

Review Article

A systematic review and meta-analysis comparing intravitreal ranibizumab with bevacizumab for the treatment of myopic choroidal neovascularisation

M. Loutfi^a, M.R.S. Siddiqui^b, A. Dhedhi^a, A. Kamal^{c,*}**Abstract**

Intravitreal injections of ranibizumab (IVR) and bevacizumab (IVB) have both been used as treatments for myopic choroidal neovascularisation. We aimed to produce a meta-analysis of published literature comparing IVR with IVB for the treatment of myopic choroidal neovascularisation, by searching electronic databases from January 1950 to March 2013. Our search produced three suitable studies that reported on 117 patients in total. The results of the meta-analysis demonstrated that the mean number of lines improvement after IVR appeared better compared with IVB [fixed effects model: SMD = 0.46, 95% CI (0.09, 0.83), $z = 2.44$, $p = 0.01$]. The number of patients who had a greater than 3 line improvement was similar between groups [fixed effects model: RR = 0.95, 95% CI (0.67, 1.32), $z = 0.33$, $p = 0.74$]. At follow up there was no difference in number of those who had an absence of leakage [fixed effects model: RR = 1.04, 95% CI (0.93, 1.16), $z = 0.64$, $p = 0.52$]. There was no statistical significance between the two groups in relation to the number of injections [random effects model: SMD = -0.25, 95% CI (-1.12, 0.61), $z = 0.57$, $p = 0.57$]. Early evidence therefore suggests that intravitreal injections of ranibizumab are comparable to intravitreal injections of bevacizumab in the treatment of myopic choroidal neovascularisation. Both treatments result in a statistically significant increase in visual acuity with high numbers of patients maintaining stable vision. Further studies are still needed to strengthen results.

Keywords: Myopic, Choroidal neovascularisation, Bevacizumab, Ranibizumab

© 2014 Production and hosting by Elsevier B.V. on behalf of Saudi Ophthalmological Society, King Saud University.
<http://dx.doi.org/10.1016/j.sjopt.2014.09.004>

Introduction

Pathological Myopia (PM) is a common cause of visual deterioration worldwide.^{1,2} It is estimated to be prevalent at a rate of 2–4% in West European populations and 9–21% in East Asian populations.¹ Rates of PM are increasing worldwide due to a variety of factors including a significant reduction in the number of hours children spend outdoors.^{2,3} PM can be defined as either: a refractive error of -6 dioptres or an axial length of 26.5 mm.⁴ Typically, its pathogenesis is associated with progressive and excessive elongation of the eyeball, leading to degenerative changes in the choroid,

sclera and retina.¹ Visual impairment caused by PM often occurs in the young to middle-aged, therefore amplifying the socioeconomic impacts of this disease.¹

The natural course of PM varies amongst individuals, leading to a variation in visual deterioration.⁵ However, without treatment visual prognosis is generally very poor.^{5–8} Degenerative changes that may occur with pathological myopia include: posterior staphyloma, diffuse or patchy chorioretinal atrophy, retinal pigment epithelial atrophy, lacquer cracks, spontaneous subretinal haemorrhages and macular choroidal neovascularisation (CNV).¹ By far the most common vision-threatening pathological process that occurs in PM is

Received 12 February 2014; received in revised form 6 July 2014; accepted 15 September 2014; available online 26 September 2014.

^a University of Liverpool Medical School, Liverpool, UK

^b Department of General Surgery, St Heliers Hospital, London, UK

^c Ophthalmology Department, Aintree University Hospital, Liverpool, UK

* Corresponding author.

e-mail address: ahmed.kamal@aintree.nhs.uk (A. Kamal).



Peer review under responsibility of Saudi Ophthalmological Society, King Saud University



Production and hosting by Elsevier

Access this article online:
www.saudiophthaljournal.com
www.sciencedirect.com

CNV, occurring in 5–10% of these eyes.^{9,10} Without treatment, CNV can have a devastating effect on vision with over 80% of patients displaying a visual acuity of 6/60 or less five years after the onset of CNV.^{5–8}

Treatment options for myopic CNV include thermal laser photocoagulation and photodynamic therapy with verteporfin (PDT) and intravitreal injections of Anti-vascular endothelial growth factor (Anti-VEGF) agents.^{1,11} In the UK, there are currently no clinically recommended treatments for myopic CNV.¹² The most widely used treatment has been photodynamic therapy with verteporfin as it demonstrated enhanced visual stabilisation compared to placebo at 12 months.¹³ However, recent studies have demonstrated unfavourable long-term results for PDT with verteporfin, where at 24 months, there was no statistically significant improvement in visual acuity or prevention of visual loss compared to placebo.^{14,15}

Anti-VEGF agents are commonly used in ocular disease due to their anti-angiogenic properties. Ranibizumab and Bevacizumab are the two most commonly used agents. In 2005, Anti-VEGF agents were first identified as having significantly positive outcomes when used in the treatment of myopic CNV.¹⁶ Many clinical studies have since examined either drug in their ability to suppress myopic CNV, consistently reporting positive outcomes in both short and long term.¹¹ Moreover, Anti-VEGF injections therapy has demonstrated superior results when compared to PDT with verteporfin.^{11,17,18}

Ranibizumab is a humanised monoclonal antibody fragment that binds to an isoform of vascular endothelial growth factor (VEGF), known as VEGF-A, preventing it from binding to its receptors.¹⁹ In 2008, it was recommended by the National Institute for Health and Clinical Excellence (NICE) for treating Age-Related Macular Degeneration (AMD) and has recently been recommended by NICE for treating Diabetic Macular Oedema and myopic choroidal neovascularisation.^{19–21} Moreover, recent clinical guidelines by the European Commission have recommended ranibizumab for the treatment of myopic choroidal neovascularisation.²² Bevacizumab is a humanised monoclonal full length antibody that also binds to VEGF-A, neutralising its activity. It was originally applied for treating metastatic cancer, however has currently been disapproved recommendation by NICE for this condition.²³ It is currently used off-label for ocular diseases such as AMD and PM.²⁴ A wide economical gap exists between both drugs with bevacizumab costing up to 100 times less.²⁵

The purpose of this meta-analysis and systematic literature review is to compare the efficacy and safety of ranibizumab and bevacizumab for the treatment myopic CNV.

