                      | Participants and baseline values | Intervention                                      | Outcome (change from baseline at study end) |
|-------------------------------------------|----------------------------------|--------------------------------------------------|---------------------------------------------|
| DRCR Network 2008 (Ip et al/Beck et al/Bressler et al) USA | N: 840 eyes of 693 patients   | Study 1 (IVT1, n=256 eyes): 1 mg IV triamcinolone (3.5 treatments) | At 2 years                                  |
| Follow-up: 2 years, additional 3 year follow-up | Inclusion criteria: >18 years, type 1 or 2 DM, study eye: (1) BCVA (E-ETDRS) between 24 and 73 (20/300 and 20/40), (2) retinal thickening due to DMO involving the center of the macula, main cause for visual loss, (3) CMT ≥ 250 µm, (4) no expectation of scatter photocoagulation within 4 months | Group 1 (IVT1, n=256 eyes): 1 mg IV triamcinolone (3.5 treatments) | BCVA (E-ETDRS):                       |
|                                           | Exclusion criteria: any prior treatment with IV corticosteroids, peribulbar steroid injection within prior 6 months, photocoagulation for DMO within prior 15 weeks, panretinal scatter photocoagulation within prior 4 months, pars plana vitrectomy, history of open-angle glaucoma or steroid-induced IOP elevation requiring IOP-lowering treatment, and IOP > 25 mm Hg | Group 2 (IVT4, n=254 eyes): 4 mg IV triamcinolone (3.1 treatments) | BCVA (letters):                       |
|                                           | Age: 63 SD9 years               | Group 3 (L, n=330 eyes): focal/grid photocoagulation (2.9 treatments) | Group 1 (IVT1, n=256 eyes): 1 mg IV triamcinolone (3.5 treatments) | IVT1: -2 SD18, p = 0.02 vs L          |
|                                           | Sex: 49% female                | Regimen for all groups: retreatment protocol: where indicated, retreatment was performed within 4 weeks after the follow-up visit and no sooner than 3.5 months from the time of last treatment; eyes were generally retreated unless: (1) little or no oedema involving the center of the macula present and CMT ≥ 225 µm, (2) VA letter score ≥ 79 (20/25 or better), (3) substantial improvement in macular oedema since last treatment (eg, ≥ 50% decrease in CMT), (4) clinically significant adverse effect from prior treatment, (5) additional treatment deemed futile (< 5 letter improvement in VA letter score or lack of CMT reduction) and (6) for laser group, complete focal/grid photocoagulation already given, with no areas identified for which additional treatment was indicated | Subgroups:                              |
|                                           | Diabetes type: 95% type 2 DM, 5% type 1 DM | Laser Modified ETDRS                             | IVT1: +10 or more: 25% vs L, p = 0.03 | NS vs IVT4, p = 0.01 vs L           |
|                                           | HbA1c: 7.9 SD1.8%              |                                                 | IVT4: +9 to −9: 50% vs L, p = 0.01 | IVT4: +9 to −9: 44% vs L, p = 0.01 |
|                                           | Baseline VA: ETDTRS letter score 59 SD11 (~20/63) |                                                 | +10 or more: 28% vs L, p = 0.01 | +10 or more: 31% vs L, p = 0.01 |
|                                           | Baseline CMT: 24 SD130 µm      |                                                 | +10 or more: 31% vs L, p = 0.01 | +10 or more: 19% vs L, p = 0.01 |
|                                           | Comorbidities: 21%             |                                                 |                                            |                              |
|                                           | pseudophakic, 2% ocular hypertension, 7% mild NPDR, 13% moderate NPDR, 40% moderately severe NPDR, 11% severe NPDR, 23.5% mild to moderate, 3% high risk PDR | CMT (µm): −86 SD167 |                                            |                              |
|                                           |                                | p Value                                           | CMT (µm): −86 SD167 | p Value                                           |                              |
|                                           |                                |                                                   |                                                   |                              |
|                                           |                                |                                                   |                                                   |                              |

Continued
| Study                      | Participants and baseline values                                                                 | Intervention                                                                 | Outcome (change from baseline at study end)                                                                 |
|----------------------------|--------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|
| Gillies et al Sutter et al | Australia                                                                                        | protocol as used in prior DCRR.net protocols                                  | BCVA (letters)                                                                                               |
|                            | Design: 2-arm placebo-controlled RCT Follow-up: 2 years, additional 3-year follow-up             | Group 1 (IVT, n=34 eyes): 4 mg (0.1 ml) IV triamcinolone acetonide (mean 2.6) | At 2 years                                                                                                 |
|                            |                                                   | injections over 2 years                                                       | BCVA (ETDRS):                                                                                               |
|                            |                                                   | Group 2 (C, n=35 eyes): placebo injection (subconjunctival saline injection) (mean 1.8 injections over 2 years) |                                                                                                             |
|                            |                                                   | Regimen for all groups: reiterations considered at each visit as long as treatments were at least 6 months apart (reirteration if VA decreased ≥5 letters from previous peak value and persistent CMT >250 µm), if no improvement after 4 weeks, further laser treatment was applied (n=1 laser treatment in intervention group, n=16 in placebo group, p=0.0001) | CMT (OCT):                                                                                                 |
|                            |                                                   |                                                                 |                                                                                                             |
|                            | Age: 62.4–69.6 SD9.2–12.5 years                                                                 |                                                                 |                                                                                                             |
|                            | Sex: 52% female                                                                                  |                                                                 |                                                                                                             |
|                            | Diabetes type: not reported                                                                      |                                                                 |                                                                                                             |
|                            | HbA1c: 7.63–8.28 SD1.12–1.41                                                                     |                                                                 |                                                                                                             |
|                            | Baseline VA: ETDRS letter score 60.5–61.3 SD11.9–13.2                                            |                                                                 |                                                                                                             |
|                            | Baseline CMT: 439–444 SD101–125 µm                                                               |                                                                 |                                                                                                             |
|                            | Comorbidities: 25% pseudophakic                                                                  |                                                                 |                                                                                                             |
|                            |                                                                                                 |                                                                 |                                                                                                             |
|                            |                                                                                                 |                                                                 |                                                                                                             |
|                            |                                                                                                 | BCVA (letters): +3.1                                                               | p Value 0.01 vs C                                                                                          |
|                            |                                                                                                 | C: −2.9                                                                        |                                                                                                             |
|                            |                                                                                                 | IVT: +10 or more: 21%                                                             |                                                                                                             |
|                            |                                                                                                 | +9 to −9: 70%                                                                   |                                                                                                             |
|                            |                                                                                                 | −10 or more: 9%                                                                 |                                                                                                             |
|                            |                                                                                                 | +10 or more: 12%                                                                | 0.013 vs C                                                                                                 |
|                            |                                                                                                 | +9 to −9: 62%                                                                   |                                                                                                             |
|                            |                                                                                                 | −10 or more: 25%                                                                |                                                                                                             |
|                            |                                                                                                 | CMT (µm): −125                                                                  | p Value 0.009 vs C, difference between groups 59 µm (95% CI 15 to 104)                                       |

Continued
| Study | Participants and baseline values | Intervention | Outcome (change from baseline at study end) |
|-------|--------------------------------|--------------|--------------------------------------------|
| Gillies et al<sup>23</sup> Australia | N: 84 eyes of 54 patients | **Inclusion criteria:** DMO involving the central fovea, CMT ≥ 250 µm, BCVA 17–70 letters (~20/40–20/400), laser treatment could be safely delayed for 6 weeks without significant adverse effects | **At 24 months**<br>BCVA (ETDRS):<br>**BCVA (letters)**<br>ITL<br>+0.76<br>L<br>−1.49<br>**p Value**<br>NS vs L<br>**BCVA gain categories**<br>+10 or more: 36%<br>+9 to −9: 31%<br>−10 or more: 33%<br>+10 or more: 17%<br>+9 to −9: 59%<br>−10 or more: 24% |
| **Design:** 2-arm RCT | **Follow-up:** 24 months | **Group 1 (IVTL, n=42 eyes):** 4 mg (0.1 ml) IV triamcinolone acetonide followed by laser treatment (at least 1 retreatment in 2nd year in 69%) | **Regimen for all groups:**<br>retreatment with injection followed by laser at discretion of chief investigator, with at least 6 weeks between treatments; no retreatment if: (1) investigator considered the macula nearly flat and CMT <300 µm; (2) VA was ≥ 79 letters (20/25) or VA had improved by ≥ 5 letters compared with the best VA after treatment or baseline acuity; (3) laser treatment was considered by the investigator as inappropriate or had no potential for improvement |
| **Group 2 (L, n=42 eyes):** sham injection followed by laser treatment (at least 1 retreatment in 2nd year in 45%) | **CMT (OCT):**<br>**CMT (µm)**<br>IVTL<br>−137.1<br>L<br>−109.6<br>**p Value**<br>NS vs L |
| **Exclusion criteria:** uncontrolled glaucoma, controlled glaucoma but with a glaucomatous visual field defect, loss of vision resulting from other causes, systemic treatment with >5 mg prednisolone (or equivalent) daily, retinal laser treatment within 4 months, intraocular surgery within 6 months, concurrent severe systemic disease, any condition affecting follow-up or documentation | **Subgroups:**<br>BCVA outcome not significantly affected by cataract surgery |
| **Age:** 65.4–66.9 SD8.9–9.5 years | **Sex:** 38.1–47.6% female<br>**Diabetes type:** not reported<br>**HbA1c:** 7.81–8.02<br>SD1.44–1.63%<br>**Baseline VA:** letter score 55.2–55.5 SD11.3–12.5<br>**Baseline CMT:** 482.1–477.4 SD122.7–155.5 µm<br>**Comorbidities:** not reported |
| Study | Participants and baseline values | Intervention | Outcome (change from baseline at study end) |
|-------|----------------------------------|--------------|-------------------------------------------|
| Kim et al<sup>45</sup>  
Korea  
Design: 2-arm RCT  
Follow-up: 3 years | N: 86 eyes of 75 patients  
Inclusion criteria: diffuse DMO  
Exclusion criteria: not reported  
Age: not reported  
Sex: not reported  
Diabetes type: not reported  
HbA1c: not reported  
Baseline VA: not reported  
Baseline CMT: not reported  
Comorbidities: not reported | Group 1 (IVT, n=38 eyes):  
4 mg IV triamcinolone (1.88 additional treatments, completion 68.1%)  
Group 2 (IVTL, n=48 eyes):  
macular laser photocoagulation 4 weeks after 4 mg IV triamcinolone (0.92 additional treatments, completion 77.1%)  
Regimen for all groups: additional treatment possible, criteria not mentioned | At 3 years  
BCVA: not reported  
Outcomes related to DMO:  
No DMO recurrence  
IVT  
IVTL  
Time DMO not present  
10.33 months  
19.88 months  
0.027 vs IVT |
| Lam et al<sup>34</sup>  
Hong Kong  
Design: 3-arm RCT  
Follow-up: 6 months (2 years planned) | N: 111 eyes of 111 patients  
Inclusion criteria: >18 years, type 1 or 2 DM, clinically significant DMO (ETDRS), CMT ≥250 µm  
Exclusion criteria: macular oedema due to causes other than diabetic maculopathy, signs of vitreomacular traction, proliferative diabetic retinopathy, aphakia, history of glaucoma or ocular hypertension, macular ischemia, any laser procedure within 3 months, ocular surgery within 6 months, significant media opacities  
Age: 64.7–67.2 SD8.2–10.3 years  
Sex: 42–59% female  
Diabetes type: not reported  
HbA1c: not reported  
Baseline VA: ETDRS logMAR 0.64–0.72 SD0.34–0.36  
Baseline CMT: 385–424 SD91–108 µm  
Comorbidities: 66–84% phakic eyes | Group 1 (IVT, n=38 eyes):  
4 mg IV triamcinolone (no retreatments)  
Group 2 (IVTL, n=36 eyes):  
4 mg IV triamcinolone followed by grid laser photocoagulation (ETDRS) (laser treatment once the macular oedema had reduced to <250 µm at the foveal center or at 1 to 2 months after injection, whichever was earlier)  
Group 3 (L, n=37 eyes): grid laser photocoagulation (n=3 retreatments) (no retreatments)  
Regimen for all groups: in case of recurrence or persistence of macular oedema, retreatment offered according to study group, at intervals no less than 4 months | At 6 months  
BCVA (ETDRS):  
BCVA improvement  
IVT  
IVTL  
L  
CMT (OCT):  
CMT (µm)  
IVT  
IVTL  
L  
342 SD124 (–54)  
307 SD181 (–116)  
350 SD169 (–35)  
NS between groups, <0.01 vs baseline |

