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New Insights into the Treatment of Wet Age-related Macular Degeneration in the Era of Anti-VEGF Therapies

A report from the 2012 Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO)

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There is general consensus among ophthalmologists that anti-vascular endothelial growth factor (VEGF)-based therapies have revolutionized the treatment of neovascular age-related macular degeneration (AMD), the leading cause of blindness in developed countries.[1] However, the use of certain anti-VEGF agents for AMD has also sparked a significant degree of debate.[2] This is largely due to the off-label use of bevacizumab in the treatment of AMD, despite only being approved for intravenous use as a cancer therapy. Adding to this discussion about the management of AMD was the regulatory approval of a new VEGF-based therapy, aflibercept, by the United States Food and Drug Administration (FDA) in late 2011. This issue of *Ophthalmology Scientific Update* provides an overview of recent evidence and developments in this fast-evolving therapeutic field that were presented at the 2012 ARVO Annual Meeting. The discussion covers the results of the VIEW 1 and VIEW 2 trials, the 2-year results from the CATT trial, and 1-year data from the highly anticipated IVAN (Inhibit VEGF in Age related choroidal Neovascularisation) trial conducted in the United Kingdom (UK).

Until recently, there were no large, randomized clinical trials assessing the efficacy of bevacizumab in preventing vision loss in patients with AMD. In 2011, the Comparison of Age-related Macular Degeneration Treatments Trial (CATT), funded by the National Institute for Health Research Health Technology Assessment (NIHR HTA) program in the UK, reported that bevacizumab provides similar efficacy as the approved gold standard AMD therapy, ranibizumab.[3] However, the CATT trial was not powered to detect small but clinically relevant differences in adverse outcomes, particularly atherothrombotic events (ATEs), which could result from the differences in the molecular structures, half-lives, and systemic absorption of the drugs.[4-6] In addition to safety-related concerns, the ophthalmology community was also left speculating whether the 1-year equivalence in efficacy between the 2 agents would be maintained during the second year. The impact of as-needed (prn) dosing regimens on visual outcomes, as well as the optical coherence tomography (OCT) findings that suggested differences in favour of ranibizumab, were also questioned.

In late 2011, a new VEGF-based therapy, aflibercept, received regulatory approval from the FDA for the treatment of neovascular AMD.[7] This decision was largely based on 1-year data from the VIEW 1 and VIEW 2 studies,[8,9] which was intended to determine whether aflibercept administered every 8 weeks was clinically equivalent in both efficacy and safety to monthly treatments with ranibizumab. It is important to note that aflibercept is not yet approved by Health Canada.

Intravitreal Aflibercept for Wet AMD: 2-Year Results from VIEW 1 and VIEW 2 Trials

Aflibercept is a fully human recombinant fusion protein that binds all isoforms of VEGF, as well as placental growth factor (PGF), thus inhibiting the binding and activation of VEGF receptors.[10] The FDA-recommended dose for aflibercept is 2 mg every 8 weeks after an induction period of 3 monthly injections.[11] The recommended treatment regimen for ranibizumab is every 4 weeks.[12]

The 2-year VIEW 1 and VIEW 2 trials are essentially identical in design.[13] While VIEW 1 was conducted in North America, the VIEW 2 trial was conducted in Europe, Asia, and Latin America. With over 2400 treatment-naïve patients enrolled, this is the largest wet AMD program conducted to date. For each trial, patients were randomly assigned in the first year to 1 of 4 groups: 0.5 mg aflibercept monthly (0.5q4), 2 mg aflibercept monthly (2q4), 2 mg aflibercept every 8 weeks after a loading dose of 3 monthly injections (q28), or 0.5 mg ranibizumab monthly (Rq4). During the second year, all 4 groups were treated prn based on monthly evaluations. All patients, however, received treatment at least every 12 weeks. The primary

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endpoint was maintenance of visual acuity (VA) at 1 year, defined as loss of <15 letters of best-corrected (BC) VA on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart (3 lines).

