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Promising Treatment Strategies for Neovascular AMD: Anti-VEGF Therapy

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1. Introduction

Age-related macular degeneration (AMD) is one of the leading causes of substantial and irreversible vision loss. The prevalence of AMD can be expected to increase along with life expectancy, which has risen steadily [1, 2]. Without treatment, the neovascular form of AMD leads to severe quality-of-life loss within a short time period and considerable economic burden.

Vascular endothelial growth factor (VEGF) is a key mediator involved in the control of angiogenesis and vascular permeability and has been shown to be induced by hypoxia in cultured human retinal pigment epithelium (RPE) [3]. VEGF-A is the most potent promoter of angiogenesis and vascular permeability within the VEGF family and its role in the pathogenesis of neovascular AMD is well recognized [4, 5]. The advent of intravitreous VEGF inhibitors has revolutionized the management of neovascular AMD. Yet, frequently, indefinite injections of VEGF blocking agents introduce a significant treatment burden for patients with neovascular AMD, and may potentially put patients in the risk of developing ocular and systemic adverse effects from injections. Many studies on modified treatment regimens have been performed in an attempt to mitigate this burden without compromise to visual acuity outcomes. Meanwhile, various randomized clinical trials on combination therapies and efforts to develop new pharmacologic agents are ongoing.

2. Therapeutic monoclonal antibodies and fragments

2.1 Intravitreal ranibizumab and bevacizumab monotherapy

2.1.1 Vascular endothelial growth factor

VEGF plays an important role in a variety of in vitro processes, including angiogenesis, microvascular permeability, and endothelial cell survival. On the other hand, these activities are all essential to survival, VEGF has been linked to a number of pathogenic conditions, including neovascular AMD, diabetic retinopathy, and cancer.

Three VEGF therapies are currently used for the treatment of patients with neovascular AMD: pegaptanib (Macugen, OSI Pharmaceuticals, USA), ranibizumab (Lucentis, Genentech, USA), and bevacizumab (Avastin, Genentech, USA).

Pegaptanib is an oligonucleotide aptamer and was the first VEGF antagonist to be approved by the US Food and Drug Administration (FDA) for use in wet AMD. However, wet AMD patients treated with pegaptanib still experience visual decline. [2, 6] The first monoclonal antibody developed to target VEGF was bevacizumab, a humanized murine monoclonal antibody. Bevacizumab was initially developed for applications in oncology, and received approval as a first-line therapy for widespread colorectal cancer from the US FDA in 2004. Bevacizumab has subsequently been approved for use in non-small cell lung cancer and breast cancer.

The successful development of VEGF as an oncology target led to interest in the potential of anti-VEGF treatment for other therapeutic indications, including ocular neovascular disorders. VEGF-A has been identified as the primary angiogenesis mediator in the eye. It is implicated in ocular neovascularization through its promotion of blood vessel formation and permeability. A role for VEGF-A in neovascular AMD is suggested by immunohistochemistry localization in human choroidal neovascular (CNV) lesions and extrapolation from other disease models [5, 7-9].

New blood vessel formation and leakage play important roles in the development of the neovascular form of AMD, and clinical trials of agents that block VEGF-A activity have produced more evidence that VEGF-A is important in development of this disease.

Ranibizumab is a humanized antibody fragment against VEGF which was specifically designed for intraocular use as a smaller antibody fragment to penetrate through the retina better. The Food and Drug Administration (FDA) approved ranibizumab for treatment of subfoveal neovascular AMD in June, 2006. It was the first drug for AMD treatment shown to improve visual acuity in a substantial percentage of patients.

Bevacizumab is a recombinant humanized monoclonal immunoglobulin antibody that inhibits the activity of VEGF. It has a similar action and is related to the ranibizumab compound with respect to its structure. Bevacizumab was approved by the FDA for the treatment of metastatic colorectal cancer in 2004, but it has not been licensed for the treatment of wet AMD or any other ocular conditions. However, it is recently used off-label worldwide not only for wet AMD but also for other ocular disease entities associated with macular edema and abnormal vessel growth.

Intraocular pharmacokinetic data derived from studies in monkeys demonstrated that through intravitreal administration, ranibizumab distributed rapidly to the retina and had a vitreous half-life of 3 days. Studies in rabbits have demonstrated that ranibizumab can rapidly penetrate through the retina to reach the choroid, just 1 hr after intravitreal admidistration [10]. In primates, serum ranibizumab levels were found to be more than 1000-fold lower than in the vitreous and aqueous humor following a single intravitreal injection [11]. These were negligible and tissue concentrations were undetectable.