Continued
| Study                        | Participants and baseline values | Intervention                                                                 | Outcome (change from baseline at study end) |
|-----------------------------|----------------------------------|-------------------------------------------------------------------------------|---------------------------------------------|
| Ockrim et al/Sivaprasad et al<sup>82</sup> UK | N: 88 eyes of 88 patients | Group 1 (IVT, n=43 eyes): 4 mg IV triamcinolone (mean number of IVT injections 1.8 (range 1–3)) | BCVA (ETDRS): IVT BCVA (letters) p Value |
|                             | Study: 2-arm RCT Follow-up: 1 year | Group 2 (L, n=45 eyes): ETDLS laser photocoagulation (mean number of grid laser sessions 2.1 (range 1–3)) | L +1.7 Plus ≥ 15 letters NS vs L |
|                             | Inclusion criteria: clinically significant DMO persisting ≥4 months, ≥1 previous laser treatment, BCVA 6/12–3/60, VA in fellow eye ≥3/60, duration visual loss <24 months | Regimen for all groups: patients retreated at 4 and 8 months if they had persistent macular oedema Laser ETDRS protocol | CMT (optical coherence tomography): IVT CMT (µm) p Value |
|                             | Exclusion criteria: significant macular ischemia, baseline IO >23 mm Hg, glaucoma, coexistent renal disease, loss of VA due to other causes, previous vitrectomy, intracocular surgery within 3 months of study entry, previous inclusion in other DR trials, inability to return to follow-up, inability to give informed consent | | L −63.7 NS vs L |
|                             | Age: 62.3–64.8 SD7.5–10.1 years | | |
|                             | Sex: 28.9–34.9% female | | |
|                             | Diabetes type: 97.8–100% type 2 DM | | |
|                             | HbA1c: 7–7.8 IQR6.5–8.7% | | |
|                             | Baseline VA: ETDRS letter score 53.0–54.6 SD13.3–14.2 | | |
|                             | Baseline CMT: 410.4–413.4 SD127.8–134.1 μm | | |
|                             | Comorbidities: 17.8–19.5% PDR, 13.3–18.6% pseudophakia, 15–17.8% posterior vitreous detachment | | |

BCVA, best corrected visual acuity; C, control; CMT, central macular thickness; CPL, control plus laser; CSME, clinically significant macular oedema; DDS, dexamethasone; DIL, dexamethasone followed by laser; DM, diabetes mellitus; DMO, diabetic macular oedema; DP, diastolic pressure; DR, diabetic retinopathy; HR QoL, health-related quality of life; IOP, intraocular pressure; IV, intravitreal; IVB, intravitreal bevacizumab; IVP, intravitreal pegaptanib; IVR, intravitreal ranibizumab; IVT, intravitreal triamcinolone; IVTl, intravitreal triamcinolone plus laser; IVTVE, intravitreal VEGF Trap-E; L, laser; MLT/MPC, macular laser therapy/macular photocoagulation; NEI VFQ-25, National Eye Institute Visual Function Questionnaire-25; NPDR, non-proliferative diabetic retinopathy; NR, not reported; OCT, optical coherence tomography; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation; RCT, randomised controlled trial; RD, ranibizumab plus deferred laser; RPL, ranibizumab plus laser; SOC, standard of care; SP, systolic pressure; SRFA, fluorocinolone; TPL, triamcinolone plus laser; VA, visual acuity; VEGF, vascular endothelial growth factor.
### Table 8  Trials assessing more than one drug

| Study                        | Participants and baseline values | Intervention                                                                 | Outcome (change from baseline at study end) |
|------------------------------|----------------------------------|-------------------------------------------------------------------------------|-----------------------------------------------|
| Ahmadieh et al[11] Iran      | N: 115 eyes of 101 patients      | Group 1 (IVB, n=41 eyes): bevacizumab 1.25 mg (0.05 ml)                        | At 24 weeks                                   |
|                              | Inclusion criteria: eyes with clinically significant DMO unresponsive to previous macular laser photocoagulation (last session >3 months prior) | Group 2 (IVB/IVT, n=37 eyes): combined bevacizumab (1.25 mg (0.05 ml)) and triamcinolone (2 mg (0.05 ml)), followed by two injections of bevacizumab alone | BCVA (Snellen chart):                         |
|                              | Exclusion criteria: visual acuity ≥20/40; history of cataract surgery within past 6 months; prior intraocular injection or vitrectomy, glaucoma or ocular hypertension; PDR with high-risk characteristics; vitreous hemorrhage; significant media opacity; presence of traction on the macula; pregnancy; serum creatinine ≥3 mg/100 ml; monocular patients | Group 3 (C, n=37 eyes): sham injection | BCVA (logMAR), 95% CI                         |
|                              | Age: 59.7 SD8.3 years (range 39–74) | Regimen for all groups: 3 consecutive IV injections at 6-week intervals     | p Value                              |
|                              | Sex: 50.5% female                 |                                                                              | −0.18 (−0.29, −0.08) (+9 letters (4, 14.5)) |
|                              | Diabetes type: not reported, 27.6–33.3% on insulin | CMT (OCT): CMT (µm), 95% CI p Value | 0.01 vs C, NS vs IVB/IVT                  |
|                              | HbA1c: 9.35–10.06%                |                                                                              | −0.21 (−0.30, −0.12) (+10.5 letters (6, 15)) |
|                              | Baseline VA: not reported         |                                                                              | 0.006 vs C                                   |
|                              | Baseline CMT: not reported        |                                                                              | −0.03 (−0.08, 0.14) (+1.5 letters (−7, 4)) |
|                              | Comorbidities: (percentage of eyes) |                                                                              |                                                  |
|                              | 13.9% history of cataract surgery, 81.7% NPDR, 4.3% early PDR, 13.9% regressed PDR; no iris neovascularisation |                                                  |                                                  |
|                              | ATEMD Oliveira Neto et al[66]    |                                                                              |                                                  |
| Multicenter                  | N: 120 eyes of 120 patients       | Group 1 (IVB, n=NR eyes): IV bevacizumab 1.25 mg (0.05 ml)                  | At 6 months                                   |
|                              | Inclusion criteria: DMO, BCVA 20/40–20/400, CMT ≥275 µm | Group 2 (IVT, n=NR eyes): 4 mg (0.1 ml) of IV triamcinolone acetoneide       | BCVA:                                         |
|                              | Exclusion criteria: PDR, laser photoocoagulation in previous 3 months, no IV corticosteroid or anti-VEGF in previous 3 months | Group 3 (IVB/IVT, n=NR eyes): 1.25 mg (0.05 ml) of IV bevacizumab plus 4 mg (0.1 ml) of IV triamcinolone acetoneide | no significant difference between groups (between 1.7 and 2.3 lines gained in the different groups in 2010 report (n=18)) |
|                              | Age: not reported                 | Regimen for all groups: monthly injections | CMT (OCT): CMT (µm), 95% CI p Value | 0.012 vs C, NS vs IVB/IVT                         |
|                              | Sex: not reported                 |                                                                              | −95.7                                         |
|                              | Diabetes type: not reported        |                                                                              | −172.2, −19.3                                 |
|                              | HbA1c: not reported               |                                                                              | −92.1                                         |
|                              | Baseline VA: not reported         |                                                                              | −154.4, −29.7                                 |
|                              | Baseline CMT: not reported        |                                                                              | 34.9 (7.9, 61.9)                               |
|                              | Comorbidities: not reported       |                                                                              |                                                  |
|                              |                                     |                                                                              |                                                  |

Continued
### Table 8  
Continued

| Study | Participants and baseline values | Intervention | Outcome (change from baseline at study end) |
|-------|----------------------------------|--------------|------------------------------------------|
| **DRCR Network 2010 (Elman et al)**<sup>21, 46</sup> USA Multicenter Design: 4-arm placebo-controlled RCT Follow-up: 1–2 years; 2 years extension (Elman)<sup>46</sup> for consenting patients | **N**: 854 eyes of 691 patients  
**Inclusion criteria**: ≥18 years, type 1 or 2 DM; study eye: (1) BCVA letter score 78–24 (20/32–20/320), (2) definite retinal thickening due to DMO assessed to be main cause of visual loss, (3) retinal thickness measured on time domain OCT ≥250 µm in central subfield (2 study eyes per patient could be included if both were eligible at study entry)  
**Exclusion criteria**: (1) treatment for DMO within the prior 3 months, (2) panretinal photocoagulation within the prior 4 months or anticipated need for panretinal photocoagulation within the next 6 months, (3) major ocular surgery within the prior 4 months, (4) history of open-angle glaucoma or steroid-induced IOP elevation, requiring IOP-lowering treatment, (5) IOP ≥25 mm Hg; systolic pressure >180 mm Hg, diastolic pressure >110 mm Hg; myocardial infarction, other cardiac event requiring hospitalisation, cerebrovascular accident, transient ischemic attack, treatment for acute congestive heart failure within 4 months before randomisation  
**Age**: median 62–64 years (25th, 75th centile 55–58, 69–70)  
**Sex**: 41–46% female  
**Diabetes type**: 6–9% type 1 DM, 89–92% type 2 DM, 2–3% uncertain  
**HbA1c**: median 7.3–7.5% (25th, 75th centile 6.5–6.7, 8.3–8.6)  
**Baseline VA**: letter score 63 SD12 (<20/63 SD2.4 lines)  
**Baseline CMT**: 405 SD134 µm  
**Comorbidities**: 60–67% prior treatment for DMO | **Group 1 (CPL, n=293 eyes)**: sham injection plus prompt (within 3–10 days after injection) focal/grid photocoagulation  
**Group 2 (RPL, n=187 eyes)**: 0.5 mg IV ranibizumab plus prompt focal/grid photocoagulation  
**Group 3 (RDL, n=188 eyes)**: 0.5 mg IV ranibizumab plus deferred (≥24 weeks) focal/grid photocoagulation  
**Group 4 (TPL, n=186 eyes)**: 4 mg IV triamcinolone plus prompt focal/grid photocoagulation  
**Regimen for all groups**: Baseline treatment 0.5 mg IV ranibizumab and 4 mg preservative free triamcinolone; study treatment every 4 weeks up to 12 weeks, then retreatment algorithm: 16 to 20 weeks, monthly retreatment unless ‘success’ criteria were met (visual acuity letter score ≥84 (20/20) or OCT central subfield thickness <250 µm); 24–48 weeks, patients subdivided (according to predefined criteria) into ‘success’, ‘improvement’, ‘no improvement’ or ‘failure’; | **At 1 year BCVA (E-ETDRS Visual Acuity Test)**:  
**BCVA (letters)** | **p Value** |
| | **CPL** | +3 SD13 |  
| | **RPL** | +9 SD11 | <0.001 vs CPL |
| | **RDL** | +9 SD12 | <0.001 vs CPL |
| | **TPL** | +4 SD13 | NS vs CPL |

Subgroups:  
▸ BCVA results in TPL group substantially better for pseudophakic eyes than for phakic eyes (comparable to results for RPL and RDL groups) (p not reported)  
▸ No difference in results according to prior treatment for DMO, baseline VA, baseline CMT, baseline level of retinopathy, focal or diffuse oedema  

| **CMT (OCT)** | **CMT (µm)** | **p Value** |
|--------------|--------------|-------------|
| **CPL** | −102 SD151 |  
| **RPL** | −131 SD129 | <0.001 vs CPL |
| **RDL** | −137 SD136 | <0.001 vs CPL |

Continued
Table 8

| Study | Participants and baseline values | Intervention | Outcome (change from baseline at study end) |
|-------|---------------------------------|-------------|------------------------------------------|
|       | DMO; 61–68% with NPDR, 26–36% with PDR or PDR scars | ‘improvement’ group continued treatment, other groups treated at investigator discretion; alternative treatment permitted if eye met criteria for ‘failure’ or ‘futility’. In the case of retreatment, ranibizumab could be given as often as every 4 weeks, and triamcinolone every 16 weeks (with sham injections as often as every 4 weeks). | TPL | −127 SD140 | <0.001 vs CPL |
|       |       | Subgroups: |       |       |       |
|       |       | ▶ pattern of CMT decrease similar for groups with CMT <400 and ≥400 µm at baseline |       |       |       |
|       |       | ▶ Significantly more patients with severe NPDR or worse improved by 2 levels or more in the ranibizumab groups (28%, no significant change in the other groups)  |
|       |       | At 2 years (expanded results, Elman 2011) |       |       |       |
|       |       | BCVA (E-ETDRS Visual Acuity Test): |       |       |       |
|       |       | Retreatment for focal/grid laser (after ≥13 weeks from previous treatment) if there was oedema involving or threatening the center of the macula and if complete laser had not been given; retreatment algorithms facilitated by web-based real-time data entry system. Median number of drug injections before 1 year visit was 8–9 for ranibizumab, 3 for triamcinolone, and 5 sham injections. Retreatment between 1 and 2 years (Elman 2011): median injections 2 in RPL group, 3 in RDL group; in TPL group 68% of eyes received at least 1 injection; at least one focal/grid laser session between 1 and 2 years: 51% CPL, 40% RPL, 29% RDL, 52% TPL |       |       |       |
|       |       |       |       |       |       |
|       |       |       |       |       |       |
|       |       |       |       |       |       |

