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Anti-VEGF therapies in the treatment of choroidal neovascularisation secondary to non-age-related macular degeneration: a systematic review

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ABSTRACT

Objectives: The aim of this study is to systematically review the evidence for anti-vascular endothelial growth factor (VEGF) therapy in choroidal neovascularisation secondary to conditions other than age-related macular degeneration.

Data sources: MEDLINE, MEDLINE in-process, EMBASE and CENTRAL databases and conference abstracts were searched (from inception to Jan 2014).

Study eligibility criteria, participants and interventions: Randomised and non-randomised comparative studies with follow-up of at least 6 months were included and were used to assess clinical effectiveness.

Study appraisal and synthesis method: Risk of bias was assessed using the Cochrane risk of bias tool and modified Newcastle-Ottawa Scale. Meta-analysis was not possible due to methodological heterogeneity.

Results: 16 studies met the inclusion criteria (1091 eyes; 963 pathological myopia, 74 other conditions). There was large variation in risk of bias across studies. An improvement in best-corrected visual acuity in anti-VEGF arms over comparators was reported in all studies. The proportion of patients improving by at least 15 letters in anti-VEGF arms ranged from 27.3% to 70%. There were no significant differences between bevacizumab and ranibizumab.

Limitations: Owing to the rarity of choroidal neovascularisation secondary to conditions other than age-related macular degeneration or pathological myopia, there are unlikely to ever be sufficiently powered trials in these populations.

Conclusions: Bevacizumab and ranibizumab appear to be effective in improving visual acuity for patients with choroidal neovascularisation secondary to conditions other than age-related macular degeneration. The evidence base is strongest for choroidal neovascularisation secondary to pathological myopia, however, based on current evidence and likely pharmacological pathways, clinicians should consider treatment with either bevacizumab or ranibizumab for rarer causes.

Strengths and limitations of this study

- A broad search has been undertaken, and data interpreted to maximise usefulness to clinicians.
- There is a lack of evidence for choroidal neovascularisation secondary to conditions other than age-related macular degeneration or pathological myopia, and there is unlikely to ever be sufficiently powered trials in these populations.
- The evidence base is strongest for pathological myopia, but based on current evidence and likely pharmacological pathways, clinicians should consider treatment with either bevacizumab or ranibizumab for rarer causes of choroidal neovascularisation.

INTRODUCTION

Choroidal neovascularisation (CNV) is a common and severe complication of a number of different diseases affecting the posterior segment of the eye, and has the potential to cause blindness. It has a significant impact on functioning and quality of life.[1] It is characterised by neovascularisation originating from the choroid which grows through Bruch's membrane and under the retinal pigment epithelium (RPE) or retina.[2] Loss of vision usually results from haemorrhage and leakage, and ultimately fibrosis.[3] Vascular endothelial growth factor (VEGF) is recognised as a key signalling molecule in this process. The most common disease associated with CNV is neovascular (wet) age-related macular degeneration (ARMD).

Pathological myopia (PM) is the commonest non-ARMD condition associated with CNV. It is estimated to affect up to 3% of the population, of which 5–11% may develop myopic CNV.[3–6] Other conditions associated with CNV include angioid streaks, multifocal choroiditis, punctate inner choroidopathy, pseudoxanthoma elasticum and presumed ocular histoplasmosis. CNV may be associated with trauma and can be idiopathic. These conditions tend to affect younger patients leading to lifelong impairment.[3] These conditions are relatively uncommon

individually, but are more frequently seen as a combination. There is only limited evidence available about their treatment.[7]

The use of anti-VEGF agents has emerged as an effective therapy for a number of ophthalmological conditions. They have been shown to be superior to photodynamic therapy (PDT) in ARMD in large randomised controlled trials (RCTs)[8–10] and in the treatment of macular oedema following retinal vein occlusion and diabetic macular oedema.[11 12] There are a number of trials that show the effectiveness of anti-VEGF antibodies in the treatment of CNV associated with PM.[13 14] Case reports and case series in the literature report improvements in vision and regression of CNV secondary to conditions other than ARMD with anti-VEGF therapy,[15–18] but there are few interventional studies.

The aim of this study is to systematically review the evidence for anti-VEGF therapy in CNV secondary to conditions other than ARMD.

METHODS

A systematic review was undertaken. The following electronic databases were searched from inception to January 2014: MEDLINE, MEDLINE In-process, EMBASE and CENTRAL. Conference abstracts from the annual meetings of the Association for Research in Vision and Ophthalmology, The Royal College of Ophthalmologists, and the American Academy of Ophthalmology for years 2011–2013 were searched using choroidal neovascularisation terms.

The search strategy for MEDLINE is shown in the online supplementary material. This was adapted for EMBASE and CENTRAL. Terms for ARMD were included in the search strategy to prevent excluding studies in which non-ARMD subgroups were included, or comparison with ARMD was used.

Eligibility criteria

Only trials with a comparative design were included. This included RCTs, controlled trials (CTs), non-randomised trials, and comparative studies. Studies including adults over the age of 18 with a diagnosis of CNV that was secondary to non-ARMD conditions were eligible for inclusion. However, studies including patients with and without ARMD with reporting of subgroups were eligible.

Included interventions were intravitreal bevacizumab, ranibizumab, pegaptanib and aflibercept. Eligible comparators were placebo/sham treatments, other pharmacological interventions, usual care and observation. There were no language restrictions. Studies with length of follow-up of less than 6 months were excluded.

Outcome measures

Outcome measures were: (A) best-corrected visual acuity (BCVA): mean change in, proportion of patients improving, and proportion of patients worsening; (B) mean change in central macular thickness (CMT) as determined by optical coherence tomography (OCT) and (C) adverse events. All BCVA data were converted to number of letters for consistency.