2.1.2 Safety

Systemic VEGF inhibition is suspected to be associated with an increased risk of hypertension and arterial thromboembolic events. Given the average age of patients requiring treatment for AMD, it is important that their treatment does not significantly increase the risk of these events. The rate of arterial thromboembolic events and

hypertension was low. Over the 24 months trial period, the rates in the ranibizumab 0.5 mg treatment group of the ANCHOR, MARINA, and PIER trials was 5.0 %, 4.6 %, and 0 %, respectively, compared with 4.2 %, 3.8 %, and 0 % in the control group.

2.1.3 Efficacy

The pivotal phase III Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA) [12] and the Anti-VEGF Antibody for the Treatment of Predominantly Classic CNV in AMD (ANCHOR) trial [13, 14] demonstrated best-corrected visual acuity (BCVA) outcomes were far superior to any previously published study in the treatment of this disease. At the end of 24 months in the MARINA trial, significantly more ranibizumab-treated patients had maintained [lost <15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters] or improved vision than sham-injected patients. Indeed, 90–95% of patients treated with 0.3 and 0.5 mg ranibizumab maintained vision compared with 53–64% of control patients. Over the same period, vision improved in 25–34% of treated eyes, compared with 4–5% of sham-injected patients.

In the ANCHOR trial, ranibizumab was compared with verteporfin photodynamic therapy (PDT) and demonstrated similar findings: 90–96% of the ranibizumab-treated versus 64–66% of the PDT-treated patients maintained vision, whereas 34–41% versus 6% of each group, respectively, gained more than 15 letters.

These outcomes were significantly better than those achieved by the control groups.

In both trials, a biphasic treatment effect was observed, with the majority of the visual gain achieved in the first 3 months of treatment (the loading phase) followed by stabilization of the gain (the maintenance phase).

Patient-reported outcomes were also assessed in the ANCHOR and MARINA trials to measure the influence of the ranibizumab-mediated improvement in visual acuity (VA) on quality of life. The data demonstrated that patients treated with ranibizumab were more likely to report improvements in near activities, distance activities, and vision specific dependency which were maintained over the 2 year duration of the trial [15, 16]. These data demonstrate that the clinical improvements seen with ranibizumab treatment translate into meaningful benefits for the patient.

More recently, the anatomical benefit of ranibizumab treatment in both the MARINA and ANCHOR studies with regard to angiographic and optical coherence tomography (OCT) characteristics has also been demonstrated. [12, 15, 16] Both functional and anatomical improvements were maintained over the 24 month study period with monthly injections.

Bevacizumab, the predecessor of ranibizumab, is a full-length monoclonal antibody that binds to and blocks the action of all VEGF isoforms. Numerous retrospective [17-20] and prospective studies [21-23] of intravitreal bevacizumab have reported its efficacy for neovascular AMD and low rates of treatment related complications [24]. Although a number of these studies were uncontrolled, relatively small in sample size, of limited follow-up, and varied with regard to outcome measures and retreatment criteria, the reported efficacy of bevacizumab coupled with its low cost when utilized as an intraocular agent has propelled its adoption worldwide.

A recent, large, multicenter, randomized prospective study (Bevacizumab for Neovascular Age-Related Macular Degeneration [ABC] trial) that demonstrated MARINA/ANCHOR-like results lends further support for its use in neovascular AMD [25, 26]. On the basis of results from the pivotal phase III clinical trials, ranibizumab dosed monthly represents the gold standard to which all other therapeutics and regimens are to be compared. In clinical practice, many retinal physicians have extrapolated the data and continued using bevacizumab. A formal head-to-head comparison of bevacizumab and ranibizumab is being conducted by the National Eye Institute of the National Institute of Health in the Comparisons of Age-Related Macular Degeneration Treatment Trials (CATTs) [27, 28]. The CATT study design includes four treatment arms: either bevacizumab or ranibizumab on a variable schedule means that monthly follow-up and evaluation of fluid based on OCT, and anti-VEGF injection when CNV becomes active and either bevacizumab or ranibizumab on a fixed monthly schedule for 1 year followed by random assignment to either continued monthly injections or a variable schedule based on the treatment response. The primary outcome measure is mean change in BCVA; secondary outcome measures include number of treatments, anatomical changes in the retina, adverse events, and cost. Preliminary results are reported in 2011 and will provide insight into how ranibizumab and bevacizumab compare with each other within the context of either a fixed monthly or traditional pro re nata (PRN) approach. At 1 year, bevacizumab and ranibizumab had equivalent effects on VA when administered according to the same schedule. Bevacizumab administered monthly was equivalent to ranibizumab administered monthly, with 8.0 and 8.5 letters gained, respectively. Bevacizumab administered as needed was equivalent to ranibizumab as needed, with 5.9 and 6.8 letters gained, respectively. Ranibizumab given as needed with monthly evaluation had effects on vision that were equivalent to those of ranibizumab administered monthly, although the comparison between bevacizumab as needed and monthly bevacizumab was inclusive. Differences in rate of serious adverse events require further study.

