Safety and Efficacy of Ranibizumab and Bevacizumab for the Treatment of Neovascular Age-related Macular Degeneration

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Abstract

Ocular anti-vascular endothelial growth factor (VEGF) therapy represents a major breakthrough in the treatment of patients with neovascular age-related macular degeneration (nvAMD). The anti-VEGF agents, ranibizumab and bevacizumab, are both widely used in the treatment of nvAMD although bevacizumab has not yet received regulatory approval for intraocular use. Bevacizumab costs considerably less than ranibizumab when administered as an intraocular injection, which has led to widespread use and studies comparing the efficacy and safety of the two drugs. Bevacizumab shares identical pharmacology with ranibizumab although structural differences result in differences in receptor affinity and rates of drug clearance. While estimates of the vitreous half-life of ranibizumab vary, it is shorter than that of bevacizumab. Furthermore, the serum half-life of bevacizumab is about 20 days, more than twice that of ranibizumab and this has led to speculation that it may present a greater risk of systemic adverse effects. Considerable clinical trial evidence exists relating to the efficacy and safety of ranibizumab. The Comparison of age-related macular degeneration treatments trials (CATT) study of the two drugs found efficacy to be equivalent for the as needed versus as needed and monthly versus monthly comparisons. Ranibizumab as needed was equivalent to monthly ranibizumab, though the bevacizumab as needed was not equivalent to monthly bevacizumab. A greater number of serious adverse events (SAEs) occurred with bevacizumab. However, the study was insufficiently powered to identify differences in drug-related adverse events. Intravitreal injection of bevacizumab is associated with a low but significant risk of acute intraocular inflammation, shown to result in significant visual loss in some patients. Finally, there are issues related to fractionating of bevacizumab that has lead to sporadic cases of blindness worldwide. The increased risk for both systemic and ocular adverse events may influence the cost-effectiveness ratio of the two drugs based on health economic models. Further comparative studies and continuous monitoring of safety data are required to examine the incidence of adverse events.

Keywords

Bevacizumab, choroidal neovascularisation, neovascular age-related macular degeneration, ranibizumab, vascular endothelial growth factor

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In developed nations, age-related macular degeneration (AMD) has been the principal cause of severe vision loss and blindness among people aged over 50 years.[1–3] AMD can be classified into dry and wet types. Angiogenesis is a key feature of neovascular AMD (nvAMD), the wet type of advanced AMD, characterised by haemorrhagic or serous liquid leakage from a subretinal neovascular membrane and the lifting of retinal layers initiating injury to the photoreceptors and retinal pigment epithelium. This abnormal growth of newly formed vessels in the macula is termed choroidal neovascularisation (CNV).[4–6]

Vascular endothelial growth factor (VEGF) is a cytokine that promotes vascular endothelial cell replication/survival and is involved in the pathogenesis of CNV in nvAMD. VEGF has therefore been a target in CNV treatment, and this has led to the development of biological agents that bind to VEGF and inhibit angiogenesis.[7–10] Several biological anti-VEGF agents have now been clinically developed, of which ranibizumab and bevacizumab are the most widely used in nvAMD therapy.

Ranibizumab (Lucentis®) is an affinity matured fragment of a humanised anti-VEGF mouse monoclonal antibody designed for use in ophthalmology and is approved in the US, Europe, Japan and other countries for nvAMD treatment.[11] Its approval was based on safety and efficacy data from large randomised controlled trials (RCTs) which demonstrated that ranibizumab improved visual acuity (VA) in a substantial proportion of treated patients with nvAMD.

Ongoing pharmacovigilance activities are in place to ensure that the safety of ranibizumab use in clinical practice is monitored.[12–16]

Bevacizumab (Avastin®) is a humanised anti-VEGF mouse monoclonal antibody that is widely used off-label in ophthalmology as an intravitreal administration. However, the drug is formulated for intravenous infusion, not intravitreal injection.[17–19] Bevacizumab is approved in the US only for the treatment of metastatic colorectal cancer.[14,20,21] Bevacizumab is a full-length antibody that is derived from the same mouse monoclonal antibody precursor as ranibizumab but without further ligand affinity improvements as were conducted with ranibizumab.

Bevacizumab has become widely used in recent years because it costs considerably less than ranibizumab when administered as an intraocular injection due to fractionation of a single bevacizumab vial into multiple unit doses.[22] The UK list price of ranibizumab is £742.[17] per vial excluding VAT, which represents a reduction from the price of £761.[20] listed in the current British national formulary (several programmes in various countries provide cost reductions), whereas bevacizumab costs £85 pre VAT per injection supplied by Moorfields pharmacy. This cost difference has led to widespread use of bevacizumab.[23,24]

Given the huge price difference between intravitreal doses of the two molecules and an assumption of non-inferiority, important data need to be generated from formal health economic evaluations that take into account incremental costs not considered when using bevacizumab, including management of increased particular adverse events, manufacturing quality, pharmacovigilance and risk management plans. The cost of a single intravitreal dose of bevacizumab is lower, but ranibizumab was developed specifically for ocular use and is manufactured according to US Pharmacopoeia specifications for intraocular injection.[22,25–29] Furthermore, there are systemic safety concerns relating to intravitreal bevacizumab injection that may be related to prolonged systemic exposure to this agent.[30,31]

This review aims to consider the molecular differences, existing safety and efficacy data of the two drugs, both in terms of ocular inflammation and systemic effects and the health economics positions associated with both of these therapies.

Molecular Differences between Ranibizumab and Bevacizumab

Direct intravitreal injection has become a common approach for delivering biological therapies to the posterior segment of the eye. Although intravitreally injected full-length antibodies penetrate the retina in a similar manner to antibody fragments,[32] their fate after entering the retina is not yet fully understood. A recent study of intravitreal ranibizumab and bevacizumab injection in rabbits found that the two drugs were cleared from the vitreous humour with half-life of 2.8 and 4.2 days, respectively, though both remained detectable until 21 and 28 days.[33] Estimates of the half-life of ranibizumab in humans vary. According to the summary of product characteristics, ranibizumab has a vitreous half-life of about nine days and a serum half-life also of nine days.[34] However, a recent report estimated the half-life of ranibizumab in humans as 4.75 days, based on published animal studies and mathematical models, but this has not been validated in clinical studies.[35] A human study found that the half-life of 1.5 mg intravitreally injected bevacizumab is 9.82 days.[36] Of greater significance is the difference in serum half-life. A study of bevacizumab in solid tumours found that its pharmacokinetic properties are consistent with that of a typical humanised monoclonal antibody, with a systemic terminal half-life in humans of approximately 20 days, double that of ranibizumab.[37]

Figure 1: Bevacizumab Concentration in the Vitreous Humour and Aqueous Humour of the Uninjected Eye After Injection of 1.25 mg of Intravitreal Bevacizumab into the Fellow Eye[39]

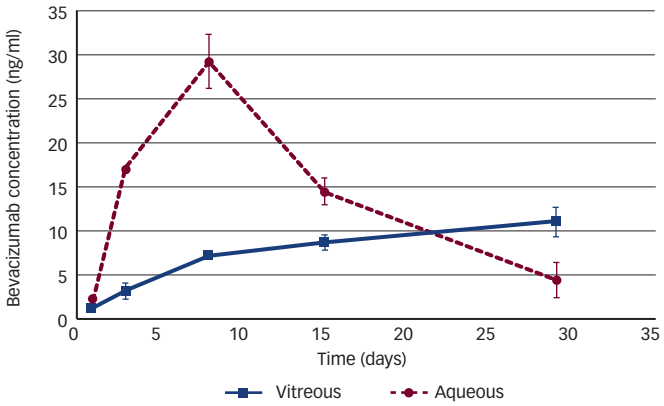
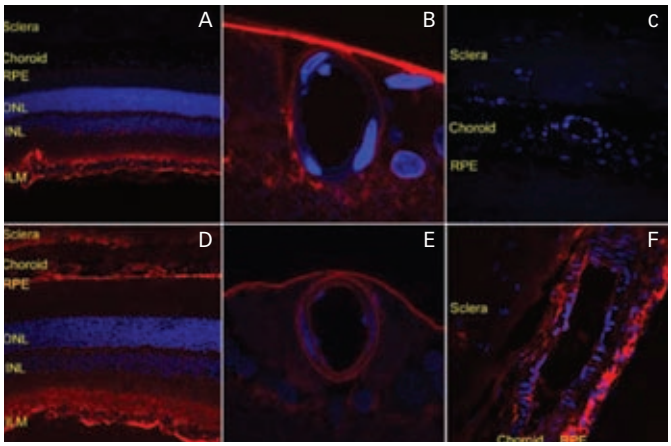


