



## New Comparative Data for Anti-VEGF Therapies in Age-Related Macular Degeneration

A report from the

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Seattle – A head-to-head trial failed to demonstrate that bevacizumab matches the efficacy and safety of ranibizumab for the treatment of neovascular age-related macular degeneration (AMD). For the primary end point of the trial, presented at the 2013 ARVO Annual Meeting, bevacizumab did not achieve the criteria for non-inferiority. In the safety analyses, no significant differences were observed in the rate of serious adverse events (SAEs), but these data conflict with a previous study in which significantly more SAEs were observed in the bevacizumab arm. When a meta-analysis was performed in pooling data from the most recent trial, called IVAN2 (Inhibition of VEGF in Age-related choroidal neovascularization) with the previous study, bevacizumab reached the non-inferiority threshold but the increased risk of SAEs persisted. The trends for differences between anti-VEGF therapies for several secondary outcomes in the IVAN2 trial further challenge equivalence within a benefit-to-risk calculation.

Chief Medical Editor: Dr. Léna Coïc, Montréal, Quebec

### New Data Contribute Little Clarification

Ranibizumab was established as a first-line treatment of AMD on the basis of large phase III trials that associated this drug with prevention of vision loss. Systemic side effects were uncommon. Bevacizumab, like ranibizumab, also inhibits VEGF but is indicated for suppression of cancer growth. It has been employed by some physicians for AMD because it can often be acquired at a lower cost, but this off-label use is controversial because the drugs differ pharmacologically, and the relative benefit-to-risk is uncertain. The controversy about off-label bevacizumab use persisted after completion of the previous CATT (Comparison of AMD Treatments Trial), which showed safety differences between bevacizumab and ranibizumab. In the new trial, IVAN2, non-inferiority on the basis of efficacy was not shown.

“The 95% confidence limit for the difference between ranibizumab and bevacizumab crosses the line of no significance and also the non-inferiority margin with a mean difference of 1.37 letters [favouring ranibizumab],” reported Dr. Simon Harding St. Paul’s Eye Unit, Royal Liverpool University Hospital, UK. In a parallel comparison of monthly to discontinuous use of anti-VEGF therapy, the difference on the primary end point also failed to meet the

definition of non-inferiority, so neither of the two IVAN2 trial hypotheses was met “by strict statistical interpretation.”

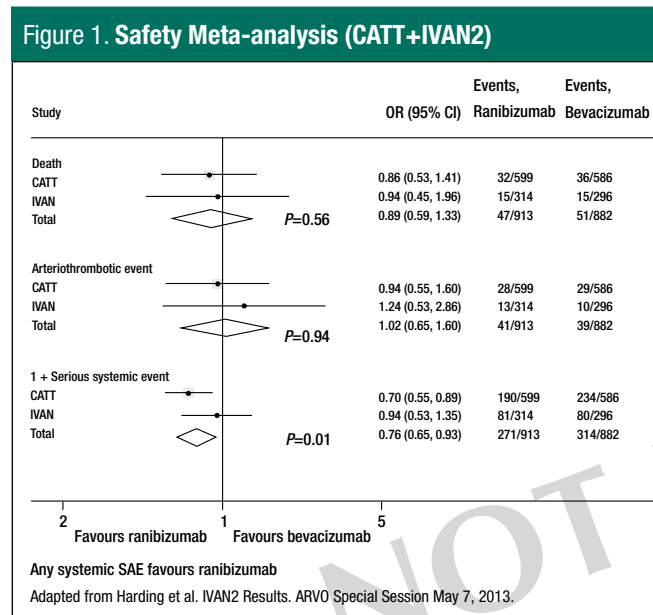
The emphasis on “strict statistical interpretation” was made because Dr. Harding contended that the failure to show non-inferiority in IVAN2 was counterbalanced by a meta-analysis of IVAN2 and CATT data, which did bring bevacizumab into a predefined non-inferiority margin despite a persistent numerical visual acuity advantage for ranibizumab. However, the pooling of data in the meta-analysis associated bevacizumab with a substantial and statistically significant increase in the risk of SAEs (35.6% vs. 29.6%;  $P=0.01$ ), so the benefit-to-risk equivalence remained in doubt by either assessment (Figure 1).