3. Modified treatment regimens

The prospect of indefinitely adhering to the monthly treatment schedules of MARINA and ANCHOR has raised ocular and systemic safety concerns as well as convenience and cost issues for patient and physician alike. The identification of alternative dosing strategies capable of reducing the number of required anti-VEGF injections while still achieving VA outcomes similar to those reached in the pivotal trials has since been a subject of great interest.

The observed biphasic treatment effect raised the possibility that, after the initial 3-months loading phase, maintenance of VA gain may be achieved with less frequent treatments. A PIER trial evaluated ranibizumab administered monthly for 3 months, followed by quarterly injections, and compared this with sham treatment. Under this schedule, ranibizumab did provide a significant VA benefit; a significantly greater number of patients achieved VA stabilization at 24 months compared with patients receiving sham treatment. However, subgroup analysis revealed that VA gains observed during the first 3 months of treatment were only maintained in 40% of patients over the duration of the trial, and for the remaining 60% quarterly dosing was not suitable [29, 30]. Results for both ranibizumab doses in the PIER trial (0.3 and 0.5mg) showed an initial mean improvement in BCVA during the initiation phase with monthly dosing, but after

month 3 in the maintenance phase with quarterly dosing, there was a gradual decline in mean BCVA to below the pretreatment baseline (2.2 letters) at 12 months, which remained unchanged at 24 months [30].

More recently, the Efficacy and Safety of Ranibizumab in Patients with Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration (EXCITE) study directly compared the PIER regimen with a fixed monthly treatment arm (0.3 mg ranibizumab) [31]. Although BCVA outcomes in the two quarterly treatment arms fared better than those in the PIER study at 12 months (2.2 and 3.1 letters gain with 0.3 and 0.5 mg ranibizumab, respectively), neither was as good as monthly dosing (0.9 letters gain). These suboptimal results demonstrate that, on average, quarterly treatment is inferior to monthly treatment; thus, it has never been adopted in practice.

Subsequently to the PIER trial, further investigation of a flexible dosing approach was carried out. The EXCITE trial directly compared a maintenance phase of quarterly injections against the monthly regimen. Consistent with previous observations, an initial gain was made in the first 3 months, after which patients receiving monthly injections contributed to gain VA, whilst those receiving quarterly injections showed a decrease from their 3 months VA levels. **(Table 1.)**

Study design	MARINA	ANCHOR	PIER	EXCITE
Study duration	24 months	24 months	24 months	12 months
Number of patients	716	423	184	353
Visit regimen in maintenance phase	Monthly	Monthly	Quarterly	Monthly for control Quarterly for study
Ranibizumab regimen in maintenance phase	Monthly	Monthly	Quarterly	Monthly for control Quarterly for study
No. of injections in maintenance phase	9	9	3	9 for control 3 for study

Table 1. Summary table of many different treatment regimen.

The current norm in clinical practice with ranibizumab or bevacizumab is to implement an initiation/induction phase followed by an individualized maintenance phase that is modeled after one of two basic approaches: traditional PRN [32] or 'treat and extend' [33, 34]. Traditional PRN involves both regular follow-up and treatment until the macula is more

or less free of exudation, with treatment thereafter during the maintenance phase only in the presence of recurrent exudation. The original prospective studies that evaluated a PRN approach to the maintenance phase were the Prospective Optical Coherence Tomography Imaging of Patients with Neovascular AMD Treated with Intra-Ocular Lucentis (PrONTO) study [35] and the Secondary to Age-Related Macular Degeneration (SAILOR) study [36]. More recently, the Study of Ranibizumab in Patients with Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration (SUSTAIN) study has contributed additional data [37]. In each of these trials, patients received three consecutive, monthly intravitreal injections of ranibizumab for induction, followed by monthly office visits. Thereafter, a PRN maintenance phase adhered to the following retreatment criteria: loss of at least five ETDRS letters, increase in central macular thickness on OCT of at least 100µm, or new hemorrhage.