Figure 2: Pharmacokinetics of Intravitreally Injected Bevacizumab and Chicken Immunoglobulin Y in Rats[40]

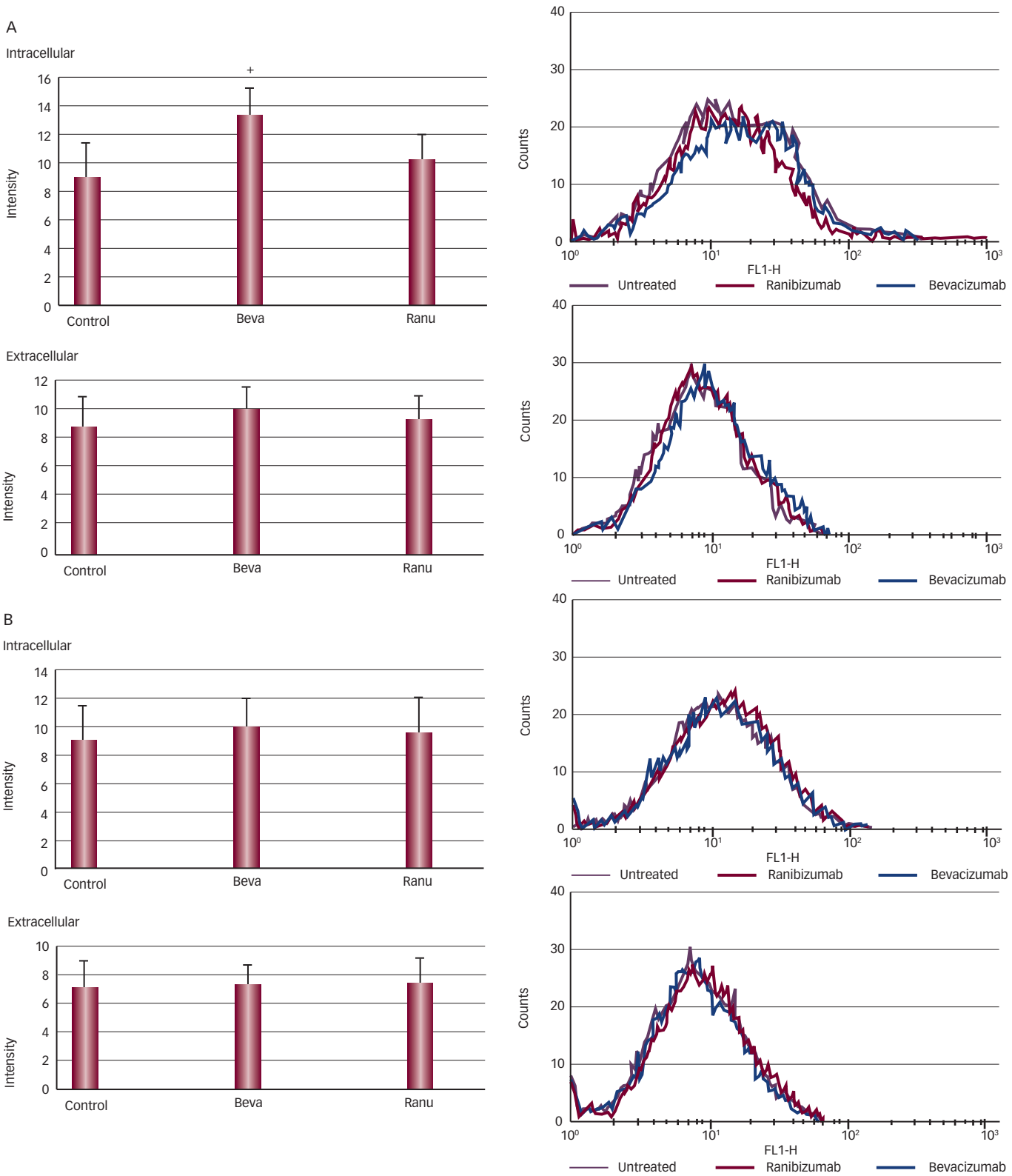


Intravitreally administered bevacizumab (immunoglobulin G [IgG]) and chicken immunoglobulin Y (IgY) overcame the inner limiting membrane barrier and diffused into deeper retinal structures (A, D). After diffusing through the retina bevacizumab crossed the blood-retina barrier and leaked into the systemic circulation (E), therefore explaining why bevacizumab is observed within the choroidal vasculature (F). The intraretinal chicken IgY was only localised along the abluminal side of the blood-retina barrier (B). Moreover, the choroidal blood vessels were negative for the presence of chicken IgY (C). ILM = inner limiting membrane; INL = inner nuclear layer; ONL = outer nuclear layer; RPE = retinal pigment epithelium.

The localised versus systemic antibody effects of the two drugs have been studied in animal models. The vitreous half-life of ranibizumab is somewhat shorter than for bevacizumab, with higher peak concentrations of drug identified in the aqueous humour of the bevacizumab-treated eye. In trials comparing the pharmacokinetics of intravitreal ranibizumab with intravitreal bevacizumab in rabbits, ranibizumab was below the limit of detection in the systemic circulation as well as in the uninjected fellow eye after intravitreal ranibizumab injection; however, after bevacizumab injection, small quantities of intravitreal bevacizumab were identified at both sites (see *Figure 1*).[38,39]

Trials in mice showed that intravitreally administered full-length immunoglobulin G (IgG) was transported across the blood-retinal barrier into the systemic circulation, indicating that systemic

Figure 3: Flow Cytometry[44]



A: 1 h clinical concentrations; B: 1 h 10 % of clinical concentrations. FL1-H = height of fluorescence intensity.

absorption after intraocular bevacizumab injection is a distinct possibility. Intravitreally injected IgGs were eliminated into the blood stream faster in laser-photocoagulated eyes versus normal control eyes owing to neonatal fragment crystallisable (Fc)-receptor upregulation in laser-photocoagulated retina. This increases the potential for Fc-mediated systemic transmission of bevacizumab from the eye into the circulation (see *Figure 2*).[21,40] It can be concluded from preclinical studies of anti-VEGF treatments that overlapping yet distinct pharmacological properties of ranibizumab and bevacizumab indicate that efficacy and safety data obtained for one drug cannot be extrapolated to the other.[41]

Bevacizumab was found to internalise and accumulate in porcine retinal pigment epithelial 42 cells *in vitro* 43. Such accumulation did not occur

with ranibizumab, implying substantial differences between the two drugs and the potential for long-term adverse effects of bevacizumab on RPE cells. Bevacizumab storage may compromise the physiological role of cells because RPE cells have significant functions in sustaining retinal homeostasis. The selective uptake of bevacizumab may be caused by the presence of fragment crystallisable (Fc) domain and sugar moieties on bevacizumab. Bevacizumab uptake may be mediated via RPE cell mannose receptors and galectins or Fc-receptor-mediated phagocytosis (see *Figure 3*).[44]

A study to evaluate VEGF plasma levels in AMD patients before and after intravitreal injections of ranibizumab or bevacizumab found a significant reduction in VEGF plasma levels during the first 28 days after intravitreal bevacizumab injection. Ranibizumab also achieved VEGF reduction at the same time-point, but not to a level of statistical significance. This difference may result in distinct systemic safety profiles.[45,46]

Efficacy of Ranibizumab and Bevacizumab

Ranibizumab

The efficacy of ranibizumab was assessed in two large phase III studies: the Minimally classic/occult trial of anti-VEGF antibody ranibizumab in the treatment of neovascular age-related macular degeneration (MARINA) trial which was a multicentre, two-year, double-masked, sham-controlled trial involving 716 patients, and the Anti-VEGF antibody for treatment of predominantly classic CNV in AMD (ANCHOR) trial. In MARINA, ranibizumab had a higher percentage of patients gaining ≥ 15 letters versus sham injections (94.5 % for 0.3 mg dose, 94.6 % for 0.5 mg dose, 62.2 % for sham, p<0.001 for both comparisons). A gain of 15 letters represents a doubling of the visual angle. Mean increases in VA were 6.5 letters in the 0.3 mg group and 7.2 letters in the 0.5 mg group, as compared with a decrease of 10.4 letters in the sham-injection group (p<0.001 for both comparisons). The VA benefit was maintained at 24 months. Ranibizumab scored higher versus sham in the National Eye Institute (NEI) Visual Function Questionnaire 25 (VFQ-25). The ranibizumab net benefit was in general larger when patients had better baseline best-corrected visual acuity (BCVA),[12,15,46,47] suggesting the greatest benefit from earlier treatment of nvAMD lesions.

