The safety of intravitreal bevacizumab monotherapy in adult ophthalmic conditions: systematic review

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ABSTRACT

Objectives: To assess the safety of intravitreal bevacizumab (IVB) as a monotherapy and to evaluate the relationship between quality of treatment and adverse events.

Data sources: Cochrane Library, Ovid MEDLINE, MEDLINE in-process, Ovid EMBASE and Toxicology Literature Online (TOXLINE) from January 2009 to May 2012. Studies included in an earlier systematic review were also assessed for inclusion.

Study eligibility criteria, participants and interventions: Randomised controlled trials (RCTs), controlled trials or observational studies including ≥10 participants reporting adverse events data following IVB monotherapy as a primary treatment in patients (aged 18 years or more) with any eye condition were included.

Study appraisal and synthesis methods: Study selection was undertaken independently by a minimum of two reviewers using pre-defined criteria. Data abstraction and quality assessment were performed by one reviewer, and then checked by a second reviewer. Study quality was assessed for only RCTs in accordance to the Cochrane Risk of Bias Tool. Additional items relating to safety data were also assessed. Results were tabulated or meta-analysed as appropriate.

Results: 22 RCTs and 67 observational studies were included. Only two RCTs reported valid safety data. Rates of serious adverse events following treatment were low. There was insufficient data to explore the relationship between the incidence of adverse events and quality of IVB injection.

Limitations: A majority of relevant existing studies were characterised by small sample sizes, unclear diagnostic criteria and reporting of safety outcomes.

Conclusions and implications of key findings: Available evidence demonstrates low rates of serious local and systemic adverse events following treatment. However, the role of IVB quality in the incidence of adverse events remains unclear. Robust evidence is needed to examine the relationship between the incidence of adverse events and variables such as injection techniques, pre-existing risk factors (e.g., immunosuppression, cross-contamination) and quality of IVB treatment.

INTRODUCTION

Age-related macular degeneration (AMD) and diabetic retinopathy (DR) have been identified as two of the three most common causes of age-specific visual impairment in England and Wales. More recently, effective treatment options have included anti-vascular endothelial growth factors (anti-VEGFs), which have been shown to both delay deterioration in vision as well as improve vision. Ranibizumab (Lucentis, Novartis) is licensed for the treatment of wet AMD and diabetic macular oedema (DMO) and costs £742.17 per injection (0.23 mL vial). Pegaptanib (Macugen; Pfizer) for treatment of AMD is available at a price of £514 per injection (300 μg vial). However, bevacizumab, which cost £242.66 for 4 mL/100 mg vial, is used as an unlicensed intervention in ophthalmic conditions. Although many doses for intravitreal administration can be produced from a single bevacizumab vial and therefore can be supplied for a much lower cost, the actual cost of dispensing smaller doses is uncertain. However, annual cost savings have been estimated if bevacizumab is used as standard treatment instead of ranibizumab in patients with AMD.
Bevacizumab remains an unlicensed ophthalmic treatment for a number of reasons. There is an on-going debate with regard to intravitreal bevacizumab (IVB) use and its quality in clinical practice. One major concern relates to the risks associated with the reformulating the drug for intravitreal injections as well as possible adverse events (AEs) associated with systemically administered anti-VEGFs. Bevacizumab is reformulated for intravitreal use to deliver a smaller volume. However, the resulting reformulated product is considered by the Medicines and Healthcare products Regulatory Agency, a UK regulatory body for medicines and medical devices, as an unlicensed product. Another concern has centred predominantly on the possible risk of serious AEs such as endophthalmitis. To date, IVB safety evidence have been inconclusive. The aim of this review was to assess the safety, in terms of rates of specific serious AEs, of IVB monotherapy in ophthalmic conditions.

METHODS
We updated an existing systematic review on AEs of intravitreal anti-VEGF reported by van der Reis et al., which searched reports from 1948 to 2009. We adapted the search strategy by including specific AE terms and omitting selected terms because the previous search strategy:

- included fewer AE terms
- used broad terms such as ‘cause’ and ‘response’ and
- applied specific study design filters, for example, in vitro studies.

Free text and subject headings or thesaurus terms relating to the intervention (eg, bevacizumab, avastin) were combined with AE floating subheadings or specific AE terms. We searched the Cochrane Library; Ovid MEDLINE; MEDLINE in-process; Ovid EMBASE; and Toxicology Literature Online (TOXLINE) from January 2009 to May 2012 because this review was part of a project commissioned by the National Institute for Health and Care Excellence (NICE) through its Decision Support Unit (DSU) between April to August 2012. We did not search clinical trial registers. No experimental and functional study design filter or language restrictions were used. Our MEDLINE search strategy presented as an on-line supplementary file 1 was translated across different databases. Reference lists of all relevant studies and systematic reviews were checked and a citation search of relevant articles was also undertaken.

Study selection
Study selection was undertaken independently by a minimum of two reviewers using pre-defined criteria. Any disagreements in the selection process were resolved by consensus or referral to a third reviewer. All published or unpublished randomised controlled trials (RCTs), controlled trials or observational studies including ≥10 participants reporting AE data following IVB monotherapy as a primary treatment in patients (aged 18 years or more) with any eye condition were included. Relevant comparators were limited to monotherapies for RCTs only. Articles were excluded if patients had received prior treatment or received IVB as an adjunctive treatment. Non-English reports, narrative reviews, editorials, letters or publications relating to preclinical and biological studies were also excluded.

Data extraction and quality assessment
Data extraction and quality assessment were performed independently by one reviewer. Disagreements were resolved by discussion with a second reviewer and if agreement could not be reached, a third reviewer was consulted. Where multiple publications of the same study were identified, data were extracted and reported as a single study. Information abstracted included study characteristics, participant details (eg, number of patients, eye condition, mean age and baseline comparability), intervention and comparator details (eg, source, dose, injection quality and frequency of treatment) and outcomes. Outcomes of interest were limited to important and serious ocular and systemic AEs as listed below:

**Systemic AEs**
- Death
- Hospitalisation
- Non ocular haemorrhage (gastrointestinal, pulmonary, other non-ocular bleeds)
- Arterial thromboembolism
- Hypertension
- Myocardial infarction
- Cerebrovascular accident (stroke)
- Transient ischaemic attack

**Ocular AEs**
- Infectious endophthalmitis (infection of the eye)
- Retinal detachment
- Retinal (pigment epithelium) tear
- Anterior chamber reaction (including acute intraocular inflammation; uveitis; inflammation of the anterior chamber and hypopyon)
- Ocular haemorrhage
- Lens damage/injury (including cataract, clouding of the lens)
- Ocular hypertension (raised intraocular pressure >21 mm Hg)
- Visual loss

For RCTs, study quality was assessed in accordance to the Cochrane Risk of Bias Tool. Additionally, we assessed items relating to safety data for RCTs; these included follow-up period greater than 6 months, definition of AE and description of method of ascertaining AE. A formal quality assessment was not undertaken for observational studies. While checklists exist for evaluating the methodological quality of a range of non-randomised studies, there is no consensus on how to incorporate a single tool to appraise different study types in a review. It was anticipated that a variety of non-randomised study designs would be identified, so criteria assessed were
limited to study design (eg, prospective or retrospective), length of follow-up and baseline comparability when appropriate.

Data analysis
A pooled analysis was undertaken using the Cochrane Review Manager software where appropriate. The relative risk was calculated for dichotomous outcomes using a fixed effects model (Mantel-Haenszel method). Otherwise, descriptive statistics were tabulated. Estimates of AE rates were calculated by dividing the number of events by the number of patients who received IVB (event rate per patient) or the number of eyes treated (event rate per treated eye).