Of the three studies, the PrONTO study demonstrated the best VA results. The PrONTO study evaluated an OCT guided, variable-dosing regimen with ranibizumab (0.5 mg) and showed that mean VA improved by 9.3 ETDRS letters at 12 months. Over a 2-year period, mean BCVA outcomes were similar to MARINA and ANCHOR with a mean of 9.9 injections (5.6 in the first year and 4.3 in the second). In comparison, results from the SAILOR study were not as good. In this study, the mean change in BCVA at 12 months from baseline was 0.5 and 1.7 letters in the treatment-naive and previously treated groups, respectively, at the 0.3 mg dose and 2.3 letters in both groups at 0.5 mg. It is worth noting that participants were not monitored as closely in SAILOR as compared with PrONTO, averaging nine visits through 1 year and a mean of 4.9 injections.

The 12-month results from SUSTAIN were slightly better than those from SAILOR (mean BCVA from baseline of 3.6 letters), yet still not as good as the monthly treatment trials. In contrast to SAILOR, participants in the SUSTAIN trial were followed monthly (more like PrONTO) and the mean number of injections over the first year was higher at 5.6.

Other relatively large studies using a traditional PRN approach have recently been published [38-40]. An analysis of these reports highlights an important trend: the best visual acuity results come from the study with the greatest mean number of treatments and closest follow-up, whereas the poorest outcomes were observed in the study with the lowest mean number of treatments and office visits. Unlike traditional PRN, a treat and extend approach initially involves regular and frequent treatment until the macula is dry, followed by a gradual extension of the treatment interval and corresponding follow-up visit. Treatment interval extension continues until there are signs of recurrence, at which point the treatment interval is then reduced.

Kang et al. [41, 42] recently published a retrospective analysis that monthly injections were not given in contrast to the three injections during the initial treatment period in the PIER and PrONTO trials. This study showed that visual acuity improved by 0.078 logMAR units and minimized the number of injections given during 12 months of follow-up (a mean of 4.07 injections were given over the 12 months). The decreased need for retreatment is of great benefit to both patients and clinicians. These results may raise doubts about the need for the three initial loading injections. They reported another study [42], the mean number of injections given in the 12 months period was 4.2 (range, 1-6). Patients were also offered reinjection with ranibizumab on an "as needed" basis. Data showed that the percentage of

patients (71.9%) with no visual loss or improved visual acuity was comparable to the percentages in the monthly injection-based studies.

In addition, Gupta et al. evaluated a treat and extend approach with bevacizumab and found nearly identical results at 12 months following a mean of 7.3 injections in the first year [40]. Although various methods for individualizing maintenance therapy have been proposed, the optimal non-monthly dosing regimen still remains unclear.

4. Combination therapy: Photodynamic therapy and antivascular endothelial growth factor therapy

The development and propagation of CNV membranes involve pro-angiogenic factors, vascular permeability molecules, and inflammatory proteins. Current standard treatment with monthly intravitreal injections of anti-VEGF monotherapy can be limited to the angiogenic component of CNV development and burdensome for both the physician and patient. Patients are subjected to increased risk of adverse effects from monthly treatments that may be lessened with treatment options given with less frequency [43]. While current monotherapy with anti-VEGF agents are effective therapy for CNV, their benefits are short-lived as they are unable to regress the lesions completely. Combination therapy with PDT proven to be effective in CNV regression may have a role not only in the treatment of CNV development but also may provide synergy through blocking adverse effects.

PDT was approved in 2000 by the FDA for the treatment of CNV secondary to AMD. Treatment involves intravenous administration of a light-sensitive dye called verteporfin followed by laser-guided, location-specific activation within the CNV membrane. Activation of the verteporfin molecules incite a phototoxic event within blood vessels, induce endothelial cell damage, platelet aggregation, and eventually lead to thrombosis of vascular channels. Treatment size is limited by the greatest linear diameter of the CNV lesion being treated [44, 45].

Variable factors within PDT treatment regimens include time of laser application and laser fluence. Standard fluence PDT (sfPDT) was commonly employed in the early studies. The Treatment of AMD with PDT (TAP) study showed stabilization but no improvement in vision with this protocol. In addition, other studies have reported that PDT may inadvertently perturb the normal choriocapillaris bordering a pathologic CNV lesion, resulting in up-regulation and expression of VEGF [46, 47]. This collateral damage may potentially be minimized with reduced-fluence PDT (rfPDT) [46]. rfPDT protocols have gained popularity because of its potential for increased CNV membrane selectivity and propensity to cause less surrounding retinal inflammation. The Verteporfin in Minimally Classic (VIM) trial employed both a standard and reduced fluence PDT protocol and showed stability of vision with either treatment over placebo, but it showed a clear trend toward a better visual outcome with rfPDT. In another comparative study, patients treated with rfPDT tended to have lower rates of severe visual loss and an overall better visual prognosis [46].

