CLINICAL STUDY

Intravitreal bevacizumab (Avastin) for age-related macular degeneration: a critical analysis of literature

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This article was presented as a scientific paper at the Asia ARVO Congress, Hyderabad, India in January 2009.

Abstract

Purpose The current medical environment demands that quality health care is delivered at an affordable cost through the use of objective, unbiased clinical data. This study was undertaken to review the current literature on bevacizumab for age-related macular degeneration and its value in determining best clinical practice.

Methods Randomised controlled trials (RCTs) and observational studies that met the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria were identified from the current literature for further analysis. Data concerning treatment dosing regimens, response to treatment, complications, and factors influencing outcome and safety were extracted and compiled into a database.

Results As of January 2009, there were 5 RCTs that compared the outcomes of bevacizumab to other treatment options and 50 studies that met the STROBE criteria with similar visual and anatomical outcomes between RCTs and observational studies. Although the doses and dosing frequencies varied between the studies, the mean gain in vision at 3 months was $+7.76 \pm 5.4$ ETDRS letters (range $+2$ to $+14.4$); an effect that was maintained at 6 months in studies with longer follow-up. Predominantly classic lesions were the most responsive of all lesion subtypes. The complication profiles/rates were similar to those reported with other anti-vascular endothelial agents.

Conclusions There is sufficient scientific and statistical evidence to advocate the effective use of OCT-guided administration of intravitreal bevacizumab for neovascular AMD. This is reflected in our study outcome measures that are comparable to findings published from recent well-conducted RCTs on intravitreal ranibizumab at the same time point.

Introduction

The concept of vascular endothelial growth factor (VEGF) inhibition and its influence on modulating the behaviour of choroidal neovascularisation (CNV) marked a turning point in the treatment of neovascular age-related macular degeneration (AMD).[1,2] Since then, two drugs, pegaptanib sodium and ranibizumab, have successfully qualified all the necessary phases of drug development to obtain licensing approval by regulatory bodies and form the mainstay of treatment for neovascular AMD. Pegaptanib sodium (Macugen; Eyetech Pharmaceuticals, New York, NY, USA) is constructed as an aptamer to target VEGF-A 165 whereas ranibizumab (Lucentis; Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA) is an antibody fragment able to target all VEGF-A isoforms when delivered intravitreally. The VISION study demonstrated that 6-weekly intravitreal pegatanib sodium stabilised vision in 70% of cases and improved vision in only 6%.[3] Subsequently, ranibizumab was shown to stabilise vision in

nearly 95% of patients with 30% experiencing improvements in visual acuity; marking the first effective intravitreal therapy with the potential to recover visual loss secondary to AMD.[4–6]

Although ranibizumab gained Food and Drugs Administration approval in June 2006; bevacizumab (Avastin; Genentech, South San Francisco, CA, USA), a recombinant humanised monoclonal antibody against all VEGF-A isoforms originally developed to treat metastatic carcinoma of the colon and rectum,[7] also showed considerable promise in improving vision albeit as an 'off label' intervention.[8–10] More specifically, a case series by Michels et al demonstrated the benefits of systemic administration of bevacizumab in the management of CNV by reducing retinal thickening and improving visual acuity;[8] which in turn encouraged further studies reporting similar outcomes when administered intravitreally.[9,10]

Furthermore under the current economic pressures and cost/benefit criteria practised in the medical environment, the provision of quality healthcare at an affordable cost through the use of objective, unbiased clinical data has become paramount. Therefore, given that bevacizumab has presented as a cheaper alternative to the more refined FDA-approved ranibizumab with presumed similar clinical outcomes, bevacizumab is now being widely administered for the treatment of neovascular AMD despite the absence of FDA and drug licensing approval for ocular use. However, in practice, various dosing/frequency regimens have been implemented either as monotherapy or in combination with other therapies making it difficult for practitioners to determine the best clinical practice based on current literature.