Screening and data extraction

Screening of titles and abstracts were undertaken independently by two authors (AS and SD). Differences were resolved through discussion with a third author (JAF). Data was extracted in a prespecified data extraction form. Non-English articles were translated.[19–21] Data extracted included baseline characteristics, mean change in BCVA, proportion of patients improving, proportion of patients worsening, mean change in CMT, and adverse events. Risk of bias for the RCTs was assessed using the Cochrane risk of bias tool.[22] A modified Newcastle-Ottawa Scale was used to assess the risk of bias for non-RCT studies. It was not possible to assess publication bias using a funnel plot because of heterogeneity and a limited number of studies.

Data were assessed for suitability for meta-analysis, but this was not possible due to methodological heterogeneity.

RESULTS

Search results

Sixteen studies met the inclusion criteria after screening 1251 titles and abstracts (figure 1).[13 19–21 23–34] The main reasons for exclusion at full text stage was the absence of a separate analysis of trial arms, ARMD as cause of CNV, absence of comparator, invalid comparator and condition not CNV.

Table 1 shows that 5 studies were RCTs and 11 were non-randomised comparative studies. Studies were from a range of different countries. Only one trial was multicentre and industry funded. Follow-up ranged from 6 to 24 months.

Across included studies, the total number of eyes was 1091 (426 in RCTs), of which 684 received an anti-VEGF. Study size ranged from 27 to 277 eyes. Mean age ranged between 35.2 and 67 years, and between 60% and 100% were female. Mean baseline BCVA was between 81 and 99 letters.

Thirteen of the studies (4 of the 5 RCTs, 1017 eyes) included participants with CNV secondary to PM. The remaining studies examined CNV associated with multifocal choroiditis, punctate inner choroidopathy, or that was idiopathic.

The treatment and comparator therapies used in the included studies were intravitreal bevacizumab (IVB), intravitreal ranibizumab (IVR), photodynamic therapy (PDT), and in one study a traditional Chinese medicine (fufang xueshuantong (FXT)). The dose used in all studies was IVR 0.5 mg or IVB 1.25 mg. All studies using PDT as comparator reported standard PDT protocol as per the verteporfin in photodynamic therapy study. The mean number of IVB/IVR injections varied from 1.5 to 4.72, and the number of PDT treatments from 1.3 to

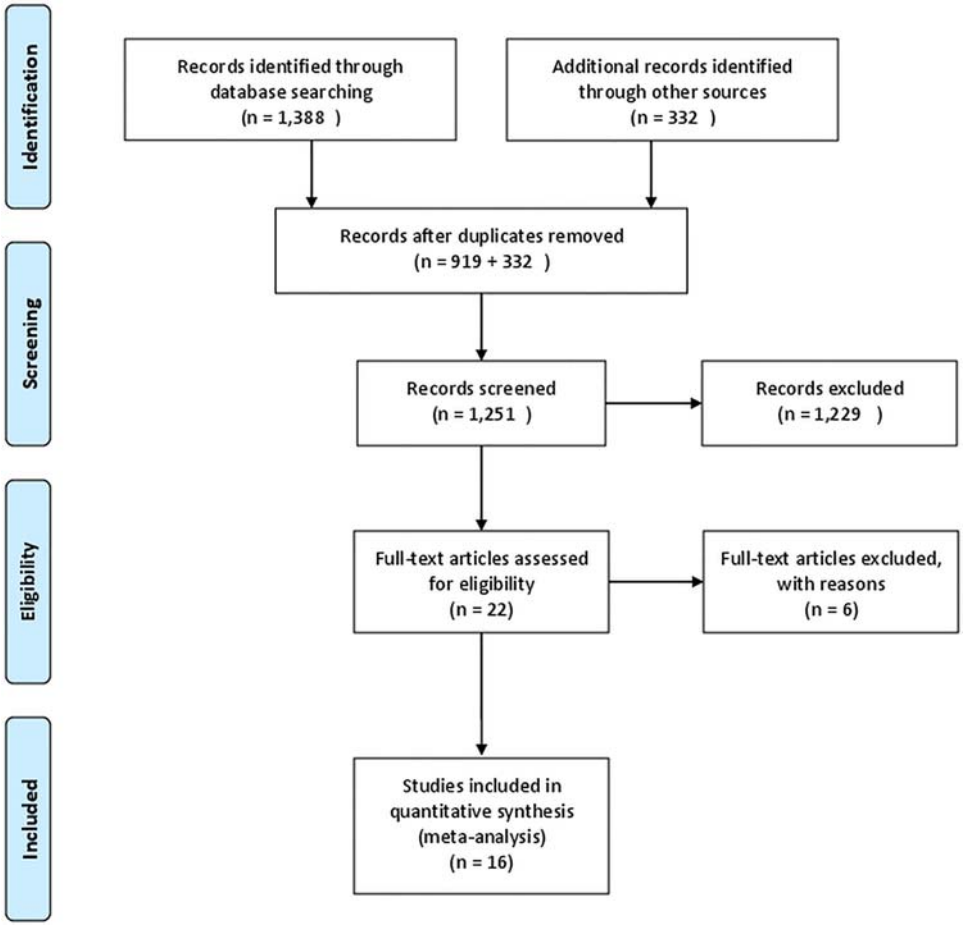

Figure 1 PRISMA 2009 flow diagram.

2.5. No studies assessing pegaptanib or aflibercept were found.

One study used a herbal agent, FXT.[19] FXT is a Chinese herbal formula used in ophthalmological conditions, and consists of *Panax notoginseng*, *Salvia miltiorrhizae*, *Astragalus membranaceus* and *Scrophularia ningpoensis*. It is purported to have a vasodilatory effect, and has been studied in the treatment of diabetic retinopathy.[35]

Risk of bias

Risk of bias was assessed separately for the RCTs and comparative studies, and detailed assessments are presented in tables 2 and 3, respectively.

Generally, the RCTs were of low or unclear risk of bias, except for blinding of participants that was high or unclear in four studies (table 2). This reflects the difficulty of blinding participants in these trials. The majority of studies used assessors who were blinded to the received interventions when evaluating visual acuity after treatment, but this was not discussed in one study.[19] Sequence generation was not reported in two studies. Two studies used sequentially numbered envelopes,[23 33] but it was unclear if these were opaque envelopes.

