Update on Age-Related Macular Degeneration

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Abstract Despite significant progress made over the past decade in the treatment of age-related macular degeneration (AMD), certain aspects of this common cause of vision loss and blindness in the elderly continue to challenge the medical community. Although treatment of neovascular AMD with vascular endothelial growth factor (VEGF) inhibition offers great promise, no clear strategy for impeding progression of “dry” AMD to the “wet” form currently is available. Clinical researchers have studied the effect of cataract surgery on AMD development and factors that influence patient response to anti-VEGF therapy. In addition, experts have examined the utility and effectiveness of ranibizumab therapy in treating wet AMD and have investigated different dosing schedules to optimize anti-VEGF therapy. Researchers also have analyzed and compared results from major trials to uncover new information on the safety and efficacy of VEGF inhibitors in treating patients with wet AMD.

Age-related macular degeneration (AMD) is the leading cause of vision loss among older Americans. Our understanding of its pathogenesis and clinical course is still in its infancy, yet significant advancements in managing this condition have been reported over the past decade. In particular, the use of agents that inhibit vascular endothelial growth factor (VEGF) offers exceptional promise in treating AMD.

At the 2013 Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO), held in Seattle, Washington, May 5–9, clinicians and scientists from all over the world presented their research on AMD. This article highlights some of the more outstanding contributions to our knowledge of this devastating disease and its management.

Identifying Risk Factors for Progression of Dry to Wet AMD

Currently, the only available treatment for AMD involves intravitreal injections of anti-VEGF agents and laser therapy for the exudative or neovascular form of the disease (“wet” AMD). Therefore, clinicians have great interest in understanding the risk factors involved in the progression of dry to wet AMD. Until a treatment or cure is available for dry AMD, stopping its progression to the exudative form will be key.

Medium-sized drusen are defined as measuring 64–125 μm in diameter, whereas any druse > 125 μm in diameter is considered to be large. Chew and others reported that in the Age-Related Eye Disease Study (AREDS), 36% of participants who had medium-sized drusen in one eye and 71% of those who had medium-sized drusen in both eyes eventually developed large drusen. In addition, at the 10-year AREDS follow-up, if the fellow eye had neovascular AMD, 40% of eyes that developed geographic atrophy (GA) also developed neovascular AMD. Thus, special attention must be paid to patients who have bilateral medium-sized drusen or one eye with neovascular AMD. Such patients should be closely monitored for conversion to wet AMD and should begin immediate treatment.

Lechanteur and others examined 275 individuals from a European genetic database who were diagnosed with neovascular AMD to attempt to identify risk factors that may help predict earlier onset of the disease. Current and past smokers developed neovascular AMD at an earlier age than did others, as did homozygous carriers of risk alleles in two genes: CFH and ARMS2.

Cataract Surgery in Patients with AMD

The interaction between cataract surgery and advanced AMD always has been controversial, with some older studies suggesting that surgical treatment of cataracts leads to AMD progression. Previously, AREDS report no. 27 demonstrated a 1.9- to 6.1-letter improvement after cataract surgery among patients having any severity of AMD. Similarly, results from the ANCHOR study and the MARINA trial also demonstrated improved visual acuity after cataract surgery among AMD patients.

Nicholson et al evaluated preoperative and postoperative characteristics of 793 patients (1,233 eyes) who underwent cataract surgery in the AREDS2 cohort. Their results showed a 10-letter improvement in 35.5% patients in the mild-AMD group, 32.3% in the moderate-AMD group, 25.7%...
in the severe-AMD group, 21.4% in the non-central GA group, and 23.5% in the advanced AMD group (central GA and/or neovascular AMD). Most importantly, there was a significant 7.5-letter improvement after cataract surgery in patients with neovascular AMD. As expected, eyes with cortical and posterior subcapsular cataracts experienced the most visual gains. Therefore, cataract surgery is a reasonable option for most patients with wet AMD for improving their vision.

■ NONRESPONDERS TO ANTI-VEGF THERAPY

The success of anti-VEGF therapy in treating wet AMD has been remarkable, yet clinicians have been frustrated by the roughly 10% of patients who are nonresponders.7 van Asten and colleagues8 evaluated 391 patients in the European genetic database known as EUGENDA. In all, 47 of 391 patients were nonresponders, as defined by a loss of ≥ 30% of letters of visual acuity from baseline. Independent risk factors for lack of response were age, visual acuity, diabetes mellitus, and accumulation of risk alleles in the CFH, ARMS2, and VEGFA genes. The investigators established a clinical risk score that may be helpful in predicting future nonresponders.