RESULTS
A flow chart of the study selection is shown in figure 1. Eighty-nine full text articles were included (n=22 RCTs, n=67 non-randomised studies). Of these 20 studies, including 1 RCT, were identified from the previous review. A total of 293 full text articles were excluded. Reasons for exclusion were wrong population, intervention or study type (n=162), unsuitable publication type (reviews, commentaries or editorials; n=34) and absence of usable data (n=97). A full list of excluded studies with reasons for exclusion is available on request.

Identified studies
A total of 22 RCTs comparing IVB with a variety of interventions as well as an observational control group with safety data were included, as presented in table 1.2,7-27 Study populations were patients with AMD (n=7 studies); DMO (n=8 studies); retinal vein occlusion (RVO) (n=4 studies) and other ophthalmic conditions (n=3). Assessment of study quality is presented as an on-line supplementary file 2. Study quality was considered to be moderate to low with only two RCTs16 19 meeting the criteria for valid safety data.

Sixty-seven observational studies were included as summarised in table 2. Most studies included patients with a single condition with fewer studies including a population with multiple conditions. Study quality was, generally, difficult to assess due to the quality of reporting. Approximately 65% of studies (n=44/67) were retrospective in design with follow-up periods of more than 6 months reported in less than a third (n=18/67) of included studies. Baseline characteristics of participants were comparable in two non-randomised studies28 29 and three case-control studies.30-32

Treatment schedule and source
Administration of 1.25 mg/0.05 mL was the most commonly reported dosage of IVB. Frequency of dosing and follow-up schedules varied across studies. Information relating to the source of IVB was reported in 35% (n=14/22) of RCTs but less than a fifth (19%; n=13/67) of observational studies.28 42-44 47 48 59 62 66 68 74 81 91 IVB was mostly provided by a local dispensing service such as the hospital’s pharmacy. There were limited data to assess quality of administered IVB.

Reporting of AEs
Ascertainment of AEs was presented more objectively in RCTs compared to observational studies. Non-RCT evidence was unclear because several studies reported absence of events as ‘no serious complications’; or ‘no ocular complications’, or ‘no adverse events were observed’, thereby providing limited information on diagnostic techniques or criteria for reported AEs. Furthermore, for AEs such as visual loss, ocular haemorrhage, hypertension and hospitalisation, the relationship between the outcomes and treatment schedule or setting remained largely unclear.

AEs reported in RCTs
Pooled 1-year data16 19 indicated that the risk of death (RR 1.38; 95% CI 0.71 to 2.68) or arteri thrombotic events (RR 0.81; 95% CI 0.42 to 1.59) were not significantly different between patients with AMD who received IVB or intravitreal ranibizumab (IVR). Furthermore, no significant difference in death between the IVB and IVR arms was observed when the CATT16 (2 year data) and IVAN19 (1 year preliminary data) clinical trials were pooled to provide long-term data analyses as shown in figure 2. Cardiac disorders, transient ischaemic attack and hospitalisation for angina were not significantly different between patients with AMD treated with IVB and IVR.19 However, serious systemic AE rates remained significantly lower in the IVG group (n=1795, RR 1.27 CI 1.09 to 1.47).

Two smaller studies, Biswas et al45 and Gharbiya et al18 with safety data for patients with AMD reported no significant AEs. No significant differences were found for death and myocardial infarction (MI) in studies that compared IVB to pegaptanib26 or sham injection2 (n=232 patients, RR 0.30; 95% CI 0.01 to 7.18).

Rates for endophthalmitis were not significantly different between IVB and IVR treatment groups for patients with AMD (1 RCT; RR 1.79; 95% CI 0.53 to 6.08).16 There were no reports of endophthalmitis,9 11 ocular hypertension,9 11 retinal detachment2 9 or vitreous haemorrhage9 11 in treatment groups comparing IVB with laser therapy in patients with DMO (n=269). In patients with DMO,21 22 25 ocular hypertension (IOP>21 mm Hg) was significantly higher in the IVT group (n=183; RR 0.13; CI 0.02 to 0.69) compared with the IVB group. A similar but non-significant trend was demonstrated in patients with RVO (n=32 patients; RR 0.08; CI 0.00 to 1.25).17

One short-term study at 3 months20 showed that posterior vitreous detachment was significantly higher in the IVB group compared with laser therapy (n=110; RR 17.00; CI 1.01 to 287.50). However, the rates of uveitis, vitreous haemorrhage, pigment epithelial tears and cataract progression were low and indicated no significant
differences between IVB and laser therapy. No significant differences in rates of foveal haemorrhage (n=81; RR 0.62; 95% CI 0.28 to 1.35) or hyphema (n=26; RR 7.8; 95% CI 0.46 to 131.62) were found in patients with RVO who had IVB or sham injection.

AEs reported in observational studies

Table 3, summarising safety data reported in observational studies, displays extensive variation in the detail of reporting of AEs with most studies not reporting or observing AEs of interest. While high event rates were reported for hospitalisation, hypertension, anterior chamber reaction and visual loss, these rates need to be interpreted with caution due to previously mentioned issues with reporting along with likely confounders.

Systemic AEs reported included death (0.4–3.8%), arterial thromboembolism (0–1.4%), hypertension (0–15.6%), MI (0–8.2%), cerebrovascular accident (0–8.7%), and transient ischaemic attack (TIA) (0.4–1.0%). Visual loss was the most commonly reported ocular event, the definition of visual loss was often unclear and occasionally associated with AEs such as anterior chamber inflammation, severe intraocular inflammation or retinal detachment. Consequently, it is uncertain whether visual loss occurred as an AE from treatment or progression of the patient’s condition. Infectious endophthalmitis was reported in 10 studies (range 0–1.0%). Three of the 13 studies in which patients received locally prepared IVB reported cases of infectious endophthalmitis. Reported rates were

