The Evidence Supporting Ranibizumab in the Treatment of Neovascular Age-related Macular Degeneration

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Abstract

The efficacy and safety of ranibizumab in neovascular age-related macular degeneration (AMD) or 'wet AMD' has been demonstrated in the large phase III ANCHOR and MARINA trials. Further studies including the PIER, PrONTO, EXCITE and SUSTAIN trials have also evaluated the optimal dosing regimen of ranibizumab. Various head-to-head studies have compared the anti-angiogenic treatments for wet AMD. The CATT and IVAN trials compared the safety and efficacy of ranibizumab with off-label use of bevacizumab and raised concern about an increased risk of ocular and systemic adverse events (AEs) in patients receiving bevacizumab compared with those receiving ranibizumab. Studies such as SAILOR and HORIZON have shown that ranibizumab has a good safety profile and is well tolerated for over 4 years with few serious ocular and systemic AEs.

Keywords

Age-related macular degeneration, aflibercept, bevacizumab, choroidal neovascularisation, ranibizumab, VEGF

Disclosure: Simon P Kelly has accepted conference travel from and has acted as a consultant and speaker for Novartis, and as consultant for Alimera and Bayer. He is currently involved in research funded by Allergan, Bayer and Novartis. Winfried Amoaku has served on the advisory board for Alcon, Alimera, Allergen, Bayer, Novartis and Thrombogenics, has received research and travel grants from Allergen, Bayer and Novartis and had involvement in clinical trials with Novartis and Pfizer.

Acknowledgements: Editorial assistance was provided by Katrina Mountfort at Touch Medical Media.

Received: 24 September 2013 **Accepted**: 6 November 2013 **Citation**: *European Ophthalmic Review*, 2013;7(2):102–8 *DOI: 10.17925/EOR.2013.07.02.102*

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Support: The publication of this article was supported by Novartis. The views and opinions expressed are those of the authors and not necessarily those of Novartis.

Age-related macular degeneration (AMD) is the leading cause of blindness in people over 60 years of age in developed countries.[1] A meta-analysis of 53 clinical studies found that approximately 41 % of patients experienced severe loss of sight (more than six lines of visual acuity [VA] lost for untreated exudative AMD) within 3 years if not treated.[2] AMD can be classified into non-exudative (dry) and exudative or neovascular (wet) forms. The latter is characterised by the formation of abnormal blood vessels known as choroidal neovascularisation (CNV), which originate from the inner choroid. The new vessels spread under the retinal pigment epithelium (RPE), and may invade the RPE and subretinal space, with subsequent exudation and bleeding. This results in scarring of the central retina and a loss of function.[3] The visual loss associated with wet AMD is progressive, with approximately one line of vision lost at 3 months, three lines at 1 year and four lines at 2 years on average.[2] Approximately 10 % of patients with AMD have the wet type of the condition. In terms of demographics, wet AMD is most common in the elderly: the 3-year incidence in people >65 years in the US is estimated to be 0.94–1.14 %.[4]

Vascular endothelial growth factor (VEGF) plays a major role in the pathology of wet AMD. It promotes angiogenesis and potentially induces vascular leakage and inflammation by triggering the proliferation and permeability of capillary endothelial cells.[5,6] As a result, VEGF has become an attractive therapeutic target in the management of wet AMD, although other cytokines may contribute to the process. Until the advent of anti-VEGF therapies, treatment of wet AMD involved physical treatments of laser photocoagulation or photodynamic therapy (PDT) with verteporfin (Visudyne®), and aimed to stabilise rather than improve vision.[7,8] In addition, such treatments were only useful in a minority of eyes. In 2006, clinical trial data on the efficacy and safety of intravitreal ranibizumab, together with the rapid adoption of off-label bevacizumab, caused a paradigm shift in AMD therapy and redefined treatment goals.[9,10] Such treatment has been shown to improve central vision, inhibit CNV and delay the progression of AMD (see *Figure 1*). Four anti-VEGF therapies are currently approved for the treatment of wet AMD: ranibizumab, bevacizumab, pegaptanib and aflibercept.