While PDT is intended to specifically target CNV vessels, collateral damage to surrounding blood vessels may lead to ischemia of healthy tissue. Following PDT of a CNV membrane, induced ischemia can lead to production of pro-angiogenic factors, especially VEGF. Therefore, combining verteporfin PDT and anti-VEGF therapy may be beneficial compared

with either modality alone, yielding longer treatment-free intervals and requiring fewer intravitreal injections [44].

The RhuFab V2 Ocular Treatment Combining the Use of Visudyne to Evaluate Safety (FOCUS) study is a multicenter, randomized, single-blind study designed to evaluate the safety and efficacy of sfPDT in combination with intravitreal ranibizumab [48, 49]. It compared sfPDT to combination sfPDT and intravitreal ranibizumab in the treatment of predominantly classic CNV secondary to AMD. One-year data showed greater visual stability in the patients treated with combination therapy and 23.8% of patients experienced improvement in visual acuity, compared with 5% of patients treated with PDT monotherapy alone. The number of re-treatments with sfPDT were decreased as well with 91% of patients treated with sfPDT monotherapy requiring repeat treatment while only 28% of patients treated with combination therapy requiring re-treatment within one year. Two-year data showed similar results with 88% of combination treated patients losing less than 15 lines of vision versus 75% of sfPDT alone treated patients. Combination therapy required an average of 0.4 repeat PDT treatments compared with an average of 3.0 in the sfPDT group [49].

5. Vascular endothelial growth factor Trap-Eye

The most effective dosing regimen and monitoring program for anti-VEGF therapy has yet to be firmly established but new treatments are aimed at extending and improving on the efficacy of ranibizumab. VEGF Trap-Eye (aflibercept, Regeneron Pharmaceuticals, USA) is a promising new anti-VEGF drug. Structurally, VEGF Trap-Eye is a fusion protein of key binding domains of human VEGF receptor 1 and 2 combined with a human IgG Fc fragment. Functionally, VEGF Trap-Eye acts as a receptor decoy with high affinity for all VEGF isoforms, binding more tightly. VEGF Trap-Eye differs from established anti-VEGF therapies in its higher binding affinity for VEGF-A and its blockage of placental growth factors-1 and -2 [50, 51].

Recently, the 1 year results of two parallel randomized, double-masked phase 3 clinical trials (VIEW 1 and VIEW 2) on the efficacy and safety of VEGF Trap-Eye for the treatment of neovascular AMD were reported [51]. Phase I data demonstrated acceptable safety and tolerability of VEGF Trap-Eye in the treatment of neovascular AMD. In Phase II study data, patients dosed in a similar fashion to the PrONTO trial demonstrated stabilization of their vision that was similar to previous studies of ranibizumab at 1 year. All dosing regimens of VEGF Trap-Eye, including 2 mg bimonthly met the primary endpoint of non inferiority compared with monthly 0.5 mg ranibizumab with regard to the percentage of patients with maintenance (loss of <15 ETDRS letters) or improvement in vision. The all treatment groups showed a mean gain of 5.3 letters at 1 year. A greater mean improvement in VA compared with monthly 0.5 mg ranibizumab at 1 year versus baseline represented the secondary endpoint of the study. In both the North American study (VIEW 1) and international study (VIEW 2), more than 95% of patients in each of the following VEGF Trap-Eye dosing groups achieved maintenance of vision compared with 94% of patients on monthly ranibizumab: 0.5 mg monthly, 2 mg monthly, and 2 mg every 2 months. In VIEW 1, patients on 2 mg monthly dosing achieved the secondary endpoint with a mean gain of 10.9 ETDRS letters compared with 8.1 for monthly ranibizumab [51].