■ ROLE OF RANIBIZUMAB IN AMD

The role of ranibizumab use in treating AMD was established in the MARINA and ANCHOR trials during the mid-2000s.4 Further, the frequency and dosing of ranibizumab for neovascular AMD were studied in the PIER, SUSTAIN, HORIZON, PrONTO, and EXCITE trials.6 Recently, therapeutic indications for ranibizumab have included diabetic macular edema and cystoid macular edema secondary to retinal vascular occlusion. Long-term data on the efficacy of this treatment currently are being studied, and some preliminary data were presented recently at the ARVO meeting.

Visual Outcomes Achieved with Ranibizumab Therapy

Kailey and colleagues10 described a retrospective study of 143 patients treated with three monthly loading doses of intravitreal ranibizumab followed by monthly review and as-needed injections of the drug. Patient loss to follow-up was similar to that of other multicenter trials (21%). Patients gained a mean of 8.07, 9.5, 8.11, and 6.24 letters at 12, 24, 36, and 48 months, respectively. Overall, 8.9% of patients lost more than 15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters, compared with 91.1% of patients who had maintained or improved vision over the 4 years.

These findings were comparable to those of large multicenter trials. For example, at 2 years of therapy in the CATT comparison of bevacizumab with ranibizumab, the group receiving monthly ranibizumab demonstrated a gain of 8.8 ETDRS letters, patients given monthly bevacizumab gained 7.8 letters, the group given as-needed ranibizumab gained 6.7 letters, and individuals given as-needed bevacizumab gained 5 letters.11 Overall, these results emphasized the role of strict monthly monitoring of patients with wet AMD, even if treatment was given on an as-needed basis.

In addition, Oshima et al12 reported that Japanese patients who gained and maintained vision with ranibizumab injections tended to have smaller neovascular lesions.

Dose and Frequency of Anti-VEGF Therapy

The results of clinical studies clearly have demonstrated the role of close monitoring of symptoms and optical coherence tomography (OCT) findings in patients with wet AMD. Optimal outcomes have been achieved with monthly injections of ranibizumab (in the pre-aflibercept era) as compared with as-needed treatment. In fact, results of the CATT study showed that as-needed treatment based on monthly follow-up was inferior to monthly injections.

Results of the AURA study,13 a retrospective analysis of the real-world use of intravitreal ranibizumab in French and German patients with wet AMD, showed that patients undergoing treatment with ranibizumab for wet AMD had, on average, poorer-than-expected visual outcomes due to monitoring performed on a less-than-monthly basis and fewer injections of ranibizumab per year.

Similarly, Schrader and others14 presented data showing that neither monthly injections of ranibizumab or bevacizumab nor a monthly follow-up based upon OCT was reimbursed by insurance companies. Treatment of the 88 eyes studied was based on vision loss at their visits. Visual acuity-guided, as-needed treatment was inferior to OCT-based monthly follow-up and as-needed treatment at 2 years. Of note, most patients required at least three injections of ranibizumab or bevacizumab even during years 3 and 4, which emphasized the role of close follow-up beyond year 2 for optimal outcomes in an as-needed treatment model.

■ THE HARBOR TRIAL

The HARBOR trial lasted for 2 years and involved 100 investigator sites and 1,098 patients with wet AMD randomized to one of four ranibizumab treatment arms: 0.5 mg monthly, three monthly loading doses followed by 0.5 mg as needed, 2.0 mg monthly, and three monthly loading doses followed by 2.0 mg as needed.15 Investigators attempted to find out whether higher doses of ranibizumab improved outcomes and whether as-needed treatment of wet AMD with ranibizumab was noninferior to monthly injections.

The rationale for the first investigation came from early AMD trials. Even in the pivotal ANCHOR trial and the MARINA study, patients given 0.5 mg of ranibizumab every month had better functional and anatomic outcomes than...
Those who received 0.3 mg of the drug monthly. At month 12 of the ANCHOR study, mean visual acuity with 0.5 mg ranibizumab improved by 11.3 ETDRS letters, compared with an 8.5-letter improvement among patients receiving the 0.3-mg dose. Similarly, at month 12 of the MARINA trial, 33.8% of patients treated with 0.5 mg of ranibizumab had a ≥15-letter gain in best-corrected visual acuity (BCVA), compared with 24.8% of patients treated with 0.3 mg of the drug. Therefore, the research teams investigated whether monthly high-dose ranibizumab therapy improved outcomes for patients with wet AMD.

