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.\(^4\) VEGF\(_{165}\) 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 photothermobic 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 MARINA\(^6\) 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 ANCHOR\(^7\) 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...
The Role of Ranibizumab in Age-related Macular Degeneration – Emerging Clinical Data

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. 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 III 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 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 uveits, 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 photopheresis 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 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 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 safe and can result in a significant reduction of retinal thickness and improvement in visual acuity.

**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.