Ranibizumab (Lucentis®) is a monoclonal antibody fragment (Fab) of a humanised anti-VEGF mouse monocloncal antibody and was designed for use in ophthalmology.[11] It was approved for the treatment of wet AMD by the US Food and Drug Administration (FDA) in 2006 and in the EU in 2007. It is administered by injection 0.5 mg into the vitreous cavity. Other approved indications include diabetic macular oedema,[12] retinal vein occlusion[13] and, more recently, myopic CNV in Europe.[14] Bevacizumab (Avastin®) is an anti-VEGF humanised mouse monoclonal antibody that is widely used for wet AMD and is not approved for intraocular use.[15] Dosage may range from 1.25 mg to 2.5 mg. Bevacizumab is approved for use by intravenous injection in metastatic colorectal cancer, non-small cell lung cancer, renal cell cancer, epithelial ovarian, fallopian

tube or primary peritoneal cancer.[16] Pegaptanib 0.3 mg (Macugen®) is pegylated anti-VEGF single-stranded DNA (ssDNA) aptamer given by intravitreal injection that was approved for wet AMD by the FDA in 2004.[17,18] Aflibercept 2 mg (Eylea®) is an anti-VEGF fusion protein that was approved by the FDA in November 2011 and by the European Medicines Agency (EMA) in November 2012 for wet AMD.[19] Several other anti-VEGF strategies are in clinical development, including new antibody fragments, designed ankyrin repeat proteins (DARPins)[20] and the use of small-interfering RNA (siRNA).[21]

A large body of clinical trial evidence supports the use of ranibizumab in wet AMD. However, there was no such high-quality evidence supporting bevacizumab, which was designed for intravenous use, until the recent publication of CATT data in the US and IVAN data in the UK and the GEFAL trial from France.[22–25] However, bevacizumab is extensively used off-label in several countries and mostly due to cost considerations.[26–28]

Various studies have compared anti-VEGF therapies but their designs have varied. Many of these studies have not shown substantial differences between treatments but it is necessary to consider the quality of the evidence and all of the data before deciding the relative merits of each therapy. This article will assess the clinical trial evidence supporting the efficacy and safety of ranibizumab

Clinical Trials Assessing the Efficacy and Safety of Ranibizumab

A number of clinical trials have evaluated ranibizumab doses, made comparisons of ranibizumab with placebo, other treatments or used ranibizumab in combination with other treatments. The major studies are summarised in *Table 1*.

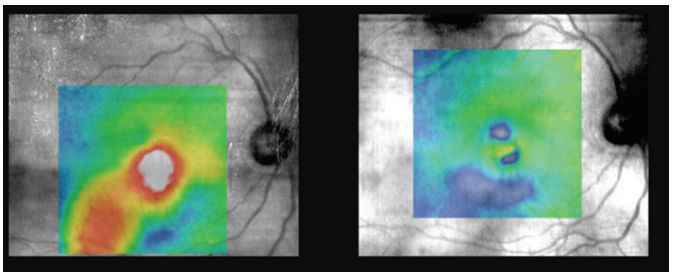
Ranibizumab Compared with Sham Injections

Several phase III trials have evaluated the safety and efficacy of ranibizumab compared with sham injections. The MARINA trial (n=716) was a multicentre, two-year, double-masked, sham-controlled trial.[9] Patients with minimally classic or occult CNV were randomised to monthly 0.3 mg or 0.5 mg ranibizumab or placebo (sham injections). Ranibizumab was superior to control in terms of maintenance and improvement of VA, and was well tolerated

The PIER study (n=184) evaluated the efficacy and safety of a 3-monthly dosing schedule.[29] Patients with AMD-related CNV were randomised to 0.3 mg or 0.5 mg ranibizumab or placebo (sham) monthly for 3 months and then quarterly. During the second year, eligible placebo group patients could crossover to 0.5 mg ranibizumab quarterly and later all eligible patients were switched to 0.5 mg ranibizumab monthly. During the first year, quarterly administration of ranibizumab was associated with loss of vision gains that had been achieved with monthly injections. The VA of placebo patients who crossed over to ranibizumab decreased across time, with an average loss of 3.5 letters 10 months after crossover. The VA of 0.3 mg and 0.5 mg group patients who rolled over to monthly ranibizumab increased for an average gain of 2.2 and 4.1 letters, respectively, 4 months after rollover.[29] Hence, quarterly treatment with ranibizumab for all patients is an inferior strategy to monthly dosing.

The question of quarterly versus monthly dosing was also examined in the EXCITE study (n=353). Patients with primary or recurrent subfoveal CNV secondary to AMD with predominantly classic, minimally classic or occult lesions were randomised to one of four dosing regimes: 0.3 mg quarterly, 0.5 mg quarterly, 0.5 mg monthly or 0.3 mg monthly.[30] Results favoured monthly dosing: after three initial monthly ranibizumab injections, both monthly and quarterly ranibizumab treatments maintained best-corrected VA (BCVA) in patients with CNV secondary to AMD. The BCVA gain in the monthly regimen was higher than that of those patients who had quarterly injections.[30]

Figure 1: Optical Coherence Tomography Imaging of Retina Before and After Ranibizumab Treatment



Left: Spectral domain optical coherence tomography (SD-OCT) images of the right eye of a male aged 78 years of age with recent distortion of vision. A pre-treatment OCT shows loss of foveal pit, visual acuity (VA) 6/12 and central retinal thickness (CRT) = 342 µm. Right: Post-treatment OCT shows recovery of foveal contour and VA 6/6, CRT = 237 µm.

