



The Role of Ranibizumab in Age-related Macular Degeneration – Emerging Clinical Data

a report by

Anna Tarantini and Paolo Lanzetta

Department of Ophthalmology, University of Udine, Italy

DOI: 10.17925/EOR.2007.00.00.62

Neovascular or wet age-related macular degeneration (AMD) is by far the leading cause of irreversible sight loss in western countries among people who are 50 years of age and older.¹ Neovascularisation in this disease sprouts from the choriocapillaries into the subretinal space, and is known as choroidal neovascularisation (CNV). CNV is the underlying cause of vision loss and is classified by fluorescein angiography into two angiographic patterns – classic and occult – that are associated with various degrees of aggressiveness of disease, vision loss and response to treatment.²

Recently, developments in treatment strategies have improved the number and efficacy of therapeutic interventions, thereby increasing the probability of avoiding vision loss or gaining vision. Several factors may initiate CNV; however, vascular endothelial growth factor A (VEGF-A), a diffusible cytokine that promotes angiogenesis and vascular permeability, has been shown to play a key role in its development.³ Four main biologically active isoforms of VEGF-A with 121, 165, 189 and 206 amino acids, respectively, have been identified.⁴ VEGF₁₆₅ is the predominant isoform involved in neovascularisation.

At present, several options exist for the management of neovascular AMD. One of these is photodynamic therapy (PDT), a photothrombotic occlusive therapy that includes the intravenous administration of a pharmacological photosensitiser (verteporfin, Visudyne®; Novartis AG, Basel, Switzerland) combined with the physical activation of the substance using a red laser light.

In the field of newer antiangiogenic approaches one new drug, ranibizumab (Lucentis®. Genentech Inc., South San Francisco, CA, US), has recently received marketing authorisation for the treatment of neovascular AMD. Ranibizumab is a recombinant humanised Fab fragment of a monoclonal antibody; by binding to the receptor-binding site of active forms of VEGF-A, it is capable of preventing 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. In animal models, ranibizumab administered intravenously easily penetrated the retina, reaching the subretinal space, and reduced retinal and choroidal neovascularisation. Ranibizumab's short half-life and rapid systemic clearance support its safety.⁵

Two randomised, double-blind, controlled, multicentre phase III trials have assessed the efficacy of intravitreal ranibizumab: the Minimally classic/occult trial of the Anti-VEGF antibody Ranibizumab In the treatment of Neovascular Age-related macular degeneration (MARINA)⁶ study and the ANTi-VEGF antibody for the treatment of predominantly classic CHORoidal neovascularisation in age-related macular degeneration (ANCHOR)⁷ study.

MARINA Study

In the MARINA⁶ study, 716 patients were enrolled and randomly assigned in a 1:1:1 ratio to receive ranibizumab at a dose of either 0.3 or 0.5mg or a sham injection monthly for two years (24 injections) in one eye. At one year, 94.5% of the patients who had received 0.3mg of ranibizumab and 94.6% of those who had received 0.5mg maintained baseline visual acuity compared with 62.2% of patients receiving sham injections. Visual acuity improved by 15 or more letters in 24.8% of the 0.3mg group and in 33.8% of the 0.5mg group compared with 5% of the sham-injection group.

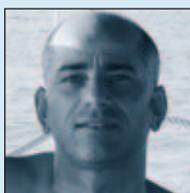
Mean increases in visual acuity were 6.5 letters in the 0.3mg group and 7.2 letters in the 0.5mg group compared with a decrease of 10.4 letters in the sham-injection group. This benefit in visual acuity was maintained at two years. Over the 24-month period, presumed endophthalmitis – defined as cases of serious post-operative inflammation treated with intravitreal antibiotics – were identified in five patients (1.0%). Four of those cases were culture-negative.

ANCHOR Study

In the ANCHOR⁷ trial, 423 patients were enrolled and randomly assigned in a 1:1:1 ratio to receive either 0.3 or 0.5mg of ranibizumab plus sham verteporfin therapy or sham intravitreal injections plus active verteporfin therapy. Ranibizumab was injected into the study eye at monthly intervals for a total of 12 injections in the first year; sham injections were administered on the same schedule. Either verteporfin or sham



Anna Tarantini works in the Department of Ophthalmology at the University of Udine, Italy. She graduated in Medicine from the University of Udine; her thesis was on the treatment of exudative age-related macular degeneration with anti-vascular endothelial growth factor. Dr Tarantini earned her degree in ophthalmology at the University of Udine, before a fellowship in oculoplastics at the University Eye Hospital in Munich.