The results of the VIEW studies come at a critical time, when clinical evidence suggests that less frequent dosing of existing anti-VEGF therapy, particularly in the first year, may yield

inconsistent visual acuity outcome. In particular, the ability to achieve maintenance or improvement in VA with a more convenient every-other-month injection without need for intervening office visits may potentiate a shift in the current management of neovascular AMD. Continuation of the VIEW studies through the second year will assess the various VEGF Trap-Eye doses administered every 3 months, or more often in the case of worsening disease, as per protocol-defined 'quarterly capped PRN' schedule. Based on phase II data, VEGF Trap-Eye seems to be generally well tolerated with no serious drug-related adverse events. In the 157 patients enrolled in phase II trial, there were two deaths (one from pre-existing pulmonary hypertension and one from pancreatic carcinoma) and one arterial thromboembolic events (patient with a history of previous stroke), but no serious systemic events occurred related to VEGF Trap-Eye [51].

In contrast to current anti-VEGF antibodies, which are rapidly cleared, the VEGF Trap-Eye is relatively degraded more slowly. Due to its high binding affinity and the ability to safely inject high doses into the eye, VEGF Trap-Eye may have longer duration of effect in the eye. Its adoption into clinical practice will depend on efficacy at 4 and 8 week intervals. If effective at 4 and 8 week intervals, VEGF Trap-Eye may offer a competitive price advantage over ranibizumab and the opportunity to significantly reduce treatment burden on patients and physicians.

6. Conclusion

Blindness secondary to AMD is common across the world and the pathogenesis of this severe condition is not fully understood. However, the advent of anti-VEGF therapy has revolutionized therapy in the management of neovascular AMD. The appropriate method, dose, regimen, types of combination therapy, and the safety of anti-VEGF remain to be investigated but randomized trials are pending and may provide a clearer answer, which hopefully can help in the treatment of resistant CNV with longer time between treatments.

7. References

[1] Bressler, N.M., *Age-related macular degeneration is the leading cause of blindness.* JAMA, 2004. 291(15): p. 1900-1.

[2] Emerson, M.V. and A.K. Lauer, *Current and emerging therapies for the treatment of age-related macular degeneration.* Clin Ophthalmol, 2008. 2(2): p. 377-88.

[3] Shima, D.T., et al., *Hypoxic induction of endothelial cell growth factors in retinal cells: identification and characterization of vascular endothelial growth factor (VEGF) as the mitogen.* Mol Med, 1995. 1(2): p. 182-93.

[4] Ferrara, N., H.P. Gerber, and J. LeCouter, *The biology of VEGF and its receptors.* Nat Med, 2003. 9(6): p. 669-76.

[5] Kliffen, M., et al., *Increased expression of angiogenic growth factors in age-related maculopathy.* Br J Ophthalmol, 1997. 81(2): p. 154-62.

[6] Gragoudas, E.S., et al., *Pegaptanib for neovascular age-related macular degeneration.* N Engl J Med, 2004. 351(27): p. 2805-16.

[7] Aiello, L.P., et al., *Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders.* N Engl J Med, 1994. 331(22): p. 1480-7.

[8] Boyd, S.R., et al., *Correlation of increased vascular endothelial growth factor with neovascularization and permeability in ischemic central vein occlusion.* Arch Ophthalmol, 2002. 120(12): p. 1644-50.

[9] Kvanta, A., et al., *Subfoveal fibrovascular membranes in age-related macular degeneration express vascular endothelial growth factor.* Invest Ophthalmol Vis Sci, 1996. 37(9): p. 1929-34.

[10] Gaudreault, J., et al., *Pharmacokinetics and retinal distribution of ranibizumab, a humanized antibody fragment directed against VEGF-A, following intravitreal administration in rabbits.* Retina, 2007. 27(9): p. 1260-6.

[11] Gaudreault, J., et al., *Preclinical pharmacokinetics of Ranibizumab (rhuFabV2) after a single intravitreal administration.* Invest Ophthalmol Vis Sci, 2005. 46(2): p. 726-33.

[12] Brown, D.M., et al., *Ranibizumab versus verteporfin for neovascular age-related macular degeneration.* N Engl J Med, 2006. 355(14): p. 1432-44.

[13] Brown, D.M., et al., *Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: Two-year results of the ANCHOR study.* Ophthalmology, 2009. 116(1): p. 57-65 e5.

[14] Rosenfeld, P.J., et al., *Ranibizumab for neovascular age-related macular degeneration.* N Engl J Med, 2006. 355(14): p. 1419-31.

[15] Kaiser, P.K., et al., *Angiographic and optical coherence tomographic results of the MARINA study of ranibizumab in neovascular age-related macular degeneration.* Ophthalmology, 2007. 114(10): p. 1868-75.

[16] Sadda, S.R., et al., *Anatomical benefit from ranibizumab treatment of predominantly classic neovascular age-related macular degeneration in the 2-year anchor study.* Retina, 2010. 30(9): p. 1390-9.

