ADIS DRUG PROFILE

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Ranibizumab

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Contents

Abstract

▲ Ranibizumab is the antigen-binding fragment of a recombinant, humanised monoclonal antibody, which binds with high affinity to, and inhibits the activity of, all active forms of vascular endothelial growth factor A, an important mediator in the development of choroidal neovascularisation.

▲ Well designed, phase III trials in patients with neovascular (wet) age-related macular degeneration (AMD) indicated that monthly intravitreal injections of ranibizumab 0.3 or 0.5mg for up to 2 years maintained or improved visual acuity to a greater extent than sham injection, verteporfin photodynamic therapy or sham photodynamic therapy.

▲ In patients with predominantly classic wet AMD who received ranibizumab in combination with verteporfin therapy, preliminary results indicate that combination therapy is superior to that of verteporfin therapy alone.

▲ Most serious ocular adverse events, which were uncommon, were associated with either the injection procedure or ranibizumab.

Features and properties of ranibizumab (Lucentis®)	
Indication	
Neovascular (wet) age-related macular degeneration (AMD)	
Mechanism of action	
Vascular endothelial growth factor A inhibitor	
Dosage and administration	
Recommended dose	0.5mg
Route of administration	Intravitreal injection
Recommended frequency	Monthly
Pharmacokinetic profile (single intravitreal injection of 0.5mg in patients with wet AMD)	
Maximum serum concentration attained ≈1 day after dose administration	0.79–2.9 ng/mL
Mean vitreous elimination half life	10 days
Adverse events	
Most frequent ocular	Conjunctival haemorrhage, eye pain, vitreous floaters, retinal haemorrhage, increased ocular pressure, vitreous detachment

Age-related macular degeneration (AMD) is the leading cause of irreversible vision loss in the elderly.[1,2] AMD comprises two types, the dry or nonexudative form, which accounts for ≈85–95% of all macular degeneration cases, and the wet or exudative form (also called neovascular), which is responsible for ≈10% of cases.[3,4]

Wet AMD is characterised by the development of abnormal blood vessels in and under the retina, called choroidal neovascularisation (CNV).[3] Until recently, the primary treatment modalities for CNV secondary to AMD included thermal laser destruction of CNV, verteporfin photodynamic therapy and a vascular endothelial growth factor (VEGF)-A inhibitor pegaptanib, which has specificity for the 165 amino acid isoform ($VEGF_{165}$).[3,5] However, these therapeutic measures show limited efficacy, with recurrence being common.[2,4-6]

Research into the pathogenesis of wet AMD shows that the underlying cause of vision loss is CNV.[7] Although CNV may be initiated by a number of factors, VEGF-A has been shown to play a key role in its development.[7,8] Therefore, the development of an antiangiogenic treatment that would selectively inhibit VEGF-A became the focus of research efforts.[6] A new molecular entity, ranibizumab (Lucentis®)[1], was subsequently developed.[3] Ranibizumab is the antigen-binding fragment of a recombinant, humanised monoclonal antibody, and was designed to bind and inhibit all active forms of VEGF-A.[3]

This profile focuses on the pharmacological properties and clinical use of intravitreal ranibizumab, which has been recently approved for use in the US, the EU, Australia, India and other countries around the world in patients with wet AMD.

1. Pharmacodynamic Profile

Mechanism of Action

- Ranibizumab is a recombinant, humanised IgG1 κ isotype monoclonal antibody fragment.[9] It is produced in an *Escherichia coli* expression system and has a molecular weight of ≈48kD.[9]
- By binding to the receptor-binding site of active forms of VEGF-A, ranibizumab prevents VEGF-A from interacting with its receptors on the endothelial cell surface, thereby reducing the proliferation of endothelial cells, vascular permeability and the formation of new blood vessels.[9]
- *In vitro*, ranibizumab dose-dependently and specifically inhibited human umbilical vein endothelial cell proliferation induced by VEGF-A isoforms (concentration range producing 50% inhibition 0.27–0.48 nmol/L; article available as an abstract).[10] By contrast, other recombinant humanised antibodies did not neutralise VEGF-isoform-induced human umbilical vein endothelial cell proliferation.[10]