Efficacy outcomes

The primary endpoint, maintenance of BCVA, achieved at 1 year in 94%, 95%, 96%, and 95% of patients in groups Rq4, 2q4, 0.5q4, and 2q8, respectively, was maintained during the second year of treatment (92%, 92%, 91%, and 92%, respectively). The mean change in BCVA from baseline to week 52, ranging from 8.3 in the 0.5q4 group to 9.3 in the 2q8 group, modestly decreased in all 4 treatment groups during the second year, ranging from 6.6 to 7.9 letters (Figure 1). The percentage of patients who maintained a BCVA gain of ≥3 lines at 96 weeks were in the range of 30%–33%, similar to the percentages achieved at 1 year. Furthermore, according to a sub-analysis of VIEW studies presented by Ho et al,[14] the proportion of patients losing <15 letters and the mean changes in BCVA were consistent across the prespecified subgroups as defined by age, baseline BCVA, and choroidal neovascularization lesion size. The decrease in central retinal thickness seen in the first year was largely maintained during the second year. Absence of fluid on OCT was seen relatively early in all treatment groups, between 4 and 8 weeks for the aflibercept 2q4 and 2q8 groups, and between 8 and 12 weeks for the aflibercept 0.5q4 and ranibizumab groups. The percentage of patients without fluid, however, decreased slightly during the second year in all 4 treatment groups (Figure 2).

Treatment experience

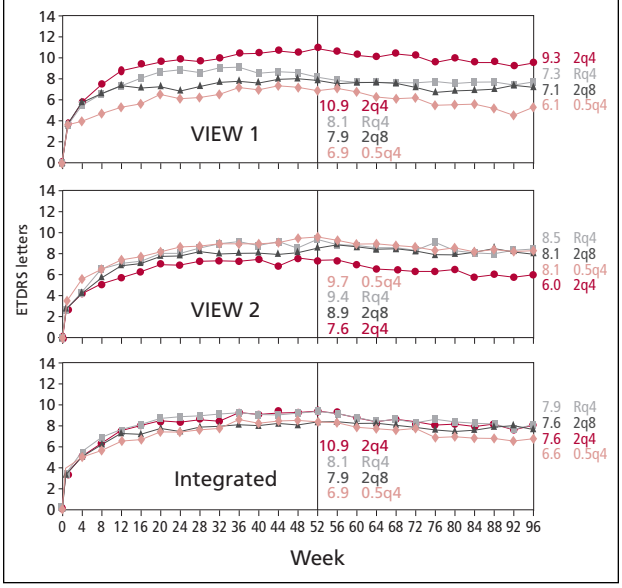
Over the course of 2 years, patients in the aflibercept 2q8 group received 11.2 injections (including 7.0 during the first year and 4.2 during the second year). Patients in the aflibercept 0.5q4 and 2q4 groups received an average of 16.2 and 16.0 injections, respectively, during the 2-year study period, and those treated with ranibizumab received 16.5 injections. Thus, patients randomized to 2q8 aflibercept achieved similar improvement in vision as those treated with ranibizumab, with an average over the course of 2 years of 5.3 fewer injections, including the first 3-month loading dose.

Notably, the mean number of injections from week 52 to week 96 was significantly lower for the aflibercept 2q4 and 2q8 groups compared to the ranibizumab group (4.1 and 4.2 versus 4.7, respectively); patients in the 0.5q4 group received a mean of 4.6 injections. The likelihood of receiving ≥6 injections during the second year was also significantly lower in both the 2q4 and 2q8 aflibercept groups compared with ranibizumab (14.0% and 15.9% versus 26.5%, respectively). In the 25% of patients who required the most intense therapy during year 2 (greatest number of injections), those assigned to the aflibercept 2q4 and 2q8 groups required an average of 1.5 and 1.4 fewer injections compared to patients treated with ranibizumab (6.5 and 6.6 versus 8.0, respectively).

Safety

The incidence of ocular adverse events was balanced across treatment groups with the most frequent events (>10% of patients) associated with the injection procedure, the underlying condition, or aging itself. The occurrence of ATEs was also similar between treatment groups: 3.2% for ranibizumab and 3.3% for the aflibercept groups combined. There were no observed dose-related adverse event signals for the aflibercept groups.

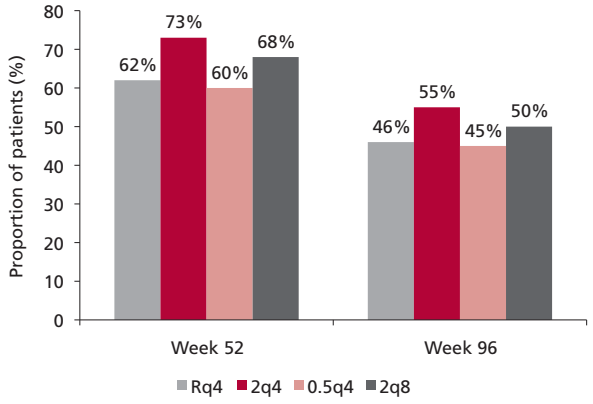
Figure 1: VIEW 1 and VIEW 2: Mean change from baseline in best-corrected visual acuity (BCVA) over 96 weeks[13]