Methods

Searching and selection

All studies examining the role of ranibizumab or bevacizumab for treating choroidal neovascularisation secondary to pathological myopia between January 1950 and March 2013 were identified. We searched the MEDLINE, EMBASE and CINAHL databases available through the NHS National Library of Health website, the Cochrane library and PubMed available online. A range of MESH words and text words are

available to describe ranibizumab, bevacizumab, pathologic myopia or choroidal neovascularisation and these terms were used in all combinations possible to search for relevant material. MESH words used were "Antibodies, Monoclonal, Humanised", "Myopia, Degenerative" and "Choroidal Neovascularisation". Text words used were "Ranibizumab", "Bevacizumab", "Short Sightedness", "Subfoveal Degenerative Myopia", "Myopi*", "New blood vessel formation in the choroid", "Lucentis", "Avastin", "Anti-VEGF", "Myopia, Degenerative" and "Choroidal Neovascularisation". Irrelevant articles, reviews and meta-analyses evident from the titles and abstracts were excluded. Relevant articles referenced in these publications were obtained and the references of identified studies were searched to identify any further studies. No language restriction was applied. A flow chart of the literature search according to PRISMA guidelines is shown in Fig. 1.²⁶

Quality assessment

The methodological quality of the trials included for meta-analysis is explained comprehensively in Tables 1 and 2.^{27–30} Assessment was performed by 2 authors independently (M.R.S.S. and M.L.).^{27–30}

Data extraction

Each included article according to our review criteria (Table 3) was reviewed by two researchers (M.R.S.S and M.L.). This was performed independently and if any conflict arose resolution was through discussion with the authors prior to analysis. Only papers examining the role of Intravitreal Injections of Anti-VEGF for treating myopic CNV in adults and comparative studies looking at Ranibizumab versus Bevacizumab for treating myopic CNV were included.

Our main outcome measures were mean number of lines improvement (assessed using an Early Treatment Retinopathy study chart test (EDTRS), the number of patients who had a greater than 3 lines improvement on ETDRS and the number of patients who had an absence of leakage at follow up. Other outcomes included number of injections, recurrence of sub/intraretinal fluid, systemic adverse events and ocular adverse events.

Data synthesis

Statistical analyses were performed using Review Manager 5.0.23 (RevMan; Cochrane Collaboration, Copenhagen).³¹ A value of $p < 0.05$ was chosen as the significance level for outcome measures. For continuous data, the Inverse-Variance method was used for the combination of standardised mean differences (SMD). Binary data were summarised as risk ratios (RR) and combined using the Mantel–Haenszel method.³² Heterogeneity of the studies was assessed according to Q and I^2 . The Q measure identifies whether the heterogeneity was statistically significant or not and the I^2 measure quantifies the heterogeneity. If the heterogeneity was significant a random effects method was used, otherwise a fixed effects method was utilised. In a sensitivity analysis, 0.5 was added to each cell frequency for trials in which no event occurred, according to the method recommended by Deeks et al.³³ Where standard deviations were not reported these were