Subsequent studies examined the feasibility of flexible dosing regimens. In the SUSTAIN study (n=513), patients were given three initial monthly ranibizumab injections (0.3 mg; patients switched to 0.5 mg ranibizumab after approval in Europe) followed by *pro re nata* (PRN) retreatment for 9 months based on pre-specified retreatment criteria.[31] The mean BCVA increased steadily from baseline to month 3 to reach +5.8 letters, decreased slightly from month 3 to 6 and remained stable from month 6 to 12, reaching +3.6 at month 12. The PrONTO study (n=40) assessed the long-term efficacy of a individualised dosing regimen of ranibizumab.[32] In this open-label study, patients were given three consecutive monthly intravitreal injections of ranibizumab (0.5 mg) followed by treatment as guided by optical coherence tomography (OCT) measures of mean VA or central retinal thickness over 2 years. At month 24, the mean VA improved by 11.1 letters. VA improved by 15 letters or more in 43 % of patients. These VA and OCT outcomes were achieved with an average of 9.9 injections over 24 months. Both studies concluded that a variable dosing regimen with intravitreal ranibizumab resulted in VA outcomes similar to those from phase III clinical studies, but fewer intravitreal injections were required.[31,32]

A recent multicentre non-interventional cohort study (SEVEN-UP, n=65) of patients who participated in the MARINA and ANCHOR trials suggested that VA declines over time: approximately 7 years after ranibizumab therapy in the ANCHOR or MARINA trials, one-third of patients demonstrated good visual outcomes, whereas another third had poor outcomes. Compared with baseline, almost half of eyes were stable, whereas one-third declined by 15 letters or more.[33] It should be noted, however, that the sample size of this study was too small to allow meaningful conclusions to be drawn. Furthermore, dosing, retreatment and monitoring frequency was highly variable in these patients, thus contributing to the less than optimal outcomes.

Ranibizumab Compared with other Treatments

The ANCHOR[34] study was a multicentre, randomised double-masked trial (n=423). Participants had predominantly classic CNV not previously treated with PDT with verteporfin or anti-angiogenic drugs. Patients were randomised to PDT with verteporfin every 3 months or as needed

Table 1: Major Clinical Studies and Quality of Evidence in the Investigation of Ranibizumab in Wet Age-related Macular Degeneration