The ANCHOR trial compared ranibizumab with photodynamic therapy (PDT) with verteporfin. Of the 423 patients enrolled in ANCHOR, 94.3 % of those given 0.3 mg of ranibizumab and 96.4 % of those given 0.5 mg ranibizumab lost fewer than 15 letters, as compared with 64.3 % of those in the verteporfin group (p<0.001 for each comparison). VA improved by ≥ 15 letters in 35.7 % of the 0.3 mg ranibizumab group and in 40.3 % of the 0.5 mg ranibizumab group, as compared with 5.6 % of the verteporfin group (p<0.001 for each comparison). As in the MARINA trial, better baseline BCVA and therefore early treatment was predictive of the greatest VA response.[13,48–50]

The Phase IIIb, multicentre, randomised, double-masked, sham Injection-controlled, two-year study of the Efficacy and safety of Ranibizumab (PIER) trial was designed to assess patients with subfoveal CNV with or without classic CNV secondary to AMD. It also examined dosing regimen to determine whether ranibizumab can be given less frequently (i.e. at three-month intervals) compared with monthly intervals. VA improved significantly at one year versus the sham group. The two-year results demonstrated that switching to monthly ranibizumab dosing provided further VA benefit, but this improvement was not observed in patients who delayed switching after more than 14 months of sham injections. This indicates that ranibizumab may not be effective as a salvage treatment in nvAMD and that optimal treatment outcomes appear to occur in patients with earlier stages, as previously also shown in MARINA and ANCHOR.[51,52]

The Efficacy and safety of ranibizumab in patients with subfoveal choroidal neovascularisation secondary to age-related macular degeneration (EXCITE) trial was a 12-month, multicentre, randomised, double-masked phase IIIb study of monthly versus quarterly ranibizumab treatment in 353 patients, with predominantly classic, minimally classic, or occult lesions. At month 12, BCVA gain in the monthly regimen was higher than that of the quarterly regimens. Increases from baseline to month 12 were 4.9, 3.8 and 8.3 letters in the 0.3 mg quarterly, 0.5 mg quarterly and 0.3 mg monthly dosing groups, respectively.[53]

Bevacizumab

A six-month study comparing bevacizumab with PDT showed improved VA gain for bevacizumab and significantly lower retina thickness on ocular coherence tomography (OCT) than PDT.[17] Before the Comparison of age-related macular degeneration treatments trials (CATT) study (see below), only one randomised, double-masked trial – the Avastin® (bevacizumab) for choroidal neovascularisation (ABC) trial – had been completed to assess the safety and efficacy of bevacizumab in nvAMD. The dosing regimen was 1.25 mg bevacizumab with three loading injections at six-week intervals followed by further treatment if required at six-week intervals. In the bevacizumab group, 32 % of patients gained ≥ 15 letters from baseline VA compared with 3 % in the standard care group (verteporfin photodynamic therapy, pegaptanib or sham) (p<0.001). Additionally, the proportion of patients who lost fewer than 15 VA letters from baseline was significantly greater among those receiving bevacizumab treatment (91 versus 67 % in the standard care group; p<0.001). Mean VA increased by 7.0 letters in the bevacizumab group with a median of seven injections compared with a decrease of 9.4 letters in the standard care group (p<0.001) and the initial improvement at week 18 (plus 6.6 letters) was sustained to week 54.[54]

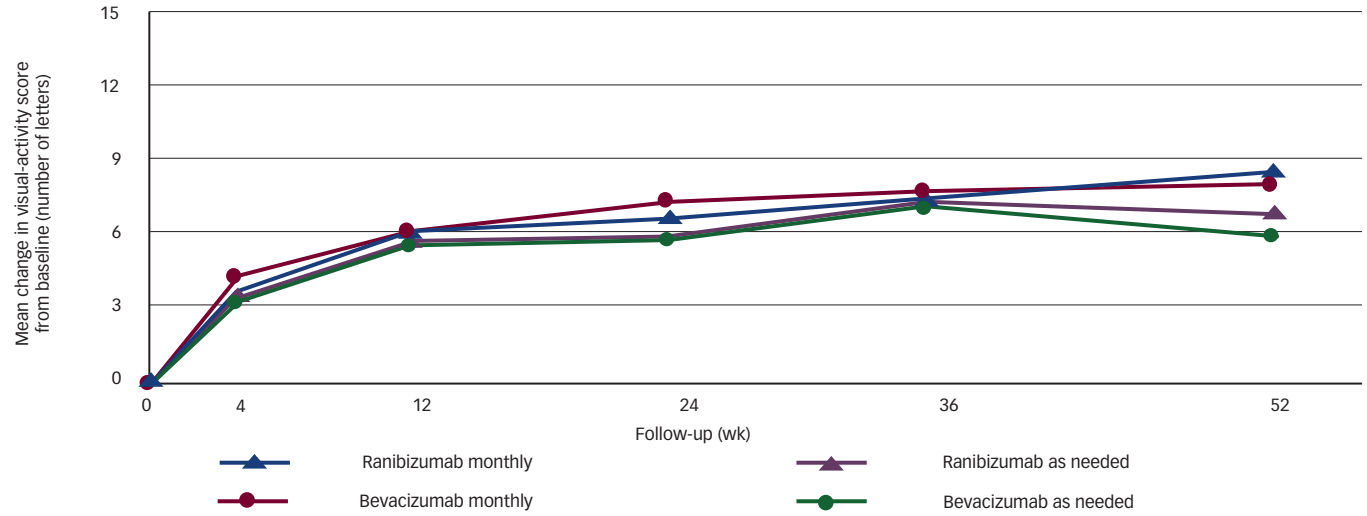
Comparative Studies of Ranibizumab and Bevacizumab

In a small prospective, double-masked randomised clinical trial comparing the efficacy of ranibizumab and bevacizumab, fifteen patients received bevacizumab and seven patients received ranibizumab. No statistically significant differences were found in visual and anatomical outcomes between the two treatments for AMD at six months or one year. The more immediate robust response in the ranibizumab group in the first three months resulted in fewer injections over time when optical coherence tomography (OCT) scans of retinal thickness were the main guides for re-treatment. Furthermore, there was a significant improvement in central subfield thickness versus baseline post-ranibizumab treatment, which was greater compared with the bevacizumab group. Further trials with larger sample sizes are warranted.[55–57]

The aim of the CATT study was to assess the relative efficacy and safety of ranibizumab and bevacizumab and to determine whether an as-needed regimen would compromise long-term visual acuity, as compared with a monthly regimen. At one year, bevacizumab and ranibizumab showed equivalent efficacy in maintaining VA. The trial also compared two dosing regimens: a monthly regimen, which is considered the standard for treatment, versus an as-needed regimen, i.e. drug administration only when signs of exudation were present.[58]

Figure 4: Change in Visual-acuity Score from Baseline to One Year[58]