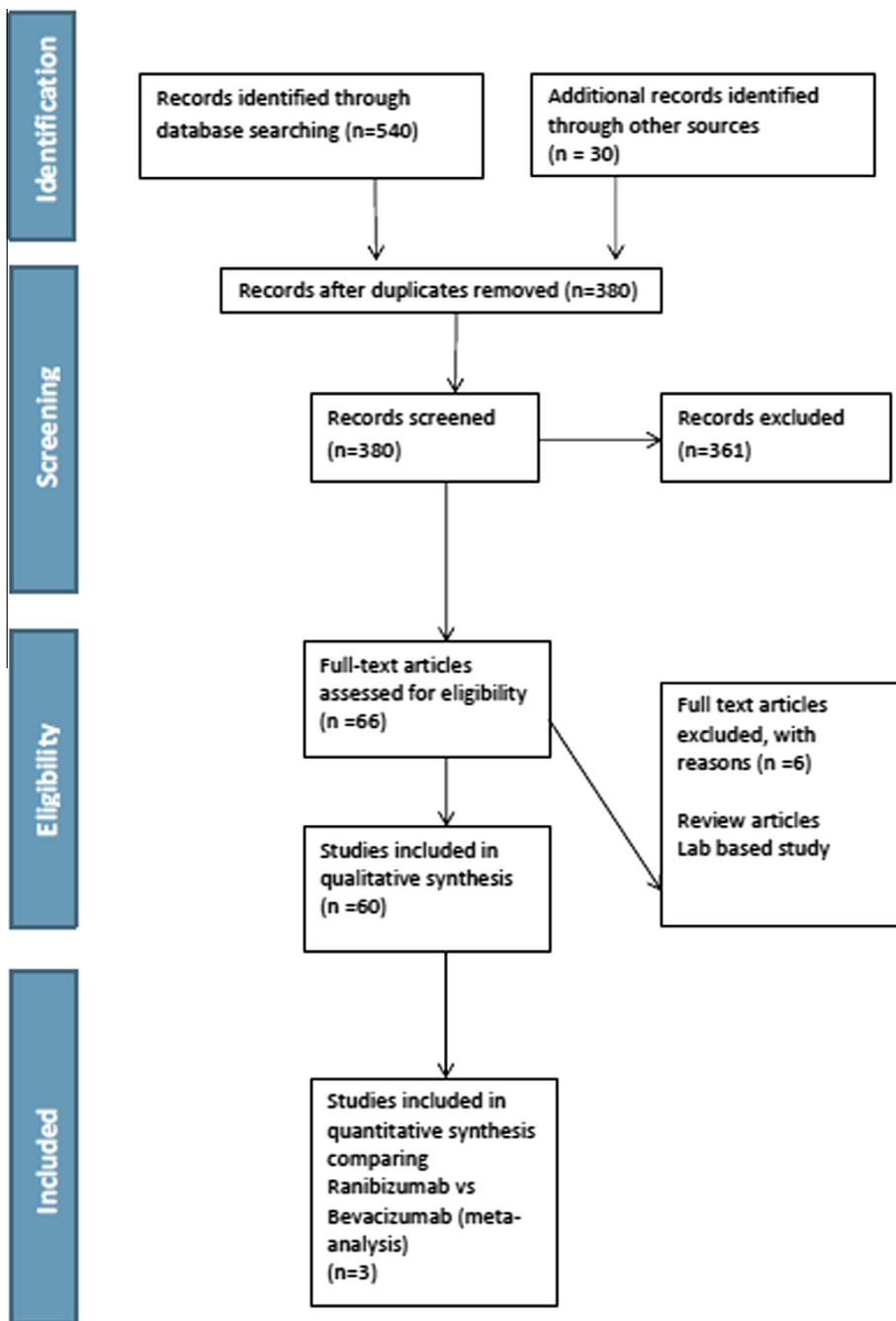


Figure 1. Search strategy.

estimated either from ranges or *p*-values. Forest plots were used for the graphical display.

Results

66 articles were screened for relevance. 41 articles were found to be relevant to our study. Three articles^{9,34,35} were found to have useful data for the summative outcome according to our inclusion criteria and thus were included in the quantitative analysis in our study (Table 1). Characteristics of each article are given in Table 4 and the results of each study are summarised in Table 5.

The three studies^{9,34,35} had a total of 54 patients in the intravitreal ranibizumab group and 63 in the intravitreal bevacizumab group (Table 4).

Overall improvement in the mean best corrected visual acuity

Three studies^{9,34,35} contributed to a summative outcome. There was no significant heterogeneity amongst trials ($Q = 2.43, df = 2, p = 0.30, I^2 = 18$). The mean number of lines improvement after IVR appeared better compared with IVB [fixed effects model: $RR = 0.46, 95\% CI (0.09, 0.83), z = 2.44, p = 0.001; Fig. 2$].

Table 1. Modified quality score for randomised controlled trials (Jaddad et al. and Chalmers et al.).^{24,25}

Quality variables	Gharbiya et al.	Iacono et al.
Was the study described as randomised such as using the words randomly, random, and randomisation? [0, 1]	1	1
Was randomisation described and appropriate? [-1, 0, 1]	1	1
Was the study described as double blind? [0, 1]	0	1
Was method of blinding appropriate? [-1, 0, 1]	0	1
Was there a description of withdrawals and dropouts? [0, 1]	1	1
Inclusion criteria	1	1
Exclusion criteria	1	1
Study period given	1	1
Appropriate statistical analysis	1	1
Hard end points	1	1
Sample size calculation	0	0
Baseline comparable	1	1
Any missing post op data	1	1
Allocation concealment	0	1
Analysis by intention to treat	0	1
Score	10	14
Score max 15. Poor = -1-5 Fair = 6-10 Good = 11-15		

Table 2. Methodological qualities of retrospective studies included in the trial. Adapted from the Scottish Intercollegiate Guidelines Network and Rangel et al.^{26,27}

Quality variables	Lai et al.
Inclusion criteria	1
Exclusion criteria	1
Demographics comparable?	1
Can the number of participating centres be determined	1
Can the number of clinicians who participated be determined	0
Can the reader determine where the authors are on the learning curve for the reported investigative procedure	1
Is the technique adequately described	1
Is there any way that they have tried to standardise the technique	1
Is the age and range given for patients	1
Do authors address whether there is any missing data	0
Were patients in each group treated along similar timelines	1
Dropout rates stated	1
Outcomes clearly defined?	1
Blind comparators	0
Analysis by intention to treat	0
Score	11
Total 15 Less than 6 – Poor quality. 6-10 – Fair quality. 11 or more – Good quality	

Table 3. Inclusion criteria.

• All studies comparing ranibizumab and bevacizumab for the treatment of myopic choroidal neovascularisation
• Trials on patients of any age or sex
• Trials in all languages
• Participants of any ethnicity

No. of patients with a best corrected visual acuity improvement of 3 lines or more

Three studies^{9,34,35} contributed to a summative outcome. There was no significant heterogeneity amongst trials ($Q = 2.01$, $df = 2$, $p = 0.37$, $I^2 = 0$). The number of patients who had a greater than 3 line improvement was similar between groups [fixed effects model: RR = 0.95, 95% CI (0.67, 1.32), $z = 0.33$, $p = 0.74$; Fig. 3].

No. of patients with an absence of leakage at follow up

Three studies^{9,34,35} reported on absence of leakage at follow up. There was no significant heterogeneity amongst trials ($Q = 3.77$, $df = 2$, $p = 0.15$, $I^2 = 47$). At follow up there was no difference in number of those who had an absence of leakage [fixed effects model: RR = 1.04, 95% CI (0.93, 1.16), $z = 0.64$, $p = 0.52$; Fig. 4].

Overall number of injections required

There was significant heterogeneity amongst trials ($Q = 10.55$, $df = 2$, $p = 0.005$, $I^2 = 81$); therefore the fixed effects model was inappropriate.^{9,34,35} There was no statistical significance between the two groups in relation to the number of injections [random effects model: SMD = -0.25, 95% CI (-1.12, 0.61), $z = 0.57$, $p = 0.57$; Fig. 5].