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**Figure 1 Summary of study selection.** This flow chart outlines the process of study selection for the systemic review based on the recommendations of the PRISMA statement. RCT, randomised controlled trial.
| Study identifier, study location | Description of study population | Number of patients (eyes) | Interventions (treatment schedule and numbers treated) | Comparators (treatment schedule and numbers treated) | Reported safety outcomes | Information relating to preparation of intravitreal bevacizumab |
|---------------------------------|----------------------------------|--------------------------|--------------------------------------------------------|--------------------------------------------------|--------------------------|----------------------------------------------------------|
| Studies including patients with age-related macular degeneration (n=7 studies) | Neovascular age-related macular degeneration BCVA, 20/50 to 20/200 Submacular scarring or haemorrhage, sparing the fovea Mean age, 74.5 years | 62 (NR) | IVB: 2.5 mg, mean 2.4 injections (n=32) | Laser therapy: mean 2.3 sessions (n=30) | Systemic adverse events Hypertension Outcomes at 6 months | IVB prepared in hospital pharmacy |
| Bashshur et al. | Lebanon | Neovascular age-related macular degeneration BCVA, 35 to 70 ETDRS letter CMT, >250μm Mean age, not reported | 60 (60) | IVB: 1.25 mg, 3 monthly injections, mean 4.3 (n=30) | IVR: 0.5 mg, 3 monthly injections, mean 5.6 (n=30) | Significant adverse events (unspecified) Outcome at 18 months | Methods of IVB preparation not reported |
| Biswas et al. | India | Choroidal neovascularisation secondary to age-related macular degeneration BCVA, 20/25 to 20/320 Mean age, 79.5 years | 1185 (1107) | IVB: 1.25 mg, monthly or as needed (n=586) | IVR: 0.5 mg, monthly or as needed (n=599) | Death Endophthalmitis Hypertension Adverse events associated with anti-VEGF treatment Arteriothrombotic adverse events Outcomes at 2 years Serious adverse events Death Arteriothrombotic events Transient ischaemic attack Hospitalised for angina Outcomes at 1 year Pigment epithelial tears Posterior vitreous detachment Thromboembolic events Cataract progression Outcomes at 3 months | Commercially re-packaged and prefilled syringes IVB |
| CATT 2012 | USA | Choroidal neovascularisation secondary to age-related macular degeneration BCVA, 20/25 to 20/320 Mean age, 79.5 years | 165 (165) | IVB, 1.25 mg as continuous or as needed treatment at 3 separate visits (n=296) | IVR, 0.5 mg as continuous or as needed treatment at 3 separate visits (n=314 eyes) | Death Endophthalmitis Hypertension Adverse events associated with anti-VEGF treatment Arteriothrombotic adverse events Outcomes at 2 years Serious adverse events Death Arteriothrombotic events Transient ischaemic attack Hospitalised for angina Outcomes at 1 year Pigment epithelial tears Posterior vitreous detachment Thromboembolic events Cataract progression Outcomes at 3 months | Commercially re-packaged and prefilled syringes IVB |
| IVAN 2012 | UK | Neovascular age-related macular degeneration; BCVA, ≥25 ETDRS letters Mean age, 77.0 years | 610 | IVB, 1.25 mg as continuous or as needed treatment at 3 separate visits (n=296) | IVR, 0.5 mg as continuous or as needed treatment at 3 separate visits (n=314 eyes) | Death Endophthalmitis Hypertension Adverse events associated with anti-VEGF treatment Arteriothrombotic adverse events Outcomes at 2 years Serious adverse events Death Arteriothrombotic events Transient ischaemic attack Hospitalised for angina Outcomes at 1 year Pigment epithelial tears Posterior vitreous detachment Thromboembolic events Cataract progression Outcomes at 3 months | Commercially re-packaged and prefilled syringes IVB |
| Lazic and Gabric | Croatia | Minimally classic or occult choroidal neovascularisation secondary to age-related macular degeneration BCVA, ≥20/400 Mean age, 75.7 years | 165 (165) | IVB, 1.25 mg (n=55) | 1. Laser therapy: according to recommended standard procedures (n=55) 2. Combination treatment, that is, laser | Death Endophthalmitis Hypertension Adverse events associated with anti-VEGF treatment Arteriothrombotic adverse events Outcomes at 2 years Serious adverse events Death Arteriothrombotic events Transient ischaemic attack Hospitalised for angina Outcomes at 1 year Pigment epithelial tears Posterior vitreous detachment Thromboembolic events Cataract progression Outcomes at 3 months | Methods of IVB preparation not reported |
| Study identifier, study location | Description of study population | Number of patients (eyes) | Interventions (treatment schedule and numbers treated) | Comparators (treatment schedule and numbers treated) | Reported safety outcomes | Information relating to preparation of intravitreal bevacizumab |
|---------------------------------|---------------------------------|--------------------------|-------------------------------------------------------|--------------------------------------------------|-------------------------|-------------------------------------------------------------|
| Schimid-Kubista et al, Austria  | Choroidal neovascularisation secondary to neovascular age-related macular degeneration; BCVA, 5 to 40 ETDRS letters | 48 (48) | IVB, 1.0 mg every 6 weeks; total of 3 injections (n=13) | therapy followed by IVB, 1.25 mg within an hour (n=55) 1. IVP, 0.3 mg every 6 weeks; total of 3 injections (n=18) 2. IVB, 1.0 mg then two injections of IVP 0.3 mg 6 weeks apart (n=17) | IOP Raised blood pressure Outcomes at 6 months | Methods of IVB preparation not reported |
| Tufail et al, UK                | Neovascular age-related macular degeneration; BCVA, 6/12 to 6/96 (Snellen equivalent) or 25 to 70 ETDRS letter scores | 131 (NR) | IVB, 1.25 mg, three loading injections at 6 week intervals followed by further treatment if required at 6 week intervals, mean injections 7.1 (n=65). | 1. Laser therapy, (n=16) 2. IVP, 0.3 mg, (n=38) 3. Sham injection, (n=12) | Endophthalmitis Uveitis Retinal detachment Retinal tear Vitreous haemorrhage Lens damage Myocardial infarction Stroke Cerebral infarction Death Outcomes at 1 year | IVB injections were prepared as single use syringes with a shelf life of 6 weeks. Syringes were placed in sealed plastic pouches |
| Studies including patients with diabetic macular oedema (n=8 studies) | | | | | | |
| Ahmadieh et al, Iran            | Diabetic macular oedema BCVA, ≤20/40 Mean age, 59.7 years | 101 (115) | IVB, 1.25 mg at baseline and weeks 6 and 12 (n=41 eyes) | 1. IVB, 1.25 mg and IVT, 2 mg at baseline, then IVB, 1.25 mg at weeks 6 and 12 (n=37 eyes) 2. Sham injection (n=37 eyes) | Endophthalmitis Death Marked anterior chamber reaction Progression of fibrous proliferation Outcomes at 24 weeks | Methods of IVB preparation not reported |
| DRCRN 2007, USA                 | Diabetic macular oedema (patients with type 1 and type 2 diabetes) BCVA, ETDRS VA letter score, 24 to 78 (20/32 to 20/320) CMT ≥275 μm Median age, 65 years | 109 (109) | 1. IVB, 1.25 mg at baseline and week 6 (n=22 eyes) 2. IVB, 2.5 mg at baseline, week 6 (n=24 eyes) | 1. Laser treatment at baseline (n=19 eyes) 2. IVB, 1.25 mg at baseline, laser treatment at week 3, then IVB, 1.25 mg at week 6 (n=22 eyes) 3. IVB, 1.25 mg at baseline, sham at week 6 (n=22 eyes) | Endophthalmitis, raised intraocular pressure, raised blood pressure, myocardial infarction, congestive heart failure Outcomes over a 70-week period | Methods of IVB preparation not reported |