The aim of this study is to review the current state of the literature on the use of bevacizumab for neovascular AMD to tease out available information that will help retinal specialist to better understand the use of the drug in this condition, although awaiting randomised controlled trials comparing ranibizumab and bevacizumab. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement[11–13] published in 2007 is a checklist of 22 standards for non-RCT studies to assess the validity/applicability of the study (Table 1) akin to the Consolidated Standards for Reporting Trials (CONSORT)[14] statement used in RCTs. A group has recently published the use of STROBE criteria for studies on bevacizumab for neovascular AMD until October 2007.[15] In this study, we have extended these findings to include RCTs and STROBE-qualified studies until January 2009.[16–71]

Materials and methods

We conducted a systematic search of MEDLINE (2005 to January 2009) and the National Institutes of Health clinical trial databases (up to January 2009) for randomised controlled trials (RCTs) and observational case series with at least 3-month follow-up, both prospective and retrospective, which met the STROBE criteria. The search strategy used both keywords and MeSH terms for the following terms or combinations: CNV; choroidal neovascularisation; anti-VEGF; bevacizumab; avastin; pegaptanib; macugen; ranibizumab; lucentis; age-related macular degeneration; age-related maculopathy. All RCTs were included. As the range of STROBE quality grade in a similar study was between 46 and 94%, this study included all studies that met at least 50% of the STROBE standards. Two reviewers assessed inclusion into this study and consensus was reached by discussion between reviewers.

The primary parameters of interest were mean change in visual acuity and central retinal thickness. The data included number of patients, treatment dose and regimen, CNV subtypes, response to treatment at specific time points, complications, and factors influencing outcome and safety. All the visual acuities were converted into equivalent ETDRS letter score for analysis. In the case of studies that sequentially reported the longer follow-up of the same series of patients, the latest study with the longest follow-up was included. Data were entered into a Microsoft Excel 2000 (Microsoft Corporation, Redmond, WA, USA) datasheet for tabulation and descriptive statistics. Data were pooled where appropriate to assess the outcome measures at specific time points and the mean number of treatments required at any particular time point.

Results

The electronic searches found a total of 349 publications that reported the clinical outcomes of bevacizumab in neovascular AMD. A total of 55 reports on clinical outcomes met the inclusion criteria. These included 5 RCTs that compared bevacizumab to other treatment options and 50 STROBE-qualified studies, of which 12 studies evaluated the combination of bevacizumab with another treatment modality. A summary of the five RCTs have been tabulated in Table 2. A meta-analysis could not be performed as a consequence of the heterogeneity in study design.

STROBE-qualified studies

There were 50 studies that met at least 50% of the STROBE criteria.[15] The total number of subjects in the studies varied from 6 to 266 (mean, 53; median, 45). Twelve of these studies assessed the effect of combination therapy of intravitreal bevacizumab with another agent. The follow-up of these studies ranged from 3 to 12 months. Nine studies had less than 6-month

Table 1 The STROBE checklist of items for evaluation of observational studies[12]

		Recommendation
Title and abstract	1a	Indicate the study's design with a commonly used term in the title or the abstract.
	1b	Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Materials and methods		
Study design	4	Present key elements of study design
Setting	5	Describe the setting or participating location
Participants	6a	Statement about institutional review board approval and consent
	6b	Give the inclusion and exclusion criteria
	6c	Describe the sources and methods of selection of participants
	6d	Describe methods of follow-up
Treatments	7a	Drug dose(s) defined
	7b	Drug administration described
Variables	8	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers
Data sources/measurement		
Visual acuity	9a	Define method of visual acuity measurement
OCT	9b	Describe technique for OCT data
Angiography	9c	Describe technique for fluorescein angiography data
Bias	10	Describe any efforts to address potential sources of bias
Study size	11	Explain how the study size was arrived at
Statistical methods	12a	Describe all statistical methods, including those used to control for confounding
	12b	Describe any methods used to examine subgroups and interactions
	12c	Explain how missing data were addressed
	12d	If applicable, explain how loss to follow-up was addressed
Results		
Participants	13a	Report the numbers of individuals at each stage of the study, eg, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
	13b	Previous treatment for nvAMD reported
	13c	Flow diagram included
Descriptive data	14a	Baseline vision and imaging data reported
	14b	Lesion type or size discussed
	14c	Indicate the number of participants with missing data for each variable of interest
	14d	Summarise follow-up time, eg, average and total amount
Main results	15	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence intervals). Make clear which confounders were adjusted for and why they were included
Adverse events	16	Adverse events reported
Other analyses	17	Report other analyses done, eg, analyses of subgroups and interactions and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for this study