In terms of dosing frequency, multiple studies (including the MARINA, CATT, and ANCHOR trials) showed excellent visual and anatomic outcomes from monthly ranibizumab injections. But a strict monthly injection schedule of ranibizumab presents a serious financial and logistical burden for most patients and health systems. In reality, most retina specialists follow and treat AMD with serial OCT guidance and as-needed treatment.

One-Year Results

At month 12, the mean change from baseline in BCVA for the four groups was +10.1 ETDRS letters for patients given 0.5 mg of ranibizumab monthly, +8.2 letters for the group given 0.5 mg as needed, +9.2 letters for patients given 2.0 mg monthly, and +8.6 letters for those given 2.0 mg as needed. Further, 34.5%, 30.2%, 36.1%, and 33.0%, respectively, gained ≥15 letters from baseline to month 12. The mean change in OCT thickness among the four groups was −172.0 μm, −161.2 μm, −163.3 μm, and −172.4 μm, respectively. The mean number of injections was 7.7 and 6.9 for the 0.5-mg as-needed and 2.0-mg as-needed groups, respectively. No significant differences in the frequency or severity of side effects among the four treatment groups were noted.

At month 12, results in the group given 2.0 mg of ranibizumab monthly were not superior to those of patients given 0.5 mg monthly, and the groups given 0.5 and 2.0 mg of ranibizumab as needed did not meet the prespecified noninferiority comparison. Therefore, results of the 1-year HARBOR trial confirmed that 0.5 mg of ranibizumab given monthly currently provides the best results in patients with wet AMD.

Anti-Therapeutic Antibodies (ATAs)

A subanalysis of results from the HARBOR study investigated the role of ATAs in nonresponders. Repeated ranibizumab administration has been associated with the development of serum ATAs over time in a small percentage of patients. In patients enrolled in the HARBOR study, a bridging enzyme-linked immunosorbent assay was used to evaluate ATA immunoreactivity to ranibizumab in serum samples collected at screening and at months 6, 12, and 24. Positive ATA status had no correlation with serum ranibizumab concentrations, change in BCVA, or change in central foveal thickness (CFT) in any of the treatment groups. Therefore, following repeated intravitreal injection up to 2 years, the presence or absence of ATAs did not affect the pharmacokinetics or efficacy of ranibizumab given to patients with wet AMD.

Visual Acuity Response

The visual acuity response to anti-VEGF injections over time in AMD patients also was investigated as part of the HARBOR study. Dreyer and others examined early versus delayed 15-letter responders to ranibizumab treatment for 12 months. At month 3, the proportion of patients gaining ≥15 letters from baseline BCVA was 24% in the group given 0.5 mg of ranibizumab monthly, 25% in the group given 0.5 mg of the drug as needed, 26% among those given 2.0 mg of ranibizumab monthly, and 26% for patients given 2.0 mg of the drug as needed. By month 12, an additional 11%–12% of patients treated with ranibizumab monthly and 7%–9% of patients treated with the drug as needed gained 15 letters of vision. This study highlighted the need for continued ranibizumab treatment, even in patients who did not experience significant early gains, and this effect was evident even with as-needed treatment.

CNV and Total Lesion Area

The underlying pathology in wet AMD is the formation of choroidal neovascularization (CNV), which leads to leakage of subretinal blood, retinal edema, formation of scar tissue, and eventual vision loss. Through the ANCHOR and MARINA trials, ranibizumab therapy helped to regress the total CNV area at 12 and 24 months.

London and colleagues presented 24-month data on the CNV area and thickness within the HARBOR study. The total lesion area and CNV area were measured by fluorescein angiography at baseline, 3 months, 6 months, 12 months, and 24 months, and the CNV thickness was measured with spectral domain OCT.
At the end of the study period, ranibizumab provided consistent regression in total lesion and CNV area over time among all four treatment arms. Complete regression was observed in 92%–96% of classic CNV lesions and 45%–63% of occult lesions.

**Two-Year Results**

Although the primary endpoint of the HARBOR trial was the mean change in BCVA at month 12, key secondary endpoints included visual change at 24 months, mean change in CFT at 24 months, and mean number of injections of ranibizumab administered. At 2 years, the mean gain in BCVA from baseline was 9.1 letters in those given 0.5 mg of ranibizumab monthly, 7.9 letters in those given 0.5 mg of the drug as needed, 8.0 letters in patients given 2.0 mg of ranibizumab monthly, and 7.6 letters in those given 2.0 mg of the drug as needed; these results were relatively similar to outcomes noted at 12 months. The mean reduction in CFT among the four groups also was statistically similar. Of note, ocular and systemic safety profiles during year 2 were similar for all four treatment groups and also were similar to those of previous ranibizumab trials.

