REVIEW

Long-term effectiveness of ranibizumab for age-related macular degeneration and diabetic macular edema

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Abstract: Neovascular age-related macular degeneration (AMD) and diabetic macular edema (DME) are major causes of visual impairment in the elderly population worldwide. With the aging population, the prevalence of neovascular AMD and DME has increased substantially over the recent years. Vascular endothelial growth factor (VEGF) has been implicated as playing an important role in the pathogenesis of both neovascular AMD and DME. Since its introduction in 2006, ranibizumab, a recombinant, humanized, monoclonal antibody fragment against all isoforms of VEGF-A, has revolutionized the treatment of neovascular AMD and DME. The efficacy and safety of ranibizumab in neovascular AMD has been demonstrated in the ANCHOR and MARINA trials. Further studies including the PIER, PrONTO, and SUSTAIN trials have also evaluated the optimal dosing regimen of ranibizumab in neovascular AMD. The CATT and IVAN trials compared the safety and efficacy of ranibizumab with off-label use of bevacizumab. Studies such as SUSTAIN and HORIZON have shown that ranibizumab has a good safety profile and is well tolerated for over 4 years with very few serious ocular and systemic adverse events. For DME, Phase II RESOLVE study and Phase III RISE and RIDE studies have demonstrated superiority of ranibizumab treatment in improving vision over placebo controls. Phase II READ and Phase III RESOLVE and REVEAL studies have shown that ranibizumab is more effective both as monotherapy and in combination with laser compared with laser monotherapy. The 3-year results from the DRCRnet protocol I study found that ranibizumab with deferred laser resulted in better long-term visual outcome compared with ranibizumab with prompt laser. This review summarizes various important clinical trials on the long-term efficacy and safety of ranibizumab in the treatment of neovascular AMD and DME. The pharmacological properties of ranibizumab, its cost effectiveness, and impact on quality of life will also be discussed.

Keywords: ranibizumab, anti-VEGF therapy, age-related macular degeneration, diabetic macular edema, safety, diabetic retinopathy, cost-effectiveness

Introduction
Neovascular age-related macular degeneration

Age-related macular degeneration (AMD) is a major cause of blindness in the elderly population. Epidemiological studies from pooled data have estimated the prevalence of early AMD and late AMD were 6.8% and 1.5% in whites aged 40 years or older, respectively.[1] Similar prevalence figures have been found in Asian populations.[2] AMD can be classified into nonexudative (dry) or neovascular (wet) forms. The former is characterized by abnormal deposits known as drusen at the macula and progressive atrophy of photoreceptors and retinal pigment epithelial cells in the macula, whereas the latter is characterized by the formation of abnormal blood vessels known as

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choroidal neovascularization (CNV). If left untreated, the visual prognosis for eyes with neovascular AMD is poor. Nearly 15% of early AMD will progress to late AMD in 15 years.[3] For neovascular AMD, the visual loss is progressive with approximately one line of vision lost at 3 months, three lines at 1 year, and four lines at 2 years.[4]

Vascular endothelial growth factor (VEGF)-A has been implicated as a major factor in the angiogenesis and progression of neovascular AMD. VEGF-A promotes the growth of vascular endothelial cells and increases vascular permeability. It plays a key role in embryonic vasculogenesis including the development of choroidal vasculature, and is an important mediator in tumor angiogenesis.[5] Previous immunohistological studies have localized VEGF in surgically resected CNV, implying VEGF plays an important role in CNV development.[6] Complement activation and inflammation, with subsequent vascular damage, is thought to play a role in the upregulation of VEGF-A in neovascular AMD.[7]

Until the advent of antivascular endothelial growth factor (anti-VEGF) therapy, treatment of neovascular AMD has been far from optimal. Photodynamic therapy (PDT) with verteporfin was first introduced for treating neovascular AMD in 2000 and treatment aimed to stabilize vision rather than improve vision.[8] It involves a two-stage process where the photosensitizing agent verteporfin is activated by an infrared laser, which then releases free oxygen radicals to damage the vascular endothelium, resulting in vascular occlusion of the CNV. Two large randomized control trials (TAP and VIP studies),[9,10] demonstrated the usefulness of PDT in preventing moderate visual loss of 3 or more lines in patients with subfoveal CNV due to AMD. However, there was still a mean decline in visual acuity (VA) of 9.8 letters over 2 years.[10]

In 2006, the efficacy of intravitreal ranibizumab injections (Lucentis; Genentech, South San Francisco, CA, USA and Novartis, Basel, Switzerland) in the treatment of predominately classic, minimally classic and occult subfoveal choroidal CNV in neovascular AMD were demonstrated by the ANCHOR and MARINA trials.[11,12] For the first time, patients can expect improvement in vision rather than maintenance of vision. Safety profile and optimal dosing schedule to reduce the frequency of injections while maintaining visual gain have been investigated in various subsequent studies including PIER, PrONTO, SUSTAIN, HORIZON, CATT, and IVAN.[13–18] Long-term studies have shown that ranibizumab is well tolerated for over 4 years and has been shown to have very few serious ocular and systemic side effects.[16]

Diabetic macula edema

Diabetic macular edema (DME) is a major complication of diabetic retinopathy (DR) and is the most frequent cause for preventable blindness in working adults in many countries.[19] A large meta-analysis has estimated the overall prevalence of any DR to be 34.6%, and the prevalence of DME was 6.8%.[20] DME is caused by leakage from the abnormal retinal capillaries leading to macular thickening and edema. If left untreated, a considerable proportion of patients with DME will suffer from visual loss. The Early Treatment for Diabetic Retinopathy Study group (ETDRS) found that without treatment, over 30% of eyes with DME developed visual loss of three lines or more at 3 years.[21] Until recently, macular laser photocoagulation had been the standard of treatment for DME. Although grid laser photocoagulation can result in a 50% risk reduction of moderate visual loss, the treatment is limited to vision stabilization or minimal mean improvement in vision.[21] Intravitreal steroids such as triamcinolone acetonide, fluocinolone, and dexamethasone has also been used in the treatment of DME, but they are associated with side effects such as cataract formation and increased intraocular pressure.[22]

VEGF has been found to play an important role in the development of DME. The hypoxic retina triggers the production of VEGF from retinal pigment epithelial cells, pericytes, and endothelial cells, which in turn causes breakdown of the blood-retinal barrier, leading to DME. Anti-VEGF therapy with ranibizumab for the treatment of DME has been established in multiple Phase II and III studies.[23–29] Based on these findings, ranibizumab has also been approved by various regulatory authorities for the treatment of DME.

In this article, we aim to review the major clinical trials regarding the long-term efficacy and safety of ranibizumab in the treatment of AMD (Table 1) and DME (Table 2). The pharmacological properties of ranibizumab, cost-effectiveness, impact on the quality of life, as well as future directions will also be discussed.

