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Update on Age-Related Macular Degeneration

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In developed countries, age-related macular degeneration (AMD) is the leading cause of irreversible legal blindness in adults ≥65 years of age. Considering the current increase in life expectancy and the projected increase in the average age of the population, AMD is likely to become a major public health concern in the future. After the sixth decade of life, the prevalence of AMD increases with each decade, such that in Canada alone, approximately 17 000 new cases of neovascular AMD and 180 000 new cases of non-neovascular AMD occur every year. In the United States, over 500 000 adults have the neovascular form of AMD with over 12% of these cases at risk each year for the development of choroidal neovascularization (CNV) in the fellow eye.[1] This issue of *Ophthalmology Rounds* reviews current treatments and future therapies for AMD.

Current pathophysiological concepts hold that the site of AMD development is the retinal pigment epithelium (RPE)–Bruch membrane (BM)–choriocapillaris (CC) complex. In the atrophic form of AMD, also known as "dry" AMD, drusen form and are associated with a variable amount of atrophy in neighbouring RPE cells, which may or may not involve the fovea. The underlying BM and CC become involved, resulting in damage to overlying photoreceptors. Depending on the exact location of these atrophic changes in relation to the fovea, this process may or may not cause distortion and/or loss of central vision. With extensive involvement of the subfoveal RPE–BM–CC complex, the effect on visual acuity (VA) can be very severe, to the point of causing legal blindness even in atrophic AMD.

In the neovascular form of AMD, new blood vessels develop from pre-existing choroidal vessels beneath BM and begin to grow toward the membrane. Where breaks are present in BM, these new blood vessels can invade the sub-RPE space or even the subretinal space, if breaks are also present in the RPE layer. These choroidal neovascular channels have poorly formed blood vessel walls and, consequently, often leak blood and fluid into the subretinal and sub-RPE spaces (Figure 1), which can lead to secondary photoreceptor damage over a wide area of macula, producing a severe loss of vision. Eventually, these choroidal neovascular channels stop growing and spreading, and undergo progressive scarring with a lower tendency to leak fluid or blood. Instead, a large subretinal or sub-RPE scar forms, sometimes called subretinal fibrosis, causing permanent and complete loss of central vision.

Since 1962, with the earliest descriptions of choroidal neovascularization seen on fluorescein angiography (FA), it has been standard practice to distinguish 3 main types of CNV: classic, occult, or a combination of the 2 depending on the FA appearance of the neovascular complex and its leakage characteristics. These leakage patterns are thought to be specific enough to reliably indicate the location of the CNV complex in either the subretinal space ("classic" leakage) or sub-RPE space ("occult leakage") or both spaces (Figure 2). This classification was initially utilized in studies of the effectiveness of photodynamic therapy (PDT) with visudyne in AMD that grouped patients according to the type and degree of "classic" CNV features as seen on FA. These subcategories were termed classic, predominantly classic, minimally classic, or occult (ie, no classic features). Recent clinical trials have continued to use this differentiation, although it is no longer thought to be of great value.[2]

Currently, management of AMD comprises both prevention and treatment. Prevention of the advanced stages of neovascular AMD is accomplished through the daily use of vitamin and mineral supplementation, particularly in patients who have already developed

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Figure 1: Retinal photograph of neovascular AMD showing submacular CNVM partially surrounded by subretinal blood.

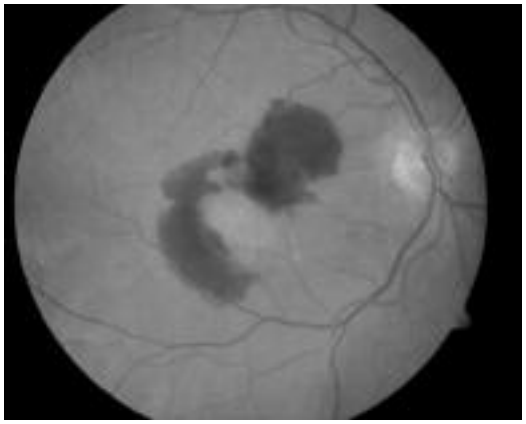
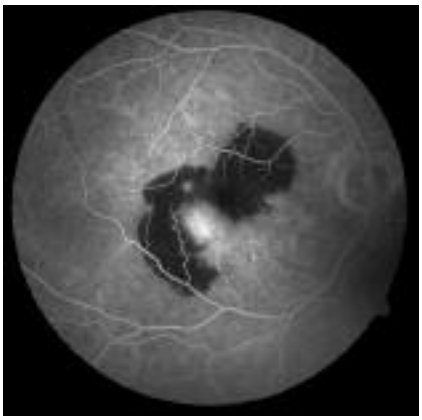


Figure 2: Fluorescein angiogram of neovascular AMD (same case) showing subretinal CNVM partially obscured by subretinal blood.