The comparative studies had low risk of bias for selecting participants from the same cohort, comparability of participants, incomplete data and selective reporting, but a high risk of bias for outcome assessment (table 3). No studies blinded assessors to the interventions received.

Treatment regimes

All studies using PDT reported using a standard regime as per the verteporfin in Photodynamic Therapy Study. After baseline treatment, all studies based re-treatment on fluoroscein angiography (FA) findings at three monthly assessments. The mean number of treatments over the duration of follow-up ranged from 1.3[31] to 3.0.[21]

All studies using anti-VEGFs reported standard doses of 0.5 mg of ranibizumab, and 1.25 mg bevacizumab intravitreally. Dosing regimens varied by study. Three studies[19 29 33] used a three monthly loading regime followed by further treatment based on clinical assessment (see table 4). All other studies based re-treatment on the findings of FA and OCT at 1–3 monthly follow-up visits. Mean number of injections over the follow-up periods ranged from 1.6 [25 31] to 4.72 injections.[23]

Clinical effectiveness

Anti-VEGF versus PDT

Ten studies compared an anti-VEGF agent to PDT, of which two were RCTs.[13 33]

Table 1 Study characteristics

Study	Study type and f/u	CNV cause	Patients	Total eyes	Treatment groups		
Pathological myopia studies							
Iacono *et al*[23]	Randomised, double-blind clinical trial, 18-month f/u	Myopia	*Mean age:* IVR 65 years, IVB 61 years *% female:* 76% *Baseline VA:* Mean letters: IVR 70±15, IVB 70±13 *Ethnicity:* NR (Italy)	48	IVR (mean number of injections 2.56, eyes=23)		IVB (mean number of injections 4.72, eyes=25)
Liu *et al*[19]	Randomised controlled trial, 12-month f/u	Pathological myopia	*Mean age:* Control group 45.1 years, treatment group 43.5 years *% female:* control group 71%; treatment group 65% *Baseline VA:** 66±16 letters(IVB +fufang xueshuantong) and 66 ±19 letters (fufang xueshuantong) *Ethnicity:* Chinese	42	FXT only (oral capsule 1.5 g TDS, eyes=20)		IVB+FXT (mean number of injections 3.86 +1.5 g oral capsule TDS, eyes=22)
Gharbiya *et al*[24]	Randomised controlled trial 6-month f/u	Pathological myopia	*Mean age:* IVR 60.63 years, IVB 59.06 years *% female:* 69% *Baseline VA:* ETDRS letters, IVR 26.44±12.58, IVB 29.50±12.98. *Ethnicity:* NR (Italy)	32	IVR 0.5 mg (mean number of injections 2.81, eyes=16)		IVB 1.25 mg (mean number of injections 2.44, eyes=16)
Wolf *et al*[13]	Randomised controlled trial, double blind, 12-month f/u	Pathological myopia	*Mean age:* DA 56.1 years, STAB 54.0 years, PDT 57.4 years *% female:* DA 75%, STAB 77.4%, PDT 72.7% *Baseline VA:* ETDRS letters, mean: DA=55.8 (12.6), STAB=55.4 (13.4), PDT=54.7 (13.8) *Ethnicity:* (International) Caucasian 58%, Asian 41%, Other 1%	277	IVR 0.5 mg (retreatment based on disease activity (DA) criteria, mean number of injections NR eyes=116)	IVR 0.5 mg (retreatment based on stabilisation criteria (STAB), mean number of injections NR, eyes=106)	PDT (mean number of treatments NR, eyes=55)
Hayashi *et al*[25]	Prospective comparative study, 12 monnth f/u	Pathological myopia	*Mean age:* PDT 53 years, IVB 56.5 years *% female:* 73% *Baseline VA:* mean letters: PDT 70±21.5, IVB 66±14.5 *Ethnicity:* Japanese	159	Controls (eyes=74)	PDT (mean number of treatments 1.43, eyes=44)	IVB 1.25 mg (mean number of injections 1.6, eyes=43)
Yoon *et al*[26]	Retrospective comparative, 12-month f/u	Myopic CNV	*Mean age:* 44.9 years *% female:* 73% *Baseline VA:* Mean letters: PDT 73±18.5, Anti-VEGF 71±23, Combination 68±18.5 *Ethnicity:* NR (South Korea)	142	PDT (mean number of treatments 2.1, eyes=51)	Anti-VEGF—IVB 1.25 mg/IVR 0.05 mg (mean number of injections 2.2, eyes=63)	Combination—IVB 1.25 mg/IVR 0.05 mg+PDT (mean number of treatments, injections=1.9, PDT=1.9, eyes=28)
El Matri *et al*[20]	Retrospective comparative study, 12-month f/u	Pathological myopia	*Mean age:* PDT 53 years, IVB 55.8 years *% female:* 61% *Baseline VA:* mean letters: 56 ±22.5 (PDT), 55±42.5 (IVB) *Ethnicity:* North African (Tunisia)	80	PDT (mean number of treatments 1.55, eyes=40)		IVB 1.25 mg (mean number of injections 1.8, eyes=40)