Clinical Data

- Early short-term, exploratory, randomised trials (three to nine doses of ranibizumab 0.3–2mg over 2–4 months) in patients with neovascular AMD indicated that visual acuity was improved (gain of ≥15 letters on the Early Treatment Diabetic Retinopathy Study [ETDRS] chart) in 44% of 27 patients[11] and in 26% of 53 patients receiving ranibizumab versus none of 11 patients receiving usual care (UC; verteporfin photodynamic therapy or observation).[12] Mean gains in visual acuity ranged from 5 to 13 letters with various dosage regimens of ranibizumab.[11-13]
- Visual acuity appeared to be retained with further ranibizumab treatment. A mean gain of 11 letters was seen at 6 months with ranibizumab versus a mean loss of 5 letters with UC (compared with a gain of 9 letters vs a loss of 5 letters at 3 months; $p < 0.01$).[12]
- A small study (n = 7) has indicated that the recurrence of CNV is common after 2 years of ranibizumab treatment (CNV was reactivated in three patients a mean of 6 months after the last dose; restarting ranibizumab was associated with a clinical response).[14]

1 The use of trade names is for product identification purposes only and does not imply endorsement.

• In the noncomparative, investigator-initiated PrONTO trial (n = 40), retreatment was given as required after three initial monthly doses; after a mean of 0.2 retreatments per eye, at 5 months after the last monthly dose, there was a mean gain from baseline in visual acuity of nine letters (vs ten at the last monthly dose; both $p < 0.001$ vs baseline).[13]

• Similarly, there was no loss of visual acuity with extended ranibizumab treatment as required (median 0.2 injections/month) for >1 year after initial monthly doses (number not reported) in a noncomparative trial (n = 66).[15]

• Ranibizumab appears to have little effect on the CNV lesion area as assessed using fluorescein angiography and fundus photography. Changes in area, leakage from the CNV and subretinal fluid were minimal after five to nine doses over 4 months in one study.[11] There were no differences between ranibizumab and UC in change in lesion area after four doses over 3 months; however, leakage was decreased versus UC ($p < 0.01$).[12]

• Nonetheless, when optical coherence tomography was used for assessment, mean central thickness measurements decreased by 190μm from baseline after three monthly doses of ranibizumab and by 158μm after a further 5 months of retreatment as required (both $p < 0.001$ vs baseline); complete resolution of retinal cysts and subretinal fluid occurred in 95% of patients.[13,16]

• Furthermore, in phase III trials (see section 3 for design details), ranibizumab 0.3 and 0.5mg doses were associated with significantly more favourable outcomes in changes from baseline in morphological characteristics of lesions at 12 months than either the active or sham comparator[17,18] and at 24 months versus sham comparator ($p < 0.001$ for each comparison).[18] Such morphological characteristics included, but were not limited to, the size of classic CNV, size of leakage area from CNV and size of lesion. Phase III trials found that the size of the lesion at baseline did not affect visual acuity treatment outcomes.[9,17,18]

• The maximum tolerated dose of ranibizumab was 0.5mg in patients with subfoveal CNV secondary to AMD (n = 27) who received single intravitreal injections of ranibizumab 0.05–1.0mg.[19] Two patients experienced dose-limiting ocular inflammation with ranibizumab 1.0mg.[19]

2. Pharmacokinetic Profile

The pharmacokinetic profile of ranibizumab has been evaluated in 120 patients with neovascular AMD who received unilateral intravitreal ranibizumab 0.05–2 mg/eye as a single dose or every 2 or 4 weeks (published as an abstract).[20] Serum ranibizumab concentrations were analysed using a homogeneous electrochemiluminescent immunoassay.[20] Some additional data were obtained from the manufacturer's prescribing information[9] and the summary of product characteristics.[21]

• Results from an *in vitro* cellular proliferation assay showed that a ranibizumab concentration of 11–27 ng/mL is necessary to inhibit the biological activity of VEGF-A by 50% (VEGF-A IC_{50}).[9] Following monthly intravitreal ranibizumab administration in patients with neovascular AMD, maximum ranibizumab serum concentrations were below the VEGF-A IC_{50} at 0.3–2.36 ng/mL.[9] In humans, following intravitreal administration, vitreal ranibizumab concentrations are predicted to be ≈90 000-fold higher than serum concentrations,[21,22] which is clinically important as extra-ocular VEGF-A is necessary for normal physiological functions.[22]