Overview of pharmacology of ranibizumab
Ranibizumab molecule

Ranibizumab is a recombinant, humanized monoclonal antibody antigen-binding fragment (Fab) directed against VEGF-A. VEGF-A belongs to a family of mitogenic glycoproteins that promote angiogenesis by the activation of cell surface VEGF receptors present in endothelial and mural cells via a tyrosine kinase (TK) signaling pathway. Besides VEGF-A, other factors in the gene family includes placental

growth factor (PlGF), VEGF-B, VEGF-C, VEGF-D, and the orf virus-encoded VEGF-E.[30] Six major isoforms of VEGF-A have been identified by alternative splicing: VEGF-121, VEGF-145, VEGF-165, VEGF-183, VEGF-189, and VEGF-206, where VEGF-165 is the predominant isoform.[31] Ranibizumab acts against all VEGF isoforms of VEGF-A and was found to be more effective in treating neovascular AMD than another anti-angiogenesis agent, pegaptanib sodium (Macugen, Pfizer/OSI Eyetech, New York, NY, USA), which is a pegylated ribonucleic acid aptamer that acts against only the VEGF-165 isoform.[32]

Ranibizumab is produced in an *Escherichia coli* expression system and has a molecular weight of around 48 kD.[33] The molecule consists of a light and heavy chain with one antibody-binding site. On a molar basis, ranibizumab is found to be 5 to 20 times more potent than the full-length antibody bevacizumab in vitro.[5] Due to the small molecular size of ranibizumab as an antibody fragment, the molecule can penetrate all layers of the retina more readily than the bevacizumab antibody (molecular weight of 148 kD).[5] The absence of the F_c portion of the antibody in ranibizumab also eliminates the possibility of complement-mediated or cell-dependent cytotoxicity triggered by interaction of the F_c receptors with inflammatory cells.[5]

Development of ranibizumab

In 1993, a murine monoclonal antibody (Mab) targeting human VEGF-A was developed and it has been shown to be able to inhibit tumor growth in vivo.[34] The humanized form of the murine Mab, which was a full-length immunoglobulin G (IgG) was later named bevacizumab.[35] Bevacizumab was approved by the US Food and Drug Administration for treatment of metastatic colorectal cancer as an adjuvant chemotherapy. However, systemic administration of bevacizumab for neovascular AMD has raised safety concerns due to the potential increased incidence of arterial thromboembolic events.[36] Therefore, an intravitreal anti-VEGF agent was developed to provide local therapy for neovascular AMD. The Fab portion of bevacizumab (Fab-12) was found to be more diffusible and demonstrated increased penetration through the retina into the choroid and was therefore used instead of the full-length antibody.[5] To increase potency and binding affinity of Fab-12 to VEGF-A molecules, five variable domain substitutions and one constant domain substitution of Fab-12 was engineered through a series of recombinant DNA and phage-display selection steps, resulting in Fab rhuFabV2 or ranibizumab which is around 100 times more potent than Fab-12.[5]

Pharmacodynamics and pharmacokinetics of ranibizumab

Ranibizumab is delivered by direct intravitreal injection into the eye through the pars plana. The drug penetrates all layers of the retina to reach the choriocapillaris, where the CNV in AMD originate. It binds to the receptor-binding site of active forms of VEGF-A and prevents VEGF-A from binding to its receptors (VEGFr-1 and VEGFr-2) on the endothelial cell surface, thus reducing vascular permeability and formation of new vessels.[37] In animal studies, it was found that ranibizumab inhibited the vascular permeability-enhancing activity of VEGF-110, VEGF-121, and VEGF-165 in human umbilical vein endothelial cell proliferation in a dose-dependent fashion.[38]

Preclinical pharmacokinetic studies performed in monkeys have demonstrated that a single injection of 0.5 mg ranibizumab reaches a peak vitreous concentration after 6 hours.[39,40] There is rapid distribution of the drug from the vitreous into either the retina or the aqueous chamber, where the concentration in the retina is around one-third of that in the vitreous. The drug is then cleared in parallel from all ocular compartments. The estimated vitreous elimination half-life of ranibizumab in humans is around 7 days,[41] and the elimination half-life from the systemic circulation is around 2 hours.[42] Following a single intravitreal injection of 0.5 mg ranibizumab in AMD patients, the maximal serum concentration was found at 1 day at a level 90,000 times less than the intravitreal ranibizumab exposure and is well below the concentration necessary to inhibit the biological activity of VEGF by 50%.[42]

Efficacy, safety, and tolerability of ranibizumab in neovascular AMD in major clinical trials
ANCHOR and MARINA

The efficacy and safety of ranibizumab in the treatment of neovascular AMD has been established in two Phase III prospective, randomized, double-blind, international multicenter clinical trials: the ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic CHORoidal Neovascularization in AMD) and MARINA (Minimally classic/occult trial of the Anti-VEGF antibody ranibizumab In the treatment of Neovascular AMD) trials.[11,12] In the ANCHOR trial, 423 patients with predominantly classic CNV due to neovascular AMD were randomized to PDT every 3 months as needed, or monthly intravitreal injection of either 0.3 mg or 0.5 mg ranibizumab.[11] Results at the end of 2 years showed

Table I Summary of clinical trials of ranibizumab in the treatment of neovascular age-related macular degeneration

Study (duration)	Patients	Study arms	Results				Average no of injections over 12 months	Safety
			VA stabilization (% < 15 letter loss)	% ≥ 15 letter gain	Mean VA change (letters)			
ANCHOR (2 years)	N = 423 Age >50 years Predominantly classic CNV	Gp 1: PDT Gp 2: 0.3 mg RNB Gp 3: 0.5 mg RNB	65.7% 90.0% 89.9%	6.3% 34.3% 41%	−9.8 +8.1 +10.7		9.6 10.8 10.7	**Ocular SAE** (endophthalmitis, severe ocular inflammation, retinal tear and detachment, vitreous hemorrhage, lens damage) Gp 1: 7.7%, Gp 2: 7.3%, Gp 3: 9.3% *Endophthalmitis* Gp 1: 0%, Gp 2: 0%, Gp 3: 2.1% **Systemic SAE** ATE Gp 1: 2.8%, Gp 2: 2.9%, Gp 3: 3.6% *Vascular deaths (APTC criteria)* Gp 1: 2.1%, Gp 2: 1.5%, Gp 3: 1.4%
MARINA (2 years)	N = 716 Age >50 years Minimally classic or occult	Gp 1: Sham Gp 2: 0.3 mg RNB monthly Gp 3: 0.5 mg RNB monthly	62.2% 92% 90.0%	3.8% 26.1% 33.3%	−14.9 +5.4 +6.6		N/A	**Ocular SAE** (endophthalmitis, severe ocular inflammation, retinal tear and detachment, vitreous hemorrhage, lens damage) Gp 1: 1.2%, Gp 2: 3.7%, Gp 3: 5.1% *Endophthalmitis* Gp 1: 0%, Gp 2: 0.8%, Gp 3: 1.3% **Systemic SAE** ATE Gp 1: 2.5%, Gp 2: 3.8%, Gp 3: 3.8% *Vascular deaths (APTC criteria)* Gp 1: 1.7%, Gp 2: 1.3%, Gp 3: 1.3%
PIER (2 years)	N = 184 Age >50 years All subfoveal CNV of all subtypes	Gp 1: Sham Gp 2: 0.3 mg RNB quarterly Gp 3: 0.5 mg RNB quarterly*	41.3% 78.3% 82%	4.8% 15% 8.2%	−21.8 −2.2 −2.3		6	**Ocular SAE** (retinal hemorrhage, macular edema) Gp 1: 3.2%, Gp 2: 3.4%, Gp 3: 0% *Endophthalmitis:* 0% **Systemic SAE** APTC ATE Gp 1: 1.6%, Gp 2: 1.7%, Gp 3: 0%
PrONTO (2 years)	N = 40 Age >50 years Subfoveal CNV CRT ≥ 300 μm BCVA 20/40-20/400	Open label, uncontrolled study. 3 monthly 0.5 mg RNB followed by injection according to criteria†	95%	35%	+11.1		5.6	No ocular or systemic adverse events reported