### IVAN2: 2-year Data

In IVAN2, 628 AMD patients were randomized at centres in the UK to receive ranibizumab 0.3 mg or bevacizumab 1.25 mg by intravitreal injection. Within these two arms, a second randomization allotted approximately half of each group to monthly injections or a discontinuous dosing strategy in which patients received injections on an as needed (PRN) schedule after an initial set of 3 monthly injections. PRN injections of ranibizumab and bevacizumab in the discontinuous arm were determined



by loss of visual acuity or clinical signs, such as active exudation. The final 2-year data of IVAN2, presented at the 2013 ARVO, included efficacy and safety analyses comparing bevacizumab to ranibizumab and monthly to discontinuous injections.



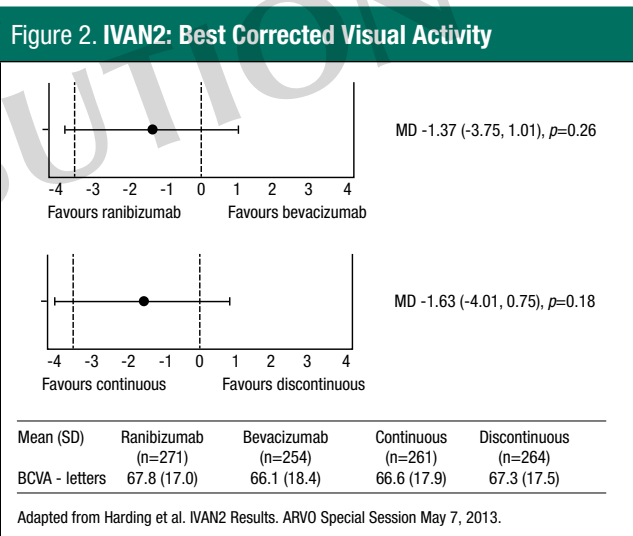
In the comparison of the anti-VEGF therapies, the primary outcome of best corrected visual acuity (BCVA) was increased by a mean 67.8 letters in the ranibizumab arm and 66.1 letters in the bevacizumab arm ( $P=0.26$ ). The 95% confidence intervals (CIs) were wide, allowing for the possibility of a more than a 3-letter decrement in visual acuity with bevacizumab relative to ranibizumab (Figure 2). This extended the relative range of difference beyond the pre-defined boundary of non-inferiority. Two of the three secondary functional outcomes and two of the three quality of life scales also favoured ranibizumab over bevacizumab, although none of these differences reached statistical significance.

On the safety analyses of the anti-VEGF agents, none of the three major outcomes, which were death, arteriothromboembolic event (ATE) and SAEs, differed significantly in IVAN2. When SAEs in major organ systems were evaluated, the greater rate of gastrointestinal SAEs on bevacizumab approached statistical significance ( $P=0.06$ ), but other rates of SAEs were generally similar. The rate of geographic atrophy (GA) was lower on ranibizumab (28.0% vs. 31.2%) but the difference was not significant ( $P=0.46$ ).

In the comparison of the continuous to discontinuous regimens, in which each arm contained a comparable distribution of ranibizumab and bevacizumab patients, the mean 1.37 letter advantage for continuous therapy did not reach statistical significance ( $P=0.26$ ). Again, the

discontinuous regimen could not be characterized as non-inferior because the 95% CI allowed for the possibility of a more than 3-letter mean relative disadvantage, which exceeded the permissible margin. Continuous therapy was also significantly superior to discontinuous therapy for two of the secondary functional outcomes (near visual acuity and contrast sensitivity).

In the safety analyses of the continuous and discontinuous regimens, continuous therapy has a borderline significance for the end point of death, producing an odds ratio (OR) of 0.47 ( $P=0.05$ ) or >50% relative reduction. The ATE rate, although not significantly different, was more than 40% lower (OR 0.56;  $P=0.13$ ). The rate of SAEs, also not statistically different, was also numerically lower in the continuous therapy group (OR 0.77;  $P=0.16$ ). However, the rate of GA was significantly lower on discontinuous therapy (25.7% vs. 33.3%;  $P=0.033$ ). The trends for greater safety with continuous therapy were called counterintuitive by the IVAN2 investigators and are now being evaluated in greater detail.