Continued
| Study identifier, study location | Description of study population | Number of patients (eyes) | Interventions (treatment schedule and numbers treated) | Comparators (treatment schedule and numbers treated) | Reported safety outcomes | Information relating to preparation of intravitreal bevacizumab |
|---------------------------------|---------------------------------|--------------------------|----------------------------------------------------------|----------------------------------------------------------|------------------------|----------------------------------------------------------|
| **Faghihi et al**, 11 Iran       | Diabetic macular oedema (patients with type 2 diabetes) BCVA, ≤20/40 CMT, >250µm Mean age, 57.5 years | 110 (130) | IVB, 1.25 mg, dosing schedule not reported (n = 42 eyes) | 1. Laser (n = 47 eyes) 2. IVB (1.25 mg) + IVT (2 mg) (n=41 eyes) | Safety assessment Vitreous haemorrhage Ocular hypertension (≥23 mm Hg) Outcome 16 weeks | Methods of IVB preparation not reported |
| **Lim et al**, 21 Korea          | Diabetic macular oedema BCVA, not reported CMT ≥300 µm Mean age, 60.0 years | 111 (120) | IVB, 1.25 mg at baseline and at week 6 (n=36) | 1. IVT, 2 mg (n=38) 2. IVB (1.25 mg)+IVT (2 mg) (n=37) | Hypertension Thromboembolic AE Serious ocular complications IOP Outcomes at 1 year IOP>22 mm Hg Cataracts Outcomes at 12 weeks | Methods of IVB preparation not reported |
| **Marey and Ellakwa**, 22 Egypt  | Clinically significant diabetic macular oedema BCVA, not reported CMT at baseline, reported per study groups Mean age, 57.7 years | 90 (90) | IVB, 1.25 mg (n=30) | 1. IVT, 4 mg (n=30) 2. IVB (1.25 mg)+IVT (4 mg) (n=30) | | |
| **Michaelides et al**, 8 UK      | Clinically significant diabetic macular oedema (in patients with type 1 or type 2 diabetes) BCVA, 35 to 69 ETDRS letters CMT ≥279µm Mean age, 57.7 years | 80 (80) | IVB, 1.25 mg at baseline, and then every 6 weeks as needed; number of injections ranged between 3 and 9 (n=42) | Laser therapy, every 4 months as needed; number of treatments, ranged between 1 and 4 (n=38) | Death IOP Loss of 30 ETDRS letters Vitreous haemorrhage Cerebrovascular accident Outcomes at 12 months | IVB prepared by Moorfields, London |
| **Shahin et al**, 25 Egypt        | Diffuse diabetic macular oedema BCVA, not reported CMT ≥292µm Mean age, 52.7 years | 32 (48) | IVB, 1.25 mg, single injection (n=24 eyes) | IVT, 4 mg, single injection (n=24 eyes) | IOP (≥23–43 mm Hg) Visually significant cataract Outcomes at 3 months | Methods of IVB preparation not reported |
| **Soheilian et al**, 2 Iran       | Diabetic macular oedema BCVA, 20/40 to 20/300 CMT, not used as inclusion criterion Mean age, 60.5 years | 129 (150) | IVB, 1.25 mg at baseline; treated repeated at 3 monthly interval on an as-needed basis (n=50 eyes) | 1. IVB, 1.25 mg+IVT, 2 mg; treated repeated at 3 monthly interval on an as-needed basis (n=50 eyes) | Death Lens opacities IOP Vitreous haemorrhage High risk proliferative | Methods of IVB preparation not reported |
| Study identifier, study location | Description of study population | Number of patients (eyes) | Interventions (treatment schedule and numbers treated) | Comparators (treatment schedule and numbers treated) | Reported safety outcomes | Information relating to preparation of intravitreal bevacizumab |
|---------------------------------|---------------------------------|--------------------------|--------------------------------------------------------|-----------------------------------------------------|--------------------------|----------------------------------------------------------|
| **Studies including patients with retinal vein occlusion (n=4 studies)** | | | | | | |
| Cekic et al,8 Turkey | Macular oedema due to branch retinal vein occlusion BCVA, ≤20/40 CMT, >250 μm Mean age, 63 years | 21 (21)* | IVB: 1.25 mg, mean 1.6 injections (n=14) | IVT: 4 mg, mean 1.4 injections (n=17) IVT+IVB (n=21) | Endophthalmitis, uveitis, thromboembolic events Outcomes at 6 months | Methods of IVB preparation not reported |
| Ding et al,17 China | Macular oedema secondary to retinal vein occlusion (unspecified) BCVA, ≤20/40 CMT, >250 μm Mean age, 54 years | 31 (32) | IVB, 1.25 mg, repeat treatment given if condition persisted or recurred (n=16 eyes) | IVT, 4 mg, repeat treatment given if condition persisted or recurred (n=16 eyes) | IOP>21 mm Hg Outcomes at 9 months | Methods of IVB preparation not reported |
| Epstein et al,12 Sweden | Macular oedema secondary to central retinal vein occlusion BCVA, 15 to 65 ETDRS letters (approx. 20/50 to 20/500) CMT ≥ 300μm Mean age, 54 years | 60 (60) | IVB, 1.25 mg at baseline and at weeks 6, 12 and 18 (n =30) | Sham injection: at baseline and at weeks 6, 12 and 18 (n=30) | Endophthalmitis Retinal tear Retinal detachment No serious non-ocular adverse events Outcomes at 6 months | IVB prepared in hospital pharmacy |
| Moradian et al,13 Iran | Acute branch retinal vein occlusion BCVA, ≤20/50 Mean age, 57.6 years | 81 (81) | IVB, 1.25 mg at baseline and 6 weeks (n=42) | Sham injection, at baseline and 6 weeks (n=39) | Foveal haemorrhage Foveal ischemia Outcomes at 12 weeks | Methods of IVB preparation not reported |
| **Studies including patients with other ophthalmic conditions (n=3 studies)** | | | | | | |
| Gharbiya et al,18 Italy | Pathologic myopia† BCVA, ≥26 ETDRS letters Mean age, 59.5 years | 32 (32) | IVB, 1.25 mg at baseline, then given as needed (n=16 eyes) | IVR, 0.5 mg at baseline, then given as needed (n=16 eyes) | Systemic adverse events Endophthalmitis Retinal detachment Vitreous haemorrhage Hypertension IOP Outcomes at 6 months | Methods of IVB preparation not reported |

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DISCUSSION

Eighty-nine studies were included in this systematic review of AEs, 22 of which were RCTs. Trials compared IVB with a number of different therapies and eye conditions, though most were in AMD, DMO and RVO. Most ocular and systemic safety measures had zero events in treatment groups or were not significantly different between groups. The quality of reporting of studies made it impossible to evaluate the impact of both known and unknown confounding factors (eg, the use of prophylactic antibiotic eye drops) on the incidence of AEs.

The most robust data for safety are from the CATT and IVAN trials which were large trials that reported longer term data. The results of these trials when meta-analysed revealed a statistically significantly higher rate of 1 or more serious systematic AE (RR 1.27; 95% CI 1.09 to 1.47) in the IVB group. In this analysis, the IVAN study alone did not show a statistically significant difference while event rates were higher in the CATT.

The recently published 2-year results of the IVAN study, which was not included in this review, has reported relatively worse safety outcomes for patients on discontinuous treatment compared to continuous treatment. In addition, there were no observed differences in mortality, frequency of thrombotic events or hospitalisation due to cardiac failure between groups of patients treated with IVB or IVR. Reported pooled analysis of the 2 years results of the CATT and IVAN studies tends to demonstrate that IVB and IVR are comparable in terms of safety. It is also important to note that AEs were more common in those patients who received discontinuous rather than patients on continuous treatment, that is, those with lower exposure to the drug experienced higher AE rates. An explanation for this observation is the possible role of immunological processes in drug interactions.

It is also important to note that the CATT study demonstrated some imbalances at baseline between randomised patients which may need further exploration. More patients randomised to IVB had had a previous TIA compared to those in the IVR arms. Similarly, more IVB patients had a history of MI. Despite these caveats, these trial designs offer the most robust assessment of AEs to date.