Recurrence of leakage

There was not enough data to produce a meaningful summative outcome. Individual studies^{9,34} showed no recurrence of CNV during the follow-up periods. No significant difference in recurrence was found between the ranibizumab and bevacizumab groups in any of the studies examined.^{9,34,35}

Complications

There was not enough data to produce a meaningful summative outcome. No ocular or systemic adverse events were recorded in the studies performed by Iacono et al. and Gharbiya et al.^{9,34} Some ocular adverse events were encountered in the Lai et al. study, with five occurring in the bevacizumab group and four in the ranibizumab group.³⁵ The most common ocular complication was a cataract (two in the bevacizumab and one in the ranibizumab group); these were treated with surgery.³⁵ Only two patients lost three or more lines on the ETDRS chart as a result of an ocular complication, both patients came from the bevacizumab group.³⁵

Discussion

Photodynamic therapy with verteporfin has been the most widely used treatment for myopic CNV as it demonstrated stabilisation of vision with short term treatment in comparison to placebo.^{13,34} However, recently it has fallen out of favour as it was shown to have poor long-term visual outcomes with a high percentage of patient developing reoccurrence of intraretinal fluid.^{14,15} Moreover, as many patients with PM had pre-existing retinal pigment epithelial atrophy,

treatment with PDT was found to exacerbate the chorioretinal atrophy.^{15,36}

Recently, VEGF has been demonstrated to play a major role in the pathogenesis of myopic CNV.^{16,37} Intravitreal Anti-VEGF injections have demonstrated significant visual and anatomical outcomes in both short-term (6 months) and long-term studies (up to 36 months).^{17,38} Moreover, Baba et al. and Yoon et al. demonstrated superior visual outcomes following Anti-VEGF therapy compared with PDT at 12 and 24 months respectively.^{18,39}

There are currently two Anti-VEGF drugs which are widely used, ranibizumab and bevacizumab. Variation between both drugs exists from a basic science perspective, suggesting a superior clinical action with ranibizumab.³⁴ The main difference between the two drugs is molecular weight, ranibizumab has a lower molecular weight (48 kDa) compared to bevacizumab (149 kDa), suggesting that ranibizumab should have higher and faster retinal penetration.³⁴ Moreover, ranibizumab is more affinity-matured than bevacizumab, suggesting that it will have more robust molecular binding with VEGF molecules.¹¹ So far, comparison of clinical data through both indirect and direct methods has failed to affirm superiority for either drug.^{40,41}

Main findings

In this meta-analysis, we quantitatively analysed three studies that directly compared ranibizumab with bevacizumab for treatment of myopic CNV. Our results demonstrate that the mean improvement in visual acuity of both groups was similar, with the summative outcome slightly favouring ranibizumab.^{9,34,35} Another visual outcome assessed was the number of patients with greater than 3 lines improvement, which demonstrated a similar outlook in both groups, across all studies.^{9,34,35} Moreover, anatomical outcomes such as absence of leakage and reoccurrence of leakage (assessed with Fluorescein Fundus Angiography (FFA) and Ocular coherence tomography (OCT)) showed very similar outcomes in both groups.^{9,34,35} Furthermore, the number of injections required was similar between the two groups in all three studies.^{9,34,35} The occurrence of ocular and systemic adverse events was infrequent, generally mild to moderate in intensity and treatable in most cases.^{9,34,35}

Importance

Anti-VEGF therapy has now been clinically recommended by several studies as a first line therapy for myopic CNV.^{11,40} Its clinical use will vary depending on a number of factors such as availability and cost.²⁵

Demonstrating similar efficacies between the two Anti-VEGF agents will further establish both agents for treating this challenging condition. This will prove useful for clinicians as it provides additional scope for drug switching and alternatives in cases where patients experience poor visual outcomes or side effects to one but not the other drug.^{9,34,35}

A number of large multi-centre randomised clinical trials examining ranibizumab and bevacizumab for treating AMD recently demonstrated comparable efficacy and safety between the two Anti-VEGF agents.^{24,42–44} Results from our study cannot be applied to AMD due to variations in the

pathogenesis. However, we may infer that VEGF agents play a similar role in generating CNV when secondary to either AMD or PM.³⁷

Appraisal of evidence

The first study to examine Anti-VEGF treatment for myopic CNV reported that bevacizumab therapy resulted in an improvement in visual acuity and reduction in sub/intra retinal fluid was provided by Nguyen et al. in 2005.¹⁶ There has since been a plethora of studies examining either ranibizumab or bevacizumab therapy for the treatment of myopic CNV, mainly from small case-series, with no randomisation or control groups.⁴ Both treatments have consistently resulted in statistically significant visual and anatomical gains at both short-term and long-term measures.¹¹ However, variation in visual outcomes between studies is profound; ranibizumab studies have demonstrated an improvement in visual acuity ranging from 8 letters to 19.3 letters improvement, while bevacizumab studies have demonstrated a range of 3.4 letter improvements to 18.2 letter improvements.⁴¹ This variation could be due to disparities in protocols, as some studies used an initial treatment of three injections (monthly) while others used only one injection (further treatment in the vast majority of studies was according to visual and anatomical findings (e.g. OCT)).¹¹ Moreover, it could be as a result of disparity in dosage, as bevacizumab therapy was used in doses of 1 mg, 1.25 mg, 1.5 mg or 2.5 mg.¹¹ Furthermore, it could be as a result of variation in the participants' baseline characteristics, presenting visual acuity, including differences in CNV dimensions, duration of symptoms or choroidal thickness.⁴⁵ In addition, there could also be intrinsic differences between drugs.