[17] Spaide, R.F., et al., *Intravitreal bevacizumab treatment of choroidal neovascularization secondary to age-related macular degeneration.* Retina, 2006. 26(4): p. 383-90.

[18] Emerson, M.V., et al., *Intravitreal bevacizumab (Avastin) treatment of neovascular age-related macular degeneration.* Retina, 2007. 27(4): p. 439-44.

[19] Cleary, C.A., et al., *Intravitreal bevacizumab in the treatment of neovascular age-related macular degeneration, 6- and 9-month results.* Eye (Lond), 2008. 22(1): p. 82-6.

[20] Yoganathan, P., et al., *Visual improvement following intravitreal bevacizumab (Avastin) in exudative age-related macular degeneration.* Retina, 2006. 26(9): p. 994-8.

[21] Avery, R.L., et al., *Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration.* Ophthalmology, 2006. 113(3): p. 363-372 e5.

[22] Bashshur, Z.F., et al., *Intravitreal bevacizumab for treatment of neovascular age-related macular degeneration: a one-year prospective study.* Am J Ophthalmol, 2008. 145(2): p. 249-256.

[23] Algvere, P.V., et al., *A prospective study on intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration of different durations.* Acta Ophthalmol, 2008. 86(5): p. 482-9.

[24] Wu, L., et al., *Twelve-month safety of intravitreal injections of bevacizumab (Avastin): results of the Pan-American Collaborative Retina Study Group (PACORES).* Graefes Arch Clin Exp Ophthalmol, 2008. 246(1): p. 81-7.

[25] Arevalo, J.F., et al., *Intravitreal bevacizumab for subfoveal choroidal neovascularization in age-related macular degeneration at twenty-four months: the Pan-American Collaborative Retina Study.* Ophthalmology, 2010. 117(10): p. 1974-81, 1981 e1.

[26] Tufail, A., et al., *Bevacizumab for neovascular age related macular degeneration (ABC Trial): multicentre randomised double masked study.* BMJ, 2010. 340: p. c2459.

[27] Martin, D.F., et al., *Ranibizumab and bevacizumab for neovascular age-related macular degeneration.* N Engl J Med, 2011. 364(20): p. 1897-908.

[28] Rosenfeld, P.J., *Bevacizumab versus ranibizumab for AMD.* N Engl J Med, 2011. 364(20): p. 1966-7.

[29] Regillo, C.D., et al., *Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1.* Am J Ophthalmol, 2008. 145(2): p. 239-248.

[30] Abraham, P., H. Yue, and L. Wilson, *Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER study year 2.* Am J Ophthalmol, 2010. 150(3): p. 315-324 e1.

[31] Schmidt-Erfurth, U., et al., *Efficacy and safety of monthly versus quarterly ranibizumab treatment in neovascular age-related macular degeneration: the EXCITE study.* Ophthalmology, 2011. 118(5): p. 831-9.

[32] Spaide, R., *Ranibizumab according to need: a treatment for age-related macular degeneration.* Am J Ophthalmol, 2007. 143(4): p. 679-80.

[33] Brown, D.M. and C.D. Regillo, *Anti-VEGF agents in the treatment of neovascular age-related macular degeneration: applying clinical trial results to the treatment of everyday patients.* Am J Ophthalmol, 2007. 144(4): p. 627-37.

[34] Chiang, A. and C.D. Regillo, *Preferred therapies for neovascular age-related macular degeneration.* Curr Opin Ophthalmol, 2011. 22(3): p. 199-204.

[35] Lalwani, G.A., et al., *A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTO Study.* Am J Ophthalmol, 2009. 148(1): p. 43-58 e1.

[36] Boyer, D.S., et al., *A Phase IIIb study to evaluate the safety of ranibizumab in subjects with neovascular age-related macular degeneration.* Ophthalmology, 2009. 116(9): p. 1731-9.

[37] Tano, Y. and M. Ohji, *EXTEND-I: safety and efficacy of ranibizumab in Japanese patients with subfoveal choroidal neovascularization secondary to age-related macular degeneration.* Acta Ophthalmol, 2010. 88(3): p. 309-16.

[38] Dadgostar, H., et al., *Evaluation of injection frequency and visual acuity outcomes for ranibizumab monotherapy in exudative age-related macular degeneration.* Ophthalmology, 2009. 116(9): p. 1740-7.