Overall, the evidence on IVB safety from observational studies was uncertain. This has previously been reported elsewhere. Included studies were frequently associated with methodological weaknesses that limited the validity of the reported findings. The majority of studies were retrospective in design with small study samples or...
| Author (year) | Study type | Condition (patients’ mean age in years) | Number of patients (number of eyes) | Baseline comparability (yes/no/unknown/not applicable) | Dosage (mg) including frequency of dosing | Number of injections/patients (mean) | Follow-up | Information on preparation of bevacizumab | Funding Notes |
|--------------|------------|----------------------------------------|------------------------------------|-------------------------------------------------|-----------------------------------------|-------------------------------------|----------|------------------------------------------|----------------|
| Abraham-Marin (2007) | Case series, (prospective) | CNV due to AMD (76) | 39 (39) | NA | 2.5 mg | 1 | 4 weeks | NR | NR |
| Arevalo (2010) | Case series, (retrospective) | CNV due to AMD (207) | 180 | NA | 1.25 mg (59.9%), 2.5 mg (40.1%) Frequency of dosing at discretion of treating physician | 5.1 (per eye) | 1, 3, 6, 12 and 24 months after the initial injection 1–7 days, 4 weeks, 8 weeks, 24 months | NR | Arevalo-Coutinho Foundation for Research in Ophthalmology, Venezuela |
| Artunay (2009) | Case series, (retrospective) | Various* (NR) | 1822 | NA | 1.25 mg once or repeated | NR | NR | NR |
| Azad (2008) | Non-randomised trial (prospective) | subfoveal CNV due to AMD (63) | 40 (40) | NA | 1.25 mg | 2.4 | 6 months | NR | NR |
| Baba (2010) | Case series (retrospective) | Myopic CNV | 40 (40) | Yes | 1.25 mg | 1.3 to 1.5 | 24 months | NR | NR |
| Bakri (2009) | Case series, (retrospective) | Various† (NR) | 35 (70) | NA | 1.25 mg | 5.9 | 39 days | NR | The Research To Prevent Blindness, New York American University of Beirut Medical Center |
| Bashshur (2009) | Nonrandomised trial, open-label, prospective (extension study) | CNV due to AMD (72.2) | 51 (51) | NA | 2.5 mg | 2.5 (3.4 during first 12 months, decreased to 1.5 during second year) | 24 months | local dispensing service | American University of Beirut Medical Center |
| Carneiro (2010) | Cohort, (prospective) | Subfoveal or juxtafoveal CNV secondary to AMD (76.9) AMD (77.8) | 97 (IVB group) | Yes (IVB:IVR) | 1.25 mg; | 7.8 | 2.3 years | NR | Sociedade Portuguesa de Oftalmologia, Hospital de Sao Joao, Switzerland National Foundation and Walter and Gertrud Sienenthaler Foundation |
| Carneiro (2011) | Cohort (retrospective):IVB vs IVR | MO due to BRVO (60.7) | 24 (25) | Yes (IVB:IVT:control; n=83) | 2.5 mg single injection then as needed | NR | 10 months (mean) | NR | Patients received IOP-lowering treatment during follow-up period if IOP ≥21 mm Hg. Anterior paracentesis was performed before IVB to reduce ocular pressure. |
| Chen (2010) | Non-randomised cohort (retrospective) | MO due to BRVO (60.7) | 24 (25) | Yes (IVB:IVT:control; n=83) | 2.5 mg single injection then as needed | NR | 10 months (mean) | NR | Patients received IOP-lowering treatment during follow-up period if IOP ≥21 mm Hg. Anterior paracentesis was performed before IVB to reduce ocular pressure. |

Continued
| Author (year)       | Study type                      | Condition (patients’ mean age in years) | Number of patients (number of eyes) | Baseline comparability (yes/no/unknown/not applicable) | Dosage (mg) including frequency of dosing | Number of injections/patients (mean) | Follow-up | Information on preparation of bevacizumab | Funding                        | Notes                                                                 |
|---------------------|---------------------------------|----------------------------------------|------------------------------------|--------------------------------------------------------|------------------------------------------|-------------------------------------|-----------|----------------------------------------|---------------------------------|---------------------------------------------------------------------|
| Cleary (2008)⁶²     | Case series (retrospective)     | Neovascular AMD (75)                   | 111 (112)                          | NA                                                     | 1.25 mg, once then as needed             | NR                                  | 4.9 (range 1–12) | Local dispensing service               | None                            | Author’s conclusion: IVB better than IVT                           |
| Costa (2006)⁶³      | Non-randomised dose escalation study (prospective) | CNV caused by AMD (74.6)               | 45 (45)                            | Yes (1.0 mg:1.5 mg:2.0 mg)                             | 1.0 mg, 1.5 mg and 2.0 mg               | NR                                  | 3                                    | Public funding (Foundation for Research Support of the State of São Paulo) | Reported as a dose escalation study but difficult to tell how many doses each participant was given and how far apart |
| Costagliola (2009)⁶⁴ | Case series (retrospective)     | CNV (subfoveal) due to AMD (73.2)      | 68 (68)                            | NA                                                     | 1.25; then monthly as per needed          | 3.87 (first 6 months); 1.09 (for remaining 6 months) | 12 | Local dispensing service               | NR                              | Exclusion criteria included previous history of thromboembolic events; uncontrolled hypertension, BP >150/90 mm Hg. Topical antibiotics prescribed for 3 days, after injection |
| Curtis (2010)⁶⁵     | Cohort (retrospective)          | AMD (median, 81.0)                     | 27 962 (IVB only; n=146 942)       | Yes (IVB:PDT: IVP: IVR)                               | NR                                      | NR                                  | 12 months                           | Research agreement between OSI Eyetech and Duke University         | Patient data were censored when at the time when a treatment which was different from initially assigned intervention was received. Between July and December 2006, study population was limited to treatment-naive patients who received bevacizumab or ranibizumab |
| Falkenstein (2007)⁶⁶| Case series (prospective)       | AMD (79.4)                             | 70 (NR)                            | NA                                                     | 1.25 mg assumed (0.05 mL)                | 1.74 (calculated from 122 injections for 70 patients) | 3,10 and 15 minutes | NR                                      | NR                              |                                                                 |
| Author (year) | Study type | Condition | Number of patients (mean age in years) | Baseline comparability (yes/no/unknown/not applicable) | Dosage (mg) including frequency of dosing | Number of injections/patients (mean) | Follow-up | Information on preparation of bevacizumab | Funding | Notes |
|--------------|------------|-----------|--------------------------------------|------------------------------------------------------|------------------------------------------|------------------------------------|-----------|----------------------------------------|---------|-------|
| Finntak (2008) | cohort (retrospective) | Various (NR) | 12 585 (IVB injections) | NR | 1.25 mg | NR | 5 days | Local dispensing service | Compounding pharmacy | Number of injections not reported |
| Fong (2008) | Case series (retrospective) | AMD (82) | 109 (109) | NA | 1.25 mg, three consecutive monthly injections then as needed | NR | 9.4 months (range 6-12) | Comming pharmacy | | |
| Frenkel 2010 | Cohort (retrospective) | AMD (80) | 47‡ | Unknown (IVB: ranibizumab: pegaptanib) | 1.25 mg | 1 | 20 minutes | | | |
| Fukami (2011) | Case series (retrospective) | AMD (77.5) | 30 (NR) | NA | 1.25 mg every 4 weeks 3 initial injections | NR | 2-4 months after last injection 9.4 months (±4.4) | | | |
| Gomi (2008) | Case series (Retrospective) | Polypoidal choroidal vasculopathy (65.4) | 11 (11) | NA | 1 mg‡ once or as needed | NR | | | |
| Good (2011) | Cohort (retrospective)** | AMD (76.6) | NR (101)†† | Yes | 1.25 mg | 7.0 | 86.6 days mean | Day 1 and after 2 week visits then at 4-week intervals. Minimum 6 months (range 4 to 12 months) | | |
| Goverdhan (2008)** | Case series (retrospective) | CNV due to AMD (79.5) | 53 (53) | NA | 1.25 mg | 1.36 | | | |
| Gower (2011)** | Cohort (retrospective) | Neovascular AMD (NR) | NR (NR) | NR (IVB:IVR) | NR | NR | | | |
| Hernandez-Rojas (2007) | Case series (prospective) | CNV due to pathological myopia (53.9) | 13 (13) (at follow-up—one patients lost to follow-up) | NA | 2.5 mg/0.1 mL once or as needed | NR | 3 months | | |
| Higashide (2012)** | Case series (retrospective) | Neovascular glaucoma (63.5) | 70 (84) | NA | 1.25 mg | 1.4 | 3 months | | |
| Hollands (2007)** | Case series (prospective) | Neovascular AMD (84.6%); DMO (6.7%); Others—histoplasmosis (8.7%) (76) | 104 | NA | 1.25 mg | 30 min | | | |