Study	Characteristics	Design/treatment					Adverse events
SUSTAIN (1 year)	N=531 Age >50 years; Active subfoveal AMD CNV; CNV ≥50% total lesion area; Total lesion size <12DA; VA ETDRS 73-24 (Snellen 20/40–20/320)	Open label, uncontrolled study. 3 monthly 0.5 mg RNB followed by injection according to criteria[††]	92.5%	+3.6	19.3%	5.3	**Ocular adverse events: 48.5%** SAE (retinal hemorrhage, cataract, RPE tear, decreased VA, vitreous hemorrhage): 1.2% **Systemic adverse events** ATE: 3.7% Death: 1.5%
SAILOR (1 year)	N=4300 Age >50 years Subfoveal AMD CNV	Gp1: 0.3 mg RNB Gp 2: 0.5 mg RNB At different dosing schedule[€€]	N/A	+0.5 (+1.7)[€] +2.3 (+2.3)[€]	14.6% (15.8%)[€] 19.3% (16.5%)[€]	4.9 (3.6)[€€]	**Key ocular SAE: <1%** Endophthalmitis: 0.1%–0.4% Uveitis: 0%–0.2% Retinal tear: 0.1% Retinal hemorrhage: 0.3%–0.9% RPED: 0.1%–0.2% VH: 0.1%–0.3% Cataract: 0.1% **Systemic SAE** APTC ATEs: 2.8% HT: 0.1% Nonocular hemorrhage: 0.6%–1.5% Vascular death: 0.9% *Risk of stroke* *0.5 mg RNB 1.2%* *0.3 mg RNB 0.7% (P=0.21)*
CATT (2 years)	N=1107 Treatment naïve; VA 20/25-20/320; subfoveal AMD CNV	Gp 1: RNB monthly Gp 2: BVC monthly Gp 3: RNB prn Gp 4: BVC prn Gp 5: RNB switched Gp 6: BVC switched[§]	93.3% 84.5% 92.8% 88.4% 90.8% 87.6%	+8.8 +7.8 +6.7 +5.0 −1.8 −3.6	32.8% 31.8% 30.7% 28.3% 4.6%** 1.7%**	11.2 11.7 6.3 3.5 5.0 5.8	**Ocular SAE** *Endophthalmitis* RNB: 0.7%, BVC: 1.2% (P=0.38) *Pseudoendophthalmitis* RNB: 0.2%, BVC: 0.2% **Systemic SAE** RNB: 31.7%, BVC 39.9% (P=0.004) *ATE* RNB: 4.7%, BVC: 5.0% (P=0.62) *Death (all cause)* RNB: 5.3, BVC: 6.1% (P=0.89)
HORIZON (4 years)	N=600 Extension study of patients from MARINA, ANCHOR, FOCUS trials	0.5 mg RNB monthly at investigator's discretion Gp 1: RNB initial Gp 2/Gp3: RNB cross over or RNB naïve groups	96.9% (80.4%)[a] 94.3% (53.4%)[a]	−7 (+2.0)[a] −2.2 (−11.8)[a]	3.1% (22.7%)[a] 5.7% (6.9%)[a]	4.2 (4.9)[aa] 3.7 (3.7)[aa]	**Ocular SAE:** Gp 1: 8%, Gp 2: 4.2% *Endophthalmitis:* Gp 1: 0.2%, Gp 2: 0% *Intraocular inflammation:* Gp 1: 0.2%, Gp 2: 0% *VH: 0.3%–0.5%* *IOP >30 mmHg:* Gp 1: 9.2%, Gp 2: 6.6% *Glaucoma:* Gp 1: 3.2, Gp 2: 4.2% *Cataract:* Gp 1: 12.5%, Gp 2: 12.1%, Gp 3: 6.3% **Systemic SAE:** Gp 1: 31.7%, Gp 2: 27.9%, Gp 3: 28.6%

(Continued)

Table I (*Continued*)

Study (duration)	Patients	Study arms	Results				Safety
			VA stabilization (% < 15 letter loss)	% ≥ 15 letter gain	Mean VA change (letters)	Average no of injections over 12 months	*Vascular deaths* Gp 1: 1.8%, Gp 2: 3.7%, Gp 3: 0% *HT* Gp 1: 11%, Gp 2: 11.1%, Gp 3: 12.7% *Nonocular hemorrhage* Gp 1: 6.3%, Gp 2: 6.3%, Gp 3: 3.2% *APTC defined ATE* Gp 1: 5.3%, Gp 2: 3.2% (*P* = 0.76)

Notes: *Initially after 1 year sham patients can cross over to receive 0.5 mg RNB monthly, subsequently all patients roll-overed to receive 0.5 RNB monthly in year 2; [†](1) VA loss of at least 5 letters with evidence of fluid on OCT; (2) increase in CRT of at least 100 μm; (3) new macular hemorrhage; (4) new area of classic CNV; or (5) persistent fluid 1 month after previous injection; [††](1) more than 5 letter loss in VA from the last visit, or (2) 100 μm increase in CRT from the lowest measurement during the first 3 months; [€]results for RNB naïve patients. Results for previously treated subjects in parenthesis; [€€]results of Cohort 1. Results of Cohort 2 in parenthesis. Cohort 1 subjects were retreated on the basis of optical coherence tomography (OCT) or VA criteria. Cohort 2 subjects received an initial RNB dose and were retreated at physician discretion; [**]compared with year 1; [§]in year 2 patients in the monthly groups were further re-randomized into monthly or prn groups giving rise to 6 treatment groups; [a]compared with month 24 results, ie, HORIZON baseline. Results compared with initial study baseline in parenthesis; [aa]mean number of injections from month 24–60 for patients who maintained VA (lost ≤ 5 letters). The mean number of injections of those who lost > 5 letters are in parenthesis.

Abbreviations: RNB, Ranibizumab; BVC, bevacizumab; PDT, photodynamic therapy; SAE, serious adverse events; ATE, arterial thromboembolic; APTC, Antiplatelet Trialists' Collaboration; DA, disc area; RPE, retinal pigment epithelium; RPED, retinal pigment epithelial detachment; VH, vitreous hemorrhage; HT, hypertension; VA, visual acuity; IOP, intraocular pressure; CNV, choroidal neovascularization; CRT, central retinal thickness; Gp, group; AMD, age-related macular degeneration; ETDRS, early treatment for diabetic retinopathy study group.

that 89.9% of the 0.3 mg and 0.5 mg ranibizumab groups lost fewer than 15 letters of VA compared with 65.7% of the PDT-treated group. In addition, 41% of the 0.5-mg-treated group and 34% of the 0.3-mg-treated group gained at least 15 letters of vision, compared with only 6.3% in the PDT-treated group. The mean VA improved by +8.1 and +10.7 letters in the 0.3 mg and 0.5 mg ranibizumab groups, respectively, while there was a 9.8-letter drop in vision in the PDT-treated group.[11]

While the ANCHOR trial assessed the efficacy of ranibizumab in predominately classic CNV, the MARINA trial assessed the efficacy and safety of ranibizumab in minimally classic or occult CNV.[12] Seven hundred sixteen patients were randomized to either monthly placebo injections, 0.3 mg or 0.5 mg ranibizumab injections over a period of 2 years. Results showed that 90% of the 0.5 mg ranibizumab-treated eyes avoided visual loss of ≥3 lines of vision, compared to 62.2% in the placebo injection group. In terms of visual gain, significantly higher proportion of patients gained ≥3 lines compared with controls, with 25% and 33.8% in the 0.3 mg and 0.5 mg ranibizumab groups, respectively. There was a mean visual gain of 6.6 letters at 2 years for the 0.5 mg ranibizumab group, compared with a mean loss of 14.9 letters in the control group ($P < 0.001$).[12]

Both the ANCHOR and MARINA trials showed that ranibizumab is generally safe and well tolerated. No significant difference in ocular and nonocular adverse events was found in the ranibizumab groups compared with PDT or placebo controls.[11,12] Serious ocular adverse events included endophthalmitis, uveitis, vitreous hemorrhage, rhegmatogenous retinal detachment, retinal tear, or lens damage. In the 2-year ANCHOR study, the cumulative incidence of endophthalmitis was 2.1%[11] and the endophthalmitis rate in the 1-year MARINA trial was 1.3%[12] In the MARINA trial, there was a small difference in arterial thromboembolic events (ATE) between the placebo and ranibizumab groups (2.5% versus 3.8%), but the difference was not statistically significant.