Study/ Reference(s)	Study Design	Number of Patients and Treatments	Major Endpoints/Findings
CATT study[23,35]	Randomised, non-inferiority multicentre, 2-year duration	n=1,107; 4 treatment groups defined by drug (ranibizumab [0.5 mg] or bevacizumab [1.25 mg]) or dosing regimen (monthly as needed)	2-year results: Comparison inconclusive, mean gain in VA similar for bevacizumab and ranibizumab: difference –1.4 letters; p=0.21. Mean visual gain better for monthly than as needed. Importantly, ranibizumab reduced the number of injections required. Patients with ≥1 systemic SAE higher with bevacizumab than ranibizumab (39.9 % versus 31.7 %; p=0.009) Endophthalmitis was rare but more frequent with bevacizumab
IVAN study[24,53]	Randomised non-inferiority factorial multicentre trial, 2-year duration	n=610; 4 treatment groups defined by drug (ranibizumab [0.5 mg] or orbevacizumab [1.25 mg]) or dosing regimen (monthly or as needed)	At 2 years, mean gain in VA was similar for both drugs (bevacizumab–ranibizumab difference: –1.4 letters; 95 % CI, –3 to – 0.8; p=0.21). Mean gain was greater for monthly than for as-needed treatment (difference: –2.4 letters; 95 % CI –4.8 to –0.1; p=0.046). Switching from monthly to as-needed treatment resulted in greater mean decrease in vision during year 2 (–2.2 letters; p=0.03). Rates of death and arteriothrombotic events were similar for both drugs (p>0.60). The proportion of patients with 1 or more systemic serious AEs was higher with bevacizumab than ranibizumab (39.9 % versus 31.7 %; adjusted risk ratio 1.30, 95 % CI 1.07–1.57; p=0.009)
ANCHOR study[34]	Multicentre, 2-year, double-masked trial. 2-year duration	n=423; 3 treatment groups: ranibizumab 0.3 mg or 0.5 mg monthly plus sham verteporfin therapy versus sham injections plus active verteporfin therapy	2-year results: 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 compared with 64.3 % of those in the verteporfin group (p<0.001 for each comparison). VA improved by 15 letters or more in 35.7 % of the 0.3 mg group and 40.3 % of the 0.5 mg group compared with 5.6 % of the verteporfin group (p<0.001 for each comparison). Mean VA increased by 8.5 letters in the 0.3 mg group and 11.3 letters in the 0.5 mg group compared with a decrease of 9.5 letters in the verteporfin group (p<0.001 for each comparison)
MARINA study[9]	Multicentre, 2-year, double-masked, sham-controlled trial. 2-year duration	n=716; 3 treatment groups: ranibizumab 0.3 mg or 0.5 mg monthly versus sham injections	2 year results: 92 % and 90 % of the patients receiving ranibizumab 0.3 mg or 0.5 mg, respectively, lost <15 letters at 2 years compared with 52.9 % in the sham-injection treatment group (p<0.0001). Patients treated with ranibizumab 0.3 mg or 0.5 mg showed a mean improvement in BCVA of 5.4 or 6.6 letters over baseline at month 24, while sham patients experienced a mean loss of 14.9 letters. 26.1 % and 33.3 % of ranibizumab 0.3 mg and 0.5 mg patients gained >15 letters at 2 years compared with 3. 8 % of patients in the sham treatment group (p<0.0001), respectively
SAILOR study[47]	12-month randomised (cohort 1) or open-label (cohort 2). multicentre clinical trial	n=4,300; cohort 1 subjects were randomised 1:1 to 0.3 mg (n=1,169) or 0.5 mg (n=1,209) ranibizumab for 3 monthly injections. Cohort 2 (n=1,922) received an initial dose of 0.5 mg ranibizumab and patients were retreated at the physician's discretion	12-month results: The incidence of vascular and non-vascular deaths during the 12-month study was 0.9 % and 0.7 % in cohort 1 (0.3 mg), 0.8 % and 1.5 % in the cohort 1 (0.5 mg), and 0.7 % and 0.9 % in cohort 2, respectively. Incidence of death due to unknown cause was 0.1 % in both cohorts 1 and 2. Stroke rates were 0.7 %, 1.2 % and 0.6 % in the 0.3 mg and 0.5 mg groups and cohort 2, respectively. Cohort 1 treatment-naïve subjects gained an average of 0.5 (0.3 mg) and 2.3 (0.5 mg) VA letters and previously treated subjects had gained 1.7 (0.3 mg) and 2.3 (0.5 mg) VA letters
EXCITE study[30]		n=353, patients randomised to 0.3 mg/ 0.5 mg quarterly, or 0.3 mg monthly ranibizumab; 3 consecutive monthly injections followed by 9-month maintenance phase (with monthly or quarterly injections)	BCVA increased from baseline to month 12 by 4.9, 3.8, and 8.3 letters in the 0.3 mg quarterly (n=104), 0.5 mg quarterly (n=88) and 0.3 mg monthly (n=101) dosing groups, respectively. Similar results were observed in the ITT population (n=353)

BCVA = best-corrected visual acuity; CI = confidence interval; ITT= intention-to-treat; SAE = serious adverse effects.

together with a monthly sham intraocular injection, or to sham PDT with verteporfin plus monthly intravitreal ranibizumab (0.3 mg or 0.5 mg) injection.[34] Results showed a substantial improvement in VA compared with verteporfin[10,34] (see *Figure 2*) over 3 and 6 months treatment with few differences in ocular or non-ocular adverse events (AEs), and efficacy and safety outcomes in the ranibizumab treatment arm were

similar to those seen in the MARINA trial. Together with the MARINA trial, these large trials of high methodological quality are regarded as pivotal studies in the development of ranibizumab.

Given the cost concerns regarding ranibizumab, comparative studies of ranibizumab and bevacizumab have attracted considerable attention. The CATT Study was a multicentre, randomised trial (n=1,107) in which treatment-naïve patients with active subfoveal CNV secondary to AMD were assigned to four treatment groups according to drug (ranibizumab (0.5 mg) or bevacizumab (1.25 mg) and treatment regimen (monthly or as needed).[23,35] At one year, patients initially assigned to monthly treatment were randomly reassigned to monthly or as needed treatment, without changing the drug assignment. The IVAN study (n=610) was a similar study in the UK that randomised patients to ranibizumab (0.5 mg) or bevacizumab (1.25 mg) monthly or as needed.[24,25]