Table 2 Continued
| Author (year) | Study type | Condition (patients’ mean age in years) | Number of patients (number of eyes) | Baseline comparability (yes/no/unknown/not applicable) | Dosage (mg) including frequency of dosing | Number of injections/patients (mean) | Follow-up | Information on preparation of bevacizumab | Funding | Notes |
|--------------|------------|----------------------------------------|-------------------------------------|-----------------------------------------------------|----------------------------------------|---------------------------------|----------|------------------------------------------|---------|-------|
| Ikuno (2009) | Case series (retrospective) | CNV due to myopia (58.4) | 63 (63) | NA | 1 mg | 2.4 | 12 months | NR | The Ministry of Education, Culture, Sports and Technology of Japan; Health and Labor Sciences Research of Japan | Re-injection considered after 2–3 months if fluorescein leakage in angiogram or subretinal fluid persisted |
| Inman (2011) | Case series (retrospective) | NR | 608 (sample included patients that received IVB, IVP and IVR) | NA | NR | Unclear (1841 injections of IVB, 428 IVP and 2421 IVR) | 4.4 years Local dispensing service | NR | This study reported incidence of infectious endophthalmitis associated with 2% topical lidocaine gel anaesthesia. No information on conditions being treated or patient demographics. During the 1-year follow-up, an average of 2.4 re-injections (range, 0–5) were administered, with a mean of 1.6 re-injections within the first 6 months (weeks 6–24) and a further 0.8 re-injections over the latter 6 months (weeks 30–48). |
| Jaissle (2009) | Case series (prospective) | MO due to BRVO (median, 68) | 23 (23) | NA | 1.25 mg (re-injection considered if macular oedema persisted in foveal area and visual acuity 20/32 or worse) | NR | 1 year. (examined every 6 weeks) | NR | German Ophthalmological Society |
| Johnson (2010) | Case series (retrospective) | Various‡‡ (76.5) | 173 (193) | NA | NR | 3.98 | Median follow-up; 40 days (range 19 to 170 days) ≥4 weeks | NR | Queen’s University, Canada |
| Jonas (2007) | Case series (retrospective) | AMD | 625 (684) | NA | 1.5 mg | 1.95 | Local dispensing service | NR | None | 534 re-injections |
| Jonas (2008) | Case series (retrospective, consecutive) | Various | NR (3818 IVB injections) | NA | 1.5 mg | NR | ≥3 months | None | None |
| Julian (2011) | Case series (retrospective) | CNV due to uveitis (median, 41.9) | 15 (15) | NA | 1.25 mg (re-treatment based on signs of active neovascularisation) | 4.25 | 17.6 (median) | NR | None | In all cases, optimum control of intraocular inflammation was achieved by the time IVB was initiated |

Continued
| Author (year) | Study type | Condition (patients’ mean age in years) | Number of patients (number of eyes) | Baseline comparability (yes/no/unknown/not applicable) | Dosage (mg) including frequency of dosing | Number of injections/patients (mean) | Follow-up | Information on preparation of bevacizumab | Funding | Notes |
|--------------|------------|----------------------------------------|-------------------------------------|-------------------------------------------------|---------------------------------------------|----------------------------------|-----------|--------------------------------------------|---------|-------|
| Kim (2009)<sup>22</sup> | Before–after study of IVB group and triamcinolone acetonide group (retrospective) | MO due to BRVO (56.9) | 50 (50) (22 received IVB and 28 received triamcinolone acetonide) | NA | 1.25 mg single dose | NR | 24 weeks | NR | NR | NR |
| Kim (2011)<sup>65</sup> | Case series (retrospective) | DMO | 48 (65) | Yes | 1.25 mg | NR | ≥12 months | NR | Grant from Kyung Hee University | NR |
| Kim (2011)<sup>29</sup> | Non-randomised controlled study (prospective, consecutive) | AMD, RVO, DMO (64.8) | 60 (60) | Yes | 1.25 mg | 1 | NR | NR | NR | NR |
| Klas (2006)<sup>66</sup> | Case-control (retrospective)§§ | AMD (NR) | 61 | Yes | 1 mg | 1 | 7 days | Local dispensing service | NR | NR |
| Krebs (2009)<sup>97</sup> | Case series (prospective) | AMD (NR) | 44 (44) | Unknown | 1.25 mg 3 monthly injections based on OCT and FA findings | 2.6 | 1 week, 1 month and 3 months | Local dispensing service | NR | L. Boltzmann Institute |
| Krechbaum (2008)<sup>28</sup> | Case series (prospective) | MO due to BRVO or CRVO (66) | 28 (29) | Unknown | 1 mg at 4-week intervals 3 intravitreal injections | 5.3 | 1, 7 and 26 months | Local dispensing service | NR | NR |
| Krishnan (2009)<sup>28</sup> | Case control (retrospective) ¶¶ | CNV due to AMD (80.5) | 14 | No | 1.25 mg | NR | 2 and 4 weeks | NR | NR | NR |
| Kumar (2012)<sup>70</sup> | Case series (retrospective) | Eales’ disease (median, 33) | 14 (14) | Unknown | 1.25 mg | 1 | 3 months | NR | NR | NR |
| Lazic (2007)<sup>71</sup> | Case series (prospective) | CNV secondary to AMD | 102 (102) | NA | 1.25 mg, once then as needed | NR | ≥1.5 months | NR | None | Follow-up was 6-weekly and ongoing Same-day bilateral injections |
| Lima (2009)<sup>72</sup> | Retrospective cohort study | Various, mostly AMD | 326 (IVB injections) 86 | NR | NR | NR | NR | NR | Macula Foundation Inc. | NR |
| Lommatzsch (2009)<sup>73</sup> | Case series (retrospective) | AMD (77.7) | 86 | NR | 1.25 mg at 6 week intervals | 1.63 | 14 | local dispensing service | None | |
| Lorenz (2010)<sup>74</sup> | Case series (prospective) | Various*** | 144 (145) | Yes | 1.25 mg | 2.2 | 6-18 months | NR | University research grant, New York. | NR |
| Mason (2008)<sup>75</sup> | Case series (retrospective) | MO due to CRVO | 15 (15) | 15 | 1.25 mg | 2.2 | 6-18 months | NR | NR | NR |
| Manayath (2009)<sup>76</sup> | Case series (prospective) | Various††† | 15 | No | 1.25 mg | 2.2 | 6-18 months | NR | University research grant, New York. | NR |
| Rasier (2009)<sup>77</sup> | Quasi-experimental ‡‡‡ | AMD (67.2) | 82 | Unknown | 1.25 mg | 1 | 6 weeks | NR | NR | NR |
| Russo (2009)<sup>78</sup> | Non-randomised controlled trial | MO due to BRVO | 15 (15) | Yes (IVB:LGP) | 1.25 mg, once or repeated as necessary | NR | 12 months | NR | NR | NR |
| Saeed (2011)<sup>79</sup> | Cohort (prospective) | Retinal vascular occlusions and other causes of CMO (88.6) | 18 | NA | 1.25 mg | NR | NR | NR | NR | NR |