AMD = age-related macular degeneration;
CNVM = choroidal neovascular membrane

neovascular AMD in one eye. Treatment methods have evolved rapidly over the last 10 years, especially with the demonstration of dramatic vision improvements in a significant percentage of neovascular AMD patients treated with intravitreal anti-vascular endothelial growth factor (VEGF) medications. Many more new treatment options are also on the horizon and these very recent advances in CNV treatment have created an atmosphere of optimism, leading to higher expectations for visual improvement in both patients and treating physicians. The definition of treatment success has changed considerably since the original AMD study. The Macular Photocoagulation Study in the 1980s considered success as no improvement in VA and <30 letters of VA loss. Studies using PDT raised the definition of success to a loss of <15 letters. Currently, randomized clinical trials investigating various treatment protocols involving periodic intravitreal injections of anti-VEGF medications regard success as achieving, at a minimum, stabilization of vision in over 95% of treated patients and improvement in vision in at least 30%-40% of cases.

The Age-Related Eye Disease Study (AREDS)

In recent years, recommendations were made by the lay press and in anecdotal reports from the medical literature concerning the type of diet and/or nutritional supplements required to produce the greatest benefit in preventing or delaying the onset of AMD for the elderly. AREDS was designed to study a particular combination of vitamins, antioxidants, and minerals in certain well-defined groups of AMD patients to determine recommendations. More specifically, AREDS examined the effectiveness of this combination of agents in decreasing the rate of progression in AMD to the more advanced neovascular or central geographic atrophy (GA) stages. Patients were randomized to receive placebo, antioxidants alone, zinc/copper alone, or a combination of antioxidants, zinc, and copper. The AREDS study concluded that, for patients over age 55 with already advanced AMD in one eye, namely, category 3 (extensive intermediate size drusen, at least 1 large drusen, noncentral GA in one or both eyes) or category 4 (advanced AMD or vision loss due to AMD in one eye), antioxidants plus zinc produced the largest reduction in risk of vision loss and in the development of advanced AMD. The measured effectiveness was a 25% risk reduction in progression to advanced AMD and a 27% reduction in the risk of losing VA as measured by loss of >15 letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart. Patients taking antioxidants alone or zinc alone also experienced some benefit, although to a lesser extent. Based upon these findings, the AREDS study recommended zinc supplementation with antioxidants as contained in the "AREDS" formula for patients with category 3 or 4 AMD. Given that the use of beta carotene increases the rate of lung cancer in cigarette smokers, an AREDS formula without beta carotene (ie, AREDS-S) was developed and is commercially available.

Further to the success of the AREDS study, AREDS-2 is currently examining the role of dietary lipids in AMD prophylaxis for selected patients at severe AMD risk. It is hypothesized that increased dietary intake of green leafy vegetables, containing lutein and zeaxanthin, and certain kinds of fish, containing omega-3 long-chain polyunsaturated fatty acids, may also help reduce the risk of developing advanced AMD.[4,5] As well, given the concerns surrounding the increased cancer risk for cigarette smokers taking beta carotene, and the concerns about a possible association between zinc and benign prostatic hypertrophy and possibly Alzheimer disease, AREDS-2 is investigating the effects that omitting beta carotene and reducing zinc to 25 mg instead of 80 mg may have on risk reduction in primary outcomes. Results of AREDS-2 are expected in 2012.