In order to assess the influence of drug and dosing regimen on the incidence of CNV in the fellow eye of patients treated for CNV with ranibizumab or bevacizumab, a cohort study of CATT enrolled patients with no CNV in the fellow eye at the time of enrolment in CATT. After 2 years, there was no statistically significant difference between ranibizumab and bevacizumab in the incidence of CNV in the fellow eye.[36]

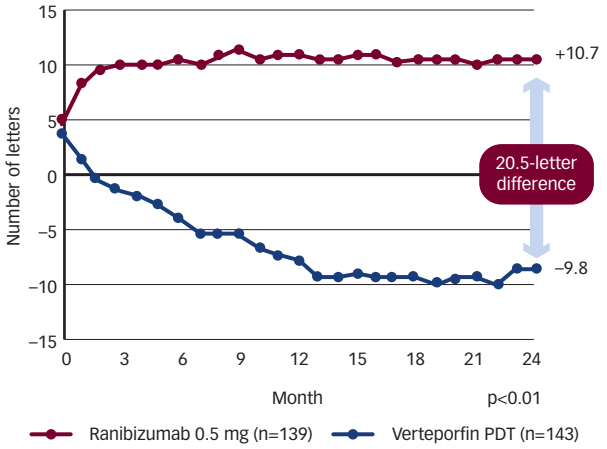
It was concluded from CATT that ranibizumab and bevacizumab had similar effects on VA over a 2-year period (see *Figure 3*). Both drugs substantially reduced fluid in or under the retina. However, there were greater reductions in total foveal thickness and retinal thickness/subfoveal fluid with ranibizumab compared with bevacizumab. Significantly more patients in the ranibizumab arms achieved a dry retina. The greater prevalence of fluid in the bevacizumab-as-needed group led to an average of 0.6 more injections during the second year than in ranibizumab-as-needed patients, and in an average of 1.5 injections more over a 2-year period. The proportion of patients with serious systemic AEs (primarily hospitalisations) was higher with bevacizumab than with ranibizumab (24.1 % versus 19.0 %). Generally, regular monthly administration of ranibizumab or bevacizumab was more effective in improving vision parameters and pathology than when administered on as-needed basis.

The IVAN study failed to show significant differences between ranibizumab and bevacizumab. VAs with continuous and discontinuous treatment were equivalent.[24] Of note, retreatment in IVAN required three consecutive injections, as opposed to retreatment in CATT, which only required one injection. Bevacizumab was associated with a lower incidence of arterio-thrombotic event or heart failure. There was no difference between bevacizumab and ranibizumab in terms of serious systemic AEs. Serum VEGF was lower with bevacizumab and higher with discontinuous treatment. The full implications of this are yet to be fully appreciated. However, a meta-analysis of 1-year data of three direct comparison trials showed that bevacizumab was associated with a significantly higher rate of ocular AEs with bevacizumab and a higher proportion of patients with serious infectious and gastrointestinal disorders.[37]

The GEFAL study was a multicentre, prospective, non-inferiority, double-masked, randomised clinical trial performed in 38 French ophthalmology centres. Recent data from the GEFAL study showed that bevacizumab was non-inferior to ranibizumab for VA at 1 year with similar safety profiles. Ranibizumab tended to have a better anatomic outcome.[22]

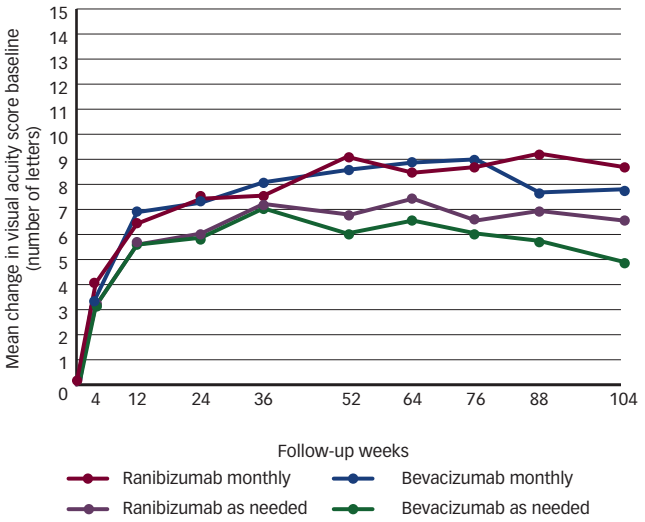
To date there is no large comparative studies of ranibizumab and pegaptanib, although results of the VISION trial[38] and post-approval

