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Update on the Management of Age-related Macular Degeneration (AMD) Part I – Neovascular AMD

By Michael H. Brent, MD, FRCSC

Age-related macular degeneration (AMD) continues to be the leading cause of severe vision loss in North America and the developed world.[1] Approximately 17,000 new cases of neovascular AMD and 180,000 cases of geographic atrophy (dry) AMD occur in Canada each year.[2] This discussion of AMD will be presented in 2 parts in *Ophthalmology Rounds*. Part 1, in this issue, will focus on new approaches to the management of neovascular AMD, as well as potential therapies on the horizon. Part 2, in the next issue, will deal with new insights into the genetics of AMD and will also provide an update on trials aimed at slowing the progression of dry AMD to its neovascular form.

The management of neovascular AMD has evolved at an unprecedented rate since the last time this topic was discussed in *Ophthalmology Rounds*[3] and there have been encouraging visual outcomes. With the advent of the Macular Photocoagulation Study[4] in the 1980s, the outcome was considered successful if visual acuity loss was <30 letters. Once photodynamic therapy (PDT) with verteporfin became available in 2000, results were deemed successful if visual acuity loss was <15 letters. Today, intravitreal injections of anti-vascular endothelial growth factor (VEGF) not only maintain, but also improve visual acuity in patients suffering from neovascular AMD. There are several new approaches on the horizon that may also contribute to managing this challenging disease.

Anti-VEGFs

The newest class of drugs that is being used today to treat neovasular AMD is directed towards inactivating VEGF. This protein is secreted by retinal pigment epithelial (RPE) and retina cells in response to ischemia, and has been identified as a key mediator of neovascularization. VEGF induces endothelial cell growth, vascular permeability, and inflamatory cell chemotaxis. Anti-VEGF drugs for ocular disease target isoforms of VEGF-A, with varying degrees of specificity. Currently available anti-VEGF drugs are given as intravitreal injections, at intervals based on their half-life.

Pegaptanib sodium

Pegaptanib sodium (Macugen,® Eyetech/OSI Pharmaceuticals) was the first anti-VEGF drug proven to be safe and effective in treating neovascular AMD.[5] Pegaptanib is a 28-base ribonucleic acid aptamer that binds and blocks the activity of extracellular VEGF-165 isoform. It is highly selective, with high specificity and affinity, and is non-immunogenic. The VEGF Inhibition Study in Ocular Neovascularization (VISION) demonstrated the safety and efficacy of pegaptanib in a prospective, randomized, double-masked, multicentre, dose-ranging, controlled, clinical trial. Patients were randomized to 1 of 3 different doses of intravitreal pegaptanib, compared with usual care plus a sham injection, at baseline and every 6 weeks for 48 weeks. At 1 year, 70% of the patients assigned to the 0.3 mg dose of intravitreal pegaptanib lost <15 letters of visual

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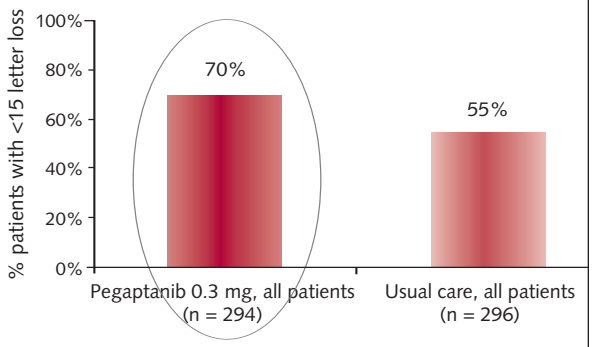
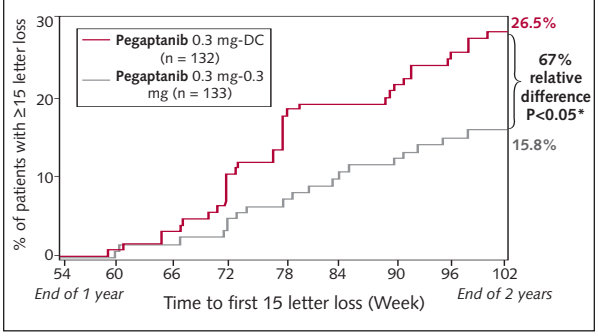
Figure 1: Patients receiving pegaptanib or usual care with or without PDT



acuity compared with 55% of patients in the usual care group (Figure 1). In other words, a larger percentage of patients in the pegaptanib-treated group met the primary endpoint of losing <15 letters on the eyechart, than did the usual-care group.

