Role of ranibizumab in management of macular degeneration

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Age-related macular degeneration (AMD) is one of the most common causes of severe vision loss in the western world. Both animal and human studies have established that vascular endothelial growth factor (VEGF) plays an important role in the pathogenesis of this process. Ranibizumab (Lucentis™, Genentech, South San Francisco, CA) is a monoclonal antibody fragment (Fab) directed toward all isoforms of VEGF-A that was specifically designed to target wet AMD. The human antibody fragment is produced by an E. coli expression system and has a molecular weight of 48kD allowing for excellent retinal penetration. The most common ocular complaints of patients receiving ranibizumab injections in randomized clinical trials were transient conjunctival hemorrhage, vitreous floaters, intraocular inflammation, increased intraocular pressure and eye pain. The rates of serious adverse events such as retinal detachment, cataract and endophthalmitis were similar to those that have been reported with other intravitreal injections and patients should always be treated under strict aseptic conditions to reduce this risk. There were no significant non-ocular events found during any study so far and the risk of thromboembolic events was less than 4% and not different than sham. The MARINA, ANCHOR and PIER studies validated the safety and efficacy of ranibizumab amongst a large population with different choroidal neovascular membrane lesion types against sham or standard of care treatment. These studies recommended monthly intravitreal ranibizumab for patients. However, the PIER study reported that an alternative dosing of every three months is acceptable but less effective than monthly injections.

**Key words:** Age-related macular degeneration, choroidal neovascular membrane, Lucentis™ (Ranibizumab injection), vascular endothelial growth factor.

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Age-related macular degeneration (AMD) is the most common irreversible cause of visual loss in the developed world. There are two distinct forms of AMD: the neovascular (wet) form and the non-neovascular (dry) form. The neovascular form of AMD accounts for 10 to 20% of the total patients with macular degeneration and is associated with the formation of neovascular membranes below the retina that release blood and fluid distorting central vision. Eventually, these neovascular lesions result in a scar leading to irreversible central vision loss. Forty-eight per cent of patients with neovascular AMD experience severe visual loss (defined as less than 20/200 visual acuity). Its impact on the quality of life and psychological stability of geriatric patients has been studied extensively and recent reports have highlighted the high rate of depression amongst patients with AMD. To date, no one etiology has been discovered and theories of the cause of AMD have included excessive oxidative stress, immune hyperreactivity and dietary deficiencies. Age, smoking status and heredity also appear to play a key role.

Over the past decade, there have been a variety of medical therapies introduced with variable success to treat the neovascular form of AMD. The Macular Photocoagulation Study (MPS) found that focal laser photocoagulation to choroidal neovascular membranes (CNVM) was beneficial to visual outcomes. However, the lesions found to be amenable to treatment had to meet strict criteria that few lesions fell into. Laser treatment was inherently destructive and created a permanent scotoma at the site of retinal ablation. Since a large proportion of CNVM lesions in AMD are subfoveal, direct laser ablation would lead to a permanent and immediate loss of central vision. Furthermore, recurrence rates were found to be 47% at five years after treatment.

Photodynamic therapy (PDT) using verteporfin (Visudyne™, Novartis, Basil, Switzerland) for selective photochemical angio-oclusion of neovascular vessels showed better results in both the treatment of ARMD with PDT (TAP) study and the verteporfin in PDT (VIP) trials. In these placebo-controlled trials, PDT treatment reduced moderate visual loss, especially in patients with predominantly classic CNV lesions, but only a few patients had improved vision. Patients with large occult lesions (greater than 4 MPS disc areas and any size minimally classic lesions) showed little benefit after PDT. Furthermore, the recurrence rate was high with over 90% of patients requiring re-treatment after three months. However, over time the treatment rates declined with an average of 3.5 treatments in the first year and 0.1 treatments in the fifth year.

**Vascular Endothelial Growth Factor (VEGF)**

Although there are several potential regulators of angiogenesis, it appears that VEGF may be one of the most important regulators of vascular development and differentiation, perhaps because it is the most specific growth factor for the vascular endothelium. VEGF is a homodimeric peptide mitogen with
narrow target cell specificity whose activity is limited to endothelial cells derived from small and large blood vessels. VEGF was originally called vascular permeability factor (VPF) and is a potent cause of vascular leakage in the retina, which is hypothesized to enhance angiogenesis by allowing translocation of plasma proteins. VEGF has also been shown to be a critical rate-limiting step in the development of ocular neovascularization. In addition, it functions as a survival factor for newly-formed blood vessels. VEGF is mainly upregulated by hypoxia and other factors. There are six isoforms of VEGF that arise from alternate splicing of the mRNA of a single gene: VEGF121, VEGF145, VEGF165, VEGF183, VEGF189 and VEGF206. VEGF165 is the predominant pathologic isoform. Inhibition of VEGF can be achieved by blocking its receptors or the molecule itself.