With regards to anatomical outcomes, the majority of studies examining Anti-VEGF for myopic CNV reported a reduction in sub/intraretinal fluid measured with FFA or OCT in $\geq 80\%$ of patients on final follow-up.⁴¹ Furthermore, all studies have demonstrated acceptable safety profiles for intravitreal Anti-VEGF injections.¹¹ However, Anti-VEGF agents are known to cause serious adverse events such as intraocular inflammation and chorioretinal atrophy.^{46–48}

Heterogeneity

Amongst the studies used in the quantitative analysis, two studies were done prospectively^{9,34} and one retrospectively.³⁵ There was heterogeneity between the studies with regards to length of study period (Gharbiya et al.: 6 months, Iacono et al.: 18 months and Lai et al.: 24 months)^{9,34,35} (Table 4). Only "end-of-study" results were analysed in this meta-analysis which is a limitation.

Patient demographics were comparable in terms of age and male:female ratio.^{9,34,35} Two studies had no statistically significant differences in baseline characteristics between the IVR and IVB groups (including mean visual acuity, lens status and refractive error)^{9,38}, while one study demonstrated statistically significant longer duration of symptoms and worse baseline visual acuity in the IVR group compared to the IVB group at baseline.³⁵ The inclusion and exclusion criteria were comparable in all of the studies; all participants had treatment-naïve myopic CNV with no other ocular disease that could affect visual acuity.^{9,34,35}

Table 4. Characteristics of trials comparing ranibizumab vs bevacizumab for the treatment of myopic choroidal neovascularisation.

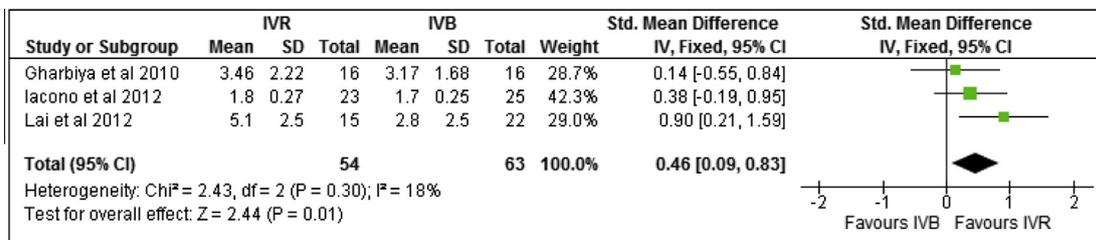
Trial	Year	Type	N	Type	f/up	Intravitreal injection protocol	Population characteristics
Gharbiya et al.	2010	Rani Bev	16 16	RCT	6	0.5 mg/0.05 mL of ranibizumab; 1.25 mg/0.05 mL of bevacizumab; Re-treatment based on presence of intra/subretinal fluid	Mean age (sd): 60.63 (10.48); m:f: 4:12 Mean age (sd) 59.06 (11.42). m:f: 6:10
Iacono et al.	2012	Rani Bev	23 25	RCT	18	0.5 mg/0.05 mL of ranibizumab; 1.25 mg/0.05 mL of bevacizumab; re-treatment based on presence of either intra/subretinal fluid, leakage or a new haemorrhage	Mean age 65 (sd 12), m:f:7:20 Mean age 61 (sd 11), m:f: 6:22
Lai et al.	2012	Rani Bev	15 22	Retro	24	0.5 mg/0.05 mL of ranibizumab; 1.25 mg/0.05 mL of bevacizumab; After 3 injections (1/month), re-treatment based on new symptoms/persistent/recurrent angiogenic leakage	Mean age 58.9 (sd 10.5), m:f:3:12 Mean age 56.3 (sd 14.6), m:f:11:11

Rani = ranibizumab; Bev = bevacizumab; f/up = follow up; Retro = retrospective; RCT = randomised controlled trial.

Table 5. Outcomes of the studies comparing ranibizumab vs bevacizumab for the treatment of myopic choroidal neovascularisation.

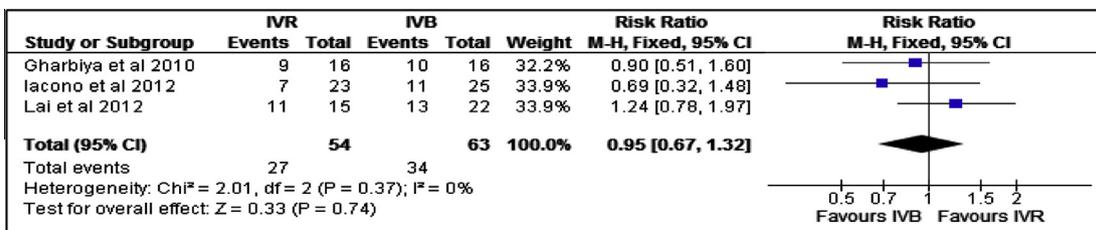
Study	Year	Type	N	Overall mean BCVA [LMC] improvement (Lines)	BCVA improved ≥ 3 lines (Overall)	Recurrence (Overall)	Absence of leakage	No. injections (Overall)	Systemic complications	Ocular adverse event
Gharbiya et al.	2010	Rani Bev	16 16	3.46 SD = 2.22 3.17 SD = 1.68	9 10	0 0	15 16	2.81 (range 1–5) 2.44 (range 1–5)	0 0	0 0
Iacono et al.	2012	Rani Bev	23 25	1.8 SD = 0.27 1.7 SD = 0.25	7 11	n/a n/a	23 21	2.56 (range 1–6) 4.72 (range 1–8)	0 0	0 0
Lai et al.	2012	Rani Bev	15 22	5.1 (P < 0.001) 2.8 (P = 0.009)	11 13	n/a 2	13 (at 3 months) 20 (at 3 months)	3.8 (range 3–6) 3.8 (range 3–9)	0 0	4 5

Rani = ranibizumab; Bev = bevacizumab; BCVA = best corrected visual acuity; LMC = LogMar Chart; SD = standard deviation.