This table is modified from Fung *et al*.[15]

Table 2 Randomised controlled trials comparing intravitreal bevacizumab with other treatment modalities

| Author (year)	Dose of bevacizumab; frequency	Number of patients in bevacizumab arm	Comparative treatment modality	Number of patients in comparator arm	Length of follow-up (months)	Visual change in bevacizumab group (ETDRS)	Visual change in comparative group (ETDRS)
Bashshur (2007)[26]	2.5 mg; PRN	32	PDT	30	6	12	−6
Hahn (2007)[44]	1 mg; 3 + PRN	10	SPDT + IVTA	10	3	12	−7
			RPDT + IVTA	10			−0.5
Lazic (2007)[51]	1.25 mg; ST	54	PDT + IVB	52	3	1	12.3
			PDT	50			0
Sacu (2009)[65]	1 mg; 3 + PRN	14	PDT + IVTA	14	12	8	−3
Weigert (2008)[70]	1 mg; 3 + PRN	14	PDT + IVTA	14	6	11	0

PRN, pro re nata; PDT, photodynamic therapy; SPDT, standard fluence PDT; RPDT, reduced fluence PDT; ETDRS, early treatment diabetic retinopathy study; IVTA, intravitreal triamcinolone; IVB, intravitreal bevacizumab; ST, single Treatment.

follow-up period whereas only three studies had completed 12-month follow-up. The doses of bevacizumab administered varied from 1 mg to 2.5 mg, although most studies used 1.25 mg/0.05 ml ($n = 36$). Two most commonly used dosing regimen included a *pro re nata* (PRN) regime guided by optical coherent tomography (OCT) and visual acuity ($n = 23$) and a loading dose of 6-weekly bevacizumab followed by an OCT-guided PRN approach ($n = 20$). The percent of STROBE criteria met ranged from 50 to 88% (mean, 68%; median, 68%). Most studies (88%) used standardised reporting of outcomes similar to RCTs on these anti-VEGF agents. Therefore, pooling of data from these studies was possible to provide a better estimate of the effect of intravitreal bevacizumab in neovascular AMD. Despite meeting STROBE criteria, some case series could not be pooled due to differing inclusion criteria. The major drawback was the lack of long-term follow-up to estimate long-term outcomes.

Visual outcomes

We compared the visual outcomes in the bevacizumab arms of all the RCTs (Figure 1), all of which reported similar results apart from that by Laziæ *et al*, with a mean gain of +6.91 ETDRS letters (range 1–12) at 3 months, +8.8 letters at 6 months (3 studies), and +8 letters at 12 months (1 study). The poorer outcome of bevacizumab reported by Laziæ *et al* at 3 months may be attributed to the single dose used in the study. The mean visual outcome improved by +6 letters ETDRS at 1 month but the effect was not sustained at 3 months. The pooled data from STROBE-selected studies showed a mean gain of +7.57 ± 4.86 SD letters at an average follow-up of 6 months.