Anti-VEGF treatments

The mainstay of current treatment for neovascular AMD is the intravitreal injection of medications that act as antagonists to circulating VEGF-A in the eye. The aim of treatment is to counteract 2 properties of VEGF-A, namely, its ability to increase vascular permeability and its role in promoting CNV. There are a number of isoforms of VEGF-A, and the most pathogenic in the eye is VEGF-A 165. Only 2 anti-VEGF agents have been approved thus far for intravitreal injection, namely, pegaptanib, which specifically targets VEGF-A 165, and ranibizumab, which targets all isoforms of VEGF-A, nonspecifically. A third agent, bevacizumab, the compound from which ranibizumab was developed, is not approved, but is widely used "off-label" as a substitute for ranibizumab because of its lower cost. Although these 3 agents are effective in counteracting the actions of VEGF-A present in the eye at the time of intravitreal injection, their duration of action is short-lived and repeat injections are required to treat AMD until the natural cycle of neovascularization and permeability subsides.

Pegaptanib

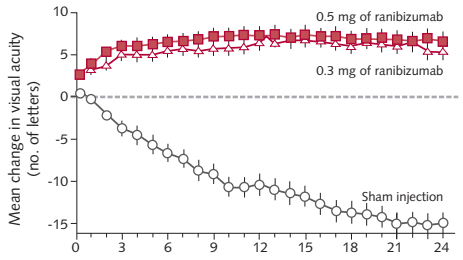
Pegaptanib is a ribonucleic acid (RNA) oligonucleotide. In the VEGF Inhibition Study in Ocular Neovascularization (VISION) trial, pegaptanib was effective in reducing moderate vision loss (MVL) and severe vision loss (SVL) in patients with all types and sizes of CNV, when given as an intravitreal injection every 6 weeks for up to 24 months.[6] Patients who received pegaptanib lost <3 lines of vision (MVL) in 65%-71% of cases versus 55% with placebo. FA revealed a reduction in CNV growth and leakage in pegaptanib patients compared with placebo injection. Adverse ocular events, such as endophthalmitis, retinal detachment, and lens injury rarely occurred. Most important, however, was the failure of pegaptanib to improve VA. Only 4%-7% of the pegaptanib group gained >3 lines of VA versus 2% in the placebo group; as a result, pegaptanib is infrequently used as a first option in the treatment of neovascular AMD.

Ranibizumab

Ranibizumab is a 48 kDa recombinant, humanized monoclonal antibody fragment (Fab portion), a derivative of the larger 149 kDa compound, bevacizumab. Ranibizumab was developed from the parent compound as a smaller molecule to more easily penetrate the retina from the vitreous and thus readily gain access to subretinal CNV where the presence of VEGF-A is at the highest concentration.

The Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA)[7] study was a 2-year, Phase III, multicentre, prospective, randomized, sham-controlled evaluation of 716 patients who received monthly ranibizumab

Figure 3: MARINA: mean changes from baseline in visual acuity over 24 months[7]



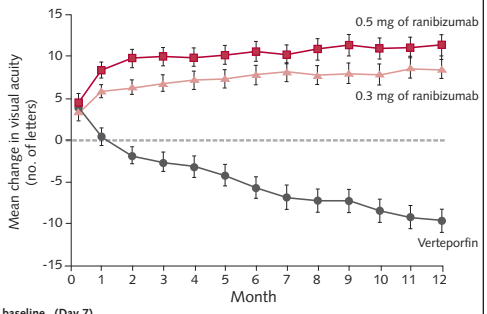
Mean change from baseline	(Day 7)								
0.5 mg of ranibizumab	+2.6	+5.9	+6.5	+7.2	+7.2	+7.4	+6.8	+6.7	+6.6
0.3 mg of ranibizumab	+2.3	+5.1	+5.6	+5.9	+6.5	+6.9	+6.1	+6.2	+5.4
Sham injection	+0.6	-3.7	-6.6	-9.1	-10.4	-11.8	-13.6	-15.0	-14.9

At each monthly assessment, $P<0.001$ for the comparison between each ranibizumab group and the sham-injection group. On Day 7, $P=0.006$ for patients receiving 0.3 mg of ranibizumab and $P=0.003$ for those receiving 0.5 mg.