VEGF has been implicated in the pathogenesis of ocular diseases such as AMD and diabetic retinopathy and supportive data have come from studies in nonhuman primates and humans including examination of excised CNVM and autopsy specimens. Studies showed that retinal pigment epithelial (RPE) cells on CNVMs over-expressed VEGF. Similarly, Frank and associates found high levels of VEGF in excised AMD-related CNVMs. The presence of VEGF has been shown in CNVM regardless of angiographic subtype. Animal studies have supported the role of VEGF in the pathogenesis of AMD. The injection of a subretinal recombinant adenovirus vector expressing VEGF in rats led to new blood vessels’ growth from the choriocapillaris, the formation of breaks in Bruch’s membrane and CNVM formation in the subretinal space.

Evidence such as this has led to the research and development of strategies to block VEGF’s effects.

Recent studies using anti-VEGF inhibitors injected into the vitreous cavity have shown promising results. The United States Food and Drug Administration (FDA) approved pegaptanib sodium (Macugen™, OSI-Eyetech, New York, NY) that binds the VEGF165 isoform in December 2004 for treatment of all neovascular AMD regardless of lesion composition. Pegaptanib is a pegylated aptamer that consists of a RNA oligonucleotide ligand that binds human VEGF165 with high affinity and specificity. Pegaptanib does not block the other isoforms of VEGF. The VEGF inhibition study in ocular neovascularization (VISION) trial examined the efficacy and safety of pegaptanib in patients with subfoveal, neovascular AMD. This randomized, controlled, double-masked, multi-center, dose-ranging trial found that 70% of subjects receiving a 0.3 mg intravitreal injection every six weeks lost <3 lines of vision versus 55% of control subjects receiving sham injection and standard care with PDT in all types of choroidal neovascularization at 12 months. Furthermore, the clinical benefits were maintained at Week 102 for pegaptanib-treated patients, with a 45% relative difference at the end of two years.

Bevacizumab (Avastin™, Genentech, South San Francisco, CA) is a full-length, recombinant, humanized, monoclonal antibody directed against all VEGF isoforms. It is the first anti-VEGF approved by the FDA for systemic administration in the treatment of colorectal cancer. Unfortunately, systemic effects such as elevation of systolic blood pressure and the potential for systemic thromboembolic events were concerns in the cancer studies. Rosenfeld reported the first patient treated with intravitreal fractionated doses of bevacizumab with impressive results in the summer of 2005. Since then there has been widespread adoption of this off-label therapy for ocular disease including AMD with a variety of case series showing good initial efficacy. Despite these studies, many still believe that bevacizumab is too large a molecule to cross the retina and be of significant benefit when injected intravitreally.

Ranibizumab

Ranibizumab (Lucentis™, Genentech, South San Francisco, CA) is a monoclonal antibody fragment directed toward all isoforms of VEGF-A. Ranibizumab has a molecular weight of 48kD and is produced by an E. coli expression system. The unique structure of ranibizumab was specifically engineered for ocular disease. This is because ranibizumab is made up of just the Fab fragment that was the basis for the full length antibody bevacizumab and has been affinity matured to have a higher binding affinity for VEGF. This confers less antigenicity and greater retinal penetration because of the smaller molecule size. The binding of ranibizumab to isoforms of VEGF-A prevents the dimerization with the VEGF receptors on cell surfaces (VEGFR1 and VEGFR2) reducing vascular leakage, angiogenesis and endothelial cell proliferation.

There are distinct differences between ranibizumab and bevacizumab. First, since ranibizumab lacks the Fc region of the antibody, it is less likely to cause complement-mediated inflammation after injection. The off-label reconstitution and formulation of bevacizumab for intravitreal use may prove to be too difficult for all clinicians to obtain and raises questions of sterility and stability. Bevacizumab has a considerably longer systemic half-life which would be worrisome if there was systemic absorption after intravitreal injection. However, there are some distinct advantages of bevacizumab over ranibizumab. As a larger molecule with a longer half-life, the dosing scheme may be longer and ranibizumab has only one binding site for VEGF while bevacizumab has two.