### A CATT and IVAN2 Meta-analysis

To expand the comparative data, the authors of IVAN2 combined their data with that of CATT, which was presented at the 2012 ARVO Annual Meeting and has been since published (Martin et al. *Ophthalmology* 2012;119:1388-98). In the much larger but similarly designed CATT, 1185 patients were randomized to ranibizumab or bevacizumab and, within these groups, to continuous or PRN therapy. In that study, the 1.4 letter advantage of ranibizumab over bevacizumab did not reach statistical significance ( $P=0.21$ ), but the 95% CI (-3.7 to +0.8 letters) did include the possibility of >3 letter disadvantage for bevacizumab. The risk of SAEs in CATT was significantly higher for bevacizumab relative to ranibizumab (OR 1.3;  $P=0.009$ ).

As the efficacy results of the trials were similar, the meta-analysis showed a similar non-significant advantage for ranibizumab for the end point of visual acuity but the 95% CIs narrowed, bringing the lower end of the 95% CI (-2.82 to +0.52) to within the predefined margin of non-inferiority. For the continuous vs. discontinuous therapy, the tighter CIs of a larger pool of data rendered the advantage of the continuous regimen statistically significant (-2.23 letters;  $P=0.01$ ). While the combined ranibizumab-bevacizumab data permitted the IVAN2 investigators to suggest that bevacizumab is non-inferior for efficacy, ranibizumab was shown in this set of data to be better tolerated.

### GEFAL: A Benefit:Risk Evaluation

Efforts to determine whether the benefit-to-risk ratio of ranibizumab and bevacizumab are similar were further complicated by another multicentre non-inferiority trial presented at the 2013 ARVO. The trial, called GEFAL (*Groupe d'Evaluation Français Avastin Lucentis*), enrolled 501 AMD patients who were randomized to PRN regimens of ranibizumab or bevacizumab. All patients initially received three monthly injections. PRN injections were administered according to visual loss or predefined clinical criteria. The primary outcome of change in visual acuity was measured at 12 months with non-inferiority defined as a difference of up to 5 letters.

The results of GEFAL complicated the ranibizumab-bevacizumab comparison because of multiple inconsistencies relative to previously presented data. In this study, unlike other studies, there was a greater gain in letters on bevacizumab even though patients on ranibizumab were more likely to have a 15-letter improvement (21.3% vs. 20.4%) and to achieve 20/20 vision (17.5% vs. 15.2%). Moreover, the mean number of injections was numerically lower on ranibizumab and most of the anatomical results, such as change in choroidal thickness and dye leakage on angiogram, favoured ranibizumab. Both drugs were well tolerated, but the authors of GEFAL expressed concern about the greater overall risk of adverse events on bevacizumab.

“When we add GEFAL data into the meta-analysis, we see more SAEs with bevacizumab but no greater risk of death or ATEs,” reported Dr. Laurent Kodjikian, Centre Hospitalier Universitaire, Lyon, France. Given the safety signal, Dr. Kodjikian, who presented the GEFAL data, concluded that bevacizumab “should be used under a risk management plan,” referring to the need to prospectively monitor and evaluate adverse events.

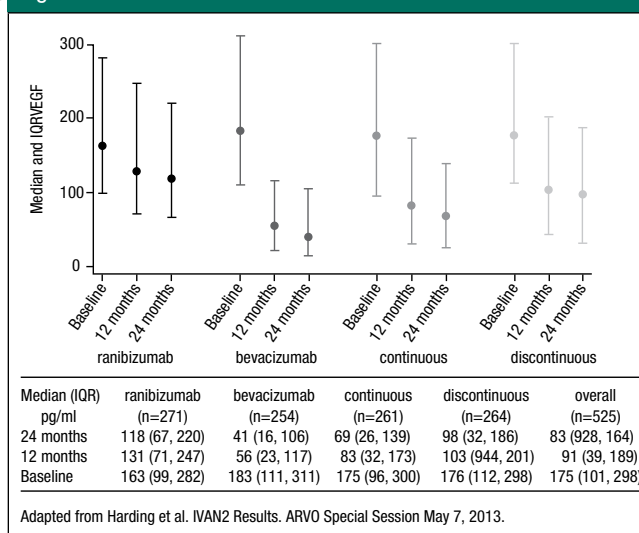
In GEFAL, bevacizumab underwent sterile preparation in hospital laboratories with a 100 mg vial in a protocol that required the unused proportion to be discarded. This

aspect of the study protocol produced criticisms that this and other trials may not be recreating circumstances in the practice setting. Reconstitution of bevacizumab, which is not available in ophthalmic doses, introduces an added risk of contamination that has been reflected in case reports of endophthalmitis. It is unclear whether the low rates of endophthalmitis in GEFAL and other trials are representative of real-world practice.