Continued
| Study | Participants and baseline values | Intervention | Outcome (change from baseline at study end) |
|-------|---------------------------------|--------------|--------------------------------------------|
| Jorge et al. \(^{1}\) Brazil | \(N: 63\) eyes of \(47\) patients | Laser Modified ETDRS protocol as used in prior DRCR.net protocols | At 48 weeks |
| Design: Prospective RCT | Inclusion criteria: Refractory cener-involving DMO | Group 1 (IVB 1.5 mg, \(n=NR\)): injections at baseline and monthly if CSFT (central subfield thickness) measured by SDOCT (spectral domain OCT) >275 µm | BCVA Mean BCVA reduction from baseline (logMAR) \(p\) Value |
| Follow-up: 24 and 48 weeks (to date, 73% and 56% of patients completed 24 and 48 weeks, respectively) | Exclusion criteria: NR | Group 2 (IVR 0.5 mg, \(n=NR\)): injections at baseline and monthly if CSFT >275 µm | IVB1.5 \(-0.21\) vs baseline \(<0.05\) at all-time points vs IVR0.5: no significant difference at all time-points |
| Sex: NR | Diabetes type: NR | CSFT Mean CSFT reduction from baseline \(p\) Value | IVR0.5 \(-0.21\) vs baseline \(<0.05\) at all time-points vs IVB1.5: no significant difference at all time-points |
| HbA1c: NR | Baseline VA: NR | | |
| Baseline CMT: NR | Comorbidities: NR | | |
| | | | |

### Continued

*Current treatments in diabetic macular oedema*
| Study | Participants and baseline values | Intervention | Outcome (change from baseline at study end) |
|-------|----------------------------------|--------------|---------------------------------------------|
| Lim et al<sup>65</sup> Korea | N: 111 eyes of 105 patients  
Inclusion criteria: eyes with clinically significant DMO based on ETDRS and DMO with central macular thickness of at least 300 µm by optical coherence tomography (OCT)  
Exclusion criteria: unstable medical status, including glycemic control and blood pressure; any previous treatment for DMO, including intravitreal, sub-Tenon injection or macular photoagulation, history of vitreoretinal surgery, uncontrolled glaucoma; proliferative diabetic retinopathy with active neovascularisation, previous panretinal photoagulation, presence of vitreomacular traction, history of systemic corticosteroids within 6 months, contraindications for bevacizumab or triamcinolone acetonide  
Age: 60.4 SD 7.4 (range 48–70) years  
Sex: 52% female  
Diabetes type: NR  
HbaA1c: 7.2 SD 1.2–7.4 SD1.2  
Baseline VA: 0.62 SD 0.23–0.65 SD 0.28 logMAR  
Baseline CMT: 447 SD 110–458 SD 92 µm  
Comorbidities: NR | Group 1 (IVB/IVT, n=36):  
IV injection of 1.25 mg (0.05 ml) IVB at 0 and 6 weeks and IV injection of 2 mg (0.05 ml) IVT at 0 weeks. Mean number of addition injection 1.28 | BCVA (logMAR)  
p Value  
IVB/IVT  
−0.15  
0.088 (between groups)  
IVB  
−0.16  
IVT  
−0.16 | Group 2 (IVB, n=38): IV injection of 1.25 mg (0.05 ml) IVB at 0 and 6 weeks. Mean number of injections 2.54.  
Group 3 (IVT, n=37): IV injection of 2 mg (0.05 ml) IVT at 0 weeks. Mean number of injections 1.04 | CMT (µm)  
p Value  
−199  
0.132 (between groups)  
−17s9  
−200 | Group 3 (IVT, n=37): IV injection of 2 mg (0.05 ml) IVT at 0 weeks. Mean number of injections 1.04 | Unclear if rescue laser was available  
IVB injections were repeated if CMT appeared >300 µm on OCT in at least 6 weeks in all three groups |
### Table 8 Continued

| Study                        | Participants and baseline values                                                                 | Intervention                                                                 | Outcome (change from baseline at study end)          |
|------------------------------|-------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|------------------------------------------------------|
| Soheilian et al. Iran        | N: 150 eyes of 129 patients<br>**Inclusion criteria:** eyes with clinically significant DMO (ETDRS criteria)<br>**Exclusion criteria:** previous panretinal or focal laser photocoagulation, prior ocular surgery or injection, history of glaucoma or ocular hypertension, VA $\geq 20/40$ or $<20/300$, iris neovascularisation, high risk PDR, significant media opacity, monocularis, pregnancy, serum creatinine $\geq 3$ mg/dL, uncontrolled DM<br>**Age:** 61.2 SD6.1 years<br>**Sex:** 47.3% female<br>**Diabetes type:** not reported<br>**HbA1c:** not reported<br>**Baseline VA:** 0.55–0.73 SD0.26–0.28 logMAR<br>**Baseline CMT:** 300–359 SD118–149 µm<br>**Comorbidities:** 94% NPDR, 6% early PDR | Group 1 (IVB, $n=50$ eyes): IV injection of bevacizumab 1.25 mg (0.05 ml) (retreatment IVB 14 eyes)<br>Group 2 (IVB/IVT, $n=50$ eyes): IV injection of combined bevacizumab (1.25 mg (0.05 ml)) and triamcinolone (2 mg (0.05 ml)), followed by two injections of bevacizumab alone (retreatment IVB/IVT 10 eyes)<br>Group 3 (MPC, $n=50$ eyes): focal or modified grid laser (retreatment MPC 3 eyes) | At 36 weeks<br>**BCVA (Snellen chart):**<br>**BCVA (logMAR), SD**<br>$0.28$ SD$0.25$ (+14 SD12.5 letters) vs IVB/IVT or MPC<br>$0.04$ SD$0.33$ (+2 SD16.5 letters)<br>$+0.01$ SD$0.27$<br>NS vs MPC<br>$+2$ lines or more: NS between groups<br>**Snellen line changes**<br>+2 lines or more: 37%<br>stable within 2 lines: 59.3%<br>$+2$ lines or more: 25%<br>stable within 2 lines: 54.2%<br>$+2$ lines or more: 14.8%<br>stable within 2 lines: 66.7%<br>$+2$ lines or more: 8.3%<br>stable within 2 lines: 33.3%<br>$+2$ lines or more: 12.5%<br>stable within 2 lines: 25.0%<br>$+2$ lines or more: 11.1%<br>stable within 2 lines: 61.1%<br>$+2$ lines or more: 10.0%<br>stable within 2 lines: 60.0%<br>$+2$ lines or more: 9.1%<br>stable within 2 lines: 59.1%<br>$+2$ lines or more: 8.2%<br>stable within 2 lines: 58.2%<br>$+2$ lines or more: 7.3%<br>stable within 2 lines: 57.3%<br>$+2$ lines or more: 6.5%<br>stable within 2 lines: 56.5%<br>$+2$ lines or more: 5.7%<br>stable within 2 lines: 55.7%<br>$+2$ lines or more: 4.9%<br>stable within 2 lines: 54.9%<br>$+2$ lines or more: 4.1%<br>stable within 2 lines: 54.1%<br>$+2$ lines or more: 3.3%<br>stable within 2 lines: 53.3%<br>$+2$ lines or more: 2.5%<br>stable within 2 lines: 52.5%<br>$+2$ lines or more: 1.7%<br>stable within 2 lines: 51.7%<br>$+2$ lines or more: 0.9%<br>stable within 2 lines: 50.9%<br>$+2$ lines or more: 0.1%<br>stable within 2 lines: 50.1%<br>$+2$ lines or more: NS between groups<br>**CMT (OCT):**<br>**CMT (µm), SD**<br>$-56$ SD$140$<br>NS vs baseline, between groups<br>$-5$ SD$113$<br>NS vs baseline, between groups<br>$-8$ SD$67$<br>NS vs baseline, between groups |
Adverse events are shown in tables 9 and 16. Conjunctival haemorrhages were higher in the ranibizumab arms compared with laser (RESTORE) or no treatment (RESOLVE). In the RESOLVE, RISE and RIDE studies, a considerably higher incidence of intraocular pressure (IOP) increase was reported in the ranibizumab arm compared to control. This increase in IOP was not demonstrated in the RESTORE study. There were no consistent differences in systemic adverse events between ranibizumab and laser or placebo.

Bevacizumab

Eight RCTs investigating the use of bevacizumab in DMO were identified (tables 4 and 8). One RCT, the BOLT study (n=80), randomised patients to laser therapy or 1.25 mg intravitreal bevacizumab. At 24 months, the mean changes in BCVA and the proportion of patients who gained 10 ETDRS letters or more was statistically significantly higher in the bevacizumab arm than in the laser arm. Faghihi et al (n=80) compared 1.25 mg bevacizumab (average 2.23 injections per patient) with 1.25 mg bevacizumab plus a single laser treatment (average 2.49 injections per patient). After 6 months, the authors found both treatments to be effective at improving BCVA, but neither treatment was found to result in a greater benefit.

Lam et al (n=52) compared two doses of bevacizumab (1.25 and 2.5 mg) in patients with diffuse DMO. Patients with focal DMO associated with localised retinal thickening were excluded. At 6 months, following 3 initial monthly injections (no treatment in the remaining 3 months), both groups showed a statistically significantly increased mean BCVA compared with baseline vision, but there was no difference between doses.

Four trials have investigated the combination of bevacizumab and triamcinolone. Ahmadieh et al (n=115) compared combined bevacizumab (three 1.25 mg injections at 6 week intervals) plus triamcinolone (2 mg baseline injection only, Triamhexal) with bevacizumab alone (three 1.25 mg at 6 week intervals) and sham injection in patients who had DMO unresponsive (definition not reported) to previous laser (last session more than 3 months previously). The combination arm and bevacizumab alone improved mean BCVA more than the sham injection. For BCVA, the combination of bevacizumab plus triamcinolone was non-statistically significantly better than bevacizumab alone.

Soheilian et al (n=150) compared combined bevacizumab (1.25 mg) plus triamcinolone (2 mg) with bevacizumab alone and laser alone in patients who were laser naive. At 36 weeks, bevacizumab alone improved BCVA more than either combination therapy or laser, although the difference was not statistically significant. Extended follow-up at 24 months showed that there was no statistically significant difference between groups for BCVA; however, the direction of effect favours the bevacizumab and combination arms more than the laser.24
### Table 9 Ranibizumab safety data

|                          | READ-2 study | RESOLVE study | RESTORE study | RISE study | RIDE study |
|--------------------------|--------------|---------------|---------------|------------|------------|
| **Number of patients**   |              |               |               |            |            |
| IVR: n=42; L: n=42; IVRL: n=42 |               |               | IVR0.3: n=51; IVR0.5: n=51; C: n=49 |               |            |
| IVR0.3: n=116; IVRL: n=118; L: n=111 |               |               | IVR0.3: 125; IVR0.5: 126; C: 123 |               |            |
| IVR0.5: n=10; L: n=12 (11%) |               |               | IVR0.3: 26%; IVR0.5: 21%; C: 19% |               |            |
| Ocular adverse events    |              |               |               |            |            |
| Eye pain                | NR           |               |               |            |            |
| IVR0.3: n=9 (18%); IVR0.5: n=9 (18%); C: n=10 (20%) |               |               | IVR0.3: 54%; IVR0.5: 52%; C: 32% |               |            |
| Conjunctival hyperaemia | NR           |               |               |            |            |
| IVR0.3: n=10 (20%); IVR0.5: n=13 (25%); C: n=7 (14%) |               |               | IVR0.3: 20%; IVR0.5: 14%; C: 2% |               |            |
| Conjunctival haemorrhage | NR           |               |               |            |            |
| IVR0.3: n=6 (12%); IVR0.5: n=15 (29%); C: n=1 (2%) |               |               | IVR0.3: 15.2%; IVR0.5: 18.5%; C: 11% |               |            |
| IOP increase            | NR           |               |               |            |            |
| IVR: n=1 (2%); L: n=4 (10%); IVRL: 3 (7%); L: n=1 (2%) |               |               | IVR0.3: 3.2%; IVR0.5: 3.2%; C: 13% |               |            |
| Vitreous haemorrhage     | NR           |               |               |            |            |
| Substantial worsening of DMO |              |               |               |            |            |
| Retinal ischaemia        | NR           |               |               |            |            |
| Retinal artery occlusion | NR           |               |               |            |            |
| Endophthalmitis          | NR           |               |               |            |            |
| Retinal detachment       | NR           |               |               |            |            |
| Neovascularisation       | NR           |               |               |            |            |
| Traumatic cataract       | NR           |               |               |            |            |
| Uveitis                  | NR           |               |               |            |            |
| Macular oedema           | NR           |               |               |            |            |
| Retinal exudates         | NR           |               |               |            |            |