Patients were re-randomized to continue or to stop treatment during the second year of the study. Treatment benefit for pegaptanib was maintained at 102 weeks for those who continued intravitreal injections every 6 weeks. Patients who were randomized to discontinue pegaptanib injections after 1 year lost more visual acuity in the second year (Figure 2). Efficacy over 2 years was observed in patients with any lesion subtype (predominantly classic, minimally classic, or occult), irrespective of lesion size or baseline visual acuity. The most serious adverse ocular event was endophthalmitis, with an incidence of 1.8% in year 1. With an amendment to the injection procedure mandating pre-injection antibiotics and proviodine iodine, use of a lid speculum, sterile drape, and sterile gloves, the endophthalmitis incidence dropped to 0.7% by the end of year 2. Pegaptanib offered the first proven alternative to PDT, with similar visual acuity outcomes. Pegaptanib had the advantage of being proven effective for all lesion

Figure 2: Patients continuing pegaptanib for 2 years experienced less vision loss



DC = discontinued; * Nominal *P* value

subtypes, of any size. The disadvantage was that it required repeated intravitreal injections every 6 weeks, for at least 2 years, and possibly for life.

Ranibizumab

Ranibizumab (Lucentis,® Genentech/Novartis) is the newest anti-VEGF drug proven in clinical trials to be effective in treating neovascular AMD. It is a recombinant, humanized, monoclonal antigen-binding fragment (Fab) that binds and neutralizes all biologically-active isoforms of VEGF-A. The MARINA[6] and ANCHOR[7] trials were both 2-year, prospective, multicentre, randomized, double-masked, sham injection-controlled studies, evaluating the safety, tolerability, and efficacy of repeated intravitreal injections of ranibizumab in patients with neovascular AMD. The Phase IIIb, multicentre, randomized, double-masked, sham Injection-controlled study of Efficacy and safety of Ranibizumab (PIER) trial was a phase IIIb study that assessed whether fewer injections of ranibizumab over 1 year would result in visual acuity outcomes that were better than in sham-injected controls.

In the Minimally classic/occult trial of the Anti-VEGF antibody Ranibizumab In the treatment of Neovascular AMD (MARINA) trial, 716 patients with minimally classic or occult subfoveal neovascularization were randomized 1:1:1 to receive either intravitreal ranibizumab 0.3 mg, or 0.5 mg, or a sham injection monthly for a total of 24 injections over 2 years (Figure 3). Prior treatment with PDT precluded study entry. After 1 year, almost 95% of patients lost <15 letters of visual acuity, when treated with ranibizumab, compared to 62% of patients in the sham injection group (Figure 4). Patients treated with ranibizumab gained an average of 7 letters in visual acuity compared with baseline, whereas the control group lost an average of 10.5 letters. In addition,

Figure 3: Ranibizumab Studies
Phase III Studies – Min. Classic/Occult

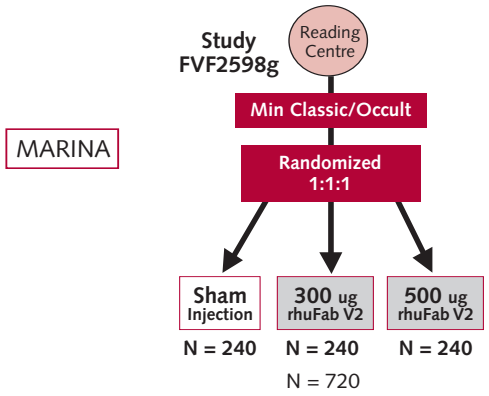
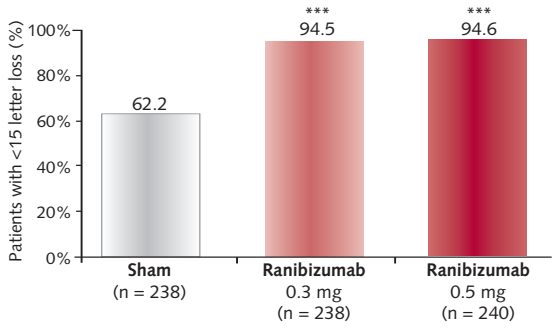


Figure 4: Primary endpoint: Ranibizumab prevents vision loss



***p<0.0001 *vs* sham

MARINA study MONTH 12

34% of patients treated with the 0.5 mg dose of ranibizumab improved vision by gaining ≥15 letters. Forty per cent of ranibizumab-treated patients achieved 20/40 vision or better at 12 months. Improvements in visual acuity in the ranibizumab group were maintained through 24 months, while there was further vision loss amongst patients in the control group.