### Exploring the Meaning of Circulating VEGF Levels

The premise behind off-label substitution of bevacizumab for ranibizumab is that these drugs function similarly, but the data in the studies conducted so far challenge that assertion. In regard to the relative specificity of activity, one potential explanation for the greater relative risk of adverse events associated with bevacizumab is the greater systemic penetration of the drug after intravitreal injection. In IVAN2, serum VEGF levels in the ranibizumab patients fell on average by about 15% from baseline at 12 months and by an additional 5% to 8% by 24 months. In contrast, serum VEGF levels in the bevacizumab group fell on average >50% by 12 months and by an additional 5% to 8% by 24 months (Figure 3).

Figure 3. IVAN2: Median VEGF Serum Level



“Giving intraocular anti-VEGF therapy produces a drop in circulating VEGF levels. We saw a greater drop with bevacizumab. We do not know whether this is due to the dose or the larger molecule,” reported one of the IVAN2 team members. “Quite what this means in terms of safety, we really don’t know.”

Five-year follow-up for the IVAN2 trial is planned, but ranibizumab remains the “standard of care” and will be used in those patients who require additional anti-VEGF

therapy, according to Dr. Usha Chakravarthy, Queen's University, Belfast, UK, who was another IVAN2 investigator. No phase III trials to license bevacizumab are underway.

### Conclusion

A 2-year trial comparing bevacizumab to ranibizumab for control of AMD was unable to demonstrate non-

inferiority. The study was the second of two multicentre studies to evaluate whether there was similar efficacy and safety of bevacizumab and ranibizumab for AMD. When data from the two studies were combined, clinically significant differences in safety were observed. Other findings from these studies, including the greater activity of bevacizumab in inhibiting VEGF outside of the eye, support the conclusion that these agents are not interchangeable. □

### Questions and Answers

*Questions and answers with Dr. Alan Cruess, Professor and Head, Department of Ophthalmology, Dalhousie University, Halifax, Nova Scotia.*

**Q: IVAN2 investigators concluded that bevacizumab was non-inferior to ranibizumab based on a meta-analysis with the CATT data even though this was not shown in their own trial. Do you agree with the conclusion?**

**A:** The science of meta-analysis is complicated and not uniformly accepted because there are problems with combining data from separate trials with separate protocols. For example, the CATT trial employed a different PRN strategy and defined a different margin for non-inferiority. In IVAN2, there was a failure to prove that bevacizumab was not worse than ranibizumab. This should be the emphasis. Ultimately, they drew a different conclusion from what their data showed.

**Q: In the meta-analysis, IVAN2 investigators acknowledged a higher rate of SAEs on bevacizumab, but suggested the mechanism was unclear and the difference was small, implying limited clinical significance. Do you agree?**

**A:** It is important to first recognize that both IVAN2 and CATT are only powered for efficacy. Safety data should be reported, but differences are a signal for further analysis. What is important to note is that this signal is consistent across a large body of data, including several observational studies. While IVAN2 investigators suggested that they were uncertain about a mechanism, the greater suppression of VEGF in the bevacizumab arm in IVAN2 is a very likely mechanism. The comparative data with bevacizumab and ranibizumab is still limited. It is important not to sweep safety signals under the rug.

**Q: In concluding remarks, the lead author of IVAN2 characterized bevacizumab as offering better value. Is this fair?**

**A:** Cost effectiveness is an important consideration, but the concept of value must include efficacy and safety. An opinion about the value of bevacizumab drawn from the IVAN2 data should not be used to circumvent the regulatory system that is in place to evaluate benefit-to-risk. It is troubling to see this system thrown under the bus. We have numerous examples of bad outcomes from off-label use of therapies. This becomes a political rather than a scientific conclusion.

**Q: Many thought the higher rate of SAEs during discontinuous use of anti-VEGF therapies to be counterintuitive. Do you agree?**

**A:** The biologic plausibility of greater risk from discontinuous use can be drawn from other physiologic processes in which intermittent suppression of one signalling factor, relative to continuous suppression, can produce a greater rise in a compensatory signal in the same pathway. Angiogenesis is complex, which is one reason to employ these drugs judiciously. As ophthalmologists, we are relatively new to using therapies with systemic effects and so may be underestimating their risks.

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