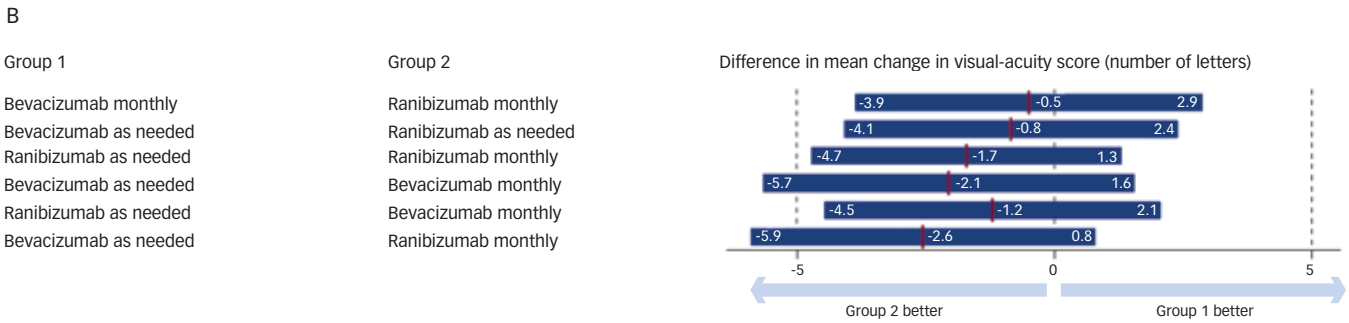
A



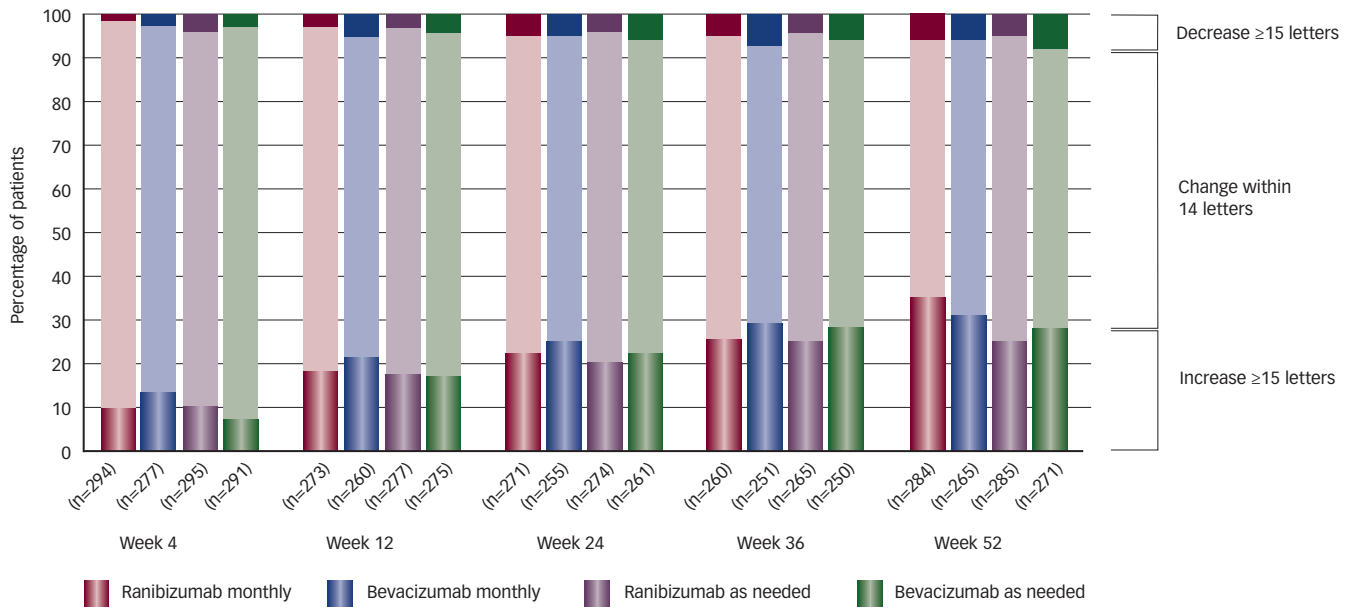
Mean (± SE) Change in Visual-Acuity Score from Baseline (number of letters)					
Ranibizumab monthly	+3.6 ± 0.5	+6.1 ± 0.7	+6.6 ± 0.8	+7.5 ± 0.9	+8.5 ± 0.8
Bevacizumab monthly	+4.3 ± 0.6	+6.1 ± 0.7	+7.3 ± 0.9	+7.7 ± 1.0	+8.0 ± 1.0
Ranibizumab as needed	+3.3 ± 0.6	+5.6 ± 0.7	+5.8 ± 0.7	+7.2 ± 0.7	+6.8 ± 0.8
Bevacizumab as needed	+3.2 ± 0.5	+5.6 ± 0.7	+5.8 ± 0.8	+7.1 ± 0.9	+5.9 ± 1.0

SE = standard error.

B



C



An as-needed regimen is used less frequently and relies on clinical judgement and imaging techniques to determine when to re-inject the drugs.[59] However, VA outcomes data from ranibizumab Phase 3 clinical studies, together with reported drug and disease modelling results, support an individualised ranibizumab therapy regimen of three initial once-monthly injections of 0.5 mg ranibizumab followed by monthly monitoring of VA and re-treatment if a VA loss of more than five letters occurs, as included on the European label.[13,15,52,60] In CATT, ranibizumab as needed was equivalent to monthly ranibizumab, although the comparison between bevacizumab as needed and monthly bevacizumab was inconclusive (see *Figure 4*).[58]

The anatomical data on efficacy, be it cessation of leak on fundus fluorescein angiography ($p<0.001$) or resolution of fluid on OCT ($p<0.001$), all highly significantly favoured monthly ranibizumab over an as-needed regime. The mean reduction in central retinal thickness was greater in the ranibizumab monthly group (196 µm) compared with all other groups (152 to 168 µm, $p=0.03$ by analysis of variance). Although the CATT study was not intended to compare monthly ranibizumab versus as needed bevacizumab and despite it being a *post-hoc* analysis, it is noteworthy that they were significantly different (8.5 ± 14.1, 5.9 ± 15.7, $p=0.04$, two-sided test). In the monthly ranibizumab group, 3 % more patients gained ≥ 3 lines, which would have been a significant difference if the group sizes were larger (n=805). However, partly due to the high variability in outcome, the trial was insufficiently powered to detect small differences.[61] If this was the patient's better eye, however, then gaining ≥3 lines equates to a considerably improved quality of life[12] for one in 30 patients, which may be an important factor for a patient choosing between ranibizumab and bevacizumab.[61] In conclusion, clinicians should consider recommending only monthly ranibizumab, rather than strict, aggressive *pro re nata* (PRN).

Safety of Ranibizumab and Bevacizumab

An electronic search was conducted to review the issue of safety associated with the use of either ranibizumab or bevacizumab. PubMed was searched for relevant terms, including bevacizumab, ranibizumab, safety, macular degeneration, intraocular pressure, endophthalmitis, inflammation, myocardial infarction, stroke and non-ocular haemorrhage. Furthermore, where relevant, safety data were documented in comparative RCTs identified from the efficacy review. Clinical trials written in English language that demonstrated robust data, e.g. well-designed RCTs that address the relevant issue, were considered for inclusion in this review. Substantial data without some factors, e.g. based on randomised studies but with deficiencies, for example lack of clearly identified primary outcomes, inclusion or exclusion criteria, or long enough follow-up, were also considered. The search excluded papers that were not about nvAMD, or used a compound other than bevacizumab or ranibizumab. The search was limited to reports published within the last six years.