Second-Year CATT Results Confirmed 1-Year Data

The 2-year CATT trial data confirmed that ranibizumab and bevacizumab had similar therapeutic effects on VA over a 2-year period.[15] Of 1185 patients with neovascular AMD who were enrolled in the CATT trial, 1107 were followed during the second year. At enrollment, participants were randomly assigned to 1 of 4 treatment groups according to agent (ranibizumab or bevacizumab) and administration schedule (monthly or prn).[3] At the end of the first year, patients who were assigned to monthly treatments were randomized to either continued treatment with a monthly regimen or be switched to a prn treatment plan. Patients initially assigned to prn treatment continued with

Figure 2: VIEW 1 and VIEW 2: Proportion of patients without fluid on time domain optical coherence tomography[13]



the regimen. The objectives were to evaluate outcomes in patients who maintained the same dosing regimen for 2 years, and to determine the effects of switching to prn treatment after 1 year of monthly dosing.

Efficacy data

For patients receiving the same monthly dosing for 2 years, the mean gain in VA was similar for both drugs, with a difference for patients treated with bevacizumab relative to those receiving ranibizumab of -1.4 letters (95% confidence interval [CI], -3.7 to 0.8; *P*=0.21) (Figure 3). The mean gain in VA was, however, significantly greater for patients treated monthly compared with prn treatment, (difference, -2.4 letters; 95% CI, -4.8 to -0.1 letters; *P*=0.046). Furthermore, switching from monthly to prn treatment resulted in a greater mean decrease in vision during the second year (-2.2 letters; *P*= 0.03). It appears, according to CATT investigators, that as soon as patients switched to a prn dosing regimen, they exhibited similar VA outcomes as patients who received prn treatment from baseline.

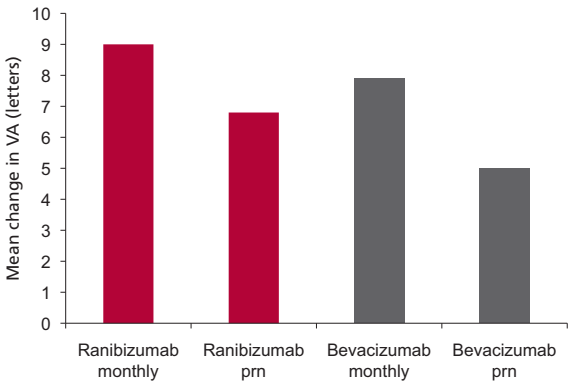
The percentage of patients without fluid on OCT (dry OCT) ranged from 13.9% in the bevacizumab prn group to 45.5% in the ranibizumab monthly-treatment group (*P*=0.0003 for drug; P<0.0001 for regimen). The greater prevalence of fluid in patients receiving prn bevacizumab led to an average of 0.6 more injections during the second year compared to the ranibizumab prn group, and an average of 1.5 injections more over a 2-year period. While the development of geographic atrophy (GA) was higher in both monthly-treated groups than in the prn groups, treatment with ranibizumab was associated with a higher detection of GA, despite its effectiveness in drying out the retina. Due to higher incidence of GA in patients receiving monthly ranibizumab, some experts speculated that a drier retina may simply make the appearance of GA more visible on OCT than if fluid was still present. Hence, the higher observations of GA with monthly ranibizumab.

Safety data

Over 2 years, the rates of death and ATEs, the major safety areas of concern, were similar for both drugs. However, the higher rate of serious adverse events (SAEs) for bevacizumab-treated patients reported in the first year was also noted during the second year. Compared with ranibizumab, bevacizumab was associated with a higher proportion of patients with ≥1 systemic SAEs (39.9% versus 31.7%; adjusted risk ratio, 1.30; 95% CI, 1.07 to 1.57; *P*=0.009). Among all organ systems, the greatest difference was in gastrointestinal disorders.

The investigators noted that it is uncertain whether the difference in SAEs was the result of chance, imbalances at baseline not captured in multivariate modeling, or truly higher risk. It is also important to keep in mind that the CATT trial was not sufficiently powered for safety analysis.