Continued
| Author (year) | Study type | Condition (patients' mean age in years) | Number of patients (number of eyes) | Baseline comparability (yes/no/unknown/not applicable) | Dosage (mg) including frequency of dosing | Number of injections/patients (mean) | Follow-up | Information on preparation of bevacizumab | Funding | Notes |
|--------------|------------|----------------------------------------|------------------------------------|----------------------------------------------------------|------------------------------------------|-------------------------------------|----------|------------------------------------------|---------|-------|
| Shah (2011)  | Cohort (retrospective) | Various | 10,958 (IVB injections) | NR | NR | NR | 6 days | NR | NR | Part-funded by Novartis (and part-funded by Canadian Institutes for Health Research) | IVR patients were on average 1.8 years older than IVB patients (78.7 vs 76.9, p = 0.01) and had slightly worse baseline vision (6/76 vs 6/64, p = 0.013). 195 out of the 351 patients that received IVR, had been treated previously with IVB (mean, 4.3 injections per patient). Prior treatment in IVB group unclear |
| Sharma (2012) | Cohort (retrospective) | AMD, DMO RVO (IVB group, 76.9) | 173 (693 IVB injections) | No difference in age and VA (IVB:IVR) | 1 mg unclear | NR | Local dispensing service |
| Shienbaum (2012) | Case series (retrospective) | AMD | 73 (74) | Yes (IVB:IVR) | NR (Monthly treatment until no intraretinal or subretinal fluid on optical coherence tomography. Treatment intervals determined by signs of exudation 1 mg Once or repeated injections | NR | 1.41 years | NR | None reported |
| Shima (2008) | Case series (retrospective) | Various§§§ | 707 (1300 injections) | NR | NR | ≥2 months | NR | Health Sciences Research Grant, Ministry of Health, Labour and Welfare, Japan |
| Shimada (2011) | Case series (retrospective) | Myopic CNV (58.4) | 74 (74) | NA | 1.25 mg At baseline, week 1, then monthly (unspecified length of time) | NR | 12 months (SD-4.3) | NR | Grants 19390441 and 19659445 from the Japan Society for the Promotion of Science, Tokyo, Japan |
| Sivkova (2010) | Case series (prospective) | CME due to DR, BRVO and CRVO (DR patients 59.7; RVO patients, 68) | 96 (107) | Unclear (DR:RVO) | 1.25 mg 3 consecutive injections at 1-monthly intervals | NR | 4 months | NR | No significant difference in adverse events between groups |
| Sohn (2011) | Case control (prospective) | DMO (54.5) | 11 | NA | 1.25 mg | NR | 1.3 months | NR | Gachon University, Incheon Korea |
Table 2 Continued

| Author (year) | Study type | Condition (patients' mean age in years) | Number of patients (number of eyes) | Baseline comparability (yes/no/unknown/not applicable) | Dosage (mg) including frequency of dosing | Number of injections/patients (mean) | Follow-up | Information on preparation of bevacizumab | Funding | Notes |
|---------------|------------|----------------------------------------|-------------------------------------|-----------------------------------------------------|--------------------------------------|-------------------------------------|-----------|------------------------------------------|---------|-------|
| Song (2011)   | Case control (retrospective)*** | DMO (57.1)                             | 35 (58)                             | Yes (IVB:IVT)                                       | 1.25 mg                               | NR                                  | 8 weeks   | NR                                       | Institute for Medicine research grant of Kosin University College of Medicine | NR     | Of 27 patients, 3 were lost to follow-up/protocol violation |
| Sonmez (2011) | Case series (prospective)     | Subfoveal CMO due to AMD (69.4)        | 24 (24)                             | NA                                                  | 1.25 mg weeks 0, 6 and 12, then every 12 weeks until week 48 | 5                                   | NR        | NR                                       | NR                  | NR |
| Spandau (2006) | Case series (retrospective, consecutive) | AMD                                      | 63                                  | NA                                                  | 1.5 mg                                | NR                                  | ≥2 months | NR                                       | NR                  | NR |
| Torres-Soriano (2012) | Case series (prospective)     | CNV PDR, RVO (NR)                      | 31                                  | NA                                                  | 2.5 mg, frequency not reported         | 1.3                                 | 1 month   | NR                                       | NR                  | NR |
| Vignalleggia (2009) | Case series (prospective)     | AMD due to AMD (75.5)                  | 324                                 | NA                                                  | 1.25 mg; then every 6 weeks. Frequency not reported | 3.3                                 | NR        | Local pharmacy                            | NR                  | NR |
| Weinberger (2007) | Case series (retropective)     | PED in exudative AMD (76)              | 31 (31)                             | NA                                                  | 1.25 mg once                          | NR                                  | 1–7 months | NR                                       | Academic institution | NR |
| Wickremasinghe (2008) | Case series (retropective)     | Neovascular AMD                         | 1278 IVB injections 1173 (1310)     | NA                                                  | 1.25 mg (16%), 2.5 mg (89%)          | 3.7 (3.3 per eye)                  | 12–15 (13.6) | NR                                       | No                  | NR |
| Wu (2008)     | Case series (retropective)     | Myopic CNV (49)                        | 26                                  | NA                                                  | 1.25 mg                               | 2                                   | 12 months | NR                                       | NR                  | Of the 40 patients included in the study, 14 received IVR |
| Yoon (2012)   | Case series (retropective)     | Myopic idiopathic CNV (50)             | 30                                  | NA                                                  | 1.25 mg                               | 2                                   | 12 months | NR                                       | NR                  | NR |
| Zhang (2012)  | Non-randomised intervention case series (prospective) | Subfoveal idiopathic CNV (32)       | 40                                  | NA                                                  | 1.25 mg                               | 2                                   | 12 months | NR                                       | NR                  | NR |

This table summarises the study characteristics of included observational studies. Data shown here include patient characteristics, interventions and outcomes reported in the included studies.

*Artunay 2009* studied patients with the following conditions: AMD, CNV due to myopic degeneration idiopathic and other secondary causes, cystoid or diffuse MO from CRVO, BRVO, diabetes, uveitis and retinitis pigmentosa proliferative retinopathies.

†Population included patients CNV due to AMD, DMO, DR, MO due to RVO or autoimmune retinopathy.

‡Forty-seven patients out of a study population of 71 received bevacizumab. A number of patients received all three anti-VEGF medications while others received just one treatment type. However, authors reported that only the first anti-VEGF injection was considered in the study.

§Gamulescu (2010) included a control group that received ranibizumab.

¶Injection in five eyes, 1 or 2 months after first injection at physician discretion.

**Good et al included a control group that received ranibizumab.

††101 eyes received bevacizumab only, 96 eyes received ranibizumab only and 18 eyes received bevacizumab and ranibizumab.

†‡Population included patients AMD, diabetes, retinal vein occlusion and other eye conditions.

§§Kiss et al included a control group that received triamcinolone acetonide.

¶¶Krishnan et al included a control group that received ranibizumab.

***Population included patients with AMD, BRVO, CRVO and myopic choroidal neovascularisation.

†††Population included patients with neovascular AMD; BRVO, CRVO; cystoid macular oedema; proliferative DR and DMO.

‡‡‡Rasier et al reported between-group comparison of hypertensive/non-hypertensive patients.

§§§Conditions included AMD, DR, CNV, BRVO, CRVO and other pathologies (unspecified).

¶¶¶Control group received triamcinolone acetonide.

AMO, age-related macular degeneration; BP, blood pressure; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; CMO, cystoid macular oedema; CNV, choroidal neovascularisation; DMO, diabetic macular oedema; DR, diabetic retinopathy; FA, fluorescein angiography; IVB, intravitreal bevacizumab; IVP, intravitreal pegaptanib; IVR, intravitreal ranibizumab; MO, macular oedema; NA, not applicable; NR, not reported; OCT, optical coherence tomography; PDT, photodynamic therapy; RVO, retinal vein occlusion; PED, pigment epithelium detachment.
inadequate follow-up periods (less than 6 months). With respect to larger studies, observational data from Curtis et al. suggest no difference in the risk of AEs between IVB and IVR once socioeconomic confounders are accounted for. On the other hand, results of an unpublished study of Medicare patients funded by Genentech found an increased risk of stroke and death in IVB patients. The available abstract, however, did not provide sufficient information to allow an in-depth analysis of the results of this study. A recently published population-based, nested case-control study reported by Campbell et al. (n=91 378) found no relationship between the risk of MI, venous thromboembolism, stroke or congestive heart failure and the administration of IVR or IVB. While the risk of systemic AEs was similar for both treatment groups, there was an increased risk of acute MI for a subgroup of patients with diabetes who received IVB.
This review highlighted the challenges of assessing the safety of IVB especially due to limited opportunities for in-depth detailed analyses of the relationship between IVB preparation and reported rates of infectious endophthalmitis. In the past, case reports have suggested contaminated batches of IVB as the primary source of infection; a published review of patient safety information held by the National Patient Safety Agency in England and Wales reported an increased risk of serious AEs including endophthalmitis following IVB treatment. The authors acknowledged that identifying the source of infection (ie, contaminated injection procedure or infected anti-VEGF) could be complex. However, Jonas et al, reporting on AE rates in a study population which included patients who had received IVB and IVT, suggested that event rates were statistically independent of drug injected (p=0.45), operating surgeon (p=0.18) and patient’s age (p=0.87).