intravitreal injections for minimally classic or occult CNV due to AMD. This landmark study found that ranibizumab was effective, independent of lesion type, baseline VA, and lesion size; further, at 2 years after beginning injections, 92% and 90% of patients receiving 0.3 or 0.5 mg of ranibizumab, respectively, lost <3 lines of vision compared with 52.9% of patients in the placebo group. There was also a significant difference in the prevention of SVL: only 3.4% and 2.5% of the 0.3 mg and 0.5 mg groups, respectively, experienced SVL at 24 months compared with 22.7% of the placebo group. Most remarkably, 26.1% and 33.3% of patients in the 0.3 mg and 0.5 mg group, respectively, gained 3 lines of VA versus 3.8% of those receiving sham injection, at 2 years (Figure 3). The average gain for patients treated with ranibizumab was 6.6 letters in VA compared with the sham injection group that lost an average of 14.9 letters. This difference of 21.0 letters represents almost 4 lines of VA difference in favour of ranibizumab versus placebo. Moreover, 34.5% and 42.1% of the 0.3- and 0.5-mg groups of ranibizumab-treated patients, respectively, achieved 20/40 vision or better at 2 years. In both groups, lesion growth and leakage, as demonstrated by FA, were reduced by ranibizumab at 2 years. Systemic adverse events and mortality rates were comparable for ranibizumab and placebo groups.

The Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD (ANCHOR)[8] study was a second landmark study involving ranibizumab. This was a 2-year, Phase III, multicentre, randomized, active-treated, controlled, double-blind study of 423 patients with classic neovascular AMD comparing monthly intravitreal injections of ranibizumab (0.3 mg or 0.5 mg) with PDT and a placebo injection. At 24 months, 90% of patients in both the 0.3 mg and 0.5 mg ranibizumab groups had lost <15 letters from baseline compared with 66% of patients in the PDT group. At 2 years, 34% and 41% of patients receiving 0.3 mg and 0.5 mg of ranibizumab, respectively, had gained >15 letters compared with only 6% in the PDT

Figure 4: ANCHOR: mean changes in the number of letters read as a measure of visual acuity from baseline through 12 months[8]



Mean change from baseline	(Day 7)												
0.5 mg of ranibizumab	+4.6	+8.4	+9.8	+10.0	+9.9	+10.2	+10.6	+10.2	+10.9	+11.4	+10.9	+11.1	+11.3
0.3 mg of ranibizumab	+2.9	+5.9	+6.4	+6.8	+7.2	+7.4	+7.9	+8.2	+7.7	+8.1	+7.8	+8.6	+8.5
Verteporfin	+3.9	+0.5	+1.8	+2.5	-3.1	-4.1	-5.6	-6.8	-7.1	-7.1	-8.3	-9.1	-9.5

P<0.001 for all monthly comparisons of each dose of ranibizumab with verteporfin.

group. The mean gain was 8.1 and 10.7 letters in the 0.3- and 0.5-mg ranibizumab groups, respectively, compared with a mean loss of 9.8 letters in the PDT group (Figure 4). In a subgroup analysis of patients who entered the study with vision between 20/80 and 20/200 and those patients with smaller lesions (<2 disc areas), 50% achieved VA gains of >15 letters. There were no cases of SVL in the ranibizumab groups, but SVL did occur in 13.3% of patients in the PDT group. Ranibizumab was more effective than PDT in all measures studied on FA as well. Systemic adverse events were equivalent between the 2 groups.

A third landmark study involving ranibizumab was the rhuFAB v2 Ocular treatment Combining the Use of visudyne to evaluate Safety (FOCUS) study.[9] This 2-year, Phase I/II, multicentre study randomized 162 patients with predominantly classic CNV to ranibizumab plus verteporfin PDT versus verteporfin PDT alone. All patients received initial treatment with PDT at baseline followed by ranibizumab or sham injection 7 days after PDT. Patients were retreated with PDT at 3-month intervals based on FA leakage as determined by the treating physician. In the first year, a relatively large number of transient cases of uveitis were observed (approximately 9%), leading to an amended protocol in the second year involving a liquid formulation of ranibizumab instead of the lyophilized formulation. At 24 months, 25% of patients receiving ranibizumab + PDT compared with 7% of PDT alone gained >3 lines of VA; the average VA difference between the 2 arms was 12.4 letters. The study concluded that ranibizumab with PDT was more effective than PDT alone and there was a low rate of associated adverse events. Recently, the suggestion that combining ranibizumab with PDT may reduce the number of required retreatments is currently under examination in a number of ongoing clinical studies.