As the inclusion criteria of the five RCTs were not significantly different, the data on visual outcomes of all the bevacizumab arms (all doses inclusive) of the five
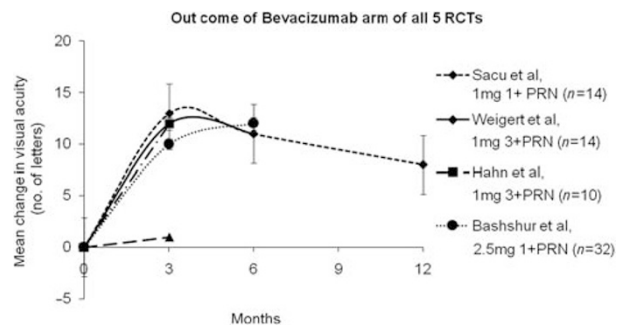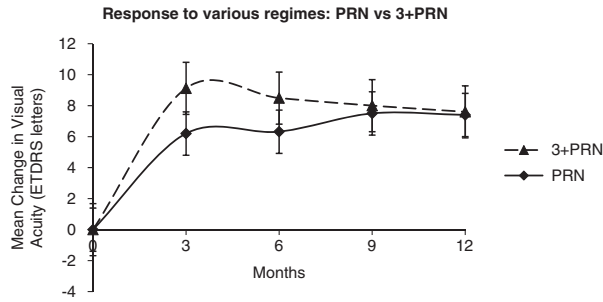

Figure 1 Mean change of visual acuity (VA) score (ETDRS letters) in the bevacizumab arms of all the five randomised controlled trials. Vertical bars represent ±1 standard error of the mean.
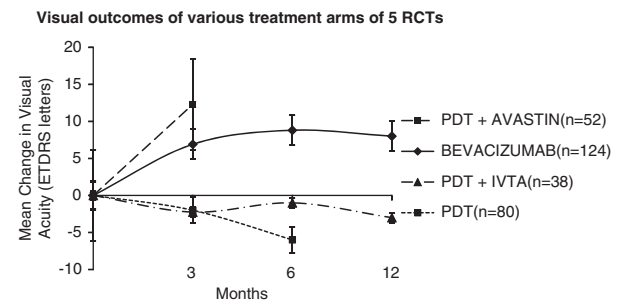
Figure 2 Mean change of visual acuity (VA) score (ETDRS letters) in various treatment arms at various time points in the five randomised controlled trials. Vertical bars represent ±1 standard error of the mean.

RCTs were pooled and then compared to the other treatment options at similar time frames (Figure 2). The other treatment options were a combination of photodynamic therapy (PDT) and bevacizumab, PDT and intravitreal triamcinolone and PDT monotherapy. Bevacizumab monotherapy and the combination of bevacizumab and PDT produced better outcomes than other treatment modalities, with combination therapy

Figure 3 Mean change of visual acuity (VA) score (ETDRS letters) over time comparing various treatment doses. Vertical bars represent ±1 standard error of the mean.

demonstrating a better outcome in the short term (3 months).

Effects of various doses of bevacizumab

The various doses of bevacizumab reported in literature are 1 mg,[41,44,65,68,70] 1.25 mg, 1.5 mg,[23,32,33,49] 2 mg,[33] 2.5 mg[22,26–28] ($n = 5$ for 1 mg; $n = 4$ for 1.5 mg; $n = 1$ for 2 mg and $n = 4$ for 2.5 mg). The pooled data of these doses indicated a dose-dependent response to the drug, whereas in higher doses they showed a better response (Figure 3). However, these data have to be further evaluated as most studies used 1.25 mg/0.05 ml with very few studies using other doses.

Effects of dosing frequency of bevacizumab on outcomes

Two dosing frequencies were commonly practised in the literature. The first regimen included a loading dose of 6-weekly intravitreal bevacizumab for three doses followed by PRN doses as administered on the treating physician's discretion; whereas the second implemented a PRN schedule from the start of the therapy guided by OCT features of recurrent or persistent fluid and/or drop in vision. Figure 4 illustrates the visual outcomes of both these dosing frequencies. The initial gain in vision appears greater in patients given a loading dose; however, this effect was not sustainable at 12 months.