Continued
| Event                              | READ-2 study | RESOLVE study | RESTORE study | RISE study | RIDE study |
|-----------------------------------|--------------|---------------|---------------|------------|------------|
| Retinal haemorrhage               | NR           | NR            | NR            | IVR0.3: 12.8%; IVR0.5: 12.7%; C: 20.3%; IVR0.3: 16.8%; IVR0.5: 11.9%; C: 14.6% | IVR0.3: 15.2%; IVR0.5: 22.6%; C: 18.9% |
| Cataract                          | NR           | NR            | NR            | IVR0.3: 13.6%; IVR0.5: 11.1%; C: 15.4% | IVR0.3: 8.8%; IVR0.5: 12.9%; C: 15% |
| Vitreous detachment               | NR           | NR            | NR            | IVR0.3: 15.2%; IVR0.5: 11.1%; C: 10.6% | IVR0.3: 3.2%; IVR0.5: 3.2%; C: 7.9% |
| Ocular hyperemia                  | NR           | NR            | NR            | IVR0.3: 12.8%; IVR0.5: 14.3%; C: 9.5% | IVR0.3: 7.2%; IVR0.5: 8.1%; C: 3.1% |
| Vitreous floaters                 | NR           | NR            | NR            | IVR0.3: 13.6%; IVR0.5: 11.1%; C: 15.4% | IVR0.3: 5.6%; IVR0.5: 5.6%; C: 3.1% |
| Eye irritation                    | NR           | NR            | NR            | IVR0.3: 10.4%; IVR0.5: 9.5%; C: 6.5% | IVR0.3: 8%; IVR0.5: 2.4%; C: 5.5% |
| Foreign body sensation in eyes    | NR           | NR            | NR            | IVR0.3: 12.8%; IVR0.5: 7.1%; C: 4.1% | IVR0.3: 3.2%; IVR0.5: 7.9%; C: 7.3% |
| Systematic adverse events         | Stroke in 1 pt (2%) in IVRL group- not related to study drug | IVR0.3: n=0; IVR0.5: n=3 (6%); C: n=2 (4%) | IVR: n=6 (5%); IVRL: n=1 (<1%); L: n=1 (<1%) | IVR0.3: 3.2% (n=1 stroke); IVR0.5: 7.9% (n=5 strokes); C: 7.3% (n=2 strokes) | IVR0.3: 1.6% (stroke), 5.6% (heart attack); IVR0.5: 2.4% (stroke), 2.4% (heart attack); C: 1.6% (stroke), 5.6% (heart attack) |
| Arterial thromboembolic events    | NR           | IVR0.3: n=4 (8%); IVR0.5: n=5 ((10%); C: n=5 (10%) | IVR: n=9 (8%); IVR0.3: n=6 (5%); IVR0.5: n=9 (8%); C: n=1 (<1%) | IVR0.3: 0.8%; IVR0.5: 3.2%; C: 0.8% | Serious IVR0.3: 1.6%; IVR0.5: 1.6%; C: 0% |
| Hypertension                      | NR           | IVR0.3: n=1 (2%); IVR0.5: n=1 (2%); C: n=0 | IVR: n=1 (<1%); IVR0.3: n=0; IVR0.5: n=1 (<1%); L: n=0 | NR | NR |
| Non-ocular haemorrhage            | NR           | NR            | NR            | NR         | NR         |
| Proteinuria                       | NR           | NR            | NR            | IVR: n=1 (<1%); IVR0.3: n=1 (<1%); L: n=0 | NR |
| Deaths                            | 1 (2%) due to CVA in IVRL group | NR            | NR            | IVR: n=2 (2%); IVR0.3: n=2 (2%); IVR0.5: n=2 (2%); C: 0.8% | IVR0.3: 3.2%; IVR0.5: 4.8%; C: 1.6% |

C, control; DMO, diabetic macular oedema; IOP, intraocular pressure; IVR, intravitreal ranibizumab; IVRL, intravitreal ranibizumab plus laser; L, laser; NR, not reported.
### Table 10  Bevacizumab safety

| Number of patients | BOLT study | Lam et al | Faghihi et al |
|--------------------|------------|-----------|--------------|
| MLT: n=38; IVB: n=42 | IVB1.25, n=26; IVB2.5, n=26 | IVB1.25 n=40 IVB 1.25 plus MLT n=40 |

#### Ocular adverse events

| Event                                | MLT | IVB |
|--------------------------------------|-----|-----|
| Loss of -15 or -30 ETDRS letters     | n=1 transient, 3 at 24 month analysis; n=4 transient | No significant ocular events (IOP increase, retinal tear, retinal detachment, endophthalmitis); no significant difference in change in cataract scores between groups |
| Vitreous haemorrhage                  | n=1; n=0 | |
| Eye pain/irritation/watering during or after injection | n=0; n=8 | |
| Red eye after injection               | n=0; n=8 | |
| Endophthalmitis                       | NR   | |
| Transient IOP increase                | ≥30 mm Hg—MLT: 0; IVB: n=4; ≥45 mm Hg—MLT: n=1; IVB: n=1 | |
| Floaters after injection              | n=0; n=2 | |
| Corneal epithelial defect             | n=0; n=1 | |
| Vitreomacular traction with macular oedema | n=1; n=0 | |

#### Systematic adverse events

| Event                                | MLT | IVB |
|--------------------------------------|-----|-----|
| Anaemia                              | n=1; n=0 | No systematic adverse effects (1 patient in 1.25 mg group with foot gangrene requiring amputation due to worsening diabetic neuropathy, considered unrelated to treatment) |
| Vomiting after FFA                   | n=0; n=0 | |
| Uncontrolled hypertension             | n=0; n=1 | |
| Polymyalgia rheumatica               | n=0; n=1 | |
| Intermittent claudication             | n=0; n=1 | |
| Gastroenteritis                      | n=0; n=1 | |
| Fall                                 | n=2; n=0 | |
| Urinary tract infection              | n=0; n=1 | |
| Chest infection                      | n=0; n=1 | |
| Headaches, dizziness, tiredness      | n=0; n=1 | |
| Bell palsy                           | n=1; n=0 | |
| Admission for diabetic foot ulcer    | n=1; n=1 | |
| Admission for cholecystectomy        | n=0; n=1 | |
| Admission for fall/loss of consciousness | n=1; n=0 | |
| Angina—hospital admission            | n=1; n=0 | |
| Cerebrovascular accident             | n=1; n=0 | |
| Myocardial infarction                | n=0; n=2 | |
| Coronary artery bypass graft         | n=0; n=1 | |
| Dyspnea, chest pain–admitted for hospital observation | n=0; n=1 | |
| Death                                | NR   | |

ETDRS, Early Treatment Diabetic Retinopathy Study; FFA, fundus fluorescein; IOP, intraocular pressure; IVB, intravitreal bevacizumab; MLT, macular laser therapy; NR, not reported.
Lim et al\textsuperscript{55} (n=111) also evaluated the combination of bevacizumab plus triamcinolone when compared with bevacizumab alone or triamcinolone alone. At 12 months, the authors found no statistically significant difference between groups for BCV A or CMT.

The Efficacy Study of Triamcinolone and Bevacizumab Intravitreal for Treatment of Diabetic Macular Oedema (ATEMD) study, currently only published in abstract form, compared combined therapy with bevacizumab (1.25 mg) and triamcinolone (4 mg) with each of these alone.\textsuperscript{56} At 6 months, they found no statistically significant difference between groups. One study comparing bevacizumab with ranibizumab is discussed above.\textsuperscript{51} No bevacizumab trials were suitable for meta-analysis because treatment arms were not comparable among included studies.

Adverse events are shown in tables 10 and 16. There was a low frequency of adverse events reported in the included trials. A higher incidence of mild anterior chamber reaction was reported in bevacizumab groups compared with controls. The incidence of IOP increase was comparable between bevacizumab and laser. Soheilian et al\textsuperscript{41} were the only authors to report the incidence of lens opacity. No patients in the bevacizumab alone group were found to have lens opacities but in four patients (8\%) in the bevacizumab plus triamcinolone group, this finding was observed over the 36-week follow-up period.

### Pegaptanib

Two studies have evaluated pegaptanib in DMO and both compared it with sham injection (table 5). Cunningham et al\textsuperscript{57} compare three doses of pegaptanib (0.3, 1 and 3 mg) and sham injection in laser-naive patients (n=172). At 6 months, patients in the 0.3 and 1 mg groups performed statistically significantly better than those in either the 3 mg or sham groups. Six injections (median) were administered in the 0.3 and 1 mg groups, whereas only five (median) injections were administered in the 3 mg group.

The second trial (n=260), reported by Sultan and colleagues in 2011, compared pegaptanib (0.3 mg) and sham injection. At 2 years, the pegaptanib group showed a statistically significantly greater improvement in mean BCV A compared with sham.\textsuperscript{40} However, there was no statistically significant difference in the proportion of patients with an improvement of 10 letters or more. Patients were allowed rescue laser at the assessors’ discretion (25.2\% of patients in the pegaptanib group and 45\% of patients in the sham group received rescue treatment). In regard to meta-analysis, data were only available to combine these trials for the proportion of patients with more than 15 letter gain. Although neither trial individually demonstrated a statistically significant difference favouring pegaptanib over sham (figure 5), when pooled together in meta-analysis, a statistically significant difference was found in favour of pegaptanib (OR 1.94, 95\% CI 1.01 to 3.71).

| Number of patients | Cunningham et al/Adamis et al\textsuperscript{57} | Sultan et al\textsuperscript{40} |
|--------------------|-----------------------------------------------|-------------------------------|
| Ocular adverse events | IVP0.3, n=44 eyes; IVP1, n=44 eyes; IVP3, n=42 eyes | IVP, n=133 eyes; C, n=127 eyes |
| Eye pain | Pegaptanib: 31%; C: 17% | IVP: 11.1%; C: 7% |
| Vitreous haemorrhage | Pegaptanib: 22%; C: 7% | IVP: 6.3%; C: 7.7% |
| Punctate keratitis | Pegaptanib: 18%; C: 17% | IVP: 11.8%; C: 6.3% |
| Cataract | Pegaptanib: 13%; C: 10% | IVP: 8.3%; C: 9.2% |
| Eye discharge | Pegaptanib: 11%; C: 10% | NR |
| Conjunctival haemorrhage | Pegaptanib: 10%; C: 0% | IVP: 22.2%; C: 14.1% |
| Vitreous opacities | Pegaptanib: 9%; C: 5% | NR |
| Blurred vision | Pegaptanib: 7%; C: 5% | NR |
| Other vitreous disorder | Pegaptanib: 7%; C: 0% | NR |
| Other visual disturbance | Pegaptanib: 7%; C: 0% | NR |
| Culture-negative endophthalmitis | Pegaptanib: n=1 | NR |
| IOP increase | NR | IVP: 17.4%; C: 6.3% |
| Retinal haemorrhage | NR | IVP: 6.3%; C: 10.6% |
| Retinal exudates | NR | IVP: 6.3%; C: 5.6% |
| Conjunctivitis | NR | IVP: 5.6%; C: 4.2% |
| Lacrimation increased | NR | IVP: 5.6%; C: 2.8% |
| Diabetic retinal oedema | NR | IVP: 11.1%; C: 17.6% |
| Macular oedema | NR | IVP: 9.7%; C: 11.6% |
| Systemic adverse events | | |
| Non-ocular hypertension | NR | IVP: 13.9%; C: 9.9% |
| Cardiac disorders | NR | IVP: 6.9%; C: 5.6% |
| Deaths | NR | IVP: n=4 |

IOP, intraocular pressure; IVP, intravitreal pegaptanib; NR, not reported.
Adverse events for pegaptanib are shown in table 11. There was a higher incidence of eye pain compared to control (31% vs 17%). Cataract formation was similar between the pegaptanib and control groups. There was a higher incidence of IOP increase in the pegaptanib arm compared to control (17.4% vs 6.3%). Other anti-VEGF A fibers have been evaluated in the Da Vinci study (n=219) (table 5). Four regimens of aflibercept (0.5 mg 4 weekly, 2 mg 4 weekly, 2 mg monthly for 3 months, then every 8 weeks, and 2 mg monthly for 3 months followed by treatment as required) were compared with laser. At 6 months, all aflibercept arms had a statistically better BCVA and CMT change than the laser arm. The regimen that resulted in the greatest BCVA gain and CMT reduction was 2 mg every 4 weeks; however, statistical significance between aflibercept arms was not reported. One year extended follow-up showed that all aflibercept arms were found to have a statistically significantly better BCVA compared to laser.

Adverse events are shown in table 12. There was a higher incidence of IOP increase and eye pain in the aflibercept group compared with laser. Other adverse events were too infrequent to draw meaningful conclusions. The incidence of cataracts was not reported.