A fourth study of ranibizumab, the Phase IIIB multicenter randomized double-masked sham Injection controlled study of the Efficacy and safety of Ranibizumab (PIER) study,[10] examined alternative dosing regimens for intravitreal ranibizumab to determine whether injections given at longer intervals than the previous standard of 4 weeks would yield the same effectiveness as the monthly dosing of the MARINA and ANCHOR studies. This 2-year study examined the results in 184 patients treated with 3 consecutive monthly intravitreal injections of ranibizumab followed by additional injections every 3 months. At 1 year, 83% and 90% (0.3 mg and 0.5 mg, respectively) lost <3 lines of VA versus the placebo group (49%); however, improvement in VA was infrequently observed. There was an initial improvement in VA during the first 3 months of treatment with 13.1% of the 0.5-mg ranibizumab group gaining ≥15 letters versus 9.5% of the sham group; however, as in the other studies, this treatment effect was lost at the 1-year follow-up, since VA tended to return to baseline with an observed gain of 0.2 letters. With injection intervals of 3 months, the treatment benefit observed in 4-week intervals was lost. The authors concluded that the PIER regimen of extending the treatment intervals to 3 months provides less benefit than continued monthly dosing.

Another study of ranibizumab that examined less-frequent dosing schedules was the Prospective OCT Imaging of Patients with Neovascular AMD with Intra-Ocular Lucentis (PrONTO) study).[11] This open-label, nonrandomized study examined 40 patients given intravitreal injections of 0.5 mg of ranibizumab. The patients were first treated for 3 consecutive months. Subsequent retreatments were done based on the presence of certain criteria: increase in retinal thickness of >100 µm on optical coherence tomography (OCT), loss of 5 ETDRS letters on VA testing, recurrent fluid on OCT, new onset of classic CNV, or new macular hemorrhage. This treatment algorithm resulted in a mean VA improvement of 10.7 letters at 24 months with improvement by ≥15 letters in 43% of patients. Patients received an average of 5.6 injections in the first year of the study, and 9.9 injections in the 2-year period. A mean injection-free interval of 4.5 months was achieved once the macula became free of subretinal fluid. This study demonstrated that monthly monitoring and the use of particular retreatment criteria resulted in VA outcomes similar to those achieved in the MARINA and ANCHOR studies, but with fewer injections.

Summary of ranibizumab studies

Significant improvements in VA are now possible in neovascular AMD, but to achieve and maintain VA improvement seems to require monthly injections. Many innovative protocols have been devised in attempts to reduce this requirement, including evidence for continued activity of neovascular AMD before retreatments and tailoring therapy according to changes in OCT thickness measurements, VA changes, or macular findings on clinical examination. These treatment algorithms are often difficult to follow, however, due to a number of contradictory findings; for example, fluid accumulation as seen on OCT does not always correlate

with VA loss, suggesting that vision loss in AMD may be due to other more difficult to measure factors that have nothing to do with fluid accumulation.

The Ranibizumab Safety in Previously Treated and Newly Diagnosed Patients with Neovascular Age-related Macular Degeneration (SAILOR) study[12] was yet another prospective, uncontrolled study to determine whether the frequency of retreatments following a loading schedule of 3 consecutive monthly injections of ranibizumab could be based on OCT measurements of 100 µm increased thickening or physician discretion. With these criteria for retreatment, SAILOR also failed to achieve the vision gains seen in MARINA and ANCHOR; thus, anatomical changes alone cannot reliably determine the need for retreatment, and other factors (eg, inflammation, cell injury, or even synapse disruption) may be involved. These other factors may be mediated by VEGF and may persistently cause damage whenever anti-VEGF treatment is withheld because OCT demonstrates no reaccumulation of fluid.

Although reliance on OCT thickness measurements alone is a poor predictor of the need for retreatment, the precise mechanisms that underlie deterioration in VA measurements remain to be elucidated. The current level of understanding about these mechanisms does not allow certainty that anti-VEGF therapy is necessarily the best remedy for a particular patient in whom VA has deteriorated following initial improvement with the standard of 3 consecutive monthly injections of ranibizumab.