Ocular Safety

In the large RCTs of ranibizumab, severe ocular events were rare. The ANCHOR trial documented a rate of 1.1 % endophthalmitis in the ranibizumab group. Among 140 patients treated with 0.5 mg of ranibizumab, presumed endophthalmitis occurred in two patients (1.4 %) and serious uveitis in just one individual (0.7 %).[13,48–50] In the MARINA trial, during 24 months of follow-up, presumed endophthalmitis was identified in five patients (1.0 %) and serious uveitis in six patients (1.3 %).[12,15,46] In the PIER trial, no ranibizumab arterial thromboembolic events (ATEs) occurred.[52] In a study to assess the safety of repeated intravitreal injections of ranibizumab, one case each of endophthalmitis, iridocyclitis and central retinal vein occlusion was reported (n=64). No serious systemic adverse events were noted.[62]

The Study of ranibizumab in patients with subfoveal choroidal neovascularisation secondary to age-related macular degeneration (SUSTAIN) was a one-year study evaluating individualised dosing of ranibizumab. Patients were initially given three mandatory monthly injections of ranibizumab 0.3 mg and then evaluated monthly. Patients switched to 0.5 mg ranibizumab after approval in Europe. The results of the SUSTAIN study indicated that an individualised, flexible-dosing regimen for ranibizumab, once monthly for three months and then as needed administration, was well tolerated but only moderately effective in patients with nvAMD. Safety results were comparable to ranibizumab tolerability profiles in prior studies. Individualised treatment with less than monthly re-treatments showed a similar safety profile as in previous RCTs with monthly ranibizumab treatment.[63]

A study of 86 patients comparing intravitreal injections of 1.25 and 2.5 mg bevacizumab for treatment of CVD-associated AMD dosing regimens of bevacizumab found similar efficacy for the two doses. However, three cases of vitreous reaction and one case of massive subretinal haemorrhage were reported in the higher dose group, suggesting that a dose of 2.5 mg may be associated with a higher rate of adverse events.[64]

The ABC trial showed relatively low rates of serious ocular adverse events among 65 patients treated with bevacizumab.[54] Intraocular inflammation graded as ≥ 1 (pooled for reported events of iritis, iridocyclitis, vitritis, uveitis and anterior chamber inflammation) occurred in two patients in the bevacizumab group and one in the standard care group. There were no cases reported of a rise in intraocular pressure requiring treatment. Regarding serious systemic adverse events, patients treated with bevacizumab had two myocardial infarction episodes (3.1 %) compared to zero in the controls.[54]

A retrospective study of 173 patients over two years reported a 1.3 % incidence of acute intraocular inflammation after intravitreal bevacizumab injection. All patients had worse VA at the end of follow-up than on the injection day. The mean VA loss was -6.1 lines (Snellen); and one patient developed inflammation-induced glaucoma that required surgical intervention.[65]

A retrospective study found that the incidence of sterile intraocular inflammation after bevacizumab injection that resolved with topical antibiotics and steroids was 0.27 % (44 of 16,166). The average number of prior bevacizumab injections in those eyes was 2.8 ± 0.4 injections with 10 cases occurring after first-time injections. The average time from injection to recovery of VA was 53 ± 18 days and from injection to resolution of inflammation was 37 ± 5 days. Thirty-six cases received subsequent intravitreal bevacizumab or intravitreal ranibizumab, and there were three episodes of recurrent inflammation with repeat intravitreal bevacizumab. The average follow-up was 17 ± 1 months.[66]

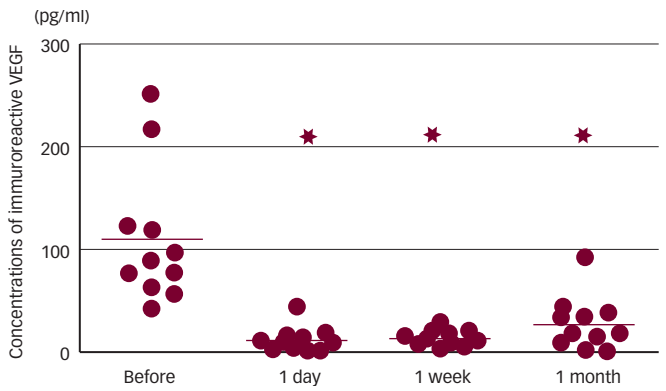
Retrospective studies in Canada of patients after three years of treatment with either ranibizumab or bevacizumab, found that patients who received bevacizumab were 12 times more likely to develop severe intraocular inflammation versus those receiving ranibizumab.[67] The high incidence of ocular inflammation in Canadian patients led Roche to release a 'Dear Healthcare Provider' letter advising of these

Table 1: Unadjusted and Adjusted Outcomes at One Year for the Comparison of Ranibizumab Therapy versus Bevacizumab Therapy[79,80]

	Number of Adverse Events/Number (%) of Patients in the Treatment Group		Hazard ratio (95 % confidence interval)	
Adverse Event	Ranibizumab	Bevacizumab	Unadjusted	Adjusted*
		July – December 2006**		
All-cause mortality	647/19,026 (4.1)	833/21,815 (4.7)	0.87 (0.76–0.99)	0.86 (0.75–0.98)
Incident myocardial infarction	170/19,026 (1.1)	227/21,815 (1.3)	0.84 (0.64–1.08)	0.83 (0.64–1.08)
Bleeding	943/19,026 (5.8)	1017/21,815 (5.6)	1.04 (0.92–1.16)	1.03 (0.92–1.16)
Incident stroke	289/19,026 (1.8)	405/21,815 (2.2)	0.80 (0.65–0.97)	0.78 (0.64–0.96)
		Exclusive Providers***		
All-cause mortality	197/4,821 (4.7)	225/6,147 (4.3)	1.11 (0.87–1.43)	1.10 (0.85–1.41)
Incident myocardial infarction	47/4,821 (1.1)	69/6,147 (1.3)	0.86 (0.53–1.41)	0.87 (0.53–1.41)
Bleeding	225/4,821 (5.3)	279/6,147 (5.2)	1.02 (0.81–1.29)	1.01 (0.80–1.28)
Incident stroke	90/4,821 (2.1)	129/6,147 (2.4)	0.88 (0.62–1.26)	0.87 (0.61–1.24)

** Hazard ratios for ranibizumab compared with bevacizumab. **By the end of the study period, almost all newly treated patients received ranibizumab or bevacizumab as first-line therapy. Therefore, in this secondary analysis, the study population was limited to newly treated patients who received ranibizumab or bevacizumab between July and December 2006. *** Patients with higher socioeconomic status may have been more likely to receive ranibizumab versus bevacizumab, so the primary analysis may have been subject to selection bias. Therefore, in this secondary analysis, the study population was limited to patients who received ranibizumab or bevacizumab in a medical practice that performed at least 20 injections and used a single drug in 95 % or more of all intravitreous injections during the third or fourth quarter of 2006.*

Figure 5: Plasma Levels of Vascular Endothelial Growth Factor Before and After an Intravitreal Injection of Bevacizumab[75]



VEGF = vascular endothelial growth factor.

adverse events and highlighting safety concerns associated with the use of intravitreal bevacizumab.[68]

One potential explanation for excessive inflammation may be its larger protein load, a result of the additional Fc fragment not present in ranibizumab.[69] This may induce an immunogenic response. Against this theory is that this Fc fragment is immune privileged. However, aflibercept (VEGF-trap) also has an Fc fragment and this inflammation is generally not seen. Another possible explanation is that bevacizumab is packaged for oncological use in 100 mg containers. When these are broken down into smaller units for ocular use, there is a risk of microbial contamination owing to incorrect handling procedures.[70]

The Royal College of Ophthalmologists has warned that when vials of bevacizumab are split to obtain the needed dose, the amount of protein administered to patients is unknown, which could lead to problems due to side effects or reduced effectiveness.[71] It has since called for a review of bevacizumab in AMD. There are significant differences in IgG concentration measured from repackaged bevacizumab syringes. Large particulate matter within some samples has been hypothesised to lead to obstruction of aqueous outflow and subsequent elevation in intraocular pressure.[42] In September 2011, the US Department of Veterans Affairs (VA) ceased ophthalmological use of Avastin pending the results of an ongoing investigation. In October 2011, interim guidelines were published which permitted the use of bevacizumab only under certain conditions of use. According to these guidelines, only one dose of medication is to be prepared from the vial and administered in a syringe. If both eyes are to be treated, a separate vial and syringe must be utilised.[72]

Systemic Safety

An interim analysis from the Safety assessment of intravitreal lucentis for AMD (SAILOR) study demonstrated a trend for an increase in the incidence of stroke in the group treated with 0.5 mg ranibizumab, compared with the 0.3 mg dose. Furthermore, the incidence of stroke was higher when pre-existing factors were present, specifically either a previous history of stroke or arrhythmia.[73,74] All other RCTs of ranibizumab showed that systemic events were rare.[13,15,47,49,52,62]

There is concern about the risk of systemic adverse events following the use of bevacizumab because of its longer systemic half life and systemic absorption after intraocular injection. Most serious drug toxicities are detected through post-marketing safety surveillance or pharmacovigilance but this procedure does not exist for drugs that have unlicensed use so the true risk of adverse events is not being reported.