• In recipients of ranibizumab 0.5mg, the mean ranibizumab vitreous elimination half-life is ≈10 days, and the maximum serum concentration of ranibizumab after 0.5 mg/month/eye, which was attained approximately 1 day after administration, was predicted to be 0.79–2.9 ng/mL.[21]

• Systemic exposure was considered negligible in one study involving 120 patients.[20] One hour after a single 0.3mg dose, 73% of patients had mean serum ranibizumab concentrations below the limit of sensitivity (0.3 ng/mL); the mean concentration in the other patients was 1.01 ng/mL. By 28 days after administration, mean serum concentrations were <0.3 ng/mL in 96% of 52 patients. Serum concentrations reached a plateau after three doses in nine patients receiving ranibizumab every 2 weeks.

- Serum ranibizumab concentrations were lower than the affinity constant of ranibizumab for VEGF in patients receiving monthly 0.3 or 0.5mg doses.[20]
- In patients with neovascular AMD, the mean estimated vitreous elimination half-life, based on the the disappearance of ranibizumab from the serum, was 9 days.[9]
- Over the ranibizumab dose range of 0.05–1.0 mg/eye, the maximum observed serum concentration was dose-proportional.[9] On the basis of population pharmacokinetic findings, the maximum serum ranibizumab concentration (1.5 ng/mL) should be reached ≈1 day after each monthly administration of intravitreal ranibizumab 0.5 mg/eye.[9] Steady-state minimum concentrations would be 0.22 ng/mL with this regimen.[9]

3. Therapeutic Efficacy

Phase III Trials

Three randomised, double-blind, controlled, multicentre phase III trials (MARINA, ANCHOR and PIER; definitions of the trial acronyms used throughout this article are shown in table I) have investigated the efficacy of intravitreal ranibizumab with respect to changes in visual acuity in patients with neovascular AMD.[9,17,18,23] Results from MARINA and the first year of ANCHOR have been fully published,[17,18] whereas results from the PIER trial are available only from the manufacturer's prescribing information and/or abstracts.[9,23,24] An abstract including some additional results from MARINA has also been included.[25]

The MARINA trial[9,18] compared ranibizumab 0.3 mg/month (n = 238) or 0.5 mg/month (n = 240) with sham injection (n = 238) for 2 years in patients with minimally classic or occult (without classic) subfoveal CNV secondary to AMD.

The ANCHOR trial[9,17,26] compared ranibizumab 0.3 mg/month (n = 140) or 0.5 mg/month (n = 140) with verteporfin photodynamic therapy given at baseline and every 3 months as required (n = 143) for 2 years in patients with predominantly classic CNV lesions; to date, only first-year results have been reported.

The PIER trial[9,23,24] compared ranibizumab 0.3 mg/month (n = 60), 0.5 mg/month (n = 61) or sham injection (n = 63) for three doses followed by the same dose at 3-monthly intervals for 2 years (results available for the first six doses, at 12 months) in patients with or without a classic CNV component.

Some results from the PIER trial are only available for patients receiving the 0.5mg dose or for both dosage groups combined. The primary outcome measure for the MARINA and ANCHOR trials was the proportion of patients maintaining their visual acuity (i.e. losing <15 letters from baseline using the ETDRS chart).[9,17,18] For the PIER trial, the primary outcome measure was the mean change in visual acuity at 12 months relative to baseline.[9,23,24]

- Visual acuity was at least maintained in 94–96% of patients receiving ranibizumab 0.3 or 0.5 mg/month at 1 year in the MARINA and ANCHOR trials[17,18] and in 92% and 90% of those receiving 0.3 or 0.5 mg/month at 2 years in the MARINA trial (figure 1). By contrast, 62% (1 year) and 53% (2 years) of sham injection recipients and 64% (1 year)