Figure 2: Changes in Visual Acuity from Baseline to 24 Months*



**Data taken from the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR) Trial.[34] PDT = photodynamic therapy.*

Figure 3: Mean Changes in Visual Acuity over 2 Years in Patients Treated with Bevacizumab and Ranibizumab in the CATT Trial



Source: CATT Research group.[23]

experience with this agent suggested that pegaptanib was inferior to ranibizumab. Pegaptanib is now rarely used. Two similarly designed, phase III studies (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD [VIEW 1, VIEW 2]) compared monthly (0.5 mg and 2 mg) and every 2 months dosing after three initial monthly doses of intravitreal aflibercept injection with monthly ranibizumab (n=2,149 combined for both trials).[19] These were designed as non-inferiority trials and found that dosing monthly or every 2 months after three initial monthly doses with aflibercept was non-inferior to monthly ranibizumab and was well tolerated. There are no data available yet on eyes treated for more than 24 months with aflibercept. In year 2, the study design was a capped PRN regimen across treatment and comparator arms. Modest decreases of BCVA ranging from 0.8 to 1.7 letters were seen in all treatment groups, with similar visual gains in the ranibizumab and aflibercept groups.[39]

The phase II MONET study (n=151) evaluated the efficacy of different dosing paradigms of the siRNA PF-04523655 (PF) versus ranabizumab.[40] Patients

were randomised to one of five treatment groups: all received ranibizumab 0.5 mg at baseline and (1) PF 1 mg (siRNA) every 4 weeks (Q4W) week 4 to 12; (2) PF 3 mg Q4W week 4 to 12; (3) PF 3 mg/2 weeks (Q2W) week 4 to 12; (4) PF 1 mg + ranibizumab (combination) Q4W baseline to week 12; and (5) ranibizumab Q4W to week 12. However, this study was underpowered and failed to meet its primary efficacy endpoints.

Ranibizumab in Combination with Other Treatments

A combined regimen was investigated in the FOCUS study (n=162), a prospective, randomised, single-masked phase II study. Patients received monthly intravitreal injections of ranibizumab 0.5 mg (n=106) or sham injections (n=56). All patients received PDT on day zero, then quarterly as needed.[41] Results indicated that through 2 years ranibizumab plus PDT was more effective than PDT alone and had a low rate of associated AEs. However, it is important to note that in this study, ranibizumab was given at fixed monthly doses and the study was not designed to compare combination therapy with ranibizumab monotherapy. There appear to be similar levels of vision preservation in the combination group in the FOCUS study and the ranibizumab monotherapy group in the ANCHOR study, but no conclusions may be drawn from this comparison – the two study populations had different baseline characteristics, including the fact that ANCHOR study subjects were treatment-naïve, whereas almost half of the subjects in the FOCUS study had received prior therapy for AMD.

The SUMMIT clinical trial programme was designed specifically to compare combination therapy with PDT and ranibizumab to ranibizumab monotherapy. The aim of the 2-year phase III DENALI study (n=321) was to demonstrate non-inferiority of ranibizumab in combination with PDT with verteporfin versus ranibizumab monotherapy in patients with subfoveal CNV secondary to AMD.[42] Patients were randomised to ranibizumab 0.5 mg, standard fluence PDT with verteporfin combination therapy or reduced fluence PDT with verteporfin combination therapy. The DENALI trial was the North American study of the SUMMIT clinical trial program, which also included the MONT BLANC study in Europe and the EVEREST study in Asia. In the MONT BLANC study (n=255), standard fluence verteporfin 6 mg/m^2 PDT and ranibizumab 0.5 mg or PRN ranibizumab monotherapy (sham infusion [5 % dextrose] PDT and ranibizumab 0.5 mg).[43] In the EVEREST study, 61 Asian patients with idiopathic polypoidal choroidal vasculopathy (IPCV) were randomised to PDT with verteporfin (standard fluence), ranibizumab 0.5 mg or the combination of both.[44] IPCV is considered by some experts to be a subtype of wet AMD but others consider it a different disease entity.[45] Results to date have failed to show that the combination of ranibizumab with verteporfin is superior to ranibizumab monotherapy. The combination may allow a treatment-free interval following initial therapy, but further studies are required to establish the benefits of a combined treatment regimen.

In summary, the combination of PDT with verteporfin with ranibizumab produced some improvement in treatment efficacy versus ranibizumab alone and was well tolerated, although the improvement was not significant in every trial. Ranibizumab is also used alone or in combination with verteporfin in IPCV.

Safety of Ranibizumab

Several studies have aimed to evaluate the safety of ranibizumab. The SECURE trial (n=234) was a phase IV open-label extension of the EXCITE and SUSTAIN studies with the objective of evaluating the long-term (24 months) safety of ranibizumab. Ranibizumab 0.5 mg was administered at the investigator's discretion if a patient experienced a BCVA loss of >5.[46] No new safety signals were identified in patients who received ranibizumab for a total of 3 years.