Paolo Lanzetta is Associate Professor of Ophthalmology at the University of Udine, Italy. He is actively involved in retinal clinical research and is an investigator in many international multicentre clinical trials on photodynamic therapy and antiangiogenic drugs. Professor Lanzetta is a major contributor to the medical literature, and has published studies on laser applications in ophthalmology. He serves on numerous scientific advisory boards, is a Member of the Programme Committee of the Association

for Research in Vision and Ophthalmology (ARVO) and addresses his research interests as an invited speaker at national and international symposia. He received his medical degree *magna cum laude* from the University of Milan, Italy, where he also completed an ophthalmology residency.

E: paolo.lanzetta@uniud.it

verteporfin was administered on day zero and then, if needed (on the basis of evaluation of angiography by the investigators), at months three, six, nine and/or 12. Of the patients who received 0.3mg ranibizumab, 94.3% lost fewer than 15 letters; for those receiving 0.5mg the figure was 96.4%. This compares with 64.3% of those in the verteporfin group.

Visual acuity improved by 15 letters or more in 35.7% of the 0.3mg group and in 40.3% of the 0.5mg group compared with 5.6% of the verteporfin group. Mean visual acuity increased by 8.5 letters in the 0.3mg group and by 11.3 letters in the 0.5mg group compared with a

The MARINA and ANCHOR trials proved for the first time that a significant proportion of patients affected with choroidal neovascularisation can improve their vision with appropriate treatment.

decrease of 9.5 letters in the verteporfin group. Presumed endophthalmitis occurred in two patients (1.4%) treated with 0.5mg ranibizumab. One case was culture-positive.

The MARINA and ANCHOR trials proved for the first time that a significant proportion of patients affected with CNV can improve their vision with appropriate treatment. This milestone was accomplished with a fixed regimen of treatment based on the monthly administration of ranibizumab. However, the monthly regimen constitutes a substantial burden for physicians, healthcare personnel, patients, care-givers and payers. Several authors have attempted to decrease the number of injections by modifying the treatment scheme.

PIER Study

The PIER study,^{8,9} a phase IIIb trial, included 182 patients with all lesion types and evaluated the efficacy and safety of ranibizumab 0.3 and 0.5mg administered monthly for three doses, followed by dosing every three months. While patients in the sham group lost a mean of 16 letters during 12 months of follow-up, patients with either dose of ranibizumab remained stable at baseline visual acuity. While short-term ranibizumab 0.5mg/month was associated with a gain in visual acuity at three months, vision generally returned to baseline during quarterly dosing. This reduction in the treatment benefit appears to highlight the need for a flexible regimen to maintain optimal results. However, of note is the fact that 40% of patients who gained visual acuity during the initial three monthly injections maintained their response at 12 months. Therefore, there is also a need to identify any factors that may be predictive of a favourable outcome.

PrONTO Study

The PrONTO¹⁰ trial investigated less frequent dosing regimens. The forty patients who were enrolled received three monthly injections during the first two months and were then re-treated using a variable dosing regimen based mainly on optical coherence tomography (OCT) patterns. Mean visual acuity improved by 7.2 and 11.3 letters in the MARINA and ANCHOR trials, respectively; in the PrONTO study there

was a mean gain of 9.3 letters. Patients in the MARINA and ANCHOR trials received 13 injections over a 12-month period, while patients in the PrONTO study, also over a 12-month period, received an average of 5.6 injections. The results from the PrONTO study suggest that an individualised treatment regimen based on OCT findings can reduce the number of injections needed while maintaining the beneficial outcomes. A decrease in the number of injections would reduce the workload, diminish the potential risk of injection-related complications and extend the injection-free interval.