In human case series, reduced blood-VEGF levels post-intravitreal bevacizumab injection showed that bevacizumab enters the general circulation, giving the potential for systemic effects (see *Figure 5*).[75] When used systemically with chemotherapeutic agents, bevacizumab can double the risk of ATEs compared with chemotherapy alone.[76]

A retrospective study of patients treated with at least one intravitreal injection of ranibizumab or bevacizumab found that ATEs occurred in 12.4 % of bevacizumab-treated patients compared with 1.4 % with ranibizumab ($p<0.0001$). In an elderly population with multiple cardiovascular risk factors, new ATEs may only in part be attributed to the intravitreal bevacizumab administration. These findings raise an issue that needs confirmation in randomised clinical trials.[77] The Canadian retrospective studies found a tendency towards a greater incidence of emergency department presentation within 30 days of

receiving an intravitreal injection for adverse cardiovascular events in patients receiving bevacizumab but not ranibizumab.[67]

In the CATT trial, the proportion of patients with serious systemic adverse events (primarily hospitalisations) was significantly higher with bevacizumab than with ranibizumab (24.1 versus 19.0 %; risk ratio, 1.29; 95 % confidence interval, 1.01 to 1.66), with excess events broadly distributed in disease categories not identified in previous studies as areas of concern.[58] On examining tables in the supplement appendix[78] if retinal, deep and hepatic vein thrombosis and pulmonary embolus were combined, then a venous thrombotic event occurred in 0.15 % of the ranibizumab group and 1.15 % of the bevacizumab group, another significant difference p<0.02.[61]

The tables accessible in the supplemental appendix of CATT,[78] that classified systemic adverse events by system organ class and treatment group, also demonstrated a greater proportion of bevacizumab patients with anaemia (2.35 versus 1 %, p<0.03). In older patients, this is a marker for gastrointestinal (GIT) bleeding. Indeed, 1.85 % of bevacizumab patients had haemorrhage or GIT ulceration versus 0.7 % of the ranibizumab patients (p<0.03). It is unlikely but possible that the same patient was entered under different but not mutually exclusive classifications. If this were the case then again venous thrombosis appeared to be significantly more frequent in the bevacizumab than ranibizumab patients.[61]

Data from the tables accessible in the supplement appendix[78] demonstrate that disabling or life-threatening events occurred in 3.51 % of the combined ranibizumab and in 5.61 % of the combined bevacizumab groups (p=0.04), 1.5 % of whom were being treated with ranibizumab and 2.5 % of whom were taking bevacizumab died.[61]

A retrospective study of a Medicare claims database of 146,942 beneficiaries has provided the largest available dataset directly comparing the safety profiles of ranibizumab and bevacizumab. After adjustment for patient characteristics, it observed significantly lower hazards of all-cause mortality and stroke with ranibizumab (n=19,026) compared with bevacizumab (n=21,815) (see *Table 1*).[79,80]

A further analysis of the Medicare claims database showed an 11 % greater overall mortality and a 57 % higher risk of haemorrhagic cerebrovascular accident for bevacizumab, over a 10-month follow up period. However the study was limited by incomplete information on important confounding factors such as smoking, lipid concentration and blood pressure levels. Compared to patients treated with ranibizumab, patients receiving bevacizumab were also more likely to have ocular inflammation and to have cataract surgery after AMD treatment. Differences in overall mortality and haemorrhagic cerebrovascular accident were attenuated in secondary analyses that included use of bevacizumab and ranibizumab based on unclassified drug codes and data back to 2006.[81]

In a post-marketing study to compare short-term (one year) survival of predominantly male subjects treated for AMD with those with dry AMD who received no treatment, it was found that mortality was unaffected by exposure to therapeutic levels of vitreous bevacizumab and ranibizumab.[82]

In a systematic review of efficacy and safety outcomes for the two anti-VEGF agents it was concluded that, in contrast to ranibizumab, current safety data for bevacizumab are incomplete and not yet robust. If the medical community remains committed to using intravitreal bevacizumab, it is critical to establish that it has an acceptable safety profile, supported by evidence-based medicine. Considerable further research is warranted to achieve this.[83]

Conclusion

There is extensive robust and consistent evidence to support the efficacy and safety of ranibizumab in nvAMD. Data suggest that bevacizumab provides efficacy in wet AMD, but the safety profile of intravitreal bevacizumab remains to be established. There is the possibility of greater systemic effects of bevacizumab, possibly be due to its longer systemic half life after administration. There are also data to suggest that bevacizumab may have a higher risk of incidence of severe intraocular inflammation and ATEs. This incremental risk for systemic and ocular adverse events may influence the cost-effectiveness ratio based on health economic models that directly compare one anti-VEGF agent to the other.

Head-to-head studies including CATT show non-inferiority in VA when both drugs are given monthly (but not PRN), but these studies may not be powered for safety, particularly for rare but possibly fatal events such as ATEs. Even if all data are pooled from main head-to-head studies this will still be insufficient to detect safety differences between ranibizumab and bevacizumab. Continuous monitoring of safety data in postmarketing will be important to examine the incidence of adverse events.

Future Developments

A number of clinical trials are currently in progress to compare the safety and efficacy of ranibizumab and bevacizumab. These include the Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation (IVAN) trial; the Prevention of vision loss in patients with AMD by intravitreal injection of bevacizumab and ranibizumab (VIBERA) trial; Avastin versus Lucentis in age-related macular degeneration (MANTA); Lucentis compared to Avastin study (LUCAS); Groupe d'evaluation Français Avastin versus Lucentis (GEFAL); and the Comparison of bevacizumab (Avastin) and ranibizumab (Lucentis) in exudative age-related macular degeneration (BRAMD) trial. Results from these trials should clarify the best practices in the management of nvAMD with anti-VEGF therapies with regard to optimal frequency of administration and duration of treatment regimen. Cost–benefit comparisons of ranibizumab and bevacizumab will also be strengthened by these upcoming data.

The outcomes from the second year of CATT and other comparative clinical studies in Europe should help to elucidate whether the multiple systemic serious adverse events experienced by more patients receiving bevacizumab are related to intravitreal anti-VEGF treatment. However there remains a requirement for large trials that are powered for safety to completely clarify the incidence of rare adverse events with ranibizumab or bevacizumab.