The influence of baseline characteristics

The outcome was better in treatment-naive lesions as compared to pretreated eyes. Pooled data indicated that patients with better baseline visual acuity fared better initially at 3 months but had no influence at 6 months. There was no correlation between the final best-achieved corrected visual acuity and the baseline central retinal thickness (data not shown). Reports that studied the response of the treatment in various angiographic subtypes of CNV were pooled to assess whether the
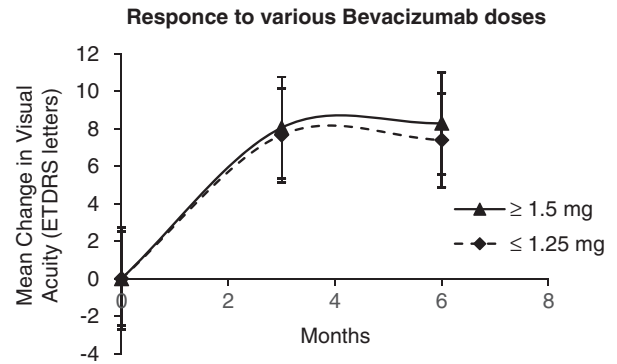
Figure 4 Mean change of visual acuity (VA) score (ETDRS letters) over time in the two treatment regimes. Vertical bars represent ±1 standard error of the mean.
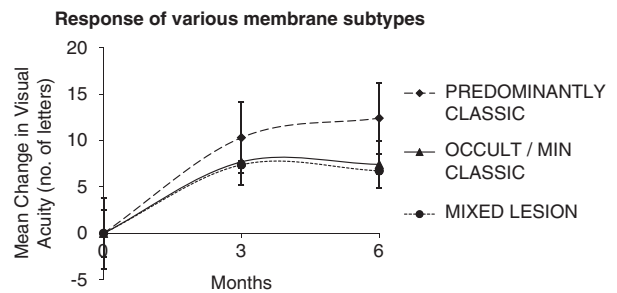
Figure 5 Mean change of visual acuity (VA) score (ETDRS letters) in various CNV subtypes. Vertical bars represent ±1 standard error of the mean.

effects of bevacizumab was dependent on the CNV subtype (Figure 5). Predominantly classic membranes were most responsive of all lesion subtypes.

Mean number of treatments

The mean number of treatments in the studies on intravitreal monotherapy was 2.94 ± 0.8 at 6 months. The different treatment protocols did not influence the number of treatments required.

Combination treatments

A total of 12 studies assessed the efficacy and safety of combining intravitreal bevacizumab with another treatment option. The most common combination tried was with PDT.[17,18,22,23,32,35,49,50,54,61,66] Intravitreal bevacizumab was administered at the same session to up to 14 days post-PDT. The mean number of PDT sessions required at 6 months was 1.4 and the average intravitreal bevacizumab therapy was 2 (range 1–4) at 6 months. The mean gain in vision was +8.85 which is similar to that obtained in the RCT by Laziæ *et al* and superior to intravitreal bevacizumab monotherapy.[51] One small

series assessed the effects of triple therapy (intravitreal triamcinolone, PDT and bevacizumab) and +17 letters gain was noted at 6 months.[17] A larger series by Augustin et al[23] studied 104 eyes treated with PDT, intravitreal dexamethasone and bevacizumab, and oral minocycline, and obtained a mean improvement of +8 letters at 10 months with a low number of retreatments. Nonetheless, this procedure required vitrectomy with retrobulbar anaesthesia.

Complications

The cumulative incidence of ocular complications reported with intravitreal bevacizumab in neovascular AMD per 100 patients include endophthalmitis −0.2, retinal pigment epithelial tears −1.8, sub retinal haemorrhage −0.21, inflammation −0.48, retinal detachment −0, vitreous haemorrhage −0, and lens injury −0.18. The cumulative incidence of thrombo-embolic phenomenon was 0.2 and death in 0.06.