Antiangiogenic therapy with ranibizumab inhibits CNV-induced leakage and reduces progressive lesion growth, but appears to have little impact on CNV persistence, which may require a permanent antiangiogenic intervention. PDT, on the other hand, occludes CNV. A combination of verteporfin therapy with an anti-VEGF adjunct may thus reduce the frequency of re-treatments, while hopefully maintaining the visual benefit offered by antiangiogenic therapy. Also, it is known that PDT induces an upregulation of VEGF, pigment epithelium-derived factor (PEDF) expression.¹¹ Administration of anti-VEGF in conjunction with PDT may counteract the upregulation of VEGF that may lead to post-treatment angiogenesis and leakage.

FOCUS Study

Year one results are available from the phase I/II randomised, multicentre, controlled FOCUS¹² study of patients with predominantly classic neovascularisation secondary to AMD. The patients received monthly intravitreal ranibizumab 0.5mg or sham injections combined with verteporfin PDT. At 12 months, combined administration of ranibizumab and verteporfin therapy resulted in 90% of patients maintaining or improving visual acuity versus 68% of patients receiving verteporfin alone. A significantly greater proportion of patients receiving ranibizumab plus verteporfin therapy gained 15 letters or more compared with their baseline visual score versus

Antiangiogenic therapy with ranibizumab inhibits choroidal neovascularisation (CNV)-induced leakage and reduces progressive lesion growth, but appears to have little impact on CNV persistence.

patients receiving verteporfin therapy alone. The most frequent ranibizumab-associated serious ocular adverse events were intraocular inflammation (11.4%) and presumed endophthalmitis (4.8%).

After a study amendment, all subjects randomised to active treatments transitioned from the lyophilised formulation to the liquid formulation of ranibizumab. Thus, the majority of second-year ranibizumab treatments used the commercially available liquid formulation Lucentis®. The protocol was amended due to a greater than anticipated number of cases of transient uveitis, most of which occurred after the first dose of the lyophilised formulation. Uveitis was present in approximately 9% of the patients treated with the lyophilised formulation during the first year. The increased number of transient

serious inflammatory cases was observed mainly after the first dose of ranibizumab. During the second year, when most eyes were treated with Lucentis, only one more case showed inflammation. The FOCUS study could not provide clear answers regarding the possible association of uveitis rates with either the lyophilised formulation or the interval between the adjunctive treatments. The results showed that further evaluations of the safety of this combined treatment were required to support larger studies of the combined therapies of verteporfin and ranibizumab.

PROTECT Study

The open-label, multicentre phase II PROTECT^{13,14} study was designed to further explore the same-day administration of standard PDT and intravitreal injection of liquid ranibizumab in patients with predominantly classic or occult lesions. In the PROTECT study, the safety results of this combined regimen did not reveal new safety concerns and showed that same-day administration of ranibizumab was not associated with an inflammatory response.

In this study, verteporfin PDT was administered at baseline and then at months three, six and nine, if required after the evaluation of lesion activity on fluorescein angiography. Ranibizumab 0.5mg was administered at baseline within one hour after verteporfin therapy, and

The PROTECT study proved that same-day administration of ranibizumab and verteporfin is safe and can result in a significant reduction of retinal thickness and improvement in visual acuity.

then monthly for three months in a total of four injections. At baseline, 93% of the patients with OCT measurements had intraretinal oedema.

During the study, retinal thickness decreased significantly at one month; this was maintained over nine months. Fundus photography and fluorescein angiography were performed, with measurements at baseline and at months three, four, six and nine. Mean lesion area, mean greatest linear dimension of CNV and fluorescein angiography

leakage were all reduced from baseline at month nine. During the nine months, 69% of patients required one initial verteporfin PDT, and only 9% required the maximum of three possible verteporfin treatments. Visual acuity outcome was similarly positive. The PROTECT study proved that same-day administration of ranibizumab and verteporfin is

Newer strategies with multiple therapies such as photodynamic therapy and ranibizumab are promising and seem to maintain the outcomes of anti-vascular endothelial growth factor monotherapy.

safe and can result in a significant reduction of retinal thickness and improvement in visual acuity with a lower number of injections.

SUMMIT Trials

The SUMMIT clinical trial programme was also designed to evaluate the safety and efficacy of verteporfin and ranibizumab when used in combination. The Denali and Mont Blanc studies will compare the efficacy and safety of ranibizumab plus verteporfin therapy administered on the same day versus ranibizumab alone.