A continuing pharmacovigilance programme for ranibizumab will ensure that clinicians and patients are notified if any significant risks appear with the long-term therapy of this agent. Substantial additional studies are necessary to attain a satisfactory safety profile for bevacizumab, proven by evidence-based medicine. ■

1. Bressler NM, Bressler SB, Congdon NG, et al., Potential public health impact of Age-Related Eye Disease Study results: AREDS report no. 11, *Arch Ophthalmol*, 2003;121:1621–4.
2. Buch H, Vinding T, Nielsen NV, Prevalence and causes of visual impairment according to World Health Organization and United States criteria in an aged, urban Scandinavian population: the Copenhagen City Eye Study, *Ophthalmology*, 2001;108:2347–57.
3. Resnikoff S, Pascolini D, Etya'ale D, et al., Global data on visual impairment in the year 2002, *Bull World Health Organ*, 2004;82:844–51.
4. Friedman DS, O'Colmain BJ, Munoz B, et al., Prevalence of age-related macular degeneration in the United States, *Arch Ophthalmol*, 2004;122:564–72.
5. Gehrs KM, Anderson DH, Johnson LV, et al., Age-related macular degeneration—emerging pathogenetic and therapeutic concepts, *Ann Med*, 2006;38:450–71.
6. Jager RD, Mieler WF, Miller JW, Age-related macular degeneration, *N Engl J Med*, 2008;358:2606–17.
7. Aiello LP, Avery RL, Arrigg PG, et al., Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders, *N Engl J Med*, 1994;331:1480–7.
8. Emerson MV, Lauer AK, Current and emerging therapies for the treatment of age-related macular degeneration, *Clin Ophthalmol*, 2008;2:377–88.
9. Kliffen M, Sharma HS, Mooy CM, et al., Increased expression of angiogenic growth factors in age-related maculopathy, *Br J Ophthalmol*, 1997;81:154–62.
10. Wells JA, Murthy R, Chibber R, et al., Levels of vascular endothelial growth factor are elevated in the vitreous of patients with subretinal neovascularisation, *Br J Ophthalmol*, 1996;80:363–6.
11. Ferrara N, Damico L, Shams N, et al., Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration, *Retina*, 2006;26:859–70.
12. Bressler NM, Chang TS, Suner IJ, et al., Vision-related function after ranibizumab treatment by better- or worse-seeing eye: clinical trial results from MARINA and ANCHOR, *Ophthalmology*, 2010;117:747–56 e4.
13. Brown DM, Kaiser PK, Michels M, et al., Ranibizumab versus verteporfin for neovascular age-related macular degeneration, *N Engl J Med*, 2006;355:1432–44.
14. Chen Y, Wiesmann C, Fuh G, et al., Selection and analysis of an optimized anti-VEGF antibody: crystal structure of an affinity-matured Fab in complex with antigen, *J Mol Biol*, 1999;293:865–81.
15. Rosenfeld PJ, Brown DM, Heier JS, et al., Ranibizumab for neovascular age-related macular degeneration, *N Engl J Med*, 2006;355:1419–31.
16. Rosenfeld PJ, Rich RM, Lalwani GA, Ranibizumab: Phase III clinical trial results, *Ophthalmol Clin North Am*, 2006;19:361–72.
17. Bashshur ZF, Schakal A, Hamam RN, et al., Intravitreal bevacizumab vs verteporfin photodynamic therapy for neovascular age-related macular degeneration, *Arch Ophthalmol*, 2007;125:1357–61.
18. Lazic R, Gabric N, Verteporfin therapy and intravitreal bevacizumab combined and alone in choroidal neovascularization due to age-related macular degeneration, *Ophthalmology*, 2007;114:1179–85.
19. Rosenfeld PJ, Moshfeghi AA, Puliafito CA, Optical coherence tomography findings after an intravitreal injection of bevacizumab (avastin) for neovascular age-related macular degeneration, *Ophthalmic Surg Lasers Imaging*, 2005;36:331–5.
20. Los M, Roodhart JM, Voest EE, Target practice: lessons from phase III trials with bevacizumab and vatalanib in the treatment of advanced colorectal cancer, *Oncologist*, 2007;12:443–50.
21. Yeung YA, Wu X, Reyes AE, 2nd, et al., A therapeutic anti-VEGF antibody with increased potency independent of pharmacokinetic half-life, *Cancer Res*, 2010;70:3269–77.
22. Rosenfeld PJ, Intravitreal avastin: the low cost alternative to lucentis?, *Am J Ophthalmol*, 2006;142:141–3.
23. BNF, British national formulary [BNF] edition 61, 2011. Available at: http://bnf.org/bnf/bnf/current (accessed 6 January 2012).
24. Brechner RJ, Rosenfeld PJ, Babish JD, et al., Pharmacotherapy for neovascular age-related macular degeneration: an analysis of the 100% 2008 medicare fee-for-service part B claims file, *Am J Ophthalmol*, 2011;151:887–95 e1.
25. Novartis, Lucentis prescribing information, 2010. Available at: http://www.gene.com/gene/products/information/pdf/lucentis-prescribing.pdf (accessed 6 January 2012).
26. Raftery J, Clegg A, Jones J, et al., Ranibizumab (Lucentis) versus bevacizumab (Avastin): modelling cost effectiveness, *Br J Ophthalmol*, 2007;91:1244–6.
27. Steinbrook R, The price of sight—ranibizumab, bevacizumab, and the treatment of macular degeneration, *N Engl J Med*, 2006;355:1409–12.
28. USP, 28/NF 23 Book Chapter <788> Particulate matter in injections. United States Pharmacopeial Convention, Inc Rockville, MD, 2005.
29. USP, 28/NF 23 Book Chapter <789> Particulate matter in ophthalmic solutions. United States Pharmacopeial Convention, Inc Rockville, MD, 2005.
30. Liew G, Mitchell P, Ranibizumab for neovascular age-related macular degeneration, *N Engl J Med*, 2007;356:747–8; author reply 9–50.
31. Wong TY, Liew G, Mitchell P, Clinical update: new treatments for age-related macular degeneration, *Lancet*, 2007;370:204–6.
32. Heiduschka P, Fietz H, Hofmeister S, et al., Penetration of bevacizumab through the retina after intravitreal injection in the monkey, *Invest Ophthalmol Vis Sci*, 2007;48:2814–23.
33. Christoforidis JB, Carlton MM, Knopp MV, et al., PET/CT imaging of I-124-radiolabeled bevacizumab and ranibizumab after intravitreal injection in a rabbit model, *Invest Ophthalmol Vis Sci*, 2011;52:5899–903.
34. Novartis, Summary of product characteristics, Lucentis®, 2011.
35. Stewart MW, What are the half-lives of ranibizumab and aflibercept (VEGF Trap-eye) in human eyes? Calculations with a mathematical model, *Eye Reports*, 2011;1, e5:12–4.
36. Krohne TU, Eter N, Holz FG, et al., Intraocular pharmacokinetics of bevacizumab after a single intravitreal injection in humans, *Am J Ophthalmol*, 2008;146:508–12.
37. Lu JF, Bruno R, Eppler S, et al., Clinical pharmacokinetics of bevacizumab in patients with solid tumors, *Cancer Chemother Pharmacol*, 2008;62:779–86.
38. Bakri SJ, Snyder MR, Reid JM, et al., Pharmacokinetics of intravitreal ranibizumab (Lucentis), *Ophthalmology*, 2007;114:2179–82.
39. Bakri SJ, Snyder MR, Reid JM, et al., Pharmacokinetics of intravitreal bevacizumab (Avastin), *Ophthalmology*, 2007;114:855–9.
40. Kim H, Robinson SB, Csaky KG, FcRn receptor-mediated pharmacokinetics of therapeutic IgG in the eye, *Mol Vis*, 2009;15:2803–12.
41. Meyer CH, Holz FG, Preclinical aspects of anti-VEGF agents for the treatment of wet AMD: ranibizumab and bevacizumab, *Eye* (Lond), 2011;25:661–72.
42. Kahook MY, Liu L, Ruzycki P, et al., High-molecular-weight aggregates in repackaged bevacizumab, *Retina*, 2010;30:887–92.
43. Klettner A, Mohle F, Roider J, Intracellular bevacizumab reduces phagocytotic uptake in RPE cells, *Graefes Arch Clin Exp Ophthalmol*, 2010;248:819–24.
44. Klettner AK, Kruse ML, Meyer T, et al., Different properties of VEGF-antagonists: Bevacizumab but not Ranibizumab accumulates in RPE cells, *Graefes Arch Clin Exp Ophthalmol*, 2009;247:1601–8.
45. Barros-Pereira R, Costa R, Falcao M, et al., Plasma Levels Of Vascular Endothelial Growth Factor Before And After Intravitreal Injection Of Bevacizumab Or Ranibizumab In The Treatment Of Neovascular Age-related Macular Degeneration, Abstract A591, *Invest Ophthalmol Vis Sci*, 2011;52:2319.