Figure 3: CATT trial: Mean change in VA* at 2 years[15]



* in patients treated with the same dosing regimen for 2 years.

Interim Analyses from the IVAN Trial: Similarities and Differences with CATT

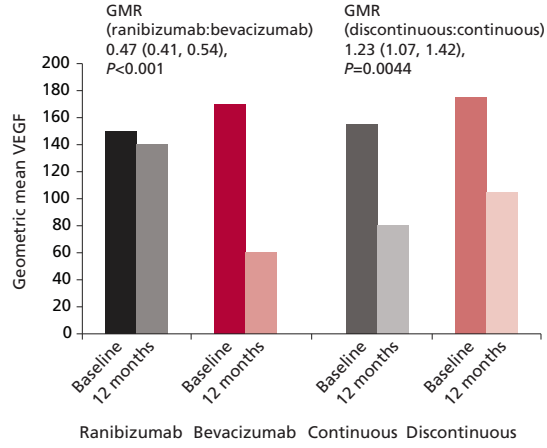
In the NIHR HTA-funded IVAN trial,[16] 610 new AMD patients aged ≥50 years from 23 hospitals and academic institutions in the UK were randomized to 1 of 4 groups: 0.5 mg ranibizumab or 1.25 mg bevacizumab, given either monthly (continuous) or prn (discontinuous). The primary outcome was distance VA at 2 years.

Efficacy data

The interim analysis of the trial, using the 3.5-letter limit, reported no significant differences between ranibizumab and bevacizumab at 1 year in BCVA (mean difference -1.99 letters; 95% CI, -4.04 to 0.06; *P*=0.056).[16] Contrary to the CATT trial, monthly dosing regimens were equivalent to prn regimens (mean difference -0.35 letters; 95% CI, -2.40 to 1.70; *P*=0.74). Anatomical findings, including fluorescein angiography (FA) and OCT, favoured monthly treatment regimens, but there were no differences between the drugs. These findings were somewhat contradictory to VA-related results which showed non-significant but greater differences between the drugs than between treatment regimens.

In accordance with other pharmacokinetic studies,[5,6] serum VEGF was lower with bevacizumab (geometric mean ratio [GMR] 0.47; 95% CI, 0.41 to 0.54; *P*<0.001) and higher with prn treatment (GMR 1.23; 95% CI, 1.07 to 1.42; P= 0.0044) (Figure 4). It is possible, according to IVAN investigators, that consequences of differential suppression of circulating VEGF will only become apparent after longer follow-up.

Figure 4: IVAN trial: Levels of serum vascular endothelial growth factor at 1 year[16]



GMR = geometric mean ratio

Safety results

Similar to CATT, slightly more systemic SAEs were reported with bevacizumab (odds ratio 1.35; 95% CI, 0.80 to 2.27; *P*=0.25). However, fewer participants receiving bevacizumab had an ATE or heart failure (odds ratio 0.23; 95% CI, 0.05 to 1.07; *P*= 0.03).

Meta-analysis

When IVAN investigators combined their findings with analysis of the data reported by Subramanian et al[17] and CATT,[3] they confirmed equivalence in VA between ranibizumab and bevacizumab, as well as between monthly and prn treatments.[16] Although the changes in lesion thickness favour ranibizumab, clinical relevance of these findings has yet to be determined. Systemic SAEs tend to occur more often with bevacizumab versus ranibizumab and in prn versus monthly treatments.

Conclusion

The emerging evidence from the VIEW 1 and VIEW 2 trials would appear to suggest that fewer injections with aflibercept may provide comparable efficacy and safety to ranibizumab in the treatment of AMD. Thus, should aflibercept obtain approval in Canada, it could become a new therapeutic option in the clinical management of AMD with differentiated benefits for patients, clinicians, and the healthcare system.

Although both the CATT and IVAN trials demonstrated equivalent efficacy between ranibizumab and bevacizumab in preventing vision loss in patients with AMD, the use of bevacizumab is likely to remain under scrutiny due to the fact that most regulatory bodies discourage the use of off-label therapies. Such polices have been created to protect both clinicians and patients while maintaining the principle of evidence-based medicine. While both the CATT and IVAN trials provide high levels of evidence in support of bevacizumab efficacy, these trials were not powered to compare safety between the 2 therapies, and the off-label use of bevacizumab might continue to present concern for clinicians. Proper pharmacoeconomic and cost effectiveness analyses are needed to assess the true costs of AMD care with a specific anti-VEGF therapy and/or dosing regimen.

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