**EMERGING ROLE OF AFLIBERCEPT: THE VIEW TRIALS AND SUBSEQUENT STUDIES**

Aflibercept, or VEGF-Trap, is a fusion protein with high VEGF affinity attributed to binding sequences from the native receptors VEGFR1 and VEGFR2. This drug, which has given retina specialists a third option for intravitreal treatment of AMD, was approved by the US Food and Drug Administration in November 2011 and by the European Medicines Agency in November 2012 for use in the treatment of wet AMD.

VIEW1 (conducted in the United States) and VIEW2 (conducted in Europe, Asia, and Latin America) were parallel trials that tested the noninferiority status of aflibercept as compared with ranibizumab in patients given 0.5 mg of ranibizumab monthly, 0.5 mg of aflibercept monthly, 2 mg of aflibercept monthly, or 2 mg of aflibercept every 2 months after receiving three monthly loading doses. Results in all three aflibercept groups were noninferior and clinically equivalent to those of patients given monthly injections of 0.5 mg of ranibizumab for the primary endpoint, which was noninferiority (margin of error, 10%) of the aflibercept regimens to ranibizumab therapy in the proportion of patients maintaining vision at week 52 (ie, losing < 15 letters on the ETDRS chart).

The efficacy and role of aflibercept in treating wet AMD still are being investigated clinically. Aflibercept is being used most commonly in patients recalcitrant to other anti-VEGF agents. Shaikh and colleagues presented data on 33 eyes of 30 patients initially treated with bevacizumab or ranibizumab for at least 6 months and subsequently treated with aflibercept for at least 6 months. Results from this retrospective study showed that although aflibercept therapy offered the benefit of decreased injection frequency (34 days between injections versus 28 days with bevacizumab and 32 days with ranibizumab), it added a significant healthcare cost to the patient.

On average, patients spent $326 for 6 months of treatment with bevacizumab and $9,720 for 6 months of aflibercept therapy. Similarly, Venzara and others looked at 86 eyes previously treated with at least three injections of bevacizumab or ranibizumab and then switched to three monthly injections of aflibercept. There was a temporary decrease in CFT on OCT among patients who were recalcitrant on prior therapy, but there was no apparent difference in visual acuity outcomes after the switch.

Furthermore, Hau and others presented their experience of 41 eyes in 35 patients with recalcitrant AMD (ie, fluid on OCT despite monthly 0.5-mg doses of ranibizumab or 1.25-mg doses of bevacizumab) who were converted to treatment with 2.0 mg of intravitreal aflibercept as needed. At 6 months, these eyes experienced a statistically significant decrease in foveal thickness (74.15 μm) and an improvement in the mean logarithm of the minimum angle of resolution (logMAR) of visual acuity from 0.46 before treatment to 0.37 at 6 months. This finding, however, was not statistically significant.

On the other hand, Barbazetto et al highlighted a small subset of patients (15%) in their aflibercept cohort who experienced a transient decrease in vision after the switch. Patients who continued to have decreased vision tended to have a lower baseline CFT. In short, the long-term effects of aflibercept on visual acuity and retinal thickness are not yet clear.

**SYSTEMIC SIDE EFFECTS OF VEGF INHIBITORS**

As the use of VEGF inhibitors for treating wet AMD increases, the local and systemic adverse effects of this class of medicines become subjects of greater interest. In the CATT trial, 39.9% of patients using bevacizumab and 31.7% of those using ranibizumab developed one or more serious systemic adverse events; the difference was statistically significant ($P = 0.004$).

To answer some questions surrounding the systemic side effects of anti-VEGF therapy, an analysis was done on 2-year data from the CATT study as well as 1-year data from the IVAN trial. The pooled analysis of both of these head-to-head studies showed that gastrointestinal disorders, venous thrombotic disease, and the occurrence of one or more adverse events were more frequent with the use of bevacizumab. Although more adverse events were noted among patients in the CATT study than among those involved in the IVAN trial, cardiovascular diseases were more prevalent at baseline among patients enrolled in the CATT study than at the start of the IVAN trial.

**CONCLUSION**

The quest to better understand the pathophysiology of AMD and to find a cure for it continues. Although the use of anti-VEGF agents currently dominates the therapeutic arena for wet AMD, the discovery and exploitation of genetic and molecular mechanisms to prevent AMD or at least halt the progression of dry AMD to advanced GA or wet AMD likely will be the focus of future research.
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