PIER

Although ranibizumab was found to be effective in the treatment of AMD, with monthly dosing, cost quickly became an issue of concern. If given monthly at the recommended dosage of 0.5 mg for neovascular AMD, the ranibizumab drug cost alone can accumulate to US$24,000 per year. In order to address this issue, the PIER study was performed to evaluate the efficacy and safety of a 3-monthly dosing regimen of ranibizumab for the treatment of neovascular AMD.[13]

One hundred eighty-four patients were randomized into placebo injection, 0.3 mg or 0.5 mg ranibizumab on a monthly or 3-monthly basis. During the second year, eligible placebo group patients could crossover to the 0.5 mg ranibizumab quarterly and later all eligible patients were switched to 0.5 mg ranibizumab monthly. At the end of 2 years, 78.3% and 82% of the 0.3 mg and 0.5 mg ranibizumab groups, respectively, lost less than three lines of vision, compared with 41.3% of the placebo injection group ($P < 0.0001$). There was a mean decrease in VA of 2.2 and 2.3 letters in the 0.3 and 0.5 mg ranibizumab groups, respectively, compared with a 21.8-letter loss in the placebo-treated group ($P < 0.0001$). Quarterly dosing of ranibizumab resulted in a slight visual decline and patients who were switched to monthly ranibizumab injections after 1 year did not benefit in terms of VA. In terms of safety, there was no endophthalmitis, severe uveitis, or lens damage during the 2-year study period. The rate of ATE was 1.6% in the placebo group and 0% in the ranibizumab group in the first year. In the second year, for the postcrossover ranibizumab treatment groups, the rate of ATE was 1.7% for the 0.3 mg group and 0% for the 0.5 mg group.

PrONTO

As the 3-monthly dosing of ranibizumab was found to be inadequate in the treatment of AMD, a variable dosing regimen was evaluated in the PrONTO (Prospective Optical Coherence Tomography Imaging of Patients with Neovascular AMD treated with intra-Ocular Ranibizumab) study.[14] It was a 2-year open-label single-center uncontrolled study in which the dosing regimen of ranibizumab was guided by optical coherence tomography (OCT) findings. Forty patients with subfoveal CNV and central retinal thickness (CRT) of at least 300 μm were treated with three consecutive loading doses of 0.5 mg ranibizumab at monthly intervals. Patients were given retreatment if any of the five criteria were met: (1) VA loss of at least 5 letters with evidence of fluid on OCT; (2) increase in CRT of at least 100 μm; (3) new macular hemorrhage; (4) new area of classic CNV; or (5) persistent fluid 1 month after previous injection. The second retreatment criterion was later amended to any qualitative increase in fluid detected on OCT. At 24 months, the mean VA improved by 11.1 letters and OCT CRT decreased by 212 μm. The mean number of injections decreased to 5.6 over 1 year and 9.9 over 2 years, compared with 24 injections as used in the ANCHOR and MARINA trials. Although the visual outcomes were better than that in the PIER trial, there was no control group in this study and it is unknown whether patients would have more visual gain with a monthly dosing regimen.

SUSTAIN

The Study of Ranibizumab in Patients with Subfoveal CNV Secondary to AMD (SUSTAIN) evaluated the safety and efficacy of 0.3 mg (which was later switched to 0.5 mg) ranibizumab of pro re nata (prn) regimen in the treatment of AMD.[15] It was a single-arm open-labeled study, with 531 patients given three initial loading injections and retreated on a monthly basis if there was: (1) more than 5 letter VA loss from the last visit, or (2) 100 μm increase in CRT from the lowest OCT measurement during the first 3 months. At the end of 12 months, the mean number of injections given was 5.3. Patients had a mean gain of 5.8 letters at 3 months, which declined to 3.6 letters in the subsequent 9 months with prn dosing. There was a mean CRT decline of 91.5 μm from baseline at month 12. The overall safety profile was satisfactory, with 1.2% of patients developing ocular adverse events including retinal hemorrhage, cataract, and retinal pigment epithelial tear. Vitreous hemorrhage and ATE were observed in 3.7% of the patients.

SAILOR

The SAILOR study (The Safety Assessment of Intravitreal Lucentis fOR AMD) was a 12-month multicenter Phase IIIb study to evaluate the safety of ranibizumab in the treatment of neovascular AMD.[43] Over 4,000 patients aged 50 years or older were divided into two treatment cohorts and received 0.3 mg or 0.5 mg ranibizumab at different dosing schedules. Results showed that ranibizumab is well tolerated with key ocular adverse events including endophthalmitis and pseudoendophthalmitis of less than 1%.[43] For systemic safety, the results showed a slightly higher trend risk of stroke in the 0.5 mg versus 0.3 mg group (1.2% versus 0.6%), but the difference was not statistically significant. Previous history of stroke, arrhythmia, and congestive heart failure were found to be risk factors for stroke in the study. However, since the study did not have a control arm, the increased stroke risk might be due to inherent risk factors for subsequent stroke rather than drug effect.

CATT and IVAN

Bevacizumab is widely used as an off-label anti-VEGF agent in the treatment of AMD due to its cheaper cost. The efficacy and safety of ranibizumab was compared with bevacizumab in the Ranibizumab and Bevacizumab for Treatment of Neovascular Age-related Macular Degeneration (CATT) study.[17,44] It was the largest head-to-head trial comparing the two anti-VEGF drugs. Treatment-naïve patients with active subfoveal CNV secondary to AMD were randomized in a

1:1:1:1 ratio into either 0.5 mg ranibizumab monthly for 1 year, 1.25 mg bevacizumab monthly for 1 year, 0.5 mg ranibizumab prn, or 1.25 mg bevacizumab prn. Patients who had prn treatment were given a single initial injection followed by prn injection every month depending on disease activity. At the end of 1 year, there was a mean gain of 8.5 and 8.0 letters for the monthly ranibizumab and bevacizumab groups, respectively, while there was a mean gain of 6.8 and 5.9 letters for the ranibizumab and bevacizumab prn groups, respectively. Bevacizumab was found to be noninferior to ranibizumab in terms of efficacy.

At the start of the second year, patients who were in the ranibizumab or bevacizumab monthly groups were rerandomized into ranibizumab or bevacizumab monthly, or switched to ranibizumab or bevacizumab prn groups, resulting in six different treatment arms.[44] At the end of the second year, there was a mean visual gain of 8.8 letters and 7.8 letters for the ranibizumab and bevacizumab monthly group, respectively, with most gain in vision occurring during the first year. There was a mean gain of 6.7 and 5.0 letters for ranibizumab and bevacizumab prn group, respectively. For patients who switched to prn dosing from monthly dosing at the first year, there was a mean decline of 2.2 letters at the second year. The CRT on OCT also increased by 31 μm in the switched ranibizumab group and 19 μm in the switched bevacizumab group ($P = 0.0004$). Overall, no significant difference in VA was seen between bevacizumab and ranibizumab groups (mean change of 1.4 letters in favor of ranibizumab). However, a small but statistically significant difference of 2.4 letters was found in favor of monthly dosing compared with prn treatment. For secondary outcomes, it was found that more patients treated with ranibizumab monthly had no subretinal fluid on OCT compared with bevacizumab prn group (46% versus 14%; $P < 0.05$), and CRT was lower in the monthly than prn groups ($P = 0.005$). In terms of safety, there were statistically significantly more systemic serious adverse events with bevacizumab compared with ranibizumab. In particular, there was a higher rate of serious adverse events for bevacizumab from the first year, which persisted into the second year, with the greatest imbalance in gastrointestinal disorders.[44] Nonetheless, the rates of death, stroke, and heart attack that might be associated with anti-VEGF agents were similar between the two drugs.