Table I. Trial acronym definitions

Acronym	Definition
ANCHOR	ANti-VEGF antibody for the treatment of predominantly classic CHORoidal neovascularisation in AMD
FOCUS	RhuFab V_2 Ocular treatment Combining the Use of Visudyne® to evaluate Safety
MARINA	Minimally classic/ocult trial of the Anti-VEGF antibody Ranibizumab In the treatment of Neovascular AMD
PIER	Phase IIIb, multicenter, randomized, double-masked, sham Injection-controlled study of the Efficacy and safety of Ranibizumab in subjects with subfoveal choroidal noevascularization with or without classic CNV secondary to AMD
PrONTO	Prospective OCT imaging of patients with Neovascular AMD Treated with intra-Ocular Luncentis
SAILOR	Safety Assessment of Intravitreal Lucentis fOR AMD

AMD = age-related macular degeneration; **CNV** = choiroidal neovasularisation; **OCT** = optical coherence tomography; **VEGF** = vascular endothelial growth factor.

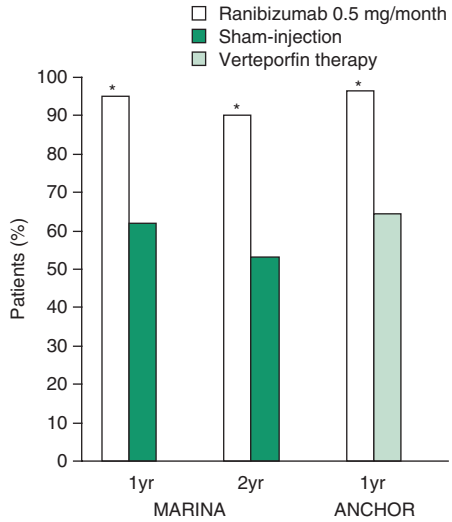

Fig. 1. Efficacy of ranibizumab in patients with wet age-related macular degeneration. Results are from the randomised, double-blind, controlled, multicentre MARINA and ANCHOR trials. The graph shows the proportion of patients receiving ranibizumab 0.5 mg/month (n = 240 and 140), sham injection (n = 238) or verteporfin therapy (n = 143) whose vision was maintained (loss of <15 letters on the ETDRS chart) relative to baseline best-corrected visual acuity score (primary endpoint).[9,17,18] * $p < 0.001$ vs comparator.

of verteporfin therapy recipients maintained visual acuity in these trials ($p < 0.001$ for each comparison).[17,18]

- Visual acuity maintenance results from subgroup analyses of ANCHOR data according to sex, age and baseline lesion size were highly consistent across the subgroups as well as with the overall results.[26]

- Visual acuity improved by ≥15 letters from baseline in 25–40% of patients receiving ranibizumab 0.3 or 0.5 mg/month at 1 year in the MARINA[18] and ANCHOR[17] trials, and by 26% and 33% at 2 years in the MARINA trial.[18] By contrast, similar improvements in visual acuity in the control arms of the MARINA and ANCHOR trials were experienced in 5–6% of patients at 1 year, and in 4% of patients at 2 years in MARINA ($p < 0.001$ for all comparisons).[9,17,18]

- Furthermore, compared with baseline, at 12 months, the proportion of ranibizumab 0.3 or 0.5mg recipients with Snellen equivalent vision of 20/40 was significantly greater ($p < 0.001$ for each ranibizumab dosage vs comparator in both trials) than those in the control arms in the ANCHOR and MARINA trials;[17,18] similar improvements on this measure were also seen in the MARINA trial at 24 months among ranibizumab recipients, compared with recipients of sham PDT ($p < 0.001$ for each ranibizumab dosage vs comparator).[18]

- By contrast, the proportion of ranibizumab 0.3 or 0.5 mg/month recipients with Snellen equivalent vision of 20/200 or worse at 12 and 24 months remained about the same as at baseline, whereas in the control groups, the proportions had significantly increased from baseline at 12 and 24 months ($p < 0.001$ for both ranibizumab dosages vs comparators).[17,18]

- While short-term ranibizumab 0.5 mg/month was associated with a gain in visual acuity at 3 months in the PIER trial, this generally returned to baseline during quarterly dosing, compared with a mean loss of 16 letters in sham injection recipients at 1 year.[9,24]