Continued

Table 1 Continued

Study	Study type and f/u	CNV cause	Patients	Total eyes	Treatment groups	
El Matri *et al*[27]	Retrospective comparative study, 24- month f/u	High myopia	*Mean age:* PDT 57 years, IVB 56 years *% female:* 65% *Baseline VA:* mean letters; PDT 56±38.5, IVB 55±17.5 *Ethnicity:* NR (France)	60	PDT (mean number of treatments 2.4, eyes=30)	IVB 1.25 mg (mean number of treatments 3.8, eyes=30)
Dethorey *et al*[21]	Retrospective comparative study, median f/u; PDT group 53 months, IVR group 13.5 months	High myopia	*Mean age:* PDT 47 years, IVR 58 years *% female:* 83% *Baseline VA:* Snellen 20/80 (PDT), 20/160 (IVR) *Ethnicity:* NR (France)	45	PDT (mean number of treatments 2.5, eyes=27)	IVR 0.5 mg (mean number of treatments 3, eyes=18)
Yoon *et al*[28]	Retrospective comparative study, 12-month f/u	Myopia	*Mean age:* 48.9 years *% female:* 82.5% *Baseline VA:* 75±13.5 letters *Ethnicity:* NR (S Korea)	40	IVR (mean number of injections 3.1, eyes=14)	IVB (mean number of injections 2.2, eyes=26)
Lai *et al*[29]	Retrospective comparative study, 24 montths f/u	Pathological myopia	*Mean age:* 57.3 years *% female:* 62% *Baseline VA:* Mean letters: IVB 66±19.5, IVR 48±21.5 *Ethnicity:* Chinese	37	IVB 1.25 mg (mean number of injections 3.8, eyes=22)	IVR 0.5 mg (mean number of injections 3.8, eyes=15)
Ikuno *et al*[30]	Retrospective comparative study, 24-month f/u	High myopia	*Mean age:* 67 years *% female:* 100% *Baseline VA:* mean letters: PDT 63±10, IVB 66±14.5, *Ethnicity:* Japanese	31	PDT (mean number of treatments 2.3, eyes=20)	IVB 1 mg (mean number of injections 2.9, eyes=11)
Baba *et al*[31]	Retrospective comparative study, 24 months f/u	Myopic CNV	*Mean age:* 62.4 years *% female:* NR *Baseline VA:* mean letters 62 ±12.5 (IVB), 68±12.5 (PDT) *Ethnicity:* Japanese	24	PDT (mean number of treatments 1.3, eyes=12)	IVB 1.25 mg (mean number of injections 1.6 eyes=12)
Non-pathological myopia studies						
Kang and Koh [32]	Retrospective comparative study, 24-month f/u	Idiopathic	*Mean age:* 35.12 years *% female:* 60% *Baseline VA:* mean letters: PDT 72±19, anti-VEGF 77±29.5 *Ethnicity:* NR (S. Korea)	29	PDT (mean number of treatments 1.33, eyes=14)	Anti-VEGF (IVR 0.05mg=2 eyes, IVB 1.25 mg=13 eyes, mean number of injections 3.71, total eyes=15)
Parodi *et al*[33]	Randomised controlled trial, 12 month f/u	Multifocal choroiditis	*Mean age:* 39 years *% female:* 66% *Baseline VA:* Mean letters; PDT 78±10, IVB 76±10 *Ethnicity:* NR (Italy)	27	PDT (mean number of treatments NR, eyes=13)	IVB (Mean number of injections NR, 'loading phase of 3 monthly injections+further re-treatments', eyes=14)
Cornish *et al*[34]	Retrospective comparative study, average f/u 14.9 months	Punctate inner choroidopathy	*Mean age:* 34.4 years *% female:* 88% *Baseline VA:* 82±15.5 mean letters *Ethnicity:* NR (Scotland)	18	IVB 1.25 mg (6 patients, mean number of injections 2.34)	IVR 0.5 mg (3 patients, mean 2.34 injections)

*Additional information taken from unpublished thesis, accessed at: http://www.docin.com/p-160870110.html.
CNV, choroidal neovascularisation; f/u, follow-up; FXT, fufang xueshuantong; IVB, intravitreal bevacizumab; IVR, intravitreal ranibizumab; NR, not reported; PDT, verteporfin photodynamic therapy, standard protocol as per verteporfin in photodynamic therapy study; TDS, three times daily; VA, visual acuity; VEGF, vascular endothelial growth factor.

Table 2 Risk of bias for randomised controlled trials

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data addressed (attrition bias)	Selective reporting (reporting bias)
Iacono *et al*[23]	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk
Liu *et al*[19]	Unclear	Unclear	High risk	Unclear	Low risk	Low risk
Gharbiya *et al*[24]	Unclear	Unclear	High risk	Low risk	Low risk	Low risk
Parodi *et al*[33]	Low risk	Unclear	High risk	Low risk	Low risk	Low risk
Wolf *et al*[13]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear

Randomised controlled trials

Pathological myopia In the RADIANCE trial (eyes=277), an RCT of ranibizumab for CNV secondary to pathological myopia, the results for the three separate treatment arms are presented from the 3-month end point, as the control group received ranibizumab thereafter.[13] Treatment arms consisted of two IVR groups re-treated based on different criteria (on the basis of assessed disease activity (DA), and on the basis of assessed disease stabilisation (STAB) and a PDT group. Mean change in BCVA was the same in both IVR groups, at a gain of 10.6 letters. The gain in letters in the PDT group was 2.2. The proportion improving (gain of ≥15 letters) was 43.1% and 38.1% in the respective IVR arms (DA and STAB), and 14.5% in the PDT group. The proportion of patients worsening was not reported. The mean decrease in CMT was 77.5, 60.9 and 12 µm between IVR DA, IVR STAB and PDT arms, respectively (statistical significance not reported). At 12 months, all three arms reported improvements in BCVA.

Other CNV causes

Parodi *et al*[33] compared the effectiveness of PDT and IVB in patients with subfoveal CNV secondary to multifocal choroiditis (eyes=27). They reported a mean gain of 9 letters in the IVB group compared with 1 letter in the PDT group at 12 months. The difference was statistically significant. The proportion of patients with a gain of >15 letters was 36% in the IVB group compared with 0% in the PDT group; 8% of patients in the PDT group had a loss of >15 letters compared with none in the IVB group (statistical significance not reported). The mean CMT change was 44 and 55 µm in the PDT and IVB groups, respectively (statistical significance not reported).

Comparative studies

Pathological myopia Seven of the eight comparative studies[20 21 25–27 30] were in PM (eyes=541). The mean change in BCVA improved for all anti-VEGF arms compared with PDT. In studies in which the gain in BCVA in anti-VEGF arms over PDT was reported as statistically significant, the gain in letters ranged from 6[30] to 12.5 letters.[31]

The proportions of patients improving by >15 letters in the anti-VEGF groups ranged from 27.3%[21] to 70%;[20] however, neither of these groups reported statistical testing. In those in which a statistically significant difference was found ($p \leq 0.05$),[25 26] the gain was 41.9% and 39.7% compared with 20.4% and 17.7% in the PDT groups, respectively.