Pharmacokinetics and Clinical Safety

The pharmacokinetics for ranibizumab was investigated in both animal and human studies. The systemic release of ranibizumab has been concerning given the possible risks for thromboembolic events seen with the related drug, bevacizumab. In animal studies, the maximum level of ranibizumab was achieved within one day with an estimated half-life in the vitreous cavity of approximately three days. Serum levels paralleled the vitreous concentration decline of ranibizumab and serum levels were found to be 2000-fold lower than in the vitreous cavity. Following monthly intravitreal injections of ranibizumab for AMD, patients’ serum concentrations of ranibizumab were low (0.3 ng/ml to 2.36 ng/ml) and far below the inhibitory concentration necessary to inhibit 50% of VEGF-A (11 ng/ml to 27 ng/ml). Population pharmacological analysis predicts that with a single 0.5 mg dose of ranibizumab, a maximum serum concentration of 1.5 ng/ml is expected one day after administration. By evaluating the elimination pharmacokinetics of ranibizumab in serum, it is predicted that ranibizumab will have a vitreous half-life of nine days.

There were no significant non-ocular events found during the ranibizumab studies. The rate of thromboembolic events was examined closely given the higher rates of thromboembolic events experienced in cancer patients receiving bevacizumab. In the first year, the rate of thromboembolic events was...
2.1% in ranibizumab-treated patients in comparison to 1.1% in sham-treated patients. However, in Year 2, the rates of thromboembolic events were not statistically different (3.0% vs. 3.2% in ranibizumab-treated patients vs. sham respectively). The most common ocular complaints of patients receiving ranibizumab injections over sham treatments were conjunctival hemorrhage, vitreous floaters, intraocular inflammation, increased intraocular pressure and eye pain. Ocular adverse events are detailed in Table 1 and did not exceed controls during the Phase I-III studies.

**Clinical Efficacy**

Data from Phase III clinical trials have shown promising results. Recently released data from the anti-VEGF antibody for the treatment of predominantly classic choroidal neovascularization in AMD (ANCHOR) study validated its efficacy in treating predominantly classic lesions. Approximately 94 to 96% of ranibizumab-treated patients maintained or improved vision (less than 15 letters loss in VA) compared with approximately 64% of patients treated with PDT during the first 12 months of the 24-month study (P <0.001), [Table 2].28,29 The minimally classic/occult trial of the anti-VEGF antibody ranibizumab in the treatment of neovascular AMD (MARINA) study demonstrated that ranibizumab was safe and effective in the management of minimally classic and occult with no classic lesions. The study found that 95% of ranibizumab-treated patients experienced visual improvement or stabilization compared with 62% of sham-treated patients after 12 months (P <0.001). Moreover, patients treated with ranibizumab experienced 15 letter increase in vision, something rarely found in studies with pegaptanib [Table 3].30,31 In both the MARINA and ANCHOR studies, patients received monthly ranibizumab injections for 24 months.

The Phase IIIb, multicenter, randomized, double-masked, sham injection-controlled study of the efficacy and safety of ranibizumab in subjects with subfoveal choroidal neovascularization with or without classic CNV secondary to AMD (PIER) study,32 evaluated an alternate dosage regimen instead of monthly injections of ranibizumab for neovascular AMD. The trial was designed to determine the safety and efficacy of a modified dosage regimen consisting of intravitreal dosage every month for three doses, then an additional injection mandated every three months thereafter. In contrast, almost all the previous ranibizumab studies had monthly dosage schemes. All lesion types were eligible for the PIER study if the active CNV accounted for at least 50% of the total lesion. Physicians within the study could not administer treatments of ranibizumab if leakage was noted between the mandated injection time points. Using this alternative dosage scheme, the mean change in visual acuity at 12 months was -16.3 letters in the sham group, -1.6 in the 0.3 mg dose and -0.2 letters with the 0.5 mg dose. Table 4 highlights the other visual outcomes of the study. Overall, both doses of ranibizumab tested showed a significant benefit over sham in the management of wet AMD. However, quarterly dosage did not appear as effective as monthly dosage, as illustrated by the results of the MARINA and ANCHOR Trials.28,30 The three-month initiation dosage resulted in similar improvements of vision as in the MARINA and ANCHOR trials, but by 12 months, the PIER patients returned to baseline study acuity while the MARINA and ANCHOR patients exhibited continual visual gain from baseline. Patients in the sham group were crossed over to quarterly dosage of 0.5mg of ranibizumab at the end of the first 12 months of the trial. The study will continue for a total of 24 months to evaluate the longer term tolerability and efficacy of ranibizumab.32