- In the MARINA and ANCHOR trials, monthly ranibizumab 0.3 or 0.5mg was associated with mean gains of 7–11 letters at 1 year and 5 and 7 letters at 2 years, versus mean losses of 10 and 15 letters with sham injection at 1 and 2 years and a mean loss of 10 letters (at 1 year) with verteporfin therapy.[9,17,18]

- Severe vision loss (≥30 letters) from baseline occurred in significantly fewer patients who received ranibizumab 0.3 or 0.5mg than those who received the sham comparator or verteporfin therapy in the MARINA[18] and ANCHOR[17] trials (0–1% vs 13% and 14% at 12 months, and 3% vs 23% (sham) at 24 months;[18] $p < 0.001$ for each comparison).

- In the MARINA trial, patient-reported vision-specific quality of life measured using the National Eye Institute Visual Function Questionnaire-25 showed that ranibizumab recipients had significantly greater improvements from baseline than sham injection recipients for near activities, distance activities and dependency ($p < 0.001$ for all three).[25]

Phase I/II Trial

Year 1 results are available from the phase I/II, randomised, single-masked, multicentre FOCUS study in patients with predominantly classic neovascularisation secondary to AMD who received intravitreal ranibizumab 0.5 mg/month plus verteporfin therapy (n = 105) for 23 months or verteporfin therapy alone (n = 56).[27] Maintenance of visual acuity was defined as a loss of <15 letters on the ETDRS chart.

The primary endpoint was the proportion of patients who, at 12 months, had maintained visual acuity relative to baseline.[27] Secondary visual acuity-related endpoints, which were measured in the first treatment year, included the proportion of patients whose visual acuity score improved by ≥15 letters, the proportion of patients whose visual acuity Snellen equivalent was ≤20/200 and the mean change from baseline in visual acuity score.[27]

- At 12 months, combined administration of ranibizumab and verteporfin therapy resulted in 90% of patients having maintained or improved visual acuity versus 68% of patients receiving verteporfin alone ($p < 0.001$).[27]
- A significantly greater proportion of patients receiving ranibizumab plus verteporfin therapy gained ≥15 letters from their baseline visual score, compared with patients receiving verteporfin therapy alone (24% vs 5%; $p = 0.003$).[27] Other visual acuity-related secondary endpoints were consistent with those for the primary endpoint.[27]

4. Tolerability

Tolerability data for ranibizumab were obtained from the phase III trials (MARINA and ANCHOR) discussed in section 3.[17,18] Results from MARINA are at 24 months and those for ANCHOR are at 12 months. Some pooled tolerability data from these trials were obtained from the manufacturer's prescribing information.[9] In addition, findings from a scheduled interim safety analysis of patients in cohort 1 of the ongoing phase IIIb SAILOR trial are also included; these results were presented in a Dear Healthcare Provider letter and specifically relate to the incidence of strokes associated with ranibizumab.[28,29] In SAILOR, patients in cohort 1 had neovascular AMD and were receiving ranibizumab 0.3 or 0.5mg;[28] frequency and patient numbers were not stated.

- Pooled tolerability data from well designed trials showed the most common ocular adverse events occurring in >20% of ranibizumab recipients were: conjunctival haemorrhage, eye pain, vitreous floaters, retinal haemorrhage, increased intraocular pressure (IOP) and vitreous detachment, and in ≥10% of ranibizumab recipients were: intraocular inflammation (generally mild), eye irritation, cataract (consistently mild or moderate), foreign body sensation in eyes, increased lacrimation, eye pruritus, visual disturbance, blepharitis, subretinal fibrosis, ocular hyperaemia, maculopathy, visual acuity blurred/decreased, detachment of the retinal pigment epithelium and dry eye.[9]
- Serious ocular adverse events in the ANCHOR trial were infrequent, occurring in 1.8% of ranibizumab recipients and 0.7% of verteporfin therapy recipients. They included presumed endophthalmitis (two patients receiving ranibizumab 0.5mg), uveitis (one patient receiving ranibizumab 0.5mg), rhegmatogenous retinal detachment (one patient each in verteporfin and ranibizumab 0.3mg groups) and vitreal haemorrhage (one patient receiving ranibizumab 0.3mg).[17]
- Similarly, few patients experienced serious adverse ocular events in the MARINA trial (4.4% of ranibizumab and 1.3% of sham injection recipients). Over 24 months of treatment, in patients in the ranibizumab 0.3mg, 0.5mg or sham injection groups, respectively, these included: presumed endophthalmitis (2, 3 and 0 patients), uveitis (3, 3, 0), rhegmatogenous retinal detachment (0, 0, 1), retinal tear (1, 1, 0), vitreous haemorrhage (1, 1, 2) and lens damage (0, 1, 0).[18] Of the serious ocular adverse events, the majority were attributable either to ranibizumab (uveitis) or to the injection procedure (presumed endophalmitis).[18]
- Within 60 minutes of injection in the ANCHOR and MARINA trials, IOP increased by ≥30mm Hg in 9–18% of ranibizumab 0.3 or 0.5mg recipients,