The IVAN study is a head-to-head trial similar to the CATT study performed in the UK to compare the efficacy and safety of bevacizumab and ranibizumab.[18] In this study, 610 patients were randomized into continuous or noncontinuous dosing of ranibizumab or bevacizumab after three initial loading doses. The primary outcome of the CATT study was replicated in the IVAN study, as there was a noninferiority comparison between bevacizumab and ranibizumab in terms of visual change. In terms of treatment regimen, both continuous and discontinuous treatment was found to be equivalent in terms of visual change. However, CRT on OCT was found to be lower with continuous treatment.

In terms of safety, the IVAN study found that fewer patients in the bevacizumab group had ATE or heart failure and there was no significant difference in patients experiencing serious adverse events between the two drugs.[18] However, a meta-analysis of 1-year data of three direct comparison trials showed a significantly higher rate of ocular adverse effects with bevacizumab (relative risk [RR] = 2.8; 95% confidence interval [CI]: 1.2–6.5) and the proportion of patients with serious infectious and gastrointestinal disorders were also higher with bevacizumab than ranibizumab (RR = 1.3; 95% CI: 1.0–1.7).[45] Therefore based on these findings, ranibizumab might provide some safety advantages compared with bevacizumab.

HORIZON

The long-term safety of ranibizumab in the treatment of AMD was assessed in HORIZON, which is an open-labeled extension of patients who have completed the MARINA, ANCHOR, and FOCUS trials.[16] Eligible patients received 0.5 mg ranibizumab at monthly intervals at the investigator's discretion for 2 years. Patients were analyzed based on three groups: patients who were randomized to the ranibizumab group in the MARINA, ANCHOR, and FOCUS trials (n = 600); patients who were in the control groups and later switched to receiving ranibizumab (n = 190); and ranibizumab-naïve group (n = 63). The main outcome measures of the study were incidence and severity of adverse events. Of the 3,552 injections in the study, there was only one case of mild endophthalmitis. There were no serious ocular adverse events such as lens damage, retinal tears, or rhegmatogenous retinal detachments. The incidence of high intraocular pressure over 30 mmHg was low and was observed in 9.2% and 6.6% of the ranibizumab-treated group and the crossover group, respectively. Cataract progression was found to be more common in the ranibizumab-treated (12.5%) and crossover (12.1%) groups than the treatment-naïve (6.3%) group, but the differences were not statistically significant ($P = 0.2$). Systemically, the difference in incidence of ATE between the ranibizumab and control groups was not statistically significant (5.3% versus 3.2%; $P = 0.76$). Therefore, the long-term use of repeated injections of ranibizumab was found to be safe in the study.

In terms of visual outcome, there was a slight mean decline in the VA gain observed with the initial studies. With less frequent follow-up (mean duration of 2 months) and less rigorous injection schedule (mean of four injections over 2 years), there was a mean gain of 2.0 letters in the ranibizumab-treated groups, and a mean loss of 11.8 letters in the pooled ranibizumab crossover group and untreated group at 48 months. Therefore, the VA for the ranibizumab treated group remained stable over 4 years, while the control groups lost vision due to delayed initial treatment. The study concluded that ranibizumab is safe in the long term, but that there is an incremental decline VA gain with longer follow-up duration and less frequent dosing schedules.

Efficacy, safety, and tolerability of ranibizumab in diabetic macula edema

Several key studies have been published on the long-term efficacy and safety of ranibizumab in the treatment of DME, including Phase II RESOLVE and READ-2 studies[23,25–27] and Phase II RISE and RIDE studies,[24] RESTORE,[28,46] REVEAL,[47] and DRCRnet protocol I.[29]

RESOLVE

In the RESOLVE study, 102 patients with DME due to type 1 or 2 diabetes were randomized to either 0.3 mg ranibizumab, 0.5 mg ranibizumab, or placebo treatment.[27] The ranibizumab-treated groups received three monthly loading doses followed by prn injection based on treatment success, disease activity, or safety criteria. After 1 month, the dose could be doubled to 0.6 mg or 1.0 mg if the CRT remained at $>300\,\mu m$ or if there was $<50\,\mu m$ reduction from the previous assessment. Results showed that at 1 year, the mean numbers of injections were 10.2 for the ranibizumab group and 8.9 for the placebo group. The primary outcome of the study was the mean average VA change from baseline (arithmetic mean of change in letter scores from month 1 through month 12) and was +7.8 letters for the pooled ranibizumab group, versus −0.1 letter in the placebo group. Secondary outcomes included the mean change in best-corrected VA at month 12, which was +10.3 letters for the ranibizumab group and −1.4 letters for the placebo group. More than 60% of the patients in the ranibizumab group gained two lines of vision versus only 9% in the placebo group. Ranibizumab was found to be safe with ocular serious adverse events being comparable between the treatment and placebo groups. Systemically, the incidence of ATEs, hypertension, and nonocular hemorrhage were also found to be comparable between the ranibizumab and placebo arms.

READ-2

In the READ-2 study,[25] ranibizumab was compared with laser or combination treatment. One hundred twenty-six patients with DME were randomized to either ranibizumab every 2 months, focal/grid laser every 3 months, or combined ranibizumab and focal/grid laser at baseline and at month 3 for the first 6 months. After 6 months, patients can crossover to ranibizumab group if the retreatment criteria were met. At 6 months, the mean change in vision was +7.2, −0.4, and +3.8 letters for the ranibizumab, laser, and combined groups, respectively. For patients who continued the study up to 2 years, most patients received ranibizumab and the mean visual gain at 2 years was 7.7, 5.1, and 6.8 letters for the ranibizumab, laser, and combined groups, respectively, with substantial improvement in the previously laser-treated group. At 3 years, the protocol was amended so that patients were monitored monthly instead of every 2 months and were given ranibizumab injections if central macular thickness (CMT) was found to be $\geq250\,\mu m$.[23] The greatest improvement in vision was seen in the ranibizumab group with more aggressive monitoring and treatment and the final mean VA improvement compared with baseline were 10.3, 1.4, and 8.9 letters for the three groups, respectively. Anatomically, all three groups showed improvement in terms of reduction in macula thickness on OCT. The study demonstrated that ranibizumab to be well tolerated with no retinal toxic effects among DME patients for up to 3 years.[23]

RISE and RIDE

RISE and RIDE studies are two parallel, 24-month, Phase III, double-masked randomized control trials comparing monthly ranibizumab versus placebo controls in the treatment of DME.[24] A total of 377 patients (RISE) and 382 patients (RIDE) were randomized to either 0.3 mg ranibizumab, 0.5 mg ranibizumab, or placebo injection. They were given monthly injections followed by potential rescue laser at 3 months. At 24 months, the placebo group also switched to the 0.5 mg ranibizumab group. The results showed that a significantly greater proportion of ranibizumab-treated patients had ≥15 letters gain in vision compared with placebo group, with 44.8% (RISE) and 33.6% (RIDE) for the 0.3 mg ranibizumab groups, 39.2% (RISE) and 45.7% (RIDE) for 0.5 mg ranibizumab groups, versus 18.1% (RISE) and 12.3% (RIDE) for the placebo groups ($P < 0.0001$). The mean change in vision was +12.5 letters (RISE) and +10.9 (RIDE) for the 0.3 mg ranibizumab groups, +11.9 letters (RISE) and +12 letters (RIDE) for the 0.5 mg ranibizumab groups versus +2.6 letters (RISE) and +2.3 letters (RIDE) in

Table 2 Summary of clinical trials of ranibizumab in the treatment of diabetic macular edema