Six of the seven comparative studies[20 21 25 27 30 31] reported the proportion of patients with worsening vision. In all studies, there was a greater proportion that deteriorated ≥15 letters in the PDT groups versus the anti-VEGF groups.

Table 3 Risk of bias of non-randomised comparative studies using modified Newcastle-Ottawa Scale

Study	Participants selected from same cohort	Comparability of participants	Assessment of outcome	Incomplete data	Selective reporting
Yoon *et al*[26]	Low risk	Low risk	High risk	Low risk	Low risk
Hayashi *et al*[25]	Low risk	Low risk	High risk	Low risk	Low risk
El Matri *et al*[20]	Low risk	Low risk	High risk	Low risk	Unclear
Dethorey *et al*[21]	Low risk	Unclear	High risk	High risk	High risk
Yoon *et al*[28]	Low risk	Low risk	Unclear	Low risk	Low risk
Lai *et al*[29]	Low risk	Low risk	Unclear	Low risk	Low risk
Ikuno *et al*[30]	High risk	Low risk	High risk	Low risk	Low risk
Baba *et al*[31]	Low risk	Low risk	High risk	Low risk	Low risk
Kang and Koh[32]	Low risk	Low risk	High risk	Low risk	Low risk
Cornish *et al*[34]	Low risk	Unclear	High risk	Low risk	Low risk

Other CNV causes

One study[32] was in idiopathic CNV (eyes=29). The gain in the anti-VEGF group was 17.5 vs 14 letters in the PDT group. In total 53.5% of patients in the anti-VEGF group compared with 42.9% of patients in the PDT group had a gain of >15 letters. No patients had a loss of >15 letters in the anti-VEGF group, compared with 21.3% in the PDT group. All differences were reported as statistically significant.

Ranibizumab versus bevacizumab

Five studies compared IVR with IVB, four in PM[23 24 28 29] and one in punctate inner choroidopathy,[34] two were RCTs.[23 24]

Randomised controlled trials

Pathological myopia Iacono *et al*[23] (eyes=48) reported no statistically significant difference in either mean letter gain, or proportion improving by at least 15 letters between IVR and IVB groups. Of those worsening, slightly more deteriorated in the IVB group at 24% versus 17% in the IVR; statistical significance was not reported.

Similarly, Gharbiya *et al*[24] (eyes=32) reported no statistically significant difference in the number of letters gained, or proportion of participants gaining more than 15 letters.

Comparative studies

Pathological myopia Yoon *et al*[28] (eyes=40; IVB=26, IVR=14) reported no statistically significant difference between intervention groups, with a mean gain of 13.5 and 14 letters in IVR and IVB groups, respectively.

Lai *et al*[29] (eyes=37, IVB=22, IVR=15) also did not report a statistically significant difference, with a mean gain of 14 and 25.5 letters between IVB and IVR groups, respectively.

Other CNV cause

Cornish *et al*[34] studied treatment of punctate inner choroidopathy (eyes=18; IVB=6, IVR=12). Mean gain in BCVA was 23 letters in the IVR group and 8.5 letters in the IVB group. Sixty-seven per cent of patients in the IVR group had a gain of at least 15 letters versus 83% in the IVR group. Statistical testing was not reported.

Other agents

Liu *et al*[19] (eyes=42) compared IVB with no IVB in patients with PM taking oral FXT. In the IVB + FXT group, there was a mean improvement of 21 letters, and in the FXT group there was a statistically significant mean improvement of 10 letters.

Adverse events

Twelve studies reported no adverse events occurring, and one study did not present adverse event data. Generally speaking, anti-VEGF therapy, compared with PDT, had fewer significant adverse events (eg, endophthalmitis, retinal detachment, systemic events). Adverse events in the RADIANCE trial were similar between IVR and PDT.[13] El Matri *et al*[27] reported two cases of endophthalmitis (6.6%) and one vitreous haemorrhage (3.3%) in the IVB group. Only one study that compared IVR with IVB reported on adverse events (worsening of cataract, increase in myopic foveoschisis, retinal detachment, macular hole, systemic events); there were similar adverse events in both groups (table 5).[29]

DISCUSSION

Statement of principal findings

Evidence from RCTs and non-randomised comparative studies shows that anti-VEGF therapies show consistent benefit in non-ARMD CNV conditions. When compared with the previous 'gold-standard' (PDT), anti-VEGFs result in greater improvements in BCVA. There was no robust evidence to suggest superiority of ranibizumab or bevacizumab.

Strengths and limitations

The search strategy was robust and broad with no language restrictions, and included grey literature. Two reviewers screened titles and abstracts. Risk of bias in studies was assessed using the Cochrane Risk of Bias