**Table 12 Aflibercept safety**

| Number of patients | DA VINCI 2010<sup>30 58</sup> |
|--------------------|--------------------------------|
| Ocular adverse events | IVVTE (all doses) n=175, laser n=44 |
| Conjunctival hemorrhage | At 6 months: Laser 18.2%, IVVTE 18.9% |
| IOP increase | At 12 months: Laser 18.2%, IVVTE 26.9% |
| Eye pain | At 6 months: Laser 2.3%, IVVTE 9.7% |
| At 12 months: Laser 2.3%, IVVTE 9.7% |
| Ocular hyperaemia | At 6 months: Laser 4.5%, IVVTE 6.3% |
| Vitreous floaters | At 12 months: Laser 4.5%, IVVTE 6.3% |
| Endophthalmitis | At 6 months: Laser 0%, IVVTE 1.1% |
| Uveitis | At 12 months: Laser 0%, IVVTE 1.1% |
| Diabetic retinal oedema | At 6 months: Laser 2.3%, IVVTE 0.6% |
| At 12 months: Laser 0%, IVVTE 0.6% |
| Visual acuity reduced | At 6 months: Laser 2.3%, IVVTE 0% |
| At 12 months: Laser 2.3%, IVVTE 0% |
| Vitreous hemorrhage | At 6 months: Laser 2.3%, IVVTE 0% |
| At 12 months: Laser 2.3%, IVVTE 0% |
| Corneal abrasion | At 6 months: Laser 0%, IVVTE 0.6% |
| At 12 months: Laser 0%, IVVTE 0.6% |
| Retinal tear | At 6 months: Laser 0%, IVVTE 0.6% |
| At 12 months: NR |
| Systematic events | |
| Hypertension | At 6 months: Laser 6.8%, IVVTE 9.7% |
| At 12 months: Laser 0%, IVVTE 1.7% |
| Myocardial infarction | At 6 months: Laser 0%, IVVTE 1.1% |
| At 12 months: Laser 0%, IVVTE 1.1% |
| Cerebrovascular event | At 6 months: Laser 0%, IVVTE 1.1% |
| At 12 months: Laser 2.3%, IVVTE 1.7% |
| Death | At 6 months: Laser 0%, IVVTE 1.7% |
| At 12 months: Laser 2.3%, IVVTE 4% |

IOP, intraocular pressure; IVVTE, intravitreal vascular endothelial growth factor Trap Eye.

Other anti-VEGF

Aflibercept has been evaluated in the Da Vinci study (n=219) (table 5). Four regimens of aflibercept (0.5 mg 4 weekly, 2 mg 4 weekly, 2 mg monthly for 3 months, then every 8 weeks, and 2 mg monthly for 3 months followed by treatment as required) were compared with laser. At 6 months, all aflibercept arms had a statistically better BCVA and CMT change than the laser arm. The regimen that resulted in the greatest BCVA gain and CMT reduction was 2 mg every 4 weeks; however, statistical significance between aflibercept arms was not reported. One year extended follow-up showed that all aflibercept arms were found to have a statistically significantly better BCVA compared to laser.

Adverse events are shown in table 12. There was a higher incidence of IOP increase and eye pain in the aflibercept group compared with laser. Other adverse events were too infrequent to draw meaningful conclusions. The incidence of cataracts was not reported.

**Steroids**

**Dexamethasone**

Two included trials assessed the use of dexamethasone to treat DMO (table 6): Haller 2010 (full text available) and Callanan (available to date only in an abstract form). Haller 2010 (n=171) compared two doses of dexamethasone, administered as an intravitreal implant (350 and 700 µm) through a 20-gauge transcleral incision, with no treatment. At 90 days only, the 700 µm group showed a statistically significantly higher proportion of patients with 10 or more letter gain...
Two trials assessed fluocinolone implant for DMO (table 6). The FAME study (n=956) compared two doses of fluocinolone (0.2 and 0.5 µg/day) with sham injection in patients with at least one prior laser treatment. Approximately 25% of patients in each group had more than one prior laser treatment. At 24 months, both doses of fluocinolone showed a statistically significant improvement in mean BCVA compared to sham. There was no modest difference between fluocinolone groups. Rescue laser was given after the first 6 weeks for persistent oedema and was allowed every 3 months. A range of 35–37% of patients in the fluocinolone group and 59% in the sham injection group required rescue laser. Extended follow-up at 36 months showed that both the fluocinolone arms continued to result in a statistically significant benefit compared with sham.

Pearson et al (n=196) compared fluocinolone (0.59 mg) with standard of care, either laser or no treatment. At 3 years, there was no statistically significant difference in the proportion of patients with 15 letter gain or more (31% fluocinolone compared with 20% standard of care) between groups and the proportion of patients losing 15 letters or more in the fluocinolone group (17% compared with 14%). Increased incidence of cataracts may have contributed to this difference.

These trials were not suitable for meta-analysis. Adverse events are shown in table 13. Following the demonstration in the FAME trial that a lower dose was about as good as higher ones, the higher doses are unlikely to be used.

### Table 13 Dexamethasone safety

| Ocular adverse events | Callanan et al | Haller et al |
|-----------------------|---------------|-------------|
| IOP elevation         | DIL: 20% (p<0.001); 1% ≥10 mm Hg; 1.6%; 0% ≥10 mm Hg | DDS350: 29.1%; DDS700: 26.4%; C: 1.8% |
| Cataract              | NR            | DDS350: 18.2%; DDS700: 9.4%; C: 3.5% |
| Anterior chamber cells| NR            | DDS350: 14.5%; DDS700: 9.4%; C: 0% |
| Anterior chamber flare| NR            | DDS350: 14.5%; DDS700: 7.5%; C: 0% |
| Vitreous haemorrhage  | NR            | DDS350: 7.3%; DDS700: 17%; C: 0% |
| Eye pain              | NR            | No significant differences in: reduced VA, eye irritation, abnormal sensation in eye, macular oedema, eye pruritus, retinal hemorrhage, DR, nonocular events |
| Vitreous floaters     | NR            | |

DIL, dexamethasone followed by laser; DDS, dexamethasone; IOP, intraocular pressure; NR, not reported.
Triamcinolone
Ten trials evaluating triamcinolone were identified (tables 7 and 8). All trials evaluated intravitreal administration of triamcinolone, but there were no trials evaluating posterior or anterior subtenon injections. Two trials used Trivaris, two trials used Kenacort, one trial used Kenalog, one trial used Trimahexal and four trials did not report the type of triamcinolone used. Three doses were assessed in the included studies (1, 4 and 8 mg) and triamcinolone has been combined with laser or bevacizumab.

Ip and colleagues (n=840) were the only authors to evaluate triamcinolone 1 mg (Trivaris). They found a statistically significant improvement in mean BCVA at 2 years in the laser group compared with the triamcinolone group and no significant difference between 1 compared with 4 mg.

Several trials compared 4 mg intravitreal triamcinolone. Ip and colleagues (n=840) found that laser therapy resulted in a greater improvement in mean BCVA at 2 years compared to 4 mg triamcinolone (Trivaris). Lam et al (n=111) found no

| Number of patients | FAME study (Campochiaro et al) | Pearson et al |
|--------------------|-------------------------------|---------------|
| IOP at 12 months   | NR                            | NR            |
| Progression of cataract | NR                           | NR            |
| Cataract           | NR                            | SRFA: 55.9%; SOC: 21.7% |
| Transient vitreous floaters | NR                           | NR            |
| Transient subconjunctival haemorrhage | NR                 | NR            |
| Cataract surgery   | SRFA0.2: 41.1% (74.9% of those without cataract surgery at baseline, 80% at 36 months); SRFA0.5: 50.9% (84.5% of those without cataract surgery at baseline, 87.2% at 36 months); C: 7% (23.1% of those without cataract surgery at baseline, 27.3% at 36 months) | NR |
| Glaucoma           | SRFA0.2: 1.6%; SRFA0.5: 2.3%; C: 0.5% | NR |
| Increased IOP      | SRFA0.2: 3.2%; SRFA0.5: 3.3%; C: 0% | SRFA: 69.3%; SOC: 11.6% |
| IOP >30 mm Hg at any point during 36 months | SRFA0.2: 18.4%; SRFA0.5: 22.9%; C: 4.3% | NR |
| Trabeculectomy     | SRFA0.2: 2.1%; SRFA0.5: 4.8%; C: 0% | NR |
| Other glaucoma surgery | SRFA0.2: 1.3%; SRFA0.5: 1.3%; C: 0.5% | NR |
| Trabecuoplasty     | SRFA0.2: 0.8%; SRFA0.5: 2.3%; C: 0% | NR |
| Vitreous haemorrhage | NR                              | SRFA: 40.2%; SOC: 18.8% |
| Abnormal sensation in eye | NR                              | SRFA: 37%; SOC: 11.6% |
| Macular oedema     | NR                            | SRFA: 34.6% |
| Eye pain           | NR                            | SRFA: 26.8%; SOC: 15.9% |
| Eye irritation      | NR                            | SRFA: 22%; SOC: 10.1% |
| Increased lacrimation | NR                             | SRFA: 22%; SOC: 8.7% |
| Photophobia        | NR                            | SRFA: 21.3%; SOC: 21.7% |
| Blurred vision     | NR                            | SRFA: 21.3%; SOC: 15.9% |
| Vitreous floaters  | NR                            | SRFA: 21.3%; SOC: 8.7% |
| Systemic adverse events | SRFA0.2: 12%; SRFA0.5: 13.2%; C: 10.3% | SRFA: 38.6%; SOC: 21.7% |
| Serious cardiovascular events | SRFA0.2 | NR |
| Pruritus           | NR                            | SRFA: 38.6%; SOC: 21.7% |
| Deaths             | NR                            | NR            |

IOP, intraocular pressure; NR, not reported; SOC, standard of care; SRFA, fluocinolone.
| Ocular adverse events                      | Number of patients | DRCR Network 2008 (Ip et al/Beck et al/ Bressler et al) | Gillies et al/Sutter et al<sup>22-61, 63, 64</sup> | Kim et al<sup>65</sup> | Lam et al<sup>64</sup> | Ockrim et al/Sivaprasad et al<sup>42-62</sup> |
|-------------------------------------------|--------------------|----------------------------------------------------------|------------------------------------------------|---------------------|---------------------|-----------------------------------------------|
| **Number of patients**                    |                    | At 2 years (or 3 years when indicated)                   | At 2 years                                       | Not reported        | –                   | At 12 months                                   |
| **IOP ≥30 mm Hg**                         |                    | IVT1: n=22; IVT4: n=53; L: n=3                            | NR                                              | NR                  | –                   | IVT: IOP significantly higher than in L group (18.2 mm Hg, range 12–26 mm Hg); no cases of glaucoma |
| **IOP >22 mm Hg**                         |                    | NR                                                       | NR                                              | NR                  | –                   | NR                                            |
| **IOP ≥10 mm Hg from baseline**           |                    | IVT1: n=41; IVT4: n=85; L: n=12                           | NR                                              | NR                  | –                   | NR                                            |
| **IOP ≥5 mm Hg**                          |                    | NR                                                       | IVT: 68% (p=0.007 vs C); C: 10%                  | NR                  | –                   | NR                                            |
| **IOP lowering medication used**          |                    | IVT1: n=31; IVT4: n=76; L: n=25                           | IVT: 44% (p=0.0002 vs C); C: 3%                 | IVT: 64% (p<0.001); L: 24% | –                   | NR                                            |
| **Cataract surgery**                      |                    | IVT1: 23% (of those phakic at baseline, 46% by 3 years (p<0.001 between all groups); IVT4: 51% (of those phakic at baseline, 83% by 3 years); L: 13% (of those phakic at baseline, 31% by 3 years) | NR                                              | –                   | –                   | NR                                            |
| **Ptosis**                                |                    | NR                                                       | NR                                              | NR                  | –                   | NR                                            |
| **Retinal detachment**                    |                    | IVT1: n=2; IVT4: n=4; L: n=2                              | NR                                              | NR                  | None                | NR                                            |
| **Retinal vein occlusion**                |                    | IVT1: n=1; IVT4: n=2; L: n=3                              | NR                                              | NR                  | –                   | NR                                            |
| **Retinal artery occlusion**              |                    | IVT1: n=0; IVT4: n=0; L: n=1                              | NR                                              | NR                  | –                   | NR                                            |
| **Anterior ischemic optic neuropathy**    |                    | IVT1: n=1; IVT4: n=0; L: n=0                              | NR                                              | NR                  | –                   | NR                                            |
| **Vitrectomy**                            |                    | IVT1: n=26; IVT4: n=19; L: n=31                           | NR                                              | NR                  | –                   | NR                                            |
| **Open angle glaucoma**                   |                    | IVT1: n=2; IVT4: n=7; L: n=2                              | NR                                              | NR                  | –                   | NR                                            |
| **Glaucoma filtering surgery**            |                    | IVT1: n=0; IVT4: n=0; L: n=0                              | NR                                              | NR                  | –                   | NR                                            |
| **Laser trabeculoplasty**                 |                    | IVT1: n=0; IVT4: n=1; L: n=0                              | IVT: n=2; C: n=0                                 | IVT: n=1            | NR                  | NR                                            |
| **Ciliary body destruction**              |                    | IVT1: n=0; IVT4: n=1; L: n=0                              | NR                                              | NR                  | –                   | NR                                            |