The Denali study will also evaluate the effect of PDT-reduced fluence on the outcome. The end-points of the SUMMIT studies will evaluate visual acuity, anatomical outcomes, number of treatments and health economics outcomes. Thus, the eventual reduced need for re-treatments, which might offer an alternative that is less time- and cost-intensive, is being evaluated by these ongoing prospective clinical trials using a combined regimen therapy.

Conclusion

In conclusion, 90% of ranibizumab-treated patients can maintain their initial visual acuity with monthly injections. Significant visual acuity improvement can occur in up to 40% of cases. Newer strategies with multiple therapies such as PDT and ranibizumab are promising and seem to maintain the outcomes of anti-VEGF monotherapy, while also reducing the number of treatments needed. ■

- Bressler NM, Age-related macular degeneration is the leading cause of blindness, *JAMA*, 2004;291:1900–1.
- Barbazzetto I, Burdan A, Bressler NM, et al., Photodynamic therapy of subfoveal choroidal neovascularization with verteporfin: fluorescein angiographic guidelines for evaluation and treatment: TAP and VIP report No. 2, *Arch Ophthalmol*, 2003;121:1253–68.
- Kliffen M, Sharma HS, Mooy CM, et al., Increased expression of angiogenic growth factors in age-related maculopathy, *Br J Ophthalmol*, 1997;81:154–62.
- Houck KA, Ferrara N, Winter J, et al., The vascular endothelial growth factor family: identification of a fourth molecular species and characterization of alternative splicing of RNA, *Mol Endocrinol*, 1991;5:1806–14.
- Ferrara N, Gerber HP, LeCouter J, The biology of VEGF and its receptors, *Nat Med*, 2003;9:669–76.
- Rosenfeld PJ, Brown DM, Heier JS, et al., Ranibizumab for neovascular age-related macular degeneration, *N Eng J Med*, 2006; 355:1419–31.
- Brown DM, Kaiser PK, Michels M, et al., Ranibizumab versus verteporfin for neovascular age-related macular degeneration, *N Eng J Med*, 2006;355:1432–44.
- Schmidt-Erfurth U, The PIER study: twelve month efficacy and safety results from a phase III study of ranibizumab 0.3 mg and 0.5 mg administered initially monthly and then every 3 months for subfoveal choroidal neovascularization secondary to age-related macular degeneration. PIER study group [abstract no. F1116], *Asian J Ophthalmol*, 2006;8(3 Suppl. 1):176.
- Brown DM, Yue H, Shams N, Ranibizumab (Lucentis) in neovascular age-related macular degeneration (AMD): subgroup analysis of year 1 PIER efficacy data, *Invest Ophthalmol Vis Sci*, 2007;48:ARVO E-Abstract 4540.
- Fung AE, Lalwani GA, Rosenfeld PJ, et al., An optical coherence tomography-guided, variable dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration, *Am J Ophthalmol*, 2007;143:566–83.
- Schmidt-Erfurth U, Schlötzer-Schrehard U, Cursiefen C, et al., Influence of photodynamic therapy on expression of vascular endothelial growth factor (VEGF), VEGF receptor 3, and pigment epithelium-derived factor, *Invest Ophthalmol Vis Sci*, 2003;44:4473–80.
- Heier J, Bayer J, Ciulla D et al., Ranibizumab combined with verteporfin photodynamic therapy in neovascular age-related macular degeneration: year 1 results of the FOCUS study, *Arch Ophthalmol*, 2006;124:1532–42.
- Schmidt-Erfurth U, Gabel P, Hohman T, PROTECT Study Group, Preliminary results from an open-label, multicenter, phase II study assessing the effects of same-day administration of ranibizumab (lucentis) and verteporfin PDT (PROTECT Study), *Invest Ophthalmol Vis Sci*, 2006;47:ARVO E-Abstract 2960.
- Wolf S, PROTECT Study Group, Nine month exploratory endpoint results from an open-label, multicenter, phase II study of same-day verteporfin and ranibizumab 0.5 mg (PROTECT Study), as measured using optical coherence tomography (OCT), fundus photography and fluorescein angiography (FA), *Invest Ophthalmol Vis Sci*, 2007;48:ARVO E-Abstract 2871.