It is also important to highlight limitations of this review. By relying on the previous systematic review as a source of evidence, it is possible that studies that were not identified in that review may have been missed in this review. Our searches were undertaken up to 2012. An updated electronic literature search was conducted up to 23 May 2014, retrieving a total of 1300 records. A preliminary shift of titles resulted in 333 potentially relevant abstracts for further detailed examination. We would prefer to have undertaken a full update. Unfortunately, this is not possible for us at present due to lack of the extensive time and resources required. Although comprehensive and up-to-date systematic reviews are desirable, a recent analysis of a sample of systematic reviews showed that the median duration of survival indicating a requirement for an update was 5.5 years (95% CI 4.36 to7.67) in systematic reviews of randomised trials of procedures or conventional drugs. Furthermore, many RCTs randomised small numbers of participants and these may have been underpowered to detect differences in AEs. Generalisability of findings may also be limited due to

| Systemic adverse events | Number of eligible studies contributing data | Percentage of eligible studies reporting zero events |
|-------------------------|---------------------------------------------|--------------------------------------------------|
| Adverse event           | Rates (%)                                   |                                                  |
| Death                   | 0.4 to 3.8                                  | Not applicable                                  |
| Hospitalisation         | 32†                                        | Not applicable                                  |
| Non-ocular haemorrhage  | 0.0                                        | 100%(n=1)‡                                      |
| Arterial thromboembolism| 0.0 to 1.35†                                | 78% (n=7)‡                                      |
| Hypertension            | 0.0 to 15.6                                 | 44% (n=4)‡                                      |
| Myocardial infarction   | 0.0 to 8.2                                  | 50% (n=5)‡                                      |
| Cerebrovascular accident| 0.0 to 8.7                                  | 45% (n=5)‡                                      |
| Transient ischaemic attack| 0.4 to 1.0                                 | 60% (n=3)‡                                      |
| Ocular adverse events   |                                            |                                                  |
| Infectious endophthalmitis| 0.0 to 1.0                                | 62% (n=19)‡                                     |
| Retinal detachment      | 0.0 to 29.0                                 | 75% (n=15)‡                                     |
| Retinal tear            | 0.0 to 15.0                                 | 42% (n=6)‡                                      |
| Anterior chamber reaction| 0.0 to 50.0                                | 57% (n=12)‡                                     |
| Ocular haemorrhage      | 0.0 to 72.0                                 | 43% (n=6)‡                                      |
| Lens damage             | 0.0 to 0.5                                  | 67% (n=6)‡                                      |
| Ocular hypertension     | 0.0 to 20.0                                 | 50% (n=8)‡                                      |
| Visual loss             | 0.0 to 50.0                                 | 11% (n=1)‡                                      |

Estimates of adverse event incidence were calculated by dividing the number of reported events by the number of patients that received IVB (event rate per patient) or the number of eyes treated (event rate per treated eye).

It is also important to highlight limitations of this review. By relying on the previous systematic review as a source of evidence, it is possible that studies that were not identified in that review may have been missed in this review. Our searches were undertaken up to 2012. An updated electronic literature search was conducted up to 23 May 2014, retrieving a total of 1300 records. A preliminary shift of titles resulted in 333 potentially relevant abstracts for further detailed examination. We would prefer to have undertaken a full update. Unfortunately, this is not possible for us at present due to lack of the extensive time and resources required. Although comprehensive and up-to-date systematic reviews are desirable, a recent analysis of a sample of systematic reviews showed that the median duration of survival indicating a requirement for an update was 5.5 years (95% CI 4.36 to7.67) in systematic reviews of randomised trials of procedures or conventional drugs. Furthermore, many RCTs randomised small numbers of participants and these may have been underpowered to detect differences in AEs. Generalisability of findings may also be limited due to

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Table 3 | Serious systemic and ocular adverse events reported in included observational studies

| Systemic adverse events | Number of eligible studies contributing data | Percentage of eligible studies reporting zero events |
|-------------------------|---------------------------------------------|--------------------------------------------------|
| Adverse event           | Rates (%)                                   |                                                  |
| Death                   | 0.4 to 3.8                                  | Not applicable                                  |
| Hospitalisation         | 32†                                        | Not applicable                                  |
| Non-ocular haemorrhage  | 0.0                                        | 100%(n=1)‡                                      |
| Arterial thromboembolism| 0.0 to 1.35†                                | 78% (n=7)‡                                      |
| Hypertension            | 0.0 to 15.6                                 | 44% (n=4)‡                                      |
| Myocardial infarction   | 0.0 to 8.2                                  | 50% (n=5)‡                                      |
| Cerebrovascular accident| 0.0 to 8.7                                  | 45% (n=5)‡                                      |
| Transient ischaemic attack| 0.4 to 1.0                                 | 60% (n=3)‡                                      |
| Ocular adverse events   |                                            |                                                  |
| Infectious endophthalmitis| 0.0 to 1.0                                | 62% (n=19)‡                                     |
| Retinal detachment      | 0.0 to 29.0                                 | 75% (n=15)‡                                     |
| Retinal tear            | 0.0 to 15.0                                 | 42% (n=6)‡                                      |
| Anterior chamber reaction| 0.0 to 50.0                                | 57% (n=12)‡                                     |
| Ocular haemorrhage      | 0.0 to 72.0                                 | 43% (n=6)‡                                      |
| Lens damage             | 0.0 to 0.5                                  | 67% (n=6)‡                                      |
| Ocular hypertension     | 0.0 to 20.0                                 | 50% (n=8)‡                                      |
| Visual loss             | 0.0 to 50.0                                 | 11% (n=1)‡                                      |
differences between study participants and patients seen in routine practice. In addition, there were concerns relating to ascertainment of exposure particularly in observational studies. The influence of excluding non-English publications in this review is unclear. Additionally, adopting a narrow focus in the definition of AEs implies that data on less serious or rare events were not presented.

CONCLUSIONS

Overall, rates of serious AEs following IVB were low when compared to other intravitreal treatments, sham injection and laser therapy with relatively higher rates being reported in head-to-head studies of IVB versus ranibizumab. Most outcomes were, however, not significantly different between treatment groups. Current evidence from observational data still remains limited due to relatively small sample sizes, unclear definition, evaluation and reporting of safety outcomes as well as adequate follow-up periods. However, an opportunity to explore the relationship between the incidence of AEs and other variables such as injection techniques, pre-existing risk factors (eg, immunosuppression, cross-contamination) and quality of IVB could offer cost-saving options in providing treatment for certain ophthalmic conditions.

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Contributors

EP coordinated the systematic review and was responsible for the conception and design, acquisition of data, analysis and interpretation of data and drafting and revision of the final manuscript. JR was responsible for the conception and design, acquisition of data, analysis and interpretation of data and drafting and revision of the final manuscript. EE-H and ME were responsible for acquisition of data, analysis and interpretation of data and drafting and revision of the final manuscript. AW contributed to the conception and design of the study, assisted with data collection analysis, interpretation of data and drafting and revision of the final manuscript. AD contributed to the conception and design of the study, assisted with analysis and interpretation of data and drafting and revision of the final manuscript.

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Competing interests

None.

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Data sharing statement

Extra data relating to references of excluded full-text articles is available by emailing Edith Poku (e.poku@sheffield.ac.uk).

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