[39] Rothenbuehler, S.P., et al., *Effects of ranibizumab in patients with subfoveal choroidal neovascularization attributable to age-related macular degeneration.* Am J Ophthalmol, 2009. 147(5): p. 831-7.

[40] Gupta, O.P., et al., *A treat and extend regimen using ranibizumab for neovascular age-related macular degeneration clinical and economic impact.* Ophthalmology, 2010. 117(11): p. 2134-40.

[41] Kang, S. and Y.J. Roh, *Ranibizumab treatment administered as needed for occult and minimally classic neovascular membranes in age-related macular degeneration.* Jpn J Ophthalmol, 2011. 55(2): p. 123-7.

[42] Kang, S. and Y.J. Roh, *One-year results of intravitreal ranibizumab for neovascular age-related macular degeneration and clinical responses of various subgroups.* Jpn J Ophthalmol, 2009. 53(4): p. 389-95.

[43] Beer, P.M., et al., *Intraocular concentration and pharmacokinetics of triamcinolone acetonide after a single intravitreal injection.* Ophthalmology, 2003. 110(4): p. 681-6.

[44] Cruess, A.F., et al., *Photodynamic therapy with verteporfin in age-related macular degeneration: a systematic review of efficacy, safety, treatment modifications and pharmacoeconomic properties.* Acta Ophthalmol, 2009. 87(2): p. 118-32.

[45] *Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: two-year results of a randomized clinical trial including lesions with occult with no classic choroidal neovascularization--verteporfin in photodynamic therapy report 2.* Am J Ophthalmol, 2001. 131(5): p. 541-60.

[46] Azab, M., et al., *Verteporfin therapy of subfoveal minimally classic choroidal neovascularization in age-related macular degeneration: 2-year results of a randomized clinical trial.* Arch Ophthalmol, 2005. 123(4): p. 448-57.

[47] Azab, M., et al., *Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: meta-analysis of 2-year safety results in three randomized clinical trials: Treatment Of Age-Related Macular Degeneration With Photodynamic Therapy and Verteporfin In Photodynamic Therapy Study Report no. 4.* Retina, 2004. 24(1): p. 1-12.

[48] Antoszyk, A.N., et al., *Ranibizumab combined with verteporfin photodynamic therapy in neovascular age-related macular degeneration (FOCUS): year 2 results.* Am J Ophthalmol, 2008. 145(5): p. 862-74.

[49] Heier, J.S., 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(11): p. 1532-42.

[50] *Aflibercept: AVE 0005, AVE 005, AVE0005, VEGF Trap - Regeneron, VEGF Trap (R1R2), VEGF Trap-Eye.* Drugs R D, 2008. 9(4): p. 261-9.

[51] Dixon, J.A., et al., *VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration.* Expert Opin Investig Drugs, 2009. 18(10): p. 1573-80.
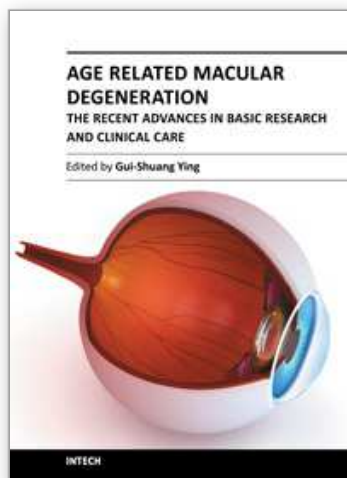
Age-related Macular Degeneration (AMD) is the leading cause of vision loss and blindness in the developed countries. In the past decade, great progress has been made in understanding the pathobiology and genetics of this blinding disease, as well as in finding new therapies for its treatment. These include the discovery of several genes that are associated with the risk of AMD, new anti-VEGF treatments for wet AMD and new imaging techniques to diagnose and monitor the AMD. All chapters in this book were contributed by outstanding research scientists and clinicians in the area of AMD. I hope this timely book will provide the basic scientists and clinicians with an opportunity to learn about the recent advances in the field of AMD.

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Young Gun Park, Hyun Wook Ryu, Seungbum Kang and Young Jung Roh (2012). Promising Treatment Strategies for Neovascular AMD: Anti-VEGF Therapy, Age Related Macular Degeneration - The Recent Advances in Basic Research and Clinical Care, Dr. Gui-Shuang Ying (Ed.), ISBN: 978-953-307-864-9, InTech, Available from: http://www.intechopen.com/books/age-related-macular-degeneration-the-recent-advances-in-basic-research-and-clinical-care/promising-treatment-strategies-for-neovascular-amd-anti-vegf-therapy

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