Study (duration)	Patients	Description	Results				Safety
			VA stabilization (% < 15 letter loss)	% ≥ 15 letter gain	Mean VA change (letters)	Mean no of injections given	
RESOLVE (1 year)	N = 102, Type 1 or 2 DM, age >18 years, CRT >300 μm, BCVA 73-39 letters	Gp 1: 0.3–1.0 mg* RNB monthly, 3 initial dose then prn Gp 2: sham	97.1% 79.6%	32.4% 10.2%	+7.8 −0.1	10.2 8.9	**Ocular adverse events** (vitreous hemorrhage, retinal ischemia, retinal artery occlusion, endophthalmitis) Gp 1: 3.9%, Gp 2: 2.0% *Endophthalmitis:* Gp 1: 2%, Gp 2: 0% **Systemic adverse events** *ATE* Gp 1: 2.9%, Gp 2: 4.1% *Hypertension:* Gp 1: 8.8, Gp 2: 10.2%
READ-2 (2 years)	N = 126, patients with DME, VA 20/40-20/320, CRT ≥ 250 μm	Initial 6 months (FU 2 monthly): Gp 1: 0.5 mg RNB 2 monthly Gp 2: focal/grid laser 3 monthly Gp 3: laser + 0.5 mg RNB (month 0 and 3) Cross over to RNB allowed after 6 months	N/A	2 year 24% 18% 26%	2 year (6 month) +7.7 (+7.24) +5.1 (−0.43) +6.8 (+3.8)	Month 6–24 9.3 5.3	**Ocular adverse events** *Vitreous hemorrhage* Gp 1: 2.3%, Gp 2: 9.5%, Gp 3: 7.1% **Systemic adverse events** 1 CVA death from Gp 3 (6 weeks after RNB, judged to be unrelated)
READ-3 (3 years)	As above, N = 74	Monthly FU instead of bi-monthly, retreatment if CRT ≥ 250 μm Gp 1: 0.5 mg RNB Gp 2: focal/grid laser Gp 3: laser + 0.5 mg RNB	N/A	32% 9% 21%	Compared with VA at 2 year +3.1 −1.6 +2.0	In year 3 2.9 5.4p 2.3p 3.3p	
RISE (2 years)	N = 377, patients with DME, VA 20/40-20/300, CRT ≥ 275 μm	Gp 1: 0.3 mg RNB monthly Gp 2: 0.5 mg RNB monthly Gp 3: sham injection	97.6% 97.6% 89.8%	44.8% 39.2% 18.1%	+12.5 +11.9 +2.6	24	**Ocular adverse events** Gp 1: 3.2%, Gp 2: 5.6%, Gp 3: 7.3% *Endophthalmitis* Gp 1: 0.8%, Gp 2: 0%, Gp 3: 0% **Systemic adverse events** Gp 1: 5.6%, Gp 2: 11.9%, Gp 3: 10.6% *Any APTC cardiovascular event* Gp 1: 2.4%, Gp 2: 8.7%, Gp 3: 4.9%
RIDE (2 years)	N = 382, patients with DME, VA 20/40-20/300, CRT ≥ 275 μm	Gp 1: 0.3 mg RNB monthly Gp 2: 0.5 mg RNB monthly Gp 3: sham injection	98.4% 96.1% 91.5%	33.6% 45.7% 12.3%	+10.9 +12.0 +2.3	24	**Ocular adverse events** Gp 1: 3.2%, Gp 2: 9.7%, Gp 3: 5.5% *Endophthalmitis* Gp 1: 0.8%, Gp 2: 1.6%, Gp 3: 0% **Systemic adverse events** Gp 1: 9.6%, Gp 2: 5.6%, Gp 3: 9.4% *Any APTC cardiovascular event* Gp 1: 8.8%, Gp 2: 5.6%, Gp 4: 5.5%

Study	Population	Group/treatment	%	Change	n	Adverse events
RESTORE (1 year)	N = 345, focal or diffuse DME, VA 20/32–20/160	Gp 1: 0.5 mg RNB†	99.1%	+6.1	7	**Ocular adverse events** Gp 1: 0%, Gp 2: 1.7%, Gp 3: 1.8% (Cataract and maculopathy) No endophthalmitis reported **Systemic adverse events** ATE Gp 1: 5.2%, Gp 2: 0.8%, Gp 3: 0.9% Hypertension Gp 1: 7.8%, Gp 2: 5%, Gp 3: 8.2%
		Gp 2: 0.5 mg RNB + laser‡	96.6%	+5.9		
		Gp 3: laser alone	91.8%	+0.8		
DRCRnet protocol I (1 year)	N = 691, CME involving fovea, VA 20/32–20/320, mean CMT 405 μm	Gp 1: 0.5 mg RNB†† + prompt laser	98%	+9	8	**Ocular adverse events** Endophthalmitis Gp 1: 1%, Gp 2: 1%, Gp 3: 0%, Gp 4: <1% Pseudoendophthalmitis Gp 1: 0%, Gp 2: 0%, Gp 3: 1%, Gp 4: <1% Elevated IOP Gp 1: 6%, Gp 2: 4%, Gp 3: 42%, Gp 4: 8% Ocular vascular event Gp 1: 1%, Gp 2: 1%, Gp 3: 2%, Gp 4: <1% Retinal detachment Gp 1: 0%, Gp 2: 1%, Gp 3: 0%, Gp 4: 0% **Systemic adverse events** Any APTC cardiovascular event Gp 1 + 2: 3%, Gp 3: 3%, Gp 4: 8%
		Gp 2: 0.5 mg RNB†† + deferred laser (6 months)	98%	+9	9	
		Gp 3: 4 mg IVTA + prompt laser	92%	+4	3	
		Gp 4: prompt laser	92%	+3	N/A	
DRCRnet protocol I (2 years)	As above, N = 691	As above€				**Ocular adverse events** Endophthalmitis Gp 1: 0.1%, Gp 2: 0.08%, Gp 3: 0%, Gp 4: 0.6% Pseudoendophthalmitis Gp 1: 0%, Gp 2: 0%, Gp 3: 1%, Gp 4: <1% Ocular vascular event Gp 1: 1%, Gp 2: 1%, Gp 3: 2%, Gp 4: 1% Retinal detachment Gp 1: 0%, Gp 2: 1%, Gp 3: 0%, Gp 4: <1% **Systemic adverse events** Any APTC cardiovascular event Gp 1 + 2: 7%, Gp 3: 8%, Gp 4: 13%
		Gp 1: 0.5 mg RNB†† + prompt laser	96%	+7§	2€€	
		Gp 2: 0.5 mg RNB†† + deferred laser (6 months)	98%	+9§	3€€	
		Gp 3: 4 mg IVTA + prompt laser	87%	+2	1€€	
		Gp 4: prompt laser	90%	+3	N/A	
DRCRN protocol I (3 years)	As above, N = 361	Gp 1: 0.5 mg RNB†† + prompt laser	94%	+7	1 (12)¶	No difference in systemic events between treatments Endophthalmitis: 0.5%–1%
		Gp 2: 0.5 mg RNB†† + deferred laser (6 months)	97%	+10	2 (15)¶	

Notes: *After month 1, the dose could be doubled to 0.1 mL if CRT remained more than 300 μm or there was less than 50 μm reduction from previous assessment; ᴾP < 0.05 between Gp 1 and Gp 2 but not between Gp 1 and Gp 3; †given on a prn basis after 2 mandatory injections; ††four initial dose given, then monthly until success criteria were met (VA 20/20 or CMT < 250); €FU extended to 8 weeks if injection can be deferred for 3 consecutive visits. The FU interval can be extended maximum up to 16 weeks. Those in Gp 3 and 4 can switch to receive RNB in year 2; €€second year only; ‡third year only, median injection over 3 years given in parenthesis; §P < 0.05 compared with Gp 4.