Bevacizumab

Bevacizumab was the first anti-VEGF compound to be used against neoangiogenesis. This 149 kDa full-length immunoglobulin antibody was originally designed for the treatment of metastatic colon cancer to bind VEGF and prevent the development of new blood vessels within a tumour. It was considered that the tumour would lack a sufficient blood supply for viability and would undergo necrosis. With this ability of bevacizumab to block VEGF, it was thought that inhibiting VEGF promotion of CNV development would be useful in AMD. The first ophthalmic use of bevacizumab in AMD involved intravenous infusion as with colon cancer, but side effects such as stroke and thrombosis presented an unacceptably high risk for elderly AMD patients. Intravitreal injection of bevacizumab was considered, but it was assumed that the large size of the molecule would prevent penetration from the vitreous into the subretinal space where VEGF is present. Nevertheless, it was tried and, in a number of noncontrolled studies, effectiveness in AMD was demonstrated. Consequently, "off-label" treatment with bevacizumab for a number of ocular disorders including neovascular AMD has become common practice. Several retrospective studies have reported good results; eg, a study of 51 eyes with bevacizumab injections for this disorder had a mean VA improvement of 7.4 letters at 12 months, which is similar to the results using ranibizumab.[13] A National Eye Institute comparative trial is currently underway to compare bevacizumab directly with ranibizumab in the Comparison of AMD Treatment Trial (CATT).[14]

Intraocular steroids

Corticosteroids have a number of properties that may be useful in the treatment of neovascular AMD. The pathogenesis of CNV involves both angiogenesis and complement-based inflammatory mechanisms. The ability of corticosteroids to act as an antiangiogenic and anti-inflammatory agent suggests possible benefits in neovascular AMD. In some animal models, corticosteroids have decreased VEGF production. The anti-inflammatory effects of corticosteroids may reduce endothelial cell migration from choroidal vessels and may also suppress matrix metalloproteinases that are present in CNV. Matrix metalloproteinases are thought to worsen CNV damage by breaking down basement membranes and extracellular matrix components that might otherwise limit the invasion of CNV into the subretinal and sub-RPE spaces.

Triamcinolone acetonide

Studies of intravitreal triamcinolone acetonide (IVTA) in neovascular AMD have found short-term improvements in VA. A prospective, nonrandomized series of 187 patients treated with 25 mg IVTA (a relatively high dose) demonstrated improvement in VA at 1 and 3 months after injection, although treatment benefit was not sustained at the 6-month follow-up.[15] Similar studies have concluded that there may be no long-lasting benefit in using IVTA for neovascular AMD, especially as monotherapy. Moreover, IVTA has many known side effects including glaucoma, cataracts, and endophthalmitis. The risk of inducing an increase in intraocular pressure requiring medical therapy is 28%-52%, with a 1% risk that this rise in pressure may require surgical intervention. Similarly, the risk of cataract formation may be as high as 45% at 1 year.

Combination therapy

Since the pathogenesis of CNV in AMD is multifactorial, involving complement-based inflammatory mechanisms, VEGF-induced neoangiogenesis, and a breakdown of RPE-BM-CC extracellular matrix, there is a theoretical basis for utilizing a combination of agents to act therapeutically against each of these mechanisms. As a result, a number of combinations have been devised. One triple-therapy combination includes PDT to close existing neovascular channels, intravitreal steroids to reduce the inflammatory component of CNV, and an anti-VEGF agent to reduce VEGF stimulation of angiogenesis and leakage. One such prospective series examined combination therapy in 104 patients; PDT was administered in a half-fluence dose (42 J/cm^2), and intravitreal injections of dexamethasone (800 µg) and

bevacizumab (1.5 mg) were given.[16] The mean increase in VA was 1.8 lines ($P<0.01$) over a mean follow-up period of 40 weeks. Spaide et al[17] demonstrated VA improvement for subfoveal CNV with fewer repeat treatments when combining PDT with IVTA. Other studies have shown similar results.[18-20] The benefit of combination therapy appears to be its ability to reduce the frequency of retreatments rather than yielding better vision outcomes when compared with monotherapy using anti-VEGF agents alone.

New treatments for neovascular AMD

Although the current practice of frequent intravitreal injections of anti-VEGF agents such as ranibizumab is effective both in stabilizing vision loss and in improving vision in approximately 30% of patients, a number of shortcomings remain with this type of therapy. The need for continuing these injections over a long time period is a result of the current anti-VEGF agents inactivating the VEGF that is present in the subretinal tissue at the time of treatment. The upstream events that lead to the production of VEGF are not addressed by this treatment approach.