IVR= Intravitreal Ranibizumab; IVB=Intravitreal Bevacizumab; SD=Standard deviation; CI=Confidence Interval; df=degrees of freedom

Figure 2. Best corrected visual acuity improvement at the end of the study periods (measured by LogMar Chart) (lines).



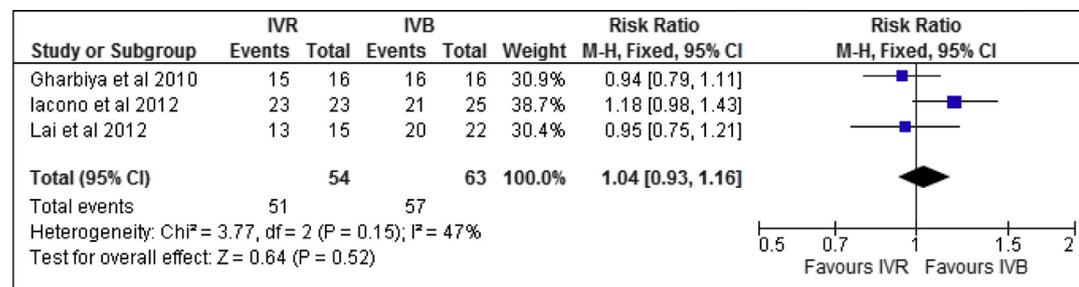
IVR= Intravitreal Ranibizumab; IVB=Intravitreal Bevacizumab; CI=Confidence Interval; df=degrees of freedom; M-H: Mantel-Haenszel

Figure 3. No. of patients with a best corrected visual acuity improvement of 3 lines or more.

The primary outcome measure was similar amongst all studies, being the best corrected visual acuity measured using the ETDRS chart, which was used in exactly the same way.^{9,34,35} FFA and OCT were employed in each study to assess for leakage sub/intraretinally.^{9,34,35} This could have

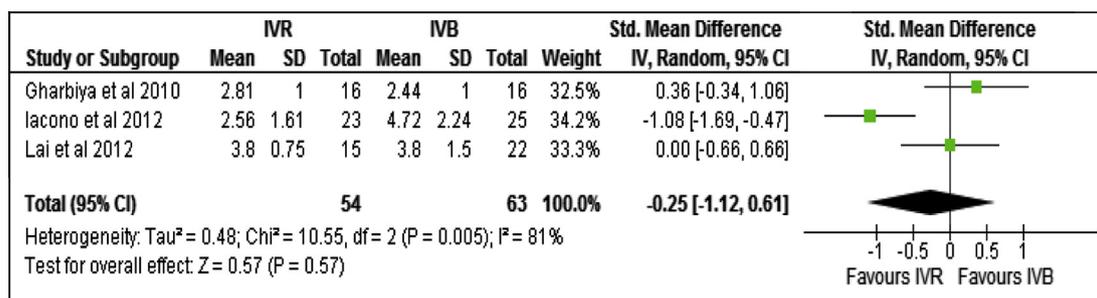
led to possible interpreter bias in our study due to having technicians and doctors of varied experience in each study examining the FFA and OCT scans.

There was no statistically significant heterogeneity in the concentrations of drug used in injections and minimal heter-



IVR= Intravitreal Ranibizumab; IVB=Intravitreal Bevacizumab; CI=Confidence Interval; df=degrees of freedom; M-H: Mantel-Haenszel

Figure 4. No. of patients with an absence of leakage at follow up.



IVR= Intravitreal Ranibizumab; IVB=Intravitreal Bevacizumab; CI=Confidence Interval; df=degrees of freedom

Figure 5. Overall number of injections required.

ogeneity in Injection methods. Retreatment varied between each study, Gharbiya et al. and Iacono et al. provided one injection and then continued on an as needed basis at monthly follow ups whereas Lai et al. treated with three injections (one each month) before providing a course of three injections (one each month) on an as needed basis.^{9,34,35}

Of the three studies included in the meta-analysis, two studies (Gharbiya et al. and Lai et al.) demonstrated similar efficacies between ranibizumab and bevacizumab for the treatment of myopic CNV, whereas Iacono et al. demonstrated enhanced efficacy when using ranibizumab compared to bevacizumab.^{9,34,35} This difference in results between studies can lead to the effect size being unstable and therefore conclusions ought to be made with a degree of caution.

Quality assessment

All studies used in the qualitative analysis scored highly in the quality assessment (Tables 1 and 2). Iacono et al’s study scored higher than Gharbiya et al’s study as it included allocation concealment, was double blinded and analysis was done on intention-to-treat basis.^{9,34}

Future studies

We did not analyse publication bias due to there being less than 10 studies included in this review. There is likely to be publication bias just by virtue of the low number of studies and this is a limitation to our review. Further prospective, long-term, multi-centre randomised clinical trials are required to determine the appropriate management of myopic CNV. Due to the small research basis that currently exists in the literature, it is inappropriate to reach a generalisable

clinical judgement between ranibizumab and bevacizumab for treating myopic CNV.

Conclusion

Evidence suggests that intravitreal Anti-VEGF injections should be first line therapy for myopic CNV. Comparative studies examining intravitreal injections of ranibizumab and intravitreal injections of bevacizumab indicate that they produce similar visual and anatomical outcomes. Both treatments result in a statistically significant increase in visual acuity with high numbers of patients maintaining stable vision. Moreover, reduction of leakage in the retinal layers following treatment is ubiquitous. Reported rates of ocular and systemic complications suggest that both treatments may be safe. However, more detailed documentation of both systemic and ocular adverse events is required in future studies. Further prospective, long term, multi-centre randomised clinical trials are still needed to elucidate the most appropriate long term management of myopic CNV.

Conflict of interest

The authors declared that there is no conflict of interest.