Abbreviations: Gp, Group; CRT, central retinal thickness; BCVA, best corrected visual acuity; RNB, ranibizumab; DME, diabetic macular edema; IVTA, intravitreal triamcinolone acetonide; APTC, Antiplatelet Trialists' Collaboration; ATE, arterial thromboembolic events; VA, visual acuity; IOP, intraocular pressure; CMT, central macular thickness; FU, follow-up; CVA, cerebrovascular accident; N/A, not applicable.

the placebo group. Ranibizumab-treated patients underwent significantly fewer macular laser procedures, with a mean of 0.3–0.8 in the ranibizumab groups compared with 1.6–1.8 for the placebo groups. In addition, ranibizumab-treated groups also had significantly greater reductions in macular edema on OCT. The treatment was found to be safe with low incidence of postinjection endophthalmitis. There was no significant increase in the incidence of deaths, nonfatal myocardial infarction, or cerebrovascular accidents, which were known possible systemic side effects of anti-VEGF therapy. Based on these results, the US Food and Drug Administration approved 0.3 mg ranibizumab for the treatment of DME in August 2012.

RESTORE

The RESTORE study is a 12-month, double-masked, multicentered, laser-controlled Phase III study which evaluated the efficacy and safety of ranibizumab versus laser therapy for DME.[28] A total of 345 patients with DME were randomized to either ranibizumab 0.5 mg, ranibizumab 0.5 mg plus laser, or laser alone. For patients receiving ranibizumab, after two mandatory injections, patients were reinjected on a prn basis according to vision stability and OCT findings. No further injections were given if vision was stable for two consecutive visits or at 20/20. For the laser group, laser therapy was given every 3 months on a prn basis. Results showed that treatment with ranibizumab both as monotherapy or combined treatment were significantly better than laser monotherapy in terms of VA functionally and OCT findings anatomically. At 1 year, the mean average change in VA from baseline was +6.1, +5.9, and +0.8 for the ranibizumab monotherapy, ranibizumab plus laser, and laser groups, respectively. Anatomically, the mean CRT decreased by 118.7 µm, 128.3 µm, and 61.3 µm for the ranibizumab, combined, and laser groups, respectively. Patients received a mean of seven injections throughout the 12 months. No significant difference was observed in terms of efficacy between the ranibizumab monotherapy group and the combined ranibizumab and laser groups. Repeated intravitreal injection of ranibizumab was found to be safe with no cases of endophthalmitis. No ocular severe adverse event was observed in the ranibizumab arm, with only one case of increased intraocular pressure, which resolved spontaneously. The pooled incidence of endophthalmitis in the RESOLVE and RESTORE trials was 1.4%, which was similar to the AMD trials. Ranibizumab was not found to be associated with increased risk of cerebrovascular or cardiovascular events in DME patients over 12 months in the study.

For the 303 patients who have completed the RESTORE core study, 240 entered an open-label extension study in which patients received 24-month of monthly 0.5 mg ranibizumab on a prn basis.[46] Results showed that a mean of 3.7 ranibizumab injections in the second year and 2.7 injections in the third year is sufficient to maintain the mean VA gained in the core study. The safety profile was also satisfactory in the long-term with no new safety concern. The results provided good evidence that long-term treatment with ranibizumab is effective and safe for the treatment of DME.

REVEAL

The REVEAL study is a multicentered Phase III study similar to RESTORE which compared the efficacy and safety of 0.5 mg ranibizumab as monotherapy or combined with laser versus laser monotherapy in Asian patients with DME.[47] Over 390 patients were randomized to the three groups and followed for 1 year. At 1 year, ranibizumab alone or combined with laser led to rapid and significant improvement in mean best-corrected VA compared with laser monotherapy ($P < 0.0001$). The mean visual gain for the ranibizumab and combined groups were 6.6 and 6.4 letters, respectively, while the laser monotherapy group gained 1.8 letters. The mean OCT CRT at 12 months for ranibizumab monotherapy or combined groups were also significantly lower compared with the laser-alone group ($P < 0.001$). In terms of safety, the incidences of ocular and nonocular serious adverse events were similar across all three treatment arms. The findings of the REVEAL are consistent with the RESTORE trial; that ranibizumab monotherapy can result in rapid and significant improvement in vision and reduction in CRT compared with laser alone.

DRCRnet protocol I

The Diabetic Research Clinical Research Network (DRCRnet) protocol I is a multicentered randomized, controlled trial which assessed the efficacy of intravitreal 0.5 mg ranibizumab combined with prompt or deferred (6 months later) focal/grid laser treatment, 4 mg triamcinolone combined with prompt laser treatment, or prompt focal/grid laser treatment alone for the treatment of central involving DME.[48] A total of 691 patients (854 eyes) with central involvement DME were recruited. In the ranibizumab arm, four initial doses were given, followed by additional monthly injection if the eye improved (CMT decreased by ≥10% or VA improved by 5 letters compared with the last visit), until success criteria were met (VA of 20/20 or CMT < 250 µm). At the end of 1 year, eyes which had intravitreal ranibizumab with prompt

or deferred laser had significantly better VA compared with prompt laser alone.

The study was subsequently extended from the original 3 years to 5 years, with eyes in the ranibizumab with prompt or deferred laser continued on their original randomization, while the triamcinolone or laser-alone groups can choose to receive ranibizumab with prompt laser treatment. In the second year, visit intervals could be extended to 8 weeks if injections could be deferred at three consecutive visits, and if ranibizumab was not resumed, the follow-up interval could be extended to every 16 weeks until ranibizumab was resumed. The 2-year visual outcomes were similar to that of the first year.[49] Compared with prompt laser alone, the mean VA was 3.7 and 5.8 letters better in the ranibizumab with prompt laser and deferred laser groups, respectively, compared with laser alone, while the triamcinolone plus prompt laser group had a mean of 1.5 letters less than the laser control group. In this trial, the median number of injections in the second year was two and three for the ranibizumab with prompt and deferred arms, respectively. This shows that patients in the second year needed substantially fewer injections to maintain the vision gain following the DRCRnet treatment algorithm.

At 3 years, the study compared the VA and OCT outcomes of eyes originally assigned to the ranibizumab prompt laser group (144 patients) versus deferred laser group (147 patients).[29] Results showed a median of one and two ranibizumab injections for the prompt and deferred laser groups, respectively. The mean VA gain from baseline was 6.8 and 9.7 letters for prompt and deferred laser groups and the difference was statistically significant ($P = 0.02$). Regarding safety, no significant difference was found between the treatment groups. The rate of injection-related endophthalmitis remained low at 0.5% and 1% in the prompt and deferred laser groups, respectively.

Using the DRCRnet protocol I retreatment algorithm, the frequency of intravitreal injections could be reduced while maintaining the VA. There was a median of six injections for first 6 months, three in the second 6 months, two or three injections in the second year, and one or two injections in the third year. Despite the decreasing frequency of injections, the VA gained in the first 6 months persisted through the 3-year study period, suggesting a long-lasting treatment effect of ranibizumab in DME by using this treatment algorithm. This contrasts with neovascular AMD where the visual benefits could not be maintained if the frequency of ranibizumab injection was decreased and illustrates the differences in the strategy in using anti-VEGF therapy for DME and neovascular AMD.