**Combination Therapy**

The two-year results from the FOCUS study33 comparing the safety and efficacy of monthly intravitreal injections of ranibizumab in combination with verteporfin PDT (Visudyne; Novartis, Hanover, NJ) versus PDT alone in the treatment of predominantly classic subfoveal CNVM due to AMD. The Phase 1/2 study involved 105 ranibizumab and PDT patients and 56 sham- and PDT-treated patients. Photodynamic therapy was given seven days before injection of either 0.50 mg ranibizumab or sham. The primary outcome measurement for the study was the proportion of patients who at 24 months had loss <15 letters from baseline BCVA. A significant change was made to the protocol during the course of the study. There were a greater number of patients who experienced transient uveitis after the injection of ranibizumab. Prior to the protocol amendment, PDT and ranibizumab had a higher rate of intraocular inflammation (13.3%) compared with after (2.9%). This was thought to be due to the lyophilized formulation used in the study and possibly due to the time interval between PDT and ranibizumab injection. The protocol

### Table 1: Adverse events of Lucentis versus controls

| Adverse event         | Lucentis % | Control % |
|-----------------------|------------|-----------|
| Conjunctival hemorrhage | 77-43      | 66-29     |
| Vitreous floaters      | 32-3       | 10-3      |
| Intraocular inflammation | 18-5       | 11-3      |
| Cataract               | 16-5       | 16-6      |
| Visual disturbance     | 14-0       | 9-2       |
| Ocular discomfort      | 8-0        | 5-0       |

### Table 2: Visual results of ANCHOR study month 12

| Outcome measure                  | Verteporfin PDT (N=143) | Lucentis 0.5 mg (N=140) |
|----------------------------------|-------------------------|-------------------------|
| Loss of less than 15 letters in visual acuity (%) | 64%                     | 96%                     |
| Gain of greater than 15 letters of visual acuity (%) | 6%                      | 40%                     |
| Mean change in visual acuity (letters) | -9.5                    | +11.3                   |

PDT - Photodynamic therapy

### Table 3: Visual results from the MARINA study month 24

| Outcome measure                          | Sham (N=238) | Lucentis 0.5 mg (N=240) |
|------------------------------------------|--------------|-------------------------|
| Loss of less than 15 letters in visual acuity (%) | 53%          | 90%                     |
| Gain of greater than 15 letters of visual acuity (%) | 4%           | 33%                     |
| Mean change in visual acuity (letters)   | -14.9        | +6.6                    |
was amended by increasing the time interval between PDT and ranibizumab injection to 28 days.

The combination of ranibizumab and PDT was safe and efficacious at year 2 in the FOCUS study. Presumed endophthalmitis occurred in 5.7% of treated patients which included both investigator reported endophthalmitis (three) and uveitis (three) cases. No overall imbalance of key arterial thromboembolic events was observed. The treatment effect of PDT and ranibizumab observed in year 1 was maintained through month 24 with 88% of subjects losing <15 letters and 25% of patients gaining >15 letters. This represented a cumulative 12.4 letter benefit in mean visual acuity change from baseline. Finally, fewer patients in the PDT and ranibizumab arm received additional PDT. Future studies will evaluate whether combination therapy will lead to less re-treatment with lucentis or PDT and greater functional outcomes over lucentis monotherapy treatment alone.33

### Conclusions and Future Perspective

Undoubtedly, the implementation of these pharmacologic developments will lead to better clinical outcomes and result in an improved quality of life for patients with AMD. Though many of these studies have demonstrated that intravitreal therapy is safe and efficacious in AMD, clinicians need to emphasize the realistic facts about these therapies to patients before starting. First, patients may need a minimum of one to two-year course of therapy before seeing benefit or changing course to other therapies. Second, the realistic outcome for most patients is stable vision or slower decline than the natural course of the disease. Patients who were previously treated with focal laser and PDT may not experience visual improvement because of the damage incurred previously but instead realize less metamorphopsia. Frequent injections (every four to six weeks) for an indefinite period of time should be expected. Thus far, the long-term safety and efficacy of these medications is unknown and should be disclosed to patients. Future randomized clinical studies with combination therapies and head to head comparisons of these medications would be helpful in determining the best modality in this devastating disease. Long-acting or slow-release versions of anti-VEGF drugs are being developed.

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