References

1. Chan WM, Ohji M, Lai TY, Liu DT, Tano Y, Lam DS. Choroidal neovascularisation in pathological myopia: an update in management. *Br J Ophthalmol* 2005;**89**(11):1522–8.
2. Morgan IG, Ohno-Matsui K, Saw SM. Myopia. *Lancet* 2012;**379**(9827):1739–48 Research Support, Non-U.S. Gov’t Review.
3. Sherwin JC, Reacher MH, Keogh RH, Khawaja AP, Mackey DA, Foster PJ. The association between time spent outdoors and myopia in children and adolescents: a systematic review and meta-analysis.

- Ophthalmology* 2012;**119**(10):2141–51 Meta-Analysis Research Support, Non-U.S. Gov't Review.
4. Neelam K, Cheung CM, Ohno-Matsui K, Lai TY, Wong TY. Choroidal neovascularization in pathological myopia. *Prog Retin Eye Res* 2012;**31**(5):495–525.
 5. Saw SM. How blinding is pathological myopia? *Br J Ophthalmol* 2006;**90**(5):525–6 [Comment Editorial Research Support, Non-U.S. Gov't].
 6. Secretan M, Kuhn D, Soubrane G, Coscas G. Long-term visual outcome of choroidal neovascularization in pathologic myopia: natural history and laser treatment. *Eur J Ophthalmol* 1997;**7**(4):307–16.
 7. Tabandeh H, Flynn Jr HW, Scott IU, Lewis ML, Rosenfeld PJ, Rodriguez F, et al. Visual acuity outcomes of patients 50 years of age and older with high myopia and untreated choroidal neovascularization. *Ophthalmology* 1999;**106**(11):2063–7.
 8. Ohno-Matsui K, Shimada N, Yasuzumi K, Hayashi K, Yoshida T, Kojima A, et al. Long-term development of significant visual field defects in highly myopic eyes. *Am J Ophthalmol* 2011;**152**(2):256 e1–65 e1 Case Reports Research Support, Non-U.S. Gov't.
 9. Iacono P, Parodi MB, Papayannis A, Kontadakis S, Sheth S, Cascavilla ML, et al. Intravitreal ranibizumab versus bevacizumab for treatment of myopic choroidal neovascularization. *Retina* 2012;**32**(8):1539–46.
 10. Ohno-Matsui K, Yoshida T, Futagami S, Yasuzumi K, Shimada N, Kojima A, et al. Patchy atrophy and lacquer cracks predispose to the development of choroidal neovascularisation in pathological myopia. *Br J Ophthalmol* 2003;**87**(5):570–3.
 11. Cohen SY. Anti-VEGF drugs as the 2009 first-line therapy for choroidal neovascularization in pathologic myopia. *Retina* 2009;**29**(8):1062–6.
 12. Excellence NifHaC. Guidance in development – Choroidal neovascularisation (pathological myopia) – ranibizumab; 2013. Available from: <<http://guidance.nice.org.uk/TA/WaveR/148#stakeholders>>.
 13. Verteporfin in Photodynamic Therapy Study G. Photodynamic therapy of subfoveal choroidal neovascularization in pathologic myopia with verteporfin. 1-year results of a randomized clinical trial-VIP report no. 1. *Ophthalmology* 2001;**108**(5):841–52 Clinical Trial Comparative Study Multicenter Study Randomized Controlled Trial.
 14. Blinder KJ, Blumenkranz MS, Bressler NM, Bressler SB, Donato G, Lewis H, et al. Verteporfin therapy of subfoveal choroidal neovascularization in pathologic myopia: 2-year results of a randomized clinical trial-VIP report no. 3. *Ophthalmology* 2003;**110**(4):667–73.
 15. Giansanti F, Virgili G, Donati MC, Giuntoli M, Pieretti G, Abbruzzese G, et al. Long-term results of photodynamic therapy for subfoveal choroidal neovascularization with pathologic myopia. *Retina* 2012;**32**(8):1547–52.
 16. Nguyen QD, Shah S, Tatlipinar S, Do DV, Anden EV, Campochiaro PA. Bevacizumab suppresses choroidal neovascularisation caused by pathological myopia. *Br J Ophthalmol* 2005;**89**(10):1368–70.
 17. Chan WM, Lai TY, Liu DT, Lam DS. Intravitreal bevacizumab (Avastin) for myopic choroidal neovascularization: six-month results of a prospective pilot study. *Ophthalmology* 2007;**114**(12):2190–6.
 18. Baba T, Kubota-Taniai M, Kitahashi M, Okada K, Mitamura Y, Yamamoto S. Two-year comparison of photodynamic therapy and intravitreal bevacizumab for treatment of myopic choroidal neovascularisation. *Br J Ophthalmol* 2010;**94**(7):864–70.
 19. Excellence NifHaC. Technology appraisal TA155 – Pegaptanib and ranibizumab for the treatment of age-related macular degeneration; 2008. Available from: <<http://www.nice.org.uk/TA155>>.
 20. Excellence NifHaC. Technology appraisal TA274 – Ranibizumab for the treatment of diabetic macular oedema (rapid review of TA237); 2013. Available from: <<http://guidance.nice.org.uk/TA274>>.
 21. Choroidal neovascularisation (pathological myopia) – ranibizumab; 2013.
 22. Novartis. Novartis drug Lucentis approved in EU as first effective anti-VEGF treatment for myopic choroidal neovascularization; 2013. <<http://www.novartis.com/newsroom/media-releases/en/2013/1714478.shtml>>.
 23. Excellence NifHaC. Technology appraisal guidance TA263 – Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer; 2012. Available from: <<http://publications.nice.org.uk/bevacizumab-in-combination-with-capecitabine-for-the-first-line-treatment-of-metastatic-breast-ta263>>.
 24. Ophthalmologists TRCo. RCOphth review concludes that Avastin and Lucentis are equally effective in treating wet AMD; 2011. Available from: [http://www.rcophth.ac.uk/news.asp?itemid=647&itemTitle=RCOphth±Review±concludes±that±Avastin±and±Lucentis±are±equally±effective±in±treating](http://www.rcophth.ac.uk/news.asp?itemid=647&itemTitle=RCOphth%20Review%20concludes%20that%20Avastin%20and%20Lucentis%20are%20equally%20effective%20in%20treating).
 25. Raftery J, Clegg A, Jones J, Tan SC, Lotery A. Ranibizumab (Lucentis) versus bevacizumab (Avastin): modelling cost effectiveness. *Br J Ophthalmol* 2007;**91**(9):1244–6.
 26. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;**339**:b2700 Consensus Development Conference Guideline.
 27. Chalmers TC, Smith Jr H, Blackburn B, Silverman B, Schroeder B, Reitman D, et al. A method for assessing the quality of a randomized control trial. *Control Clin Trials* 1981;**2**(1):31–49 Clinical Trial Randomized Controlled Trial Research Support, U.S. Gov't, P.H.S..
 28. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;**17**(1):1–12 [Meta-Analysis].
 29. Network SIG. SIGN Guidelines. 1st of December 2012; Available from: <<http://www.sign.ac.uk/guidelines/fulltext/50/checklist3.html>>.
 30. Rangel SJ, Kelsey J, Colby CE, Anderson J, Moss RL. Development of a quality assessment scale for retrospective clinical studies in pediatric surgery. *Journal of pediatric surgery* 2003;**38**(3):390–6 Research Support, Non-U.S. Gov't Validation Studies, discussion -6.
 31. Copenhagen: The Nordic Cochrane Centre TCC. Review Manager 5.2 ed; 2012.
 32. Egger MDSG, Altman DG. *Systematic reviews in healthcare*. London: BMJ Publishing; 2006.
 33. Deeks JJAD, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger MDSG, Altman DG, editors. *Systematic reviews in health care: meta-analysis in context*. 2nd ed. London (UK): BMJ Publication Group; 2001.
 34. Gharbiya M, Giustolisi R, Allievi F, Fantozzi N, Mazzeo L, Scavella V, et al. Choroidal neovascularization in pathologic myopia: intravitreal ranibizumab versus bevacizumab – A randomized controlled trial. *Am J Ophthalmol* 2010;**149**(3):458 e1–64 e1.
 35. Lai TY, Luk FO, Lee GK, Lam DS. Long-term outcome of intravitreal anti-vascular endothelial growth factor therapy with bevacizumab or ranibizumab as primary treatment for subfoveal myopic choroidal neovascularization. *Eye (Lond)* 2012;**26**(7):1004–11.
 36. Parodi MB, Da Pozzo S, Ravalico G. Retinal pigment epithelium changes after photodynamic therapy for choroidal neovascularization in pathological myopia. *Acta Ophthalmol Scand* 2007;**85**(1):50–4.
 37. Chan WM, Lai TY, Chan KP, Li H, Liu DT, Lam DS, et al. Changes in aqueous vascular endothelial growth factor and pigment epithelial-derived factor levels following intravitreal bevacizumab injections for choroidal neovascularization secondary to age-related macular degeneration or pathologic myopia. *Retina* 2008;**28**(9):1308–13.
 38. Gharbiya M, Cruciani F, Parisi F, Cuzzo G, Altimari S, Abdolrahimzadeh S. Long-term results of intravitreal bevacizumab for choroidal neovascularisation in pathological myopia. *Br J Ophthalmol* 2012;**96**(8):1068–72.
 39. Yoon JU, Byun YJ, Koh HJ. Intravitreal anti-VEGF versus photodynamic therapy with verteporfin for treatment of myopic choroidal neovascularization. *Retina* 2010;**30**(3):418–24.
 40. Lai TY. Anti-vascular endothelial growth factor therapy for myopic choroidal neovascularization: do we need more evidence? *Retina* 2012;**32**(8):1443–5.
 41. Ng DS, Kwok AK, Chan CW. Anti-vascular endothelial growth factor for myopic choroidal neovascularization. *Clin Experiment Ophthalmol* 2012;**40**(1):e98–e110.
 42. Research G, Martin DF, Maguire MG, Fine SL, Ying GS, Jaffe GJ, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology* 2012;**119**(7):1388–98 Comparative Study Multicenter Study Randomized Controlled Trial Research Support, N.I.H., Extramural.
 43. Investigators IS, Chakravarthy U, Harding SP, Rogers CA, Downes AJ, Lotery AJ, et al. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. *Ophthalmology* 2012;**119**(7):1399–411.