The SAILOR study (n=4,300) evaluated the efficacy and safety of ranibizumab and comprised a 12-month randomised study (cohort 1) and an open-label study (cohort 2).[47] Patients in cohort 1 (n=2,378) were randomised to 0.3 mg or 0.5 mg intravitreal ranibizumab for three-monthly loading doses. Patients in cohort 2 (n=1922) were given initial intravitreal dose of 0.5 mg ranibizumab and retreated at physician discretion. The results showed that ranibizumab is well tolerated, and ocular AEs were rare, with an incidence of less than 1 %. In terms of systemic safety, a slightly higher risk of stroke was seen in the 0.5 mg versus 0.3 mg group, but the difference was not statistically significant.[47] Since the study did not have a control arm, the significance, if any, of increased stroke risk is unknown.

The HORIZON study (n=853), an open-label, 2-year extension study, enrolled participants who completed 24 months in the MARINA, ANCHOR or FOCUS trials with the aim of evaluating the long-term safety and efficacy of ranibizumab. Ranibizumab 0.5 mg was administered at monthly intervals at the investigator's discretion for 2 years.[48] The main outcome measures of the study were incidence and severity of AEs. Results showed that multiple ranibizumab injections were well tolerated for ≥4 years. Of the 3,552 injections in the study, there was only one case of mild endophthalmitis. There were no serious ocular AEs, such as lens damage, retinal tears or rhegmatogenous retinal detachments.[39]

A low rate (0.02–0.049 %) of endophthalmitis following intravitreal injections of anti-VEGF agents was observed, typically within 3 days of injection. Streptococcus species was the most common bacteria isolated, and streptococcal isolates were approximately three times more frequent after intravitreal anti-VEGF injection than after intraocular surgery. Endophthalmitis is generally associated with poor visual outcomes.[49,50] Strategies to avoid oropharyngeal droplet transmission may include avoiding talking, coughing and sneezing or wearing surgical masks.

In contrast to the off-label use of bevacizumab, ranibizumab is undergoing continued systematic safety evaluation by periodic safety update reports and a risk management programme and has an estimated cumulative exposure of >1.8 million patient treatment-years. Its safety in routine clinical practice is also assessed by the LUMINOUS programme, which comprises a prospective observational study assessing ranibizumab 'real-world' safety and clinical effectiveness across licensed indications worldwide and an annual retrospective pooled safety analysis from completed wet AMD ranibizumab registries.[51] There is no large-scale systematic collection of data in association with intravitreal bevacizumab for neovascular AMD.

Discussion

As a result of the large body of clinical evidence of their efficacy and safety, anti-VEGF drugs remain the mainstay treatment for neovascular AMD for the foreseeable future, despite the rapid increase in potential new treatments. The question of whether AEs differ between off-label bevacizumab and licensed ranibizumab can only be answered on the basis of large head-to-head trials or randomised controlled trials for indirect comparison with reasonable follow-up times and sample sizes. While AEs associated with intravitreal anti-VEGF are rare, they can

be serious (e.g. stroke). Furthermore, they may be difficult to detect in clinical trials due to insufficient patient numbers or the inclusion of non-representative patients.

To date, the main head-to-head trials comparing ranibizumab with bevacizumab have been non-inferiority trials. The safety results of CATT and IVAN showed significantly more serious side effects with bevacizumab than with ranibizumab. CATT showed an increased number of hospitalisations for bevacizumab compared with ranibizumab, but for clinical reasons not generally associated with anti-VEGF drugs. However, neither CATT nor the IVAN trials were powered to detect small but clinically relevant adverse outcomes, such as stroke. Future studies should be powered not only for efficacy, but also for defined safety outcomes. Long-term pharmocovigelence and post-marketing surveillance is also required to assess such outcomes. As bevacizumab is not licensed for intraocular use it is unlikely such data will emerge.