Continued
| Table 15  | DRCR Network 2008 (Ip et al/Beck et al/Bressler et al) | Gillies et al/ Sutter et al\(^2\) 136–138 | Gillies et al\(^3\) | Kim et al\(^5\) | Lam et al\(^4\) | Ockrim et al/ Sivaprasad et al\(^2\) 62 |
|----------|----------------------------------------------------|------------------------------------------|-------------------|-----------------|-----------------|---------------------------------|
| Endophthalmitis | IVT: n=0; IVT4: n=0 L: n=0 | (Infectious) IVT: n=1; C: NR | (Culture-negative) IVTL: n=1 | None | (sterile) IVT: n=1 |
| Pseudoendophthalmitis | IVT: n=0; IVT4: n=0 L: n=0 | NR | NR | NR | NR |
| Chemosis | NR | NR | NR | NR | NR |
| Percentage of increase in cataract scores | NR | NR | NR | NR | NR |
| Ocular hypertension (>21 mm Hg) | NR | NR | NR | NR | NR |
| Cataract progression | NR | NR | NR | NR | NR |
| Cataract surgery | NR | IVT: NR; C: n=1 | NR | NR | NR |
| Corneal decompensation | NR | IVT: NR; C: n=1 | NR | NR | NR |
| Vitreous haemorrhage | NR | IVT: n=1 | NR | NR | NR |
| Lens opacity | NR | IVT: n=1 | NR | NR | NR |
| Deaths | N=33, unrelated to study treatment | IVT: n=1; C: n=2 | IVT: n=2; L: n=1 | NR | NR |

CPL, control plus laser; IOP, intraocular pressure; NR, not reported; IVT, intravitreal triamcinolone; IVTL, intravitreal triamcinolone plus laser; RDL, ranibizumab plus deferred laser; RPL, ranibizumab plus laser; TPL, triamcinolone plus laser.
| Number of patients | Ahmadieh31 (Oliveira Neto et al)56 | ATEMD 2011 | DRCR Network 2010 (Elman et al.,)51, 46 | Lim et al65 | Soheilian et al87, 41 |
|--------------------|------------------------------------|------------|------------------------------------------|------------|---------------------|
| Ocular adverse events | | | | | |
| Mild anterior chamber reaction | IVB: 19.5% (n=8 eyes), resolved after 1 week of no treatment; IVB/IVT: 18.9% (n=7 eyes), resolved after 1 week of no treatment | NR | NR | NR | IVB: 20% (n=10 eyes), resolved after 1 week; IVB/IVT: 18% (n=9 eyes), resolved after 1 week |
| Marked anterior chamber reaction | IVB: n=1 (topical corticosteroid and cycloplegic drops) | NR | NR | NR | IVB: n=1 (topical corticosteroids and cycloplegic drops); IVB: n=1 with no sign of retinal traction |
| Progression of fibrous proliferation | IVB: n=1 with no sign of retinal traction | NR | NR | NR | |
| Vitreous haemorrhage | IVB/IVT: n=1 after third injection (excluded from study) | NR | NR | NR | |
| OIP rise | IVB: 23, 22 and 28 mm Hg at 6, 12 and 18 weeks (anti-glaucoma drops) | NR | IOP elevation more frequent with triamcinolone + PL | IVB/IVT: 8.3% | NR |
| IOP ≥10 mm Hg from baseline | NR | NR | CPL: n=16; RPL: n=10; RDL: n=5; TPL: n=70 | NR | |
| IOP ≥30 mm Hg from baseline | NR | NR | CPL: n=3; RPL: n=2; RDL: n=4; TPL: n=46 | NR | |
| Initiation of IOP lowering treatment at any visit | NR | NR | CPL: n=9; RPL: n=5; RDL: n=4; TPL: n=41 | NR | |
| Iris neovascularisation | None | NR | NR | NR | |
| Lens opacity | None | NR | NR | NR | |
| Endophthalmitis | NR | NR | CPL: n=1; RPL: n=1; RDL: n=1; TPL: n=0 | NR | |
| Pseudoendophthalmitis | NR | NR | CPL: n=1; RPL: n=0; RDL: n=0; TPL: n=1 | NR | |
| Ocular vascular event | NR | NR | CPL: n=1; RPL: n=1; RDL: n=0; TPL: n=2 | NR | |
| Retinal detachment | NR | NR | CPL: n=0; RPL: n=1; RDL: n=1; TPL: n=0 | NR | |
| Vitrectomy | NR | NR | CPL: n=7; RPL: n=0; RDL: n=3; TPL: n=0 | NR | |
| Vitreous haemorrhage | NR | NR | CPL: n=15; RPL: n=3; RDL: n=4; TPL: n=2 | NR | |

Continued
Table 16  Continued

|                                             | Ahmadieh\textsuperscript{31} | ATEMD 2011 (Oliveira Neto et al)\textsuperscript{56} | DCR Network 2010 (Elman et al)\textsuperscript{21, 46} | Lim et al\textsuperscript{66} | Soheilian et al\textsuperscript{37, 41} |
|--------------------------------------------|-------------------------------|------------------------------------------------------|------------------------------------------------------|-------------------------------|--------------------------------------|
| Cataract surgery                           | NR                            | NR                                                   | CPL: 11 (of those phakic at baseline); RPL: 6 (of those phakic at baseline); RDL: 8 (of those phakic at baseline); TPL: 19 (of those phakic at baseline) | NR                            | NR                                   |
| Glaucoma surgery                           | NR                            | NR                                                   | NR                                                   | NR                            | NR                                   |
| Retinal neovascularisation                 | NR                            | NR                                                   | NR                                                   | NR                            | NR                                   |
| Development of early PDR                   | NR                            | NR                                                   | NR                                                   | NR                            | NR                                   |
| Progression to high-risk PDR              | NR                            | NR                                                   | NR                                                   | NR                            | NR                                   |
| Ocular hypertension (≥23 mm Hg)            | NR                            | NR                                                   | NR                                                   | NR                            | NR                                   |
| Systemic adverse events                    |                               |                                                      |                                                      |                               |                                      |
| Acute myocardial infarction                | N=1, considered not to be related to the study drug | No specific systemic adverse events that could be attributed to chance | No significant blood pressure increase, no thromboembolic events |                               |                                      |
| Deaths                                     | C: n=1                        |                                                      |                                                      |                               |                                      |

C, control; CPL, control plus laser; DMO, diabetic macular oedema; IOP, intraocular pressure; IVB, intravitreal bevacizumab; IVR, intravitreal ranibizumab; IVRL, intravitreal ranibizumab plus laser; IVT, intravitreal triamcinolone; L, laser; NR, not reported; PDR, proliferative diabetic retinopathy; RDL, ranibizumab plus deferred laser; RPL, ranibizumab plus laser; TPL, triamcinolone plus laser.
statistically significant difference between laser and triamcinolone at 6 months (triamcinolone type not reported). When these two trials were pooled through meta-analysis, the treatment effect favoured laser but the differences were not statistically significant (figure 6). Ockrim et al 62 (n=88) compared 4 mg intravitreal triamcinolone (Kenalog) with laser alone. At 12 months, they found no statistically significant BCVA improvement between the triamcinolone and laser groups. Gillies et al 32 (n=69) compared 4 mg of triamcinolone (Kenacort) with sham injection. Mean BCVA improved statistically significantly with triamcinolone at 24 months compared with sham injection (3.1 letter gain compared with 2.9 letter loss, p=0.01).

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**Table 2. Mean change in BCVA**

| Study or Subgroup | Ranibizumab 0.5 mg (Mean ± SD) | Laser alone (Mean ± SD) | Std. Mean Difference IV, Random, 95% CI | Std. Mean Difference IV, Random, 95% CI |
|-------------------|--------------------------------|-------------------------|----------------------------------------|----------------------------------------|
| READ-2 2009       | 0.14 ± 0.17                    | -0.01 ± 0.16            | 0.24 ± 0.16                            | 0.34 [0.21, 0.48]                      |
| RESTORE 2011      | 0.12 ± 0.13                    | 0.02 ± 0.17             | 0.25 ± 0.16                            | 0.35 [0.22, 0.48]                      |
| Total (95% CI)    | 152                            | 0.13 ± 0.17             | 0.24 ± 0.16                            | 0.46 [0.25, 0.67]                      |

**Figure 2** Ranibizumab 0.5 mg alone versus laser alone. (A) Mean change in best corrected visual acuity. (B) Proportion with >15 letter gain. (C) Central macular thickness.

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**Table 3. Proportion with >15 letter gain**

| Study or Subgroup | Ranibizumab 0.5 mg (Mean ± SD) | Laser alone (Mean ± SD) | Odds Ratio M-H, Random, 95% CI | Odds Ratio M-H, Random, 95% CI |
|-------------------|--------------------------------|-------------------------|--------------------------------|--------------------------------|
| READ-2 2009       | 0.08 ± 0.18                    | 0.14 ± 0.12             | 0.79 [0.50, 1.26]              | 0.80 [0.51, 1.27]              |
| RESTORE 2011      | 0.12 ± 0.16                    | 0.13 ± 0.13             | 0.89 [0.50, 1.60]              | 0.90 [0.51, 1.50]              |
| Total (95% CI)    | 160                            | 158                     | 0.76 [0.49, 1.19]              | 0.80 [0.51, 1.27]              |

**Figure 3** Ranibizumab 0.5 mg plus laser versus ranibizumab 0.5 mg alone. (A) Mean change in best corrected visual acuity. (B) Proportion with >15 letter gain. (C) Central macular thickness.
Lam et al. (n=111) compared triamcinolone 4 mg alone with 4 mg of triamcinolone plus laser or laser alone. At 6 months, the authors found no difference in BCV A between any of the groups. Elman et al. (n=854) compared 4 mg of triamcinolone (Trivaris) plus laser with ranibizumab plus prompt (within 3–10 days) or deferred (more than 24 week) laser and laser alone. At 2 years, they found a statistically significant difference in mean BCV A between ranibizumab plus prompt/deferred laser compared with laser alone (7 letter gain/9 letter gain compared with 3 letter gain), but no difference with triamcinolone plus laser compared with laser alone (2 letter gain compared with 3 letter gain). Neto et al. (n=120) compared 4 mg triamcinolone alone (triamcinolone type not reported) with 4 plus 1.25 mg bevacizumab. At 6 months, they found no statistically significant difference between groups.

The Elman and Lam studies were suitable for meta-analysis, which showed non-statistically significant improvements in mean BCV A between triamcinolone plus laser compared with laser alone (figure 7).

Adverse events are shown in tables 15 and 16. Triamcinolone was associated with consistently higher incidences of IOP increase and cataracts. Gilles and colleagues reported a cataract rate of over 50% by 3 years in patients treated with triamcinolone.

Other pertinent studies
Only one study in abstract form directly compared bevacizumab with ranibizumab. Bevacizumab and ranibizumab have been compared through an indirect comparison of five trials. There was no evidence of a difference between the drugs; however, wide credible intervals meant that the superiority of either drug could not be excluded.

Two-year results of the CATT (Comparison of AMD Treatment Trials) and 1 year results of the IVAN (Inhibit VEGF in Age-related choroidal Neovascularisation), recently published, have demonstrated a good safety profile of anti-VEGF therapies when used to treat patients with age-related macular degeneration. The CATT study randomised 1208 patients with AMD to monthly or as required injection of either ranibizumab or bevacizumab. At 1 year, the mean BCVA was similar in

**Figure 4** Ranibizumab 0.5 mg plus laser versus laser alone. (A) Mean change in best corrected visual acuity. (B) Proportion with >15 letter gain. (C) Central macular thickness.

**Figure 5** Pegaptanib 0.3 mg versus sham injection. (A) Proportion with >15 letter gain.
both groups (8 letter gain in bevacizumab and 8.5 in ranibizumab). Over 2 years, the rates of deaths, myocardial infarction and stroke did not differ between the ranibizumab and bevacizumab treatment groups. However, there was a higher rate of serious adverse events in the bevacizumab group compared with the ranibizumab group. This increased event rate was driven mainly by hospitalisations (RR 1.29, 95% CI 1.01 to 1.66). However, the hospitalisations were not caused by known adverse events of bevacizumab. Arteriothrombotic events and heart failure occurred in less than 2% of participants in the IV AN, and they were more often observed in the ranibizumab group than in the bevacizumab group (p=0.03). Further data from other ongoing clinical trials may provide more insight on the safety or anti-VEGF treatment and possible differences on this respect among available drugs.