Table 4 Frequency of injection

Study	Study type and f/u	Interventions	Treatment regime	Mean number of injections/treatments over f/u period
Pathological myopia				
Iacono *et al*[23]	Randomised, double-blind clinical trial, 18-month f/u	IVR	Re-treatment PRN, criteria not specified	2.56±1.61
		IVB		4.72±2.24
Liu *et al*[19]	Randomised controlled trial, 12-month f/u	IVB+FXT	Three initial monthly loading injections. FA review at 3 months, re-treatment based on leakage	4.23±2.02
		FXT	Three initial monthly loading injections. FA review at 3 months, re-treatment based on leakage. Plus oral FXT 1.5 g TDS for initial 3 months	1.95±1.90
Gharbiya *et al*[24]	Randomised controlled trial 6-month f/u	IVR	Assessed for re-treatment monthly based on presence of fluorescein leakage on FA or subretinal fluid on OCT	2.81
		IVB		2.44
Wolf *et al*[13]	Randomised controlled trial, double blind, 12-month f/u	IVR (DA group)	Day 1, thereafter based on DA criteria	2.0
		IVR (STAB group)	Day 1, month 1, thereafter based on STAB criteria	4.0
		PDT	Day 1, then treated with IVR or PDT at 3-month f/u based on investigator discretion	2.0
Hayashi *et al*[25]	Prospective comparative study, 12-month f/u	PDT	At baseline, re-treatment as per VIP and TAP protocols	1.43±0.78
		IVB	Assessed at 1 week, 1 month, and monthly after each additional injection. Re-treatment based on dye leakage on FA	1.6±0.7
		Controls	NA	N/A
Yoon *et al*[26]	Retrospective comparative, 12 mth f/u	PDT	Re-treatment 3 monthly if leakage on FA or subretinal fluid on OCT	2.1±1.4
		Anti-VEGF (IVB/IVR)	Assessed at 1 week, 1 month and 3 monthly thereafter. Re-treatment based on leakage on FA or subretinal fluid on OCT	2.2±2.0
		Combination tx	PDT, followed by IVB/IVR at one hour. Assessed at 1 week, 1 month and 3 monthly thereafter. Re-treatment based on leakage on FA or subretinal fluid on OCT	PDT 1.9±1.3 Anti-VEGF 2.5±1.9
El Matri *et al*[20]	Retrospective comparative study, 12-month f/u	PDT	Assessed 3 monthly by FA, re-treatment based on presence of fluid on OCT or leakage on FA	1.55
		IVB	Assessed monthly, re-treatment based on persistence of metamorphosia, decrease in BCVA or leakage/fluid on FA	1.8
El Matri *et al*[27]	Retrospective comparative study, 24-month f/u	PDT	Assessed 3 monthly, re-treatment based on presence of fluid on OCT or leakage on FA	2.4
		IVB	Re-treatment at intervals of 4–6 weeks as needed based on signs of disease activity	3.8
Dethorey *et al*[21]	Retrospective comparative study, median f/u; PDT group 53 months, IVR group 13.5 months	PDT	Re-treatment based on clinical progression, leakage on FA, and fluid on OCT	3.0
		IVR		3.0
Yoon *et al*[28]	Retrospective comparative study, 12-month f/u	IVR	Assessed at 1 week, 1 month, and monthly thereafter.	3.1±2.4
		IVB	Re-treatment based on decreased VA, increased metamorphosia or change of OCT FA findings	2.2±1.5

Continued

Table 4 Continued

Study	Study type and f/u	Interventions	Treatment regime	Mean number of injections/treatments over f/u period
Lai *et al*[29]	Retrospective comparative study, 24-month f/u	IVB	Three initial loading doses at 0, 1 and 2 months. Re-treatment with course of 3 injections at monthly intervals in eyes with new symptoms/recurrent angiographic leakage	3.8
		IVR		3.8
Ikuno *et al*[30]	Retrospective comparative study, 24-month f/u	PDT	Assessed at 3 months with FA, re-treatment based on CNV persistence. Re-treatment interval 3 monthly	2.3±1.2
		IVB	Assessed monthly by OCT, and injections repeated until resolution of subretinal fluid	2.9±2.4
Baba *et al*[31]	Retrospective comparative study, 24-month f/u	PDT	Assessed 3 monthly, treatments repeated if BCVA decreased by >2 lines, or retinal oedema on OCT	1.3
		IVB		1.6
Other causes of CNV				
Kang and Koh [32]	Retrospective comparative study, 24-month f/u	PDT	Assessed 3 monthly, Re-treatment based on leakage on FA/ subretinal fluid on OCT	1.33±1.01
		Anti-VEGF (IVB/IVR)	Assessed at 1 week, 1 month, thereafter 3 monthly. Re-treatment based on leakage on FA or subretinal fluid on OCT—maximum monthly PRN	3.71±0.38
Parodi *et al*[33]	Randomised controlled trial, 12-month f/u	PDT	Assessed 3 monthly by FA, re-treatment based on leakage	1.7±0.7
		IVB	Loading phase of 3 monthly injections, thereafter re-treatment based on fluid on OCT/leakage on FA at monthly assessment	3.8±1.1
Cornish *et al*[34]	Retrospective comparative study, average f/u 14.9 months	IVR	n=2, 3 monthly loading course, monthly PRN thereafter n=1, variable dosing of single injections PRN	2.9±1.7
		IVB	Single injections PRN at monthly intervals, based on presence of subretinal fluid on OCT	

BCVA, best-corrected visual acuity; CNV, choroidal neovascularisation; DA, disease activity; f/u, Follow-up; FA, fluoroscein angiography; FXT, fufang xueshuantong; IVB, intravitreal bevacizumab; IVR, intravitreal ranibizumab; NA, not applicable; OCT, optical coherence tomography; PDT, verteporfin photodynamic therapy, standard protocol as per verteporfin in photodynamic therapy study; PRN, as required; TAP, treatment of age-related macular degeneration; TDS, three times daily; VEGF, vascular endothelial growth factor; VIP, verteporfin in photodynamic therapy.