In the ANti-VEGF antibody for treatment of predominantly classic CHORoidal neovascularization in AMD (ANCHOR) trial, 423 patients with predominantly classic subfoveal neovascularization were randomized 1:1:1 to receive either intravitreal ranibizumab 0.3 mg, or 0.5 mg monthly for a total of 24 injections over 2 years, or PDT at baseline and every 3 months as necessary according to standard guidelines for 2 years (Figure 5). For those patients receiving PDT, a sham injection was performed every month for 2 years. For patients randomized to ranibizumab, a sham PDT was performed at baseline and every 3 months as necessary according to standard guidelines. At 1 year, 96% of the patients treated with ranibizumab 0.5 mg lost <15 letters of visual acuity, compared to 64% of those patients treated with PDT (Figure 6). There was an average *gain* of 11.3 letters in the 0.5 mg group, compared to an average *loss* of 9.5 letters in the PDT-treated group. In the ranibizumab 0.5 mg group, 40% of patients gained ≥15 letters of visual acuity, compared to 6% in those treated with PDT. Visual acuity of 20/40 or better was achieved by 39% of the ranibizumab 0.5 mg group compared with only 3% of patients treated with PDT.

In both the MARINA and ANCHOR trials, the most common serious adverse ocular events were registered in <1% of patients and included endophthalmitis and uveitis. Serious systemic adverse events were rare, with a slightly, but not statistically significant, increase in myocardial infarction (MI) and cerebral vascular events in the ranibizumab group. Ranibizumab produced early anatomical benefits, with reduction in central retinal thickness at day 7, as measured by optical coherence tomography, and improvement in angiographic stability at 3 months. Early benefits in mean visual acuity were demonstrated at 1 month. The MARINA and ANCHOR trials demonstrated the safety and efficacy of ranibizumab in treating all lesion subtypes of neovascular AMD. It is a quantum leap in the management of wet AMD since it is the first treatment to improve visual acuity for a significant proportion of patients, across all lesion subtypes. It has been approved by the FDA in the USA, and is in use today south of the border. Ranibizumab has not yet been approved in Canada, but it has been given priority review status by the Federal Health Protection Branch. A decision regarding the approval of ranibizumab should be made no later than July 2007.

In the PIER trial, 184 patients with subfoveal neovascular AMD, with or without a classic component, were randomized 2:1 to receive either ranibizumab 0.5 mg intravitreally, or a sham injection. In the ranibizumab group, patients were injected monthly for 3 months, and then every 3 months for 24 months. The 1-year results showed an initial

Figure 5: Ranibizumab Studies
Phase III Studies – Classic CNV

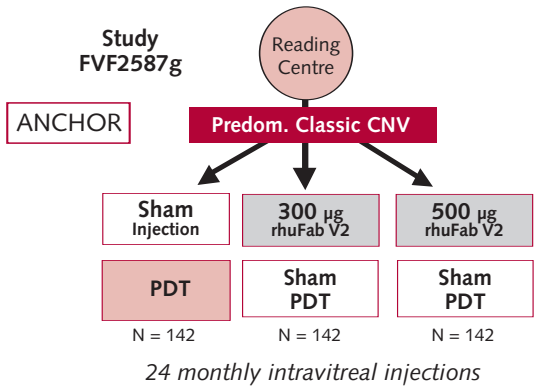
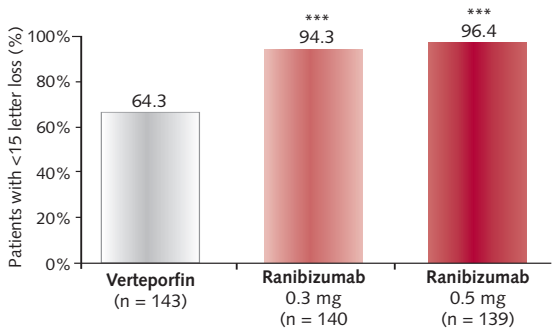


Figure 6: Primary endpoint: ranibizumab preserves vision



ANCHOR study MONTH 12

***p<0.0001 *vs* verteporfin

improvement in visual acuity for 3 months, and then a gradual loss of gained vision back to baseline by 1 year. This trial demonstrated that initial gains in vision achieved by monthly intravitreal injections of ranibizumab can be lost if the dosing interval is lengthened.