Campbell et al conducted a population-based nested case–control study of 91 378 older adults with a history of physician-diagnosed retinal disease. The authors found that neither ranibizumab nor bevacizumab was associated with significant risks of ischaemic stroke, acute myocardial infarction, congestive heart failure or venous thromboembolism.

A recent systematic review specifically assessing adverse events in anti-VEGF drugs found a low incidence of serious (below 1 in 100) and non-serious ocular events (below 1 in 500) from ranibizumab, bevacizumab and pegaptanib.60 Fung et al61 used an internet-based survey of clinicians to assess the safety of bevacizumab. The survey covered over 5000 patients and found that bevacizumab was associated with an infrequent incidence of adverse events (all less than 0.21%).

One study, which assessed diclofenac, did not meet the inclusion criteria (follow-up for only 12 weeks).71 The authors randomised 32 patients to either intravitreal diclofenac or triamcinolone and found that both diclofenac and triamcinolone reduced CMT, but a statistically significant visual improvement was observed only in the triamcinolone group.

Sfikakis et al undertook a 30-week randomised cross-over trial comparing infliximab and placebo. The study failed to meet our inclusion criteria (only 11 patients included). The authors found that infliximab resulted in a 28.6% improvement in vision compared with 4.3% with placebo. The improvement seen with placebo could be due to a ‘carry over effect’, seen in cross-over trials.

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial was primarily a study to see if the lipid-lowering agent fenofibrate could reduce macrovascular and microvascular events in type 2 diabetes.73

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### Figure 6

Triamcinolone 4 mg versus laser alone. (A) Mean change in best corrected visual acuity. (B) Proportion with >15 letter gain.

### Figure 7

Triamcinolone 4 mg plus laser versus laser alone. (A) Mean change in best corrected visual acuity. (B) Proportion with >15 letter gain.
However, a substudy within FIELD recruited 1012 patients to a retinopathy study. The primary outcome in the main study was need for laser therapy (3.4% on fenofibrate vs 4.9% on placebo), but the substudy used retinal photography to assess progression of retinopathy or development of macular oedema. The HR at 6 years for DMO was 0.69 (95% CI 0.54 to 0.87) in the fenofibrate group compared to placebo.

Ruboxistaurin is another oral agent which has been assessed for the treatment of DMO. Aiello and colleagues randomised 686 patients to receive placebo or one of three doses of ruboxistaurin. There was no statistically significant difference in delay to sight-threatening DMO in any ruboxistaurin group compared to placebo. The authors suggest that differences in laser treatment between groups may have contributed to the non-significant finding.

**Assessment of heterogeneity within meta-analysis**

Heterogeneity was assessed methodologically and statistically. Methodological heterogeneity was assessed by comparing the study population, interventions, outcome measures and follow-up. Studies that were not methodologically comparable were excluded from the meta-analysis. For example, bevacizumab trials were not pooled because Soheilian et al included patients who were laser naive and Ahmadi et al included patients who were unresponsive to laser. Some analyses were also excluded because sufficient details were not reported in the studies. For example, several studies failed to report SDs.

Statistical heterogeneity was assessed through $I^2$ scores. High statistical heterogeneity was found in two analyses (2.3 and 4.3). Therefore, these results should be interpreted with due caution. Moderate heterogeneity was found in three analyses (2.2, 3.1 and 3.2). Low heterogeneity was found in the remaining eight analyses.

**Ongoing trials**

There are numerous ongoing studies listed in appendix 2. The most salient studies include a study to compare ranibizumab and bevacizumab (Schmidt-Erfurth), a study investigating rescue ranibizumab treatment for patients who have failed on bevacizumab (Chaudhry), a study evaluating two algorithms for ranibizumab, ‘treat and extend’ and ‘as required’ (RETAIL), further studies of Trap-eye (VIVID and VISTA) and trials which are examining the use of NSAIDs, such as diclofenac and nepafenac (NEVANAC and Soheilian).

**DISCUSSION**

It appears that anti-VEGF treatment is effective in DMO, especially ranibizumab and bevacizumab. Meta-analysis of available short-term data (up to 2 years) suggests that ranibizumab is superior to laser and that adding laser to ranibizumab treatment does not confer additional benefit. Steroid treatment has demonstrated mixed success and, almost uniformly, increased the incidence of cataracts and IOP. The licence for fluocinolone takes note of this and it is positioned as a treatment when others have failed.

**Strengths and limitations of the review**

There are a number of strengths of this review. A robust systematic review methodology was used. Reliability was improved by excluding trials with small sample sizes or short follow-up. Since a number of trials included similar intervention arms, consistent treatment effects further improve reliability. Validity was improved by assessing the quality of trials using the Cochrane risk of bias tables. Including abstracts from ARVO provided up-to-date results. Pooling results through meta-analysis provided further evidence. The random effects model was used throughout to allow for heterogeneity among studies.

This review, however, has limitations. Although the inclusion of abstracts provides more up-to-date results, the studies contained in these abstracts could not be assessed for risk of bias and should therefore be interpreted with caution. In addition, reporting of quality assessment criteria was variable. Allocation concealment was especially poorly reported. There was only one study which compared different anti-VEGFs and none that compared steroids (fluocinolone vs dexamethasone vs triamcinolone). Therefore, it is difficult to assess the effectiveness within drug classes. As with any meta-analysis, questions of heterogeneity arise. Follow-up periods varied among studies. A difference of 6 months was allowed for studies to be pooled for meta-analysis, but this could have still resulted in heterogeneity. High statistical heterogeneity was found in a quarter of the analyses. Furthermore, because of the low number of trials included, publication bias could not be assessed by funnel plot analysis. The manufacturers funded most of the trials for ranibizumab, pegaptanib, dexamethasone and fluocinolone, whereas trials for bevacizumab and triamcinolone were generally funded by non-pharmaceutical organisations. Generally, non-commercial studies had smaller numbers, perhaps because of the funding restraints.

It is important to note that there may be differences in laser treatment protocol between studies. This applies to trials which combine drug treatments with laser or include laser as a comparator. All studies referred to the ETDRS protocol or a modified version of it. In the ETDRS, once a diagnosis of clinically significant macular oedema was made, an angiogram was obtained to identify ‘treatable lesions’. ‘Treatable lesions’ included discrete points of retinal hyperfluorescence or leakage (most of these are often microaneurysms), areas of diffuse leakage within the retina related to microaneurysms, intraretinal microvascular abnormalities, diffusely leaking retinal capillary bed and retinal avascular zones. In the ETDRS protocol, treatment of lesions closer than 500 microns from the centre of the macula was not required initially; however, if vision was less than 20/40 and the oedema and leakage persisted, treatment up to 300 microns from the centre of the macula was
recommended unless there was capillary dropout; in the latter case, treatment was not recommended as it may lead to further loss of perifoveal capillaries.

However, in routine clinical practice, clinicians generally use lighter and less intense treatment than specified in the ETDRS protocol. In addition, some centres do not use fluorescein angiography (unlike the ETDRS study) to guide treatment. The exact adherence to the ETDRS protocol within studies is unclear. For example, in the BOLT study, a modified ETDRS protocol was used. One of the aims of the protocol was ‘not darkening/whitening of microaneurysms’, which is not consistent with the ETDRS protocol.

Interpretation of the results

The anti-VEGF drugs appear to be clinically effective in treating DMO in short-term studies (up to 2 years). Ranibizumab has the most robust evidence base and has shown superiority compared to laser and sham injection in all trials and meta-analyses, except for the proportion of patients with 10 or more letter gain in the DRCR.net study published by Elman et al at 2 years follow-up. Adding laser to ranibizumab conferred no benefit. Bevacizumab has also been shown to be superior to laser. Three doses have been used (1.25, 1.5 and 2.5). The higher dose does not appear to add further benefit, and most studies in the literature use 1.25 mg. The addition of triamcinolone to bevacizumab did not provide further benefits. Pegaptanib has only been compared to sham injection. Mean change in BCVA favoured pegaptanib, but only through meta-analysis did the proportion of patients with more than 15 letter gain favour pegaptanib. Further published data are required before drawing conclusions on aflibercept. However, although the anti-VEGF drugs are a significant advance, they fail to improve BCVA by 10 or more letters in half or more patients, and so they do not provide a complete answer to DMO.

Steroid treatments have inconsistent results and are undoubtedly associated with increased IOP and cataract. The effects of dexamethasone appear to peak at 3 months. At 6 months, there was no significant difference compared with laser. This might imply that earlier retreatment is needed if the beneficial effect is to be maintained, but increasing the number of treatments would very likely increase the associated complications, especially with the relatively large needle size. The addition of laser did not appear to add further benefit. There was no significant difference in cataract formation at 6 months with dexamethasone compared to observation, but it is likely that a higher incidence of cataracts would be seen with longer follow-up. Significantly more patients suffered increased IOP in the dexamethasone group compared with observation. Fluocinolone has been shown to be effective compared with sham injection (FAME); however, when compared to standard of care (laser or observation at clinician’s discretion), there was no significant difference in the proportion of patients with a 15 letter or more gain. Both studies reported higher incidence of cataract formation in the fluocinolone group, with over 80% at 3 years at the higher dose. Results for triamcinolone are inconsistent. Ip et al found that laser was more effective, while others have found no statistically significant difference. Triamcinolone combined with laser, however, seemed to have similar efficacy as ranibizumab combined with laser in pseudophakic eyes. Triamcinolone is more effective than sham injection. Triamcinolone has consistently been associated with increased incidence of cataract and raised IOP.

Steroids and laser therapy may affect CMT in a different manner from anti-VEGF drugs. For example, when ranibizumab alone is compared with ranibizumab plus laser, it appears to be more effective in terms of mean change in BCVA and proportion of patients with more than 15 letter gain. However, ranibizumab plus laser is more effective at reducing CMT. Furthermore, when triamcinolone plus laser is compared with ranibizumab plus laser, the latter appears to be more effective in terms of change in BCVA and proportion of patients with more than 15 letter gain, but triamcinolone plus laser is more effective at reducing CMT. The reasons for this are unclear. There is a weak correlation between CMT and BCVA. However, the long-term benefits of reducing CMT are currently unknown.

No large observational studies were identified that compared anti-VEGF drugs. Using an internet-based survey, Fung et al found the incidence of adverse events in bevacizumab to be low. One small outbreak of sterile endophthalmitis was reported with a single batch of bevacizumab in Canada, emphasising the need for sterility when preparing aliquots. Curtis et al carried out a very large retrospective cohort study in 146 942 patients aged 65 and over with age-related macular degeneration (AMD). Their aim was to examine cardiovascular outcomes in patients treated with the four options: photodynamic therapy (PDT), pegaptanib, bevacizumab and ranibizumab. The authors reported that one of their comparisons showed an increase in overall mortality and stroke risk with bevacizumab compared to ranibizumab, with HRs of 0.86 (95% CI 0.75 to 0.98) and 0.78 (0.64 to 0.96), respectively. However, owing to the very large cost differences between bevacizumab and ranibizumab, the authors noted that selection bias might be operating, with poorer people (with poorer health) more likely to be treated with bevacizumab. They therefore carried out another analysis using only ophthalmological clinics which used only one drug, to avoid selection bias. This analysis showed no significant difference: overall mortality HR for ranibizumab 1.10 (95% CI 0.85 to 1.14); MI 0.87 (0.53 to 1.14); stroke 0.87 (0.61 to 1.24).

Gower et al analysed 77 886 anti-VEGF injections from Medicare data (46% ranibizumab and 54% bevacizumab). Results have only been published in abstract form. The authors found an increased risk of overall mortality and cerebrovascular events in the bevacizumab group compared with the ranibizumab group, with HRs of 1.10 (95% CI 1.01 to 1.19) and 1.10 (95% CI 1.02 to 1.19), respectively. However, the authors noted that selection bias might be operating, with poorer people (with poorer health) more likely to be treated with bevacizumab. They therefore carried out another analysis using only ophthalmological clinics which used only one drug, to avoid selection bias. This analysis showed no significant difference: overall mortality HR for ranibizumab 1.10 (95% CI 0.85 to 1.14); MI 0.87 (0.53 to 1.14); stroke 0.87 (0.61 to 1.24).
group (HR 1.11 99% CI 1.01 to 1.23 and 1.57, 1.04 to 2.37, respectively). There was no statistically significantly increased risk in the ranibizumab group. The authors acknowledge that a limitation of the study is a failure to adjust for important confounding factors (such as smoking, hypertension and hyperlipidaemia). Considering the cost difference, it is likely that patients treated with bevacizumab would have been in a lower socioeconomic class and therefore at high risk of mortality and vascular disease.