Table 5 Study results

Study	Study type and f/u	Interventions	Numbers	Outcomes				
				Change in mean BCVA	Proportion improving	Proportion worsening	Decrease in mean CMT (µm)	Adverse events
Results: pathological myopia group								
Iacono *et al*[23]	Randomised, double-blind clinical trial, 18-month f/u	IVR	23	+9±1.3 letters	30% (at least 15 letters)	17% (≥5 letters)	NR	None
		IVB	25	+8.5±1.25 letters*	40% (at least 15 letters)*	24% (≥5 letters)†	NR	
Liu, *et al*[19]	Randomised controlled trial, 12-month f/u	IVB+FXT	22	+21±10 letters	NR	NR	43.41	None
		FXT	20	+9.75±9.5 letters‡	NR	NR	22.65‡	
Gharbiya *et al*[24]	Randomised controlled trial 6-month f/u	IVR	16	+17.31±11.10 letters	56.2% (≥15 letters)	None	45	None
		IVB	16	+15.87±8.41 letters*	62.5% (≥15 letters†	None	52*	
Wolf *et al*[13]	Randomised controlled trial, double blind, 12-month f/u	IVR (DA group)	116	+10.6 letters	43.1% (gain of ≥15 letters)	NR	77.5	*Retinoschisis*: 1 (0.85%) *Cataract*: 2 (1.69%) *Vitreous detachment:* 1 (0.94%)
		IVR (STAB group)	106	+10.6 letters	38.1% (gain of ≥15 letters)	NR	60.9	*Cataract:* 1 (0.96%)
		PDT	55	+2.2 letters†	14.5% (gain of ≥15 letters)†	NR	12†	*Cataract:* 1 (6.67%) *Vitreous detachment:* 1 (6.67%)†
Yoon *et al*[26]	Retrospective comparative study, 12-month f/u	PDT	51	−3.1 letters	17.7% (gain of ≥15 letters)*‡	NR	NR	None
		Anti-VEGF (IVB/IVR)	63	+12.2 letters	39.7% (gain of ≥15 letters)‡	NR	NR	
		Combination tx	28	+4.6 letters‡	21.4% (gain of ≥15 letters)*	NR	NR	
Hayashi *et al*[25]	Prospective comparative study, 12-month f/u	PDT	44	+4 letters	20.4% (gain of >15 letters)	9.1% (>15 letter loss)	NR	None
		IVB	43	+11.5 letters	41.9% (gain of >15 letters)‡	4.7% (>15 letter loss)†	NR	
		Controls	74	+14.5 letters‡	NR	NR	NR	
El Matri *et al*[20]	Retrospective comparative study, 12-month f/u	PDT	40	+1 letters	22.5% (≥15 letters)	30% (≥15 letters)	41	None
		IVB	40	+15 letters‡	70% (≥15 letters)†	10% (≥15 letters)†	115.5‡	
El Matri *et al*[27]	Retrospective comparative study, 24-month f/u	PDT	30	NR	6.6% (≥15 letters)	13.3% (≥15 letters)	45.5	*None*
		IVB	30	NR *(But reports statistically significant improvement in BCVA in IVB group over PDT group at 24 months)*	36.6% (≥15 letters)*	10% (≥15 letters)†	121.7	*Endophthalmitis:* Two eyes (6.6%) *Vitreous haemorrhage:* One eye, 3.3% *Systemic events:* Two hypertensive crises (6.6%)
Dethorey *et al*[21]	Retrospective comparative study, median f/u; PDT group 53 months, IVR group 13.5 months	PDT	(27) At 12 months, eyes=26	No change	23.1% (≥15 letters)	34.6% (≥15 letters)	NR	NR
		IVR	(18) At 12 months, eyes=11	+15 letters*	27.3% (≥15 letters)†	9.1% (≥15 letters)†	59†	

Continued

Table 5 Continued

Study	Study type and f/u	Interventions	Numbers	Outcomes				
				Change in mean BCVA	Proportion improving	Proportion worsening	Decrease in mean CMT (μm)	Adverse events
Yoon *et al*[28]	Retrospective comparative study, 12-month f/u	IVR	14	+13.5±11.5 letters	NR	NR	NR	None
		IVB	26	+14±12 letters*	NR	NR	NR	
Lai *et al*[29]	Retrospective comparative study, 24-month f/u	IVB	22	+14 letters	NR	NR	NR	*Worsening of cataract:* 2 (9%) *Increase in myopic foveoschisis:* 1 (4.5%) *Retinal detachment:* 1 (4.5%) *Macular hole:* 1 (4.5%) *Systemic events:* None
		IVR	15	+25.5 letters*	NR	NR	NR	*Worsening of cataract:* 1 (6.6%) *Increase in myopic foveoschisis:* 1 (6.6%) *Cellophane maculopathy:* 1 (6.6%) *Systemic events:* none
Ikuno *et al*[30]	Retrospective comparative study, 24-month f/u	PDT	20	9 letter loss	0% (≥15 letters)	20% (≥15 letters)	NR	*Subretinal haemorrhage:* 1 (5%)
		IVB	11	+6 letters‡	36% (≥15 letters)†	18% (≥15 letters)†	NR	None
Baba *et al*[31]	Retrospective comparative study, 24-month f/u	PDT	12	+0.5 letters	41.7% (>5 letters)	NR	107	None
		IVB	12	+12.5 letters‡	66.7% (>5 letters)†	NR	93*	
Non-pathological myopia group								
Kang and Koh[32]	Retrospective comparative study, 24-month f/u (idiopathic)	PDT	14	+7 letters	42.9% (15 letters)	21.3% (15 letters)	NR	None
		Anti-VEGF (IVR/IVB)	15	+17.5 letters‡	53.5% (15 letters)‡	0%‡	NR	
Parodi *et al*[33]	Randomised controlled trial, 12-month f/u (Multifocal choroiditis)	PDT	13	+1 letter	0% (gain of >15 letters)	8% (loss of >15 letters)	44	None
		IVB	14	+9 letters‡	36% (gain of >15 letters)‡	0% (loss of >15 letters)†	55†	
Cornish, *et al*[34]	Retrospective comparative study, average f/u 14.9 months (punctate inner choroidopathy)	IVR	3	+23 letters	67% (15 letters)	33% (15 letters)	NR	None
		IVB	6	+8.5 letters†	83% (15 letters)†	16% (15 letters)†	NR	

*No statistically significant difference between intervention groups.
†Statistical significance not reported.
‡Statistically significant difference between intervention groups ($p \leq 0.05$).
BCVA, best-corrected visual acuity; CMT, central macular thickness; DA, disease activity; f/u, follow-up; FXT, fufang xueshuantong; IVB, intravitreal bevacizumab; IVR, intravitreal ranibizumab; NR, not reported; PDT, verteporfin photodynamic therapy, standard protocol as per verteporfin in photodynamic therapy study; VEGF, vascular endothelial growth factor.