Bevacizumab

Bevacizumab (Avastin;® Genentech) is a full-length, monoclonal IgG antibody that binds and neutralizes all biologically-active isoforms of VEGF-A. Bevacizumab and ranibizumab are derived from the same mouse monoclonal anti-VEGF antibody,[8] but bevacizumab (148kd) is 3 times larger than ranibizumab (48kd). Bevacizumab has 2 binding sites to ranibizumab's one, but ranibizumab has a much higher affinity for VEGF-A. Initial primate studies raised concerns about bevacizumab's ability to penetrate through the retina from the vitreous.[9-11] Therefore, research was directed towards developing a similar drug, with a smaller molecular weight that could easily penetrate the internal limiting membrane of the human retina. Bevacizumab was approved for treatment of colorectal cancer in 2004 and became available for off-label use. The rationale for using intravitreal bevacizumab was based on the promising success of ranibizumab in early trials and the overall similarity between the 2 drugs.

Philip Rosenfeld et al first reported the use of bevacizumab systemically and intravitreally for treatment of neovascular AMD.[12,13] Intravenous administration of bevacizumab 5 mg/kg at 2-week intervals produced a significant reduction in retinal thickening and an improvement in visual acuity in a small series of patients. Intravitreal injection of bevacizumab 1 mg was found to cause a marked reduction in retinal thickening, without short-term toxicity. Systemic administration of bevacizumab is associated with an increased risk of stroke and MI in patients with cancer. The dose of intravitreal bevacizumab injected into the vitreous is 1/400th of the intravenous dose. It has been assumed that this should translate into a lower risk of developing systemic adverse effects. Fung et al recently published an international, intravitreal bevacizumab, internet-based self-reporting safety survey.[14] The total number of injections reported was 7,113 in 5,228 patients. Results demonstrated no increased rate of drug-related ocular or systemic effects. These short-term results suggest that intravitreal bevacizumab is safe.

Subsequent to Rosenfeld's initial reports, the use of bevacizumab rapidly spread worldwide. To date, there have been no prospective, multicentre, clinical trials reported to determine the safety and efficacy of bevacizumab. Several case reports and pilot studies have been published in peer-reviewed journals supporting anatomical improvements with concomitant improvement in visual acuity. Bevacizumab is considerably less expensive than ranibizumab and, due to its larger size, bevacizumab appears to have a longer half-life. This allows intravitreal bevacizumab injections to be given every 6-8 weeks, rather than every 4 weeks for ranibizumab. Although intravitreal bevacizumab appears to be effective as a treatment for neovascular AMD, it is unknown whether it is as effective as intravitreal ranibizumab. The National Eye Institute (NEI) has announced that it will sponsor a trial to compare the 2 drugs. Since ranibizumab has not yet been approved in Canada, bevacizumab is in widespread use by retina specialists across the country.

Combination therapy

There is a growing trend internationally to consider the use of more than one drug to treat neovascular AMD. Similar to the approach in oncology, different drugs can be used to effectively target the underlying physiological pathways responsible for neovascularization, its recurrence, and subsequent subretinal fibrosis. Currently, the mechanism of action of PDT with verteporfin is to cause vaso-occlusion and thrombosis of the neovascular complex. As a result of vessel closure, however, hypoxia develops in the surrounding tissue, VEGF is upregulated, and there is release of inflammatory cytokines. VEGF upregulation promotes endothelial cell proliferation and vascular permeability. The result is recurrence of the neovascular complex. This explains why it takes several sessions of PDT with verteporfin to eventually close the neovascular complex. During this time, however, subretinal fibrosis develops and this is likely the most responsible cause of the moderate visual acuity loss seen in patients treated with PDT monotherapy.

Anti-VEGF drugs bind and neutralize extracellular VEGF and extinguish the drive for neovascularization. They help to prevent the development of subretinal fibrosis. They do not, however, cause vaso-occlusion and, once anti-VEGF therapy is withdrawn, neovascularization often recurs. This has been illustrated in the

VISION trial using pegaptanib monotherapy. Patients who stopped intravitreal pegaptanib in year 2 of the study developed recurrent neovascularization with a concomitant decrease in visual acuity. In the PIER study, initial visual acuity gains were lost when the interval between ranibizumab injections was increased from monthly to every 3 months. The rationale for combination therapy is to use visudyne to initiate vaso-occlusion, but also to inject an intravitreal anti-VEGF agent to prevent upregulation of VEGF, revascularization, and subsequent subretinal fibrosis. Some retina specialists are also adding intravitreal dexamethasone in attempt to extinguish any inflammatory response caused by the release of inflammatory cytokines during neovascular involution. This triple therapy approach is in its early stages of clinical application. The hope is that combination therapy will decrease the frequency and number of treatments necessary, maintain or improve visual acuity, and prevent subretinal fibrosis.