The ANCHOR and MARINA trials included assessment of vision-related function quality of life. While VA provides an objective assessment of the treated eye, tools such as the National Eye Institute Visual Function Questionnaire 25 (NEI VFQ-25) provides information about the individual's overall function.[52] Improvement in NEI VFQ-25 scores generally correlates with improvement in vision – an analysis of MARINA and ANCHOR data found that a 4- to 6-point change in NEI VFQ-25 scores represents a clinically meaningful improvement.[53] The mean changes in the NEI VFQ-25 score in the MARINA study were 8.2 for the ≥15 letters gained group, 3.0 for the <15 letters gained or lost group and –6.3 for the ≥15 letters lost group. In the ANCHOR study, the mean changes were 11.1 for the ≥15 letters gained group, 4.4 for the <15 letters gained or lost group and –1.2 for the ≥15 letters lost group.[53] The VFQ-25 tool is a useful measure of the overall impact of therapies on the vision-specific quality of life and function of retinal patients and merits inclusion in the design of future clinical studies.
In comparative studies of ranibizumab and bevacizumab, some studies have yielded differences in retinal anatomy findings (e.g. total foveal thickness and retinal thickness).[37] When comparing the ANCHOR results with the FOCUS results, it can be concluded that the combination of ranibizumab with PDT does not necessarily result in better VA outcomes, and the use of PDT may reduce the VA benefits achieved with ranibizumab alone. It thus seems unlikely that such combination therapy provides any significant advantage over ranibizumab alone. As a safer, and more cost-effective alternative to the traditional monthly treatments, individualised anti-VEGF treatment regimens have merit.

Overall, there have been a large number of studies investigating treatments for wet AMD and there is substantial evidence that ranibizumab is an effective, safe and well-tolerated treatment option. However, there remains a lack of high-quality comparative data that provide ophthalmologists with the information needed to fully inform their treatment choices. Further well-designed studies are needed to better assess the relative efficacy and safety of the treatments currently available. Ranibizumab, bevacizumab and aflibercept are effective. Monthly clinical assessments and monthly intravitreal injections are often troublesome for patients and exercising for providers. In clinical practice, patients are predominantly treated using PRN regimens or treat and extend regimens.

As treatment with anti VEGF agents expands to include clinical indications additional to wet AMD, there will be increasing focus on the burden on medical retinal services in healthcare systems. A growing body of clinical data has confirmed the transformational profile of ranibizumab in wet AMD. In addition, aflibercept (Eylea) is an emerging and promising alternative anti-VEGF agent in the treatment of AMD. Aflibercept has received its EMA authorisation and has recently been approved by National Institute for Health and Care Excellence (NICE). Its role will become more clear in the future. Recent publications from Denmark, Germany, Israel and UK demonstrate a reduction of blindness certifications and or visual impairment measurements attributable to wet AMD since the introduction of anti-VEGF agents in Europe. Such publications suggest ranibizumab has made a difference at population levels.[54–59] It is likely that ranibizumab will remain the cornerstone of AMD therapy for the foreseeable future. ■

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Definition of Clinical Trials Investigating the Efficacy and Safety of Ranibizumab in Wet Age-related Macular Degeneration

ANCHOR = Treatment of Predominantly Classic CHORoidal Neovascularization in AMD; CATT = Comparison of Age-related macular degeneration Treatment Trials; DENALI = Verteporfin plus ranibizumab for choroidal neovascularization in age-related macular degeneration; EXCITE = Efficacy and Safety of Ranibizumab in Patients With Subfoveal Choroidal Neovascularization (CNV) Secondary to Age-related Macular Degeneration; EVEREST = Visual Outcome in Patients With Symptomatic Macular PCV Treated With Either Ranibizumab as Monotherapy or Combined With Verteporfin Photodynamic Therapy; FOCUS = Ranibizumab combined with verteporfin photodynamic therapy in neovascular age-related macular degeneration; GEFAL = French Evaluation Group Avastin Versus Lucentis; HORIZON = Open-Label Extension Trial of Ranibizumab for Choroidal Neovascularization Secondary to Age-Related Macular Degeneration; IVAN = Inhibition of VEGF in Age-related choroidal Neovascularisation; MARINA = Minimally classic/occult trial of anti-VEGF antibody ranibizumab in the treatment of neovascular age-related macular degeneration; MONET = Phase II Open Label Multicenter Study For Age Related Macular Degeneration Comparing PF-04523655 Versus Lucentis In The Treatment Of Subjects With CNV; MONT BLANC = Verteporfin plus ranibizumab for choroidal neovascularization in age-related macular degeneration; PIER = Ranibizumab in subjects with subfoveal CNV with or without classic CNV secondary to AMD; SAILOR = Safety Assessment of Intravitreal Lucentis fOR AMD; SECURE = phase IV open-label extension of the EXCITE and SUSTAIN studies; SEVEN-UP = Seven Year Update of Macular Degeneration Patients; SUMMIT = Clinical trial programme comprising EVEREST, MONT BLANC and DENALI; SUSTAIN = Study of ranibizumab in patients with subfoveal CNV secondary to AMD; VIEW = VEGF trap-eye: Investigation of Efficacy and Safety in Wet AMD.