46. Chang TS, Bressler NM, Fine JT, et al., Improved vision-related function after ranibizumab treatment of neovascular age-related macular degeneration: results of a randomized clinical trial, *Arch Ophthalmol*, 2007;125:1460–9.
47. Boyer DS, Antoszyk AN, Awh CC, et al., Subgroup analysis of the MARINA study of ranibizumab in neovascular age-related macular degeneration, *Ophthalmology*, 2007;114:246–52.
48. Bressler NM, Chang TS, Fine JT, et al., Improved vision-related function after ranibizumab vs photodynamic therapy: a randomized clinical trial, *Arch Ophthalmol*, 2009;127:13–21.
49. Brown DM, Michels M, Kaiser PK, et al., Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: Two-year results of the ANCHOR study, *Ophthalmology*, 2009;116:57–65 e5.
50. Kaiser PK, Brown DM, Zhang K, et al., Ranibizumab for predominantly classic neovascular age-related macular degeneration: subgroup analysis of first-year ANCHOR results, *Am J Ophthalmol*, 2007;144:850–7.
51. Abraham P, Yue H, Wilson L, Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER study year 2, *Am J Ophthalmol*, 2010;150:315–24 e1.
52. Regillo CD, Brown DM, Abraham P, et al., Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1, *Am J Ophthalmol*, 2008;145:239–48.
53. Schmidt-Erfurth U, Eldem B, Guymer R, et al., Efficacy and safety of monthly versus quarterly ranibizumab treatment in neovascular age-related macular degeneration: the EXCITE study, *Ophthalmology*, 2011;118:831–9.
54. Tufail A, Patel PJ, Egan C, et al., Bevacizumab for neovascular age related macular degeneration (ABC Trial): multicentre randomised double masked study, *BMJ*, 2010;340:c2459.
55. Subramanian ML, Abedi G, Ness S, et al., Bevacizumab vs ranibizumab for age-related macular degeneration: 1-year outcomes of a prospective, double-masked randomised clinical trial, *Eye* (Lond), 2010;24:1708–15.
56. Subramanian ML, Abedi G, Ness S, et al., Bevacizumab vs Ranibizumab: One Year Outcomes of a Head to Head, Prospective, Double-Masked, Randomized Clinical Trial, Abstract A163, *Invest Ophthalmol Vis Sci*, 2010;51:517.
57. Subramanian ML, Ness S, Abedi G, et al., Bevacizumab vs ranibizumab for age-related macular degeneration: early results of a prospective double-masked, randomized clinical trial, *Am J Ophthalmol*, 2009;148:875–82 e1.
58. Martin DF, Maguire MG, Ying GS, et al., Ranibizumab and bevacizumab for neovascular age-related macular degeneration, *N Engl J Med*, 2011;364:1897–908.
59. Lalwani GA, Rosenfeld PJ, Fung AE, et al., A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTO Study, *Am J Ophthalmol*, 2009;148:43–58 e1.
60. Holz FG, Korobelnik JF, Lanzetta P, et al., The effects of a flexible visual acuity-driven ranibizumab treatment regimen in age-related macular degeneration: outcomes of a drug and disease model, *Invest Ophthalmol Vis Sci*, 2010;51:405–12.
61. Beaumont P, Bevacizumab: not as good with more adverse reactions?, *Clin Experiment Ophthalmol*, 2011;39:588–90.
62. Heier JS, Antoszyk AN, Pavan PR, et al., Ranibizumab for treatment of neovascular age-related macular degeneration: a phase I/II multicenter, controlled, multidose study, *Ophthalmology*, 2006;113:633 e1–4.
63. Holz FG, Amoaku W, Donate J, et al., Safety and efficacy of a flexible dosing regimen of ranibizumab in neovascular age-related macular degeneration: the SUSTAIN study, *Ophthalmology*, 2011;118:663–71.
64. Modarres M, Naseripour M, Falavarjani KG, et al., Intravitreal injection of 2.5 mg versus 1.25 mg bevacizumab (Avastin) for treatment of CNV associated with AMD, *Retina*, 2009;29:319–24.
65. Johnson D, Hollands H, Hollands S, et al., Incidence and characteristics of acute intraocular inflammation after intravitreal injection of bevacizumab: a retrospective cohort study, *Can J Ophthalmol*, 2010;45:239–42.
66. Chong DY, Anand R, Williams PD, et al., Characterization of sterile intraocular inflammatory responses after intravitreal bevacizumab injection, *Retina*, 2010;30:1432–40.
67. Sharma S, Johnson D, Abouammoh M, et al. , A retrospective analysis of the comparative safety and efficacy of intravitreal bevacizumab versus ranibizumab, Presented at: ASRS Conference, Vancouver, 2010.
68. Barron H, Dear Healthcare Provider letter. Important drug warning regarding Avastin® (bevacizumab), 2006.
69. Georgopoulos M, Polak K, Prager F, et al., Characteristics of severe intraocular inflammation following intravitreal injection of bevacizumab (Avastin), *Br J Ophthalmol*, 2009;93:457–62.
70. Berger AR, Sharma S, Severe intraocular inflammation/endophthalmitis following off-label treatment with intravitreal bevacizumab, Report by the Department of Ophthalmology and Vision Sciences, Faculty of Medicine, University of Toronto, *Ophthalmol Scientific Update*, 2009;1–8.
71. Kmietowicz Z, Doctors warn against using Avastin for macular degeneration, *BMJ*, 2010;340:c2483.
72. PBM PBMS, *Ophthalmology*, Specialty Care and Surgical Services, Intravitreal Bevacizumab (Avastin®) Therapy Update to Interim Guidance, National PBM Bulletin 2011.
73. Boyer DS, Heier JS, Brown DM, et al., A Phase IIIb study to evaluate the safety of ranibizumab in subjects with neovascular age-related macular degeneration, *Ophthalmology*, 2009;116:1731–9.
74. Mitchell P, Korobelnik JF, Lanzetta P, et al., Ranibizumab (Lucentis) in neovascular age-related macular degeneration: evidence from clinical trials, *Br J Ophthalmol*, 2010;94:2–13.
75. Matsuyama K, Ogata N, Matsuoka M, et al., Plasma levels of vascular endothelial growth factor and pigment epithelium-derived factor before and after intravitreal injection of bevacizumab, *Br J Ophthalmol*, 2010;94:1215–8.
76. Scappaticci FA, Skillings JR, Holden SN, et al., Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab, *J Natl Cancer Inst*, 2007;99:1232–9.
77. Carneiro AM, Barthelmes D, Falcao MS, et al., Arterial thromboembolic events in patients with exudative age-related macular degeneration treated with intravitreal bevacizumab or ranibizumab, *Ophthalmologica*, 2011;225:211–21.
78. Martin DF, The CATT Research Group, Maguire MG, et al., Ranibizumab and bevacizumab for neovascular age-related macular degeneration, *N Engl J Med*, 2011;364(20):1897–908.
79. Curtis LH, Hammill BG, Schulman KA, et al., Errors in Table in: Risks of Mortality, Myocardial Infarction, Bleeding, and Stroke Associated With Therapies for Age-Related Macular Degeneration, *Arch Ophthalmol*, 2010;128:1623.
80. Curtis LH, Hammill BG, Schulman KA, et al., Risks of mortality, myocardial infarction, bleeding, and stroke associated with therapies for age-related macular degeneration, *Arch Ophthalmol*, 2010;128:1273–9 Erratum in: *Arch Ophthalmol*, 2010;128(12):1623.
81. Gower EW CS, Chu L, Varma R, Klein R, Adverse event rates following intravitreal injection of Avastin or Lucentis for treating age-related macular degeneration, Poster 6644, Presented at: ARVO 2011, Fort Lauderdale, Florida, 1–5 May, 2011.
82. French DD, Margo CE, Age-related macular degeneration, anti-vascular endothelial growth factor agents, and short-term mortality: a postmarketing medication safety and surveillance study, *Retina*, 2011;31:1036–42.
83. Mitchell P, A systematic review of the efficacy and safety outcomes of anti-VEGF agents used for treating neovascular age-related macular degeneration: comparison of ranibizumab and bevacizumab, *Curr Med Res Opin*, 2011;27:1465–75.