44. Krebs I, Schmetterer L, Boltz A, Told R, Vecsei-Marlovits V, Egger S, et al. A randomised double-masked trial comparing the visual outcome after treatment with ranibizumab or bevacizumab in patients with neovascular age-related macular degeneration. *Br J Ophthalmol* 2013;**97**(3):266–71.
45. Ahn SJ, Woo SJ, Kim KE, Park KH. Association between Choroidal Morphology and Anti-Vascular Endothelial Growth Factor Treatment Outcome in Myopic Choroidal Neovascularization. *Invest Ophthalmol Vis Sci* 2013;**54**(3):2115–22.
46. Ghasemi Falavarjani K, Nguyen QD. Adverse events and complications associated with intravitreal injection of anti-VEGF agents: a review of literature. *Eye (Lond)* 2013;**27**(7):787–94.
47. Saint-Geniez M, Kurihara T, Sekiyama E, Maldonado AE, D'Amore PA. An essential role for RPE-derived soluble VEGF in the maintenance of the choriocapillaris. *Proc Natl Acad Sci U S A* 2009;**106**(44):18751–6.
48. Kurihara T, Westenskow PD, Bravo S, Aguilar E, Friedlander M. Targeted deletion of Vegfa in adult mice induces vision loss. *J Clin Invest* 2012;**122**(11):4213–7.