Different treatment approaches are under investigation and designed to act at sites or steps in the process of CNV development that may produce a longer lasting benefit for a given therapeutic intervention. One current research direction involves the limitation of angiogenesis by targeting the proliferating endothelial cell with medications known as microtubule disruptors. Also, intracellular inhibitors including protein kinase inhibitors and nucleic acid therapies may be used to block cell-signalling pathways that give rise to VEGF production. Other agents may work in the extracellular space by blocking receptor binding (including VEGF), or blocking other cellular components including integrins, platelet-derived growth factor (PDGF), complement, and cytokines. Research in these areas has given rise to the production of a number of compounds that are currently investigated for possible clinical use.

Bevasiranib

Small interfering ribonucleic acid (siRNA) induces the catalytic destruction of a fragment of messenger RNA by targeting a specific codon sequence used by mRNA for VEGF protein synthesis. Theoretically, this type of gene-silencing therapy should prevent VEGF production over a long time and be more efficient in reducing the amount of VEGF produced in the CNV area rather than simply removing available VEGF. A number of practical issues must be addressed in developing therapeutic agents of this type including the challenge of incorporating this siRNA into retinal cells that are nondividing cells. The Cand5 Anti-VEGF RNAi Evaluation (CARE) study[21] evaluated the safety and efficacy of intravitreal siRNA, bevasiranib, in patients with neovascular AMD. Patients were randomized to receive variable doses (0.2, 1.5, or 3.0 mg) of intravitreal bevasiranib and followed for 12 weeks; overall, 78% of patients lost <15 letters at the 12-week endpoint, while 6% in the 3.0-mg group gained >5 letters of VA. These results are in line with the benefits achieved by anti-VEGF agents such as ranibizumab, but more study will be required before this siRNA agent can be recommended for clinical use.

VEGF Trap

In this approach, a soluble receptor "decoy" is used to bind to all isoforms of VEGF-A. The VEGF trap binds VEGF-A with higher affinity than other anti-VEGF drugs. One agent was studied in a multicentre, masked trial where subjects were randomized to 5 doses of VEGF trap in the study eye:[22] Group A received 0.5 mg every 4 weeks; Group B, 2.0 mg every 4 weeks; Group C, 0.5 mg every 12 weeks; Group D, 2.0 mg every 12 weeks; and Group E received 4.0 mg every 12 weeks. A significant mean reduction in retinal thickness was observed after 12 weeks compared with baseline. Almost all patients (99%) maintained or improved their vision at 12 weeks.

Other approaches

A number of upstream events in the production of VEGF and other factors that determine the integrity of neovascular channels in AMD are targeted as possible sites for pharmacological intervention. Tyrosine kinase inhibitors can be used to block intracellular signalling by inhibiting tyrosine kinase to reduce the available cell energy necessary for RNA transport and protein synthesis. Complement plays a role in the inflammatory component of neovascular AMD, and complement inhibitors, including C3 inhibitor peptide C5aR small molecule and C5 antibody, are under investigation as possible targets in AMD treatment. Microtubule inhibitors, including combretastatin drops and small-molecule tubulin inhibitor drops such as mammalian target of rapamycin (mTOR) reveal promise as possible therapeutic agents in blocking production of VEGF. PDGF is needed for the production of endothelial cell pericytes that grow around endothelial cells to enhance the integrity of neovascular channels produced by VEGF stimulation. A PDGF aptamer that strips pericytes from newly formed neovascular channels may make these neovascular channels more sensitive to other therapeutic agents and thus reduce neovascularization.

Safety issues

The risk of causing harm with frequent intravitreal injections of VEGF antagonists can be broken down into the risk from the injection itself and the risk from possible systemic absorption of the injected material from the vitreous deposit.

Steps should be taken to ensure that the risk of intraocular infection from the injection is as low as possible. The consensus suggests that an eyelid speculum is necessary to prevent eyelash contact with the injection

site and topical agents (eg, povidone iodine or fluoroquinolone eyedrops) are indicated to reduce the number of infectious agents possibly present in tears at the time. Other measures such as sterilizing the skin of the eyelids, the use of antibiotic drops several days before and/or after treatment, and the use of gloves are not universally accepted because their utility is not well established. These precautions result in an approximate 1/1000 risk of serious intraocular infection for each injection. Other complications such as vitreous hemorrhage, acute intraocular pressure elevation, and retinal detachment are similarly rare.