Implications for clinicians

The anti-VEGF drugs appear to be a significant advance in the treatment of DMO and are regarded now as the treatment of choice for patients affected by this condition. Studies assessing the effectiveness of steroids have reported mixed results. The high rates of cataract and increased IOP are a drawback. Triamcinolone combined with laser may be a good option for pseudophakic patients and may be more cost-effective than treatment with ranibizumab. However, the need for fewer administrations, potentially one every 3 years with fluocinolone, is advantageous. From an administration perspective, some patients might prefer infrequent steroid injections with a sizeable risk of cataract, and a small, but existent, risk of glaucoma, to frequent anti-VEGF injections, even if the potential gain may not be fully comparable. Steroids may also be considered for patients who do not adequately respond to anti-VEGFs. Currently, the role of laser in the treatment of DMO is debatable. Short-term data from available trials have demonstrated the superiority of anti-VEGF with regard to laser treatment but have failed to demonstrate a benefit of combining both treatment approaches. It is possible that some ophthalmologists may still opt to offer laser treatment to patients with very focal areas of leakage.

Currently, there is more evidence for the effectiveness of ranibizumab and bevacizumab than for pegaptanib and VEGF-trap eye. The results of direct head to head trials of ranibizumab and bevacizumab are awaited. Bevacizumab is not licensed for intraocular use but costs considerably less than other forms of therapy. Ranibizumab is licensed and more expensive, but its use is supported by large manufacturer-funded trials demonstrating its clinical effectiveness. In the UK, the General Medical Council recommends that unlicensed medications should only be prescribed if ‘an alternative, licensed medicine would not meet the patient’s needs’ and there is ‘a sufficient evidence base and/or experience of using the medication to demonstrate its safety and efficacy’. The FDA says that when using a drug ‘off-label’, clinicians ‘have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product’s use and effects’. Patients should be fully aware of the use of any unlicensed medication and consent to any safety or efficacy uncertainties.

The place of intravitreal steroids needs consideration now that we have the anti-VEGFs drugs, as does the role of laser. The anti-VEGFs drugs may now be the first-line treatment in place of laser, with laser being used selectively for focal lesions, and in sequence after anti-VEGF therapy once the retinal thickness has been reduced. However, it should be noted that about half of the patients do not get good results with anti-VEGFs. In RESTORE, only 50% of patients had gains in VA of 10 or more letters. So the anti-VEGFs are ‘game-changers’, but their impact should not be overestimated.

In those who do not respond to anti-VEGFs or laser, there remains a place for steroids, despite their high adverse effect rates. The European licence for fluocinolone recognises this, by stating that it should be used when other therapies have not had sufficient effect. The commonest adverse effect is cataract, but that is very common in people with diabetes, and many are already pseudophakic when treatment of DMO is required.

Vitreoretinal surgery for the treatment of DMO was not included in our review. Laidlaw reviewed the literature and only found evidence for vitrectomy when there were signs of clinical or OCT traction. However, even in these cases, the evidence was not strong.

Implications for policy makers

In the UK, the National Institute of Health and Clinical Excellence (NICE) has recently made the decision not to recommend ranibizumab for the treatment of DMO. NICE concluded that ranibizumab, although clinically effective, was not cost-effective compared to laser therapy. Bevacizumab is less than a tenth of the cost of ranibizumab but is unlikely to be licensed. This beckons the question as to whether policy makers should recommend cheaper unlicensed medications over a more expensive licensed alternative when their efficacy and side effects appear to be similar.

Unanswered questions

Several unanswered questions remain. Studies evaluating the effectiveness of ranibizumab compared with bevacizumab are needed. Although the anti-VEGFs are clinically effective and a major step forward in the management of DMO, it has to be noted that they have little effect in a large number of patients. Generally speaking, the proportion of patients who have demonstrated 10 or more letter gain using anti-VEGFs is between 30% to 50% in the trials that demonstrate the greatest effectiveness. Most of these patients would not achieve the 20/40 visual acuity required for driving. More effective treatments, or combinations of treatments, are required.

There is a lack of specific evidence for the use of anti-VEGF drugs or steroids in patients with macular ischaemia secondary to DMO. A number of trials excluded patients with macular ischaemia. The RESTORE trial included patients with macular...
ischaemia and undertook a subgroup analysis. The authors compared patients with (n=34) and without (n=35) macular ischaemia at baseline. They found that those without macular ischaemia responded better to ranibizumab (mean average change in BCVA at 12 months 7.2 letters gain compared with 6.3 letters). Larger trials are needed to assess the use of anti-VEGF drugs and steroids in patients with macular ischaemia.

The duration of treatment is as yet uncertain. Most of the included studies use a retreatment protocol based on clinical need or OCT results. For example, in the BOLT study, patients received a median of nine injections of bevacizumab over 24 months. However, it is not yet known for how frequent long-term maintenance injections will be needed and whether laser treatment in sequence could potentially reduce the number of anti-VEGF injections required. Other treatment strategies to apply laser, such as using laser power at subthreshold levels, may prove more effective. Future trials should use active comparators which are used in routine clinical practice and avoid placebo-controlled trials.

CONCLUSION

This review evaluated current treatments for DMO. Undoubtedly, the use of anti-VEGFs heralds a new era for patients who suffer from DMO. Currently, the anti-VEGFs ranibizumab and bevacizumab have consistently shown good clinical effectiveness without major unwanted side effects. Steroid results have been mixed and are usually associated with cataract formation and IOP increase. Based on the short-term data available, adding laser therapy to anti-VEGFs does not appear to confer additional benefit.

Despite the current wider spectrum of treatments for DMO, only a small proportion of patients recover good vision (≥20/40), and thus the search for new therapies to prevent and manage DMO needs to be continued.

Contributors JAF screened titles, checked data extraction, performed the meta-analysis and drafted the manuscript. NL conceived the idea, interpreted the results and provided clinical expertise throughout. PR performed the literature search, updated the searches, screened the titles and managed the references. CC extracted data from the studies. DS screened the titles and checked the meta-analysis. NW designed the review and supervised the running of the study. All authors contributed to the final draft.

Competing interests None.

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Data sharing statement No additional data are available.

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132. Kuppermann BD, Blumenkranz MS, Haller JA, et al. Randomized controlled study of an intravitreal dexamethasone drug delivery system in patients with persistent macular edema. Arch Ophthalmol 2007;125:309–17.

133. Beyer DS, Faber D, Gupta S, et al. Dexamethasone intravitreal implant for treatment of diabetic macular edema in vitrectomized patients. Retina 2011;31:915–23.

134. Campochiaro PA, Hafiz G, Shah SM, et al. Sustained ocular delivery of fluocinolone acetonide by an intravitreal insert. Ophthalmology 2010;117:1393–9.
corticosteroid* or dexamethasone or fluocinolone or triamcinolone or anti-VEGF* or anti-vascular endothelial growth factor*) AND Title=(diabetic macular edema or diabetic macular oedema or diabetic retinopathy or diabetic maculopathy) AND Title=(random*)

Searches for systematic reviews
Ovid MEDLINE(R) Daily Update 11 July 2012, Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations 11 July 2012
1. Diabetic Retinopathy/dt (Drug Therapy)
2. Macular Edema/dt (Drug Therapy)
3. (diabet* adj2 macular adj (edema or oedema)).tw.
4. (diabet* adj2 maculopathy).tw.
5. (diabet* adj2 retinopathy).tw.
6. 1 or 2 or 3 or 4 or 5
7. (ranibizumab or lucentis or bevacizumab or avastin or pegaptanib or macugen or aflibercept or vegf trap-eye or steroid* or cortico-steroid* or dexamethasone or fluocinolone or triamcinolone or anti-VEGF* or anti-vascular endothelial growth factor*).tw.
8. exp Vascular Endothelial Growth Factor A/
9. exp Fluocinolone Acetonide/
10. exp Triamcinolone/
11. 7 or 8 or 9 or 10
12. 6 and 11
13. (systematic review or meta-analysis or pubmed or medline).tw.
14. meta-analysis.pt.
15. cochrane.af.
16. 13 or 14 or 15
17. 12 and 16
Cochrane Database of Systematic Reviews and Technology Assessments Database, Cochrane Library July Issue, 2012
Ranibizumab or lucentis or bevacizumab or avastin or pegaptanib or macugen or aflibercept or vegf trap-eye or steroid* or corticosteroid* or dexamethasone or fluocinolone or triamcinolone or anti-VEGF* or anti-vascular endothelial growth factor* in Record Title and diabetic macular edema or diabetic macular oedema or diabetic retinopathy or diabetic maculopathy in Record Title

Searches for safety and adverse events
Ovid MEDLINE(R) Daily Update 11 July 2012, Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations 11 July 2012; EMBASE 1980–2012 week 27
1. (ranibizumab or lucentis or bevacizumab or avastin or pegaptanib or aflibercept or vegf trap-eye or macugen or dexamethasone or fluocinolone or triamcinolone or anti-VEGF* or anti-vascular endothelial growth factor*).m_titl.
2. (diabetic macular edema or diabetic macular oedema or diabetic retinopathy or diabetic maculopathy).m_titl.
3. 1 and 2
4. (risk or safety or adverse or harm or pharmacovigilance).tw.
5. (side-effect* or precaution* or warning* or contraindication$ or contra-indication* or tolerability or toxic*).tw.
6. 4 or 5
7. 3 and 6

Searches of the annual meeting abstracts (for trials, reviews and safety studies)
► ARVO (Association for Research in Vision and Ophthalmology) (2002–2012)
► ADA (American Diabetes Association) (2002–2012)
► EASD (European Association for the Study of Diabetes) (2002–2012)

Other searches
Web sites of the following
► Drugs@FDA: FDA Approved Drug Products
► European Medicines Association
► ClinicalTrials.gov
► EU Clinical Trials Register
► National Institute for Health and Clinical Excellence

APPENDIX 2: ONGOING TRIALS IN CLINICALTRIALS.GOV
► Schmidt-Erfurth and colleagues are comparing ranibizumab and bevacizumab in DME (NCT00545870)
► TRIASTIN study is comparing ranibizumab, triamcinolone and sham injection (NCT00682539)
► Maturi and colleagues are comparing bevacizumab plus dexamethasone with bevacizumab alone (NCT01309451)
► IBeTA study (Jorge and colleagues) is comparing bevacizumab (1.5 mg) plus laser, triamcinolone (4 mg) plus laser with laser alone (NCT00997191)
► Chaudhry and colleagues are evaluating ranibizumab in patients who have failed with 3–6 injections of bevacizumab (NCT01253694)
► MIDME study (Pfizer) is comparing pegaptanib 0.3 mg with sham injection (NCT01175070)
► Figueiredo and colleagues are comparing pegaptanib plus laser with laser alone (NCT01281098)
► RESPOND (Novartis) is comparing ranibizumab (0.5 mg) alone with ranibizumab plus laser or laser alone (NCT0135914)
► RETAIN (Novartis) study is comparing two different ranibizumab algorithms; ‘treat and extend’ versus as needed (NCT01171976)
► RED-ES (Novartis) is comparing ranibizumab with laser in patients with visual impairment due to DME (NCT00901186)
► READ 3 study (Do and colleagues) are comparing two doses of ranibizumab 0.5 and 2 mg (NCT01077401)
► VIVID-DME and VISTA DME studies (Bayer) are comparing aflibercept with laser. (NCT01331681 and NCT01363440)
► Gillies and colleagues are comparing bevacizumab with dexamethasone (NCT01288076)
► Soheilian and colleagues are performing a phase I study looking at the use of diclofenac compared with bevacizumab in DME (NCT00999791)
► López-Miranda and colleagues are comparing the use of bevacizumab before and after laser therapy (NCT00804206)
► NEVANAC study is comparing triamcinolone alone with triamcinolone plus nepafenac (NSAID) (NCT00780780)
► Elman and colleagues are comparing laser alone, laser combined with an intravitreal injection of triamcinolone, laser combined with an intravitreal injection of ranibizumab, or intravitreal injection of ranibizumab alone (NCT00444600)
► BRDME (Schlingemann and colleagues) study is comparing the use of bevacizumab and ranibizumab in the treatment of patients with DME (OCT central area thickness > 275 µm) (NCT01635790)
► Wile and colleagues are comparing bevacizumab and ranibizumab in patients with DME in at least one eye (NCT01610557)
► Protocol T study (Wells and colleagues) is comparing effectiveness of a aflibercept, bevacizumab and ranibizumab for DME (NCT01627249)
► Allergan-funded study comparing safety and efficacy of 700 µg dexamethasone implant against 0.5 mg ranibizumab in patients with DME (NCT01492400)
► Pfizer-funded study comparing effectiveness of 0.3 mg pegaptanib against sham injection (NCT01100307)
► Allergan-funded study comparing safety and efficacy of an intravitreal dexamethasone implant (700 and 350 µg) against sham in patients with DME (NCT00168329)
► Allergan-funded study comparing safety and efficacy of an intravitreal dexamethasone implant (700 and 350 µg) against sham in patients with DME (NCT00168337)