Currently, there is a multicentre Canadian and an American registry in place to collect data on the safety and efficacy of combination PDT and intravitreal bevacizumab for the treatment of neovascular AMD. Novartis has also announced that it will sponsor a prospective, randomized, double-masked, controlled, multicentre, phase IIIb combination therapy study. The DENALI trial will assess the safety and efficacy of PDT with verteporfin administered in conjuction with ranibizumab, versus ranibizumab monotherapy, in patients with subfoveal choroidal neovascularization secondary to AMD. There will be 8 sites in Canada participating in the DENALI trial, along with centres in the USA. The trial is scheduled to start in Spring 2007.

Future therapies

Several new approaches to the management of neovascular AMD are currently in development and may be available within the next few years. Feeder vessel therapy involves identifying feeder vessels in the choroid that propagate the neovascular complex. These are identified using high-speed indocyanine green (ICG) angiography, taking up to 30 frames per second. Once identified, ICG-mediated thrombosis of the feeder vessels is achieved using thermal laser. This results in complete closure of the whole neovascular complex. This technology is currently in Phase 2 clinical trials.

The VEGF trap[15] is a soluble protein that acts as a decoy VEGF receptor, and prevents VEGF interaction with its target receptors. The VEGF trap binds VEGF-A with a higher affinity than does pegaptanib, ranibizumab, or bevacizumab. Phase III clinical trials are slated to start soon.

RNA interference[16] is a novel approach to treating neovascular AMD by inhibiting the production of VEGF at the intracellular level. Cells can inhibit specific protein production by silencing genes coding for a particular protein. A double-stranded RNA molecule is incorporated into the cell cytoplasm, that is then cleaved to form an RNA-induced silencing complex. This complex binds to messenger RNA for a particular protein, such as VEGF, to inhibit its production. In effect, the small interfering RNA (siRNA) eliminates VEGF synthesis.

Squalamine lactate is derived from the cartilage of the dogfish shark.[15] It is an intravenously-administered, antiangiogenic, small molecule that blocks the action of a number of angiogenic growth factors, including VEGF. It is currently being tested in a phase 3 clinical trial in patients with neovascular AMD.

Finally, small molecule receptor tyrosine kinase inhibitors bind all VEGF receptors and prevent signal transduction and gene expression.[15] This effectively prevents VEGF synthesis. Clinical trials are in early phases.

Conclusion

Management of neovascular AMD is changing quickly, with multifaceted approaches and innovative new therapies targeting different stages of angiogenesis. The next few years should be very exciting in bringing us closer to controlling this very prevalent and devastating disease.

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Upcoming events

March 1, 2007 VPP Dr. Jurij Bilyk, Philadelphia, Pennsylvania
"Advances in Orbital Imaging"

March 8, 2007 VPP Dr. Joseph Mikhael, PMH, Toronto
"Physician/Patient Communication — More than Just Talking"

March 30, 2007 18th annual Jack Crawford Day
Hospital for Sick Children
Contact: Ms. Karen Martin 416-978-2719

April 12, 2007 Retina VPP (TBA)

April 14, 2007 International Mini-Symposium on Diabetic Retinopathy
"NeuroVascular Dysfunction in Diabetes: The Eye as Window"
Course Director: Dr. Shelley Boyd
Location: MaRS Bldg.
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http://www.cme.utoronto.ca/education/neurovascular.asp

April 26, 2007 VPP – Dr. Janet Davis, Miami, Florida
"Local and Systemic Therapy for Uveitis"

May 3, 2007 VPP – Dr. Arif Samad, Halifax, Nova Scotia
"The Evolution of Retinal Anti-Angiogenic Therapy"

May 10, 2007 VPP – Dr. Mina Chung, Rochester, New York
"Adaptive Optics Imaging of the Retina"

May 17, 2007 VPP – Dr. William Macrae
"Quality Assurance Rounds"

May 31, 2007 VPP – Dr. Thomas Freddo, U of Waterloo (Ocular Pathology)

June 15, 2007 48th Annual Departmental Research Day
Location: JJR McLeod Auditorium, Medical Sciences Building, U of Toronto
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Note: This year's (September 2006 to May 2007) VPP rounds will be held at Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, 'E' Wing, Ground Fl, Room EG61 at 5:30PM – 7:30PM.

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