Discussion

It may be argued that the gold standard for evidence-based medicine is a systematic review of RCTs. However, intravitreal bevacizumab is widely used in various ocular conditions in the absence of rigorous drug development phases or regulatory licensing protocols. Thus the basis of such clinical practice in this particular circumstance is not based on the highest quality of clinical evidence; however, a recent study that applied the STROBE standards on studies that reported clinical outcomes on bevacizumab for neovascular AMD demonstrated that although the average reporting score of these studies were lower than that of RCTs on the whole, some studies did indeed obtain higher STROBE scores.[15] Hence, this demonstrates that there are useful studies with considerable evidence-based bearing that are available on this treatment effect outside RCTs and that the pooling of data from well-conducted RCTs and STROBE-qualified studies alike are useful under these circumstances.

There are five RCTs that compared bevacizumab to other treatment modalities. Although the doses and dosing frequency varied between these studies, the mean gain in vision at 3 months was similar to that achieved with monthly intravitreal ranibizumab at the same time point in well-conducted RCTs. This effect was maintained at 6 months in studies with longer follow-up. However, there are no long-term data on the sustained effect of this drug.

Based on this study, the visual outcomes with bevacizumab does not differ significantly to the MARINA and ANCHOR studies on ranibizumab for neovascular AMD.[4,5] The predominantly classic lesions did better with both drugs. The profile and rate of complications were also similar with both agents.

Furthermore a dose-response relationship was also noted with bevacizumab, whereby higher doses of 2.5 mg showed a better treatment outcome compared to 1 mg dosing. However, as most studies implemented a 1.25 mg/0.05 ml regimen it is not clear if these may have biased our findings and it would be invaluable for us to further evaluate the optimal dose of bevacizumab in neovascular AMD.

There have been a number of schools of thought as to the optimal administration protocol for this drug in the management of CNV. This analysis supports the notion that a loading dose of three injections followed by an OCT-guided retreatment criterion provides better visual outcomes than the PRN schedule. These findings are in keeping with the rationale of the PrONTO study, which demonstrated that treatment benefits similar to monthly treatments of ranibizumab could be achieved by a loading dose of three injections and minimising the number of injections using a OCT-guided treatment algorithm.[40,75] This regimen may also potentially reduce the ocular or systemic adverse effects of prolonged and constant VEGF inhibition.

A two-prong approach combining PDT and intravitreal bevacizumab is worth exploring, as the analysis indicates significant visual gain and reduced retreatment rates. Although, this can be explained by the synergistic effects of the different mechanisms of action of these treatment options, a similar effect has not been noted with well-conducted randomised trials involving ranibizumab and pegaptanib.

Despite higher doses used in some studies, bevacizumab was well tolerated and the safety profile was no different from other recent surveillance reports[72–74] or indeed other published RCTs on ranibizumab.[4,5] However, the actual incidence may be subject to publication bias.

Conclusion

Analyses of the available STROBE-qualified studies and RCTS have shown that the clinical outcomes and safety profile of intravitreal bevacizumab are similar to those from well-conducted trials of intravitreal ranibizumab in neovascular AMD in the short term. However, the optimal dose and the long-term outcomes need further evaluation. We await the 2-year outcomes of the ongoing randomised clinical trials comparing various treatment strategies of intravitreal bevacizumab to ranibizumab in neovascular AMD, the NEI funded CATT trial in the United States, and the HTA-funded IVAN trial in the United Kingdom.

Conflict of interest

The authors declare no conflict of interest.

Summary

What was known before
- Bevacizumab is unlicenced for intraocular use.
- Several studies have used bevacizumab in neovascular age related macular degeneration
- The outcomes differ between studies.

What this study adds
- This study is a comprehensive review of studies that assessed the outcomes of bevacizumab in neovascular age related macular degeneration.
- Only studies that met the CONSORT and STROBE quality grades were reviewed allowing for a detailed assessment of several aspects of the outcomes of bevacizumab in neovascular age related macular degeneration.
- The study provides useful and unbiased clinical data on the drug while outcomes of the CATT and IVAN trials are awaited.

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