4% of verteporfin therapy recipients and 3% of sham injection recipients.[17,18]

- Ranibizumab was associated with an increased frequency of cataract formation in the ANCHOR trial (11% and 13% for ranibizumab 0.3 and 0.5mg vs 7% for verteporfin therapy),[17] but not in the MARINA trial (16% for both doses vs 16% for sham injection).[18] Visual acuity outcomes in patients with cataract formation were not notably different relative to other patients in the respective groups in the two studies.[17,18]

- Non-ocular adverse events from pooled phase III data included hypertension (5–23% of ranibizumab 0.3mg or 0.5mg recipients vs 8–23% of controls), nasopharyngitis (5–16% vs 5–13%), arthralgia (3–11% vs 0–9%), headache (2–15% vs 3–10%), bronchitis (3–10% vs 2–8%) and cough (3–10% vs 2–7%).[9]

- Results from a scheduled interim safety analysis of patients in the SAILOR trial (patient numbers not stated), showed that patients receiving the intravitreal ranibizumab 0.5mg dose had a significantly higher incidence of strokes than those receiving the 0.3mg dose (1.2% vs 0.3%; p = 0.02); frequency of administration not stated.[28] Genentech subsequently issued a Dear Health Care Provider letter via the FDA.[28] Noted in the letter, was that patients with a previous history of stroke appeared to be at higher risk for subsequent stroke, and that the overall safety of intravitreal ranibizumab 0.3 or 0.5mg was consistent with that observed during phase III trials described in the manufacturer's prescribing information.[28]

- However, the rate of arterial thromboembolic events occurring in ranibizumab-treated patients was low and not significantly different from the rate occurring in either verteporfin or sham-comparator recipients.[17,18] In the Dear Health Care Provider letter,[28] the rate of arterial thromboembolic events, including myocardial infarction or vascular death, was not significantly different between ranibizumab 0.3mg or 0.5mg recipients in the ongoing SAILOR tolerability trial (patient numbers not stated).

5. Dosage and Administration

In the US, the recommended dosage of ranibizumab in patients with neovascular AMD is 0.5mg administered intravitreally once a month.[9] After the first four injections, if monthly administration is not feasible, treatment may be reduced to one injection every 3 months.[9] However, compared with continued monthly administration, on average, the quarterly administration is less effective, with a decline in visual acuity benefit of about five letters over the following 9 months.[9]

In the EU, the recommended dosage of ranibizumab in patients with neovascular AMD is 0.5mg administered intravitreally monthly for the first 3 months followed by a flexible treatment regimen guided by visual acuity outcomes.[21]

For detailed information on contraindications, drug interactions, warnings and precautions, and use in special patient populations, local prescribing information should be consulted.

6. Ranibizumab: Current Status

Ranibizumab has recently been approved by the US FDA, is licensed in the EU, Switzerland, Australia, India, Indonesia, Peru, Argentina and Mexico, and is preregistration in Canada and other markets throughout the world for the treatment of patients with neovascular AMD.

In well designed, randomised, controlled trials, intravitreal administration of ranibizumab 0.3 or 0.5mg for up to 2 years reduced vision loss and improved visual acuity and vision-related visual functioning, and was generally well tolerated, in patients with neovascular AMD.[9]

Disclosure

During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

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