Tool for RCTs and a modified Newcastle-Ottawa Scale for comparative studies. Only studies with at least 6 months of follow-up were included to increase meaningfulness of outcomes.

A major limitation of this review was that the majority of evidence pertains to CNV caused by PM, however, this reflects the available evidence base in the literature. The included non-PM CNV conditions such as PIC, and POHS are of such rarity that it is unlikely there will ever be large RCTs of their treatment. Many of the non-randomised comparative studies were small and of low quality. There was one large industry-funded trial assessing ranibizumab, but none assessing bevacizumab.

Methodological heterogeneity between studies was too high to allow meta-analysis. Baseline BCVA varied considerably between studies, as did treatment regimes. No study reported on vision-related quality of life as an outcome measure, arguably the most important. Studies were powered for clinical efficacy, not to detect adverse events.

The largest RCT included in our review (RADIANCE)[13] was limited by the fact that although the entire follow-up period was 12 months, after 3 months, patients were eligible to cross over into other arms of the study. We therefore have presented only 3-month data, as the relevance of the data after this point is questionable.

Context of these results

This is the first systematic review to include all causes of CNV except ARMD. Wang *et al*[36] undertook a systematic review of anti-VEGFs in CNV secondary to only PM. It did not include the RADIANCE study[13] or undertake as broad a search. The authors concluded that the evidence supported anti-VEGF agents as first-line treatment, which supports our findings.

Ranibizumab remains the only drug licensed for the treatment of CNV secondary to PM, and its short-term (up to 24 months) safety has been demonstrated in numerous studies.[8–10 37] National Institute for Health and Care Excellence (NICE) has recently approved ranibizumab as an option for treatment for CNV secondary to PM, where it is provided at a discount through a patient-access scheme.[38] The appraisal committee noted that while there was little long-term evidence, it had shown greater clinical effectiveness than the current standard treatment of PDT.

Bevacizumab has a similar mechanism of action, and is considerably cheaper. However, due to commercial reasons, it is unlikely ever to be licensed for intravitreal use. The CATT study demonstrated that bevacizumab and ranibizumab have equivalent effects on visual acuity in neovascular ARMD.[39] A total of 1185 patients were randomised to receive either bevacizumab or ranibizumab, and at 24-month follow-up the authors found similar effects on visual acuity and no difference in rates of death or systemic arteriothrombotic events. In 2012, NICE evaluated 89 studies and concluded that there was no significant difference in adverse events between bevacizumab and ranibizumab.[40] A recent systematic review of the treatments for macular oedema secondary to central retinal vein occlusion examined anti-VEGF agents, including bevacizumab and ranibizumab, and concluded that they were similar in improving visual acuity, and there was no evidence of difference in adverse events.[11]

Anti-VEGF agents are used off-label for the treatment of CNV secondary to conditions other than ARMD or PM. There are multiple case series that support their effectiveness. All case series are subject to several methodological weaknesses, most importantly, publication bias and lack of comparator groups. Troutbeck *et al*[17] reported on the use of IVR in 41 patients with a range of conditions complicated by CNV, including multifocal choroiditis, peripapillary CNV, angioid streaks, central serous chorioretinopathy, macular telangiectasia and idiopathic CNV. They reported that 25–43% of patients experienced 15 letter or greater improvement in vision. Chang *et al*[16] used bevacizumab in 39 eyes in the treatment of CNV associated with either multifocal choroiditis, angioid streaks, myopic and also idiopathic CNV. Median BCVA improved from 76 letters at baseline, to 85 letters at mean follow-up of 58.8 weeks, and there were no adverse events.

What do these results mean for clinical practice?

The evidence for the use of anti-VEGF in the treatment of CNV associated with ARMD and, recently, PM is well established. The evidence for the use of these agents in the treatment of CNV complicating other diseases is mixed. This represents a heterogeneous group of conditions, often found in younger people and frequently with devastating visual outcomes. Despite a limited evidence base, the use of anti-VEGF therapy is likely to provide the best outcomes for patients. Patients expect and demand treatment in advance of best evidence being available, and healthcare planners and commissioners need to make decisions about the use of anti-VEGF molecules in these circumstances with limited evidence base for the relatively rare cases. Marginal cost–benefit analysis is often used in these circumstances, and this is likely to be favourable if it takes account of the overall costs to society and the individual patient in the event of a devastating loss of vision. Given that anti-VEGFs are superior to PDT and its use is off-label in treatment of CNV secondary to conditions other that ARMD and PM, considering the cheapest drug (sourced and administered) would prove to be the most cost effective and affordable option for clinical commissioners.

Further research

While the use of anti-VEGFs in ARMD and, recently, PM has been investigated in a number of large robustly conducted RCTs, there is a corresponding lack of high-quality, long-term evidence for the use of these drugs in CNV of other causes.

Large RCTs with head-to-head comparison of anti-VEGFs and other standard treatments are unlikely to be conducted in CNV secondary to conditions other than ARMD or PM, because of the heterogeneous and rare nature of these conditions. It may also be unethical to randomise participants to PDT considering the evidence that currently exists, and that the scientific equipoise is more in favour of anti-VEGFs. High-quality multicentre comparative studies which compare different anti-VEGFs are needed, especially considering the cost difference. This will become more important with the advent of aflibercept which has recently been licensed for choroidal neovascularisation secondary to pathological myopia.[41] Further, small case series are unlikely to change clinical practice. Further studies are needed to establish the place of each anti-VEGF in the treatment pathway, and the frequency of injection.

CONCLUSIONS

Bevacizumab and ranibizumab appear to be more effective in improving visual acuity in patients with CNV secondary to pathological myopia. Based on the current knowledge of the condition, small RCTs, non-randomised comparative studies and robust RCT data from other conditions, clinicians should consider bevacizumab or ranibizumab as an option for treating patients with CNV secondary to other rarer causes. There is no evidence of difference in outcomes between bevacizumab and ranibizumab.

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Search strategy

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3. choroidal neovascular membrane.mp.
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