Cost-effectiveness of ranibizumab treatment
Age-related macular degeneration

As AMD is one of the leading causes of blindness worldwide, the burden of disease associated with visual impairment is enormous. Multiple studies have been conducted to estimate the cost-effectiveness of ranibizumab for AMD, and was found to be cost-effective compared with usual care, no treatment, or placebo in Canada, Germany, UK and US when outcomes were calculated on a long-term (>10 year) basis.[50] Most cost-effectiveness studies used data from the MARINA and ANCHOR trials with monthly ranibizumab injections. In the UK, the incremental cost-effectiveness ratio (ICER), or cost per quality-adjusted life year (QALY) gained for ranibizumab for the treatment of classic CNV, ranged from approximately US$266,035 for the 2-year model to approximately US$50,386 for the 10-year model.[51] Similarly, the ICERs for ranibizumab for patients with minimally classic and occult CNV, compared with usual care, ranged from approximately US$152,464 for the 2-year model to US$25,098 for the 10-year model.[51] In Canada, the Canadian Agency for Drugs and Technologies in Health evaluated the manufacturer's cost-effectiveness data and found that ranibizumab was cost-effective if the Product Listing Agreement was implemented, ie, the manufacturer pays for additional treatments if the number of injections exceeds nine in the first year and six in the second and third years.[50]

Markov modeling has been used to simulate real-life treatment patterns and effectiveness of ranibizumab treatment for neovascular AMD in Germany.[52] It predicted VA and costs of patients treated with ranibizumab over 10 years, assuming five injections per year over 2 years versus costs per year of legal blindness avoided (vision year gained) and per QALY. The calculated ICER from the study was approximately US$17,798–67,562 for all subtypes of CNV.

Diabetic macula edema

The cost effectiveness of ranibizumab in DME was evaluated from evidence gathered in the RESTORE trial.[53] Using a Markov model simulating a 15-year time frame for treating DME in one eye using 2010 price levels, it was found that the ICER of ranibizumab monotherapy was approximately US$39,072 compared to laser monotherapy. This is equivalent to a 64% probability of being cost-effective. For the combined laser ranibizumab and laser therapy, it resulted in an ICER of approximately US$7,635 with a 42% probability of being cost effective. Therefore, it was concluded that ranibizumab monotherapy appears to be cost effective in

relation to laser monotherapy, while the cost-effectiveness of combined ranibizumab plus laser therapy was less certain.

Comparative vision gains and impact on quality of life after ranibizumab treatment
Age-related macular degeneration

Patients reported vision-related function and quality of life in the ANCHOR and MARINA trials were assessed using the National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25).[54] It was found that at 12 months, patients treated with 0.3 mg and 0.5 mg ranibizumab had mean improvements in NEI VFQ-25 composite scores of 5.9 and 8.1 points, respectively, compared with 2.2 points improvement in the PDT group. This improvement was seen up to 24 months as ranibizumab-treated patients were more likely to report improved visual function in near and distant related activities and reduced vision-related dependency.[54] This finding appeared to be valid regardless of whether the treated eye was the better or worse seeing eye at the onset of treatment.[55] In addition, treatment of neovascular AMD with ranibizumab increased the proportion of patients who have at least 20/40 vision and they were more likely to be driving (78.4% in ranibizumab-treated versus 67.2% in placebo control groups in MARINA; 91.4% in ranibizumab-treated versus 71.6% in PDT groups in ANCHOR), as well as reported to have better driving perception.[56]

In a prospective noncomparative consecutive case series, ranibizumab treatment for 3 months was found to improve the near vision of neovascular AMD patients by 33% compared with baseline, with 44% increase in reading speed and 33% improvement in their central visual field.[57] The quality of life assessed by the NEI VFQ-25 also showed improvement for both distance and near activities. The improvement however was more marked for near activities compared with distance activities.

Quality of life measures following ranibizumab therapy has also been compared with bevacizumab in the IVAN study.[15] It found that the ranibizumab- and bevacizumab-treated groups did not differ in terms of quality of life scores, contrast sensitivity, and reading index. However, bevacizumab seemed to fare slightly worse in terms of near VA, but the difference failed to reach statistical significance ($P = 0.058$).[18]

Diabetic macular edema

The use of ranibizumab has been found to provide health-related quality of life gains in patients with DME. In the RESTORE study, vision-related quality of life gains assessed using the NEI VFQ-25 questionnaire showed significant improvement in patients treated with ranibizumab (monotherapy or combined with laser).[53] At 1 year, the composite scores increased by 5.0 and 5.4 points in the ranibizumab monotherapy and ranibizumab plus laser groups, respectively, compared with a small gain of 0.6 point in the laser monotherapy group. Vision improved in the ranibizumab group for both distant and near activities. At 12 months, 46% and 50% of patients in the ranibizumab monotherapy and combined ranibizumab plus laser groups reported excellent-to-good eyesight (21% and 23% at baseline), compared with 24% in the laser-only group with a baseline of 22%.

Conclusions and future directions

The long-term safety and efficacy in the use of ranibizumab for the treatment of neovascular AMD and DME is now being evaluated through the LUMINOUS program.[58] The study will be a 5-year prospective multicentered noninterventional study to assess the long-term safety, efficacy, treatment patterns, and health-related quality of life outcomes in patients being treated with ranibizumab. With a planned sample size of 30,000 subjects worldwide, the study will help to evaluate the long-term safety and efficacy in addition to understanding the treatment patterns and outcomes of ranibizumab for neovascular AMD and DME in the real-world clinical setting.

More recently, VEGF-trap aflibercept (Eylea, Regeneron, Tarrytown, NY, USA; Bayer Pharma AG, Berlin, Germany), a fusion protein which inhibits both VEGF-A, VEGF-B and PlGF has been approved by various regulatory authorities for the treatment of neovascular AMD. The approval was based on two Phase III randomized controlled trials, VIEW-1 and VIEW-2,[59] which evaluated the efficacy and safety of aflibercept in the treatment of neovascular AMD. It compared the use of 0.5 mg aflibercept monthly, 2 mg aflibercept monthly, 2 mg aflibercept bimonthly doses after three initial doses, and 0.5 mg ranibizumab monthly for 2 years. The results showed that all aflibercept treatment groups were noninferior compared with ranibizumab monthly treatment, offering the potential for decreasing the frequency of injection and follow-up visits while maintaining vision gain with the use of aflibercept. Aflibercept has also been reported to result in rapid resolution of persistent macular thickening due to CNV despite multiple prior ranibizumab injections.[60] Therefore, aflibercept might provide an alternative treatment option for treatment failures following ranibizumab therapy. The long-term safety of aflibercept however remains to be evaluated. An European public assessment report on aflibercept recently

published by the European Medicines Agency has reported a higher number of cerebrovascular events in the aflibercept group compared with ranibizumab group, especially in the subgroup of patients ≥85 years (9.5% for aflibercept versus 3.4% for ranibizumab at 2 years).[61] A noninterventional postmarketing study on the use of aflibercept will be conducted to address the risk of arterial thromboembolic events, cerebral vascular accidents, and transient ischemic attacks in the near future.

Based on the various studies with long-term follow-up, there is good evidence that ranibizumab is an effective, safe, and well-tolerated treatment option for both neovascular AMD and DME. Ranibizumab provides not only visual stabilization but also vision gain in neovascular AMD, which has never been achieved with previous treatment modalities. In the long-term, ranibizumab also improves patients' quality of life in various activities and has been shown to be cost-effective in both neovascular AMD and DME compared with usual care. Its main drawback is the monthly dosing regimen, which escalates the medical burden of treatment. This is particularly troublesome for neovascular AMD patients as visual deterioration is observed with less frequent dosing of ranibizumab. For DME, the initial gain in VA could be maintained in the long-term with patients requiring much fewer injections after the first year. With numerous new drugs being developed in the research pipeline, treatment options which require less frequent dosing while offering long-term control of disease activities will be more promising therapeutic options for neovascular AMD and DME. However, for the time being, ranibizumab will remain the gold-standard treatment for neovascular AMD and DME due to its good long-term efficacy and safety profiles and will be the yardstick for new treatments to compare with.

Disclosure

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