From the cardiovascular point of view, the main risk is stroke. The Phase III Food and Drug Administration (FDA) reports from the initial trials of ranibizumab revealed a small increase in stroke development when comparing the 0.3-mg dose (0.7%) with the 0.5-mg dose (3.3%). Nevertheless, these stroke rates are still lower than the stroke rates found in many other epidemiological studies of nonocular diseases; therefore, it is unclear that intravitreal ranibizumab increases the risk of stroke beyond the age-related risk alone. For those with a history of previous stroke, the incidence of new stroke was much higher (9%), although the absolute numbers in these studies were small. For patients with AMD and diabetes, data indicate an increased risk of stroke with bevacizumab, but not with pegaptanib or ranibizumab. As a result, it is important to take a past history of stroke into consideration when recommending intravitreal injections of a VEGF antagonist.

Currently, there are conflicting reports about adverse cardiovascular events with these agents. The incidence of stroke, myocardial infarction (MI), and nonocular hemorrhage in ANCHOR, MARINA, and SAILOR trials did not reach statistical significance. A meta-analysis[23] of patients with a prior history of stroke by Genentech, however, revealed a statistically significantly higher rate of stroke in patients receiving intravitreal injections of ranibizumab.

The difficulty in determining whether there is a definite increased systemic risk for patients receiving intravitreal injections of VEGF antagonists is highlighted by the healthier patients enrolled in the MARINA and ANCHOR studies than an age-matched group represented in the Medicare database.[24] Patients in the Medicare database without AMD had a 2-year MI risk of 3.5% compared with the MARINA sham group that had an MI risk of 1.7%. Patients in these 2 studies with neovascular AMD had an MI rate of 4.38%, whereas the rate among patients with non-neovascular AMD was 4.09%. Moreover, the average annual death rate was $<2\%$ in MARINA and ANCHOR versus 5% in the Medicare database.

In addition to cardiovascular complications, there may be long-term effects from systemic absorption of currently used VEGF antagonists affecting other bodily systems. For example, VEGF is known to be neuroprotective and blocking VEGF may promote neurodegenerative conditions. If there is a risk, it has not been detected in any data reviewed to date by the FDA and must therefore come from postmarketing surveillance and reports submitted to the FDA or the pharmaceutical companies by treating physicians.

Surgical treatment of neovascular AMD

For some time, there was a great deal of enthusiasm about surgical treatment in AMD. Several approaches were described, including surgical removal of the choroidal neovascular membrane (CNVM), pneumatic displacement of subretinal blood (with or without subretinal tissue plasminogen activator [tPA] injection), and macular translocation surgery.

Surgical removal of CNVM appeared promising after its introduction by de Juan and Machemer in 1988.[25] The procedure involved a 3-port pars plana vitrectomy to gain access to the macula. Immediately, a small retinotomy was created close to the macula where the CNVM is located and a balanced salt solution (BSS) injected into the subretinal space to safely remove the CNVM with forceps. The Submacular Surgery Trial (SST),[26] involving 336 patients with AMD and submacular CNVM, found no benefits with surgery; there was a primary successful outcome of 41% for the observation arm and 44% for the surgery arm. Today, the procedure is seldom performed.

Macular translocation surgery (MTS) is another surgical procedure for AMD, first reported by Machemer and Steinhorst in 1993.[27] Because the initial procedure involved complete cutting of the retina in the periphery and rotating the retina, particularly the macula, away from the submacular CNVM, many retina surgeons tried to develop a less extensive method of translocation. Results from both complete and limited macular translocation procedures have yielded mixed results, but neither technique has gained much enthusiasm and macular translocation surgery is seldom performed for neovascular AMD.

Low-vision treatments

For patients who do not respond to, or are unsuitable for, any of the current AMD treatments, there remains the option of low-vision assistance. A number of new approaches have been developed, including improvements in magnifying devices for both near and distance vision, vision training to help patients utilize a nonfoveal preferred retinal locus, computer-assisted magnification of text, and even the insertion of intraocular implants, utilizing telescopic magnification principles either in the implant itself or in the combination of implant plus spectacle correction. The theory and practice of these low-vision treatments are beyond the scope of this article, but are important as rehabilitative methods for many AMD patients where no other treatment methods have helped.

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