Editorial

Anti-vascular endothelial growth factor treatment for neovascular age-related macular degeneration: CATT 5 year outcomes and implication for clinical practice

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Results from the Five-Year Outcomes with Anti-Vascular Endothelial Growth Factor Treatment of Neovascular Age-Related Macular Degeneration Comparison of Age-related Macular Degeneration Treatments Trials (CATT 5)(1) provided an interesting read. This trial funded by the United States National Institute of Health, is the largest non-industry funded clinical trial that have subsequently characterised patients' outcomes after 5 years. Few trials have managed to obtain long term patient outcomes following cessation of study. In the follow up study, only a small number of patients continued to receive the originally assigned drug or dosing schedule after study cessation, hence the 5 year outcomes from the CATT study provide information primarily on overall treatment outcomes with Anti-vascular endothelial growth factor (Anti-VEGF) and does not give any new guidance on the effects of different drugs or its regimens beyond the 2 year results.

In the original CATT study,(2) patients with active choroidal neovascularization (CNV) secondary to Age-related Macular Degeneration (AMD) with no previous treatment were assigned randomly to 0.50 mg ranibizumab (Lucentis, Genentech) or 1.25 mg bevacizumab (Avastin, Genentech) and to either monthly or as needed (pro re nata [PRN]) dosing regimens. At 2 years, VA improved from baseline in all four groups, with most of the improvement during the first 6 months.(2) Ranibizumab and bevacizumab had similar effects on VA, with the PRN regimen resulting in slightly less gain in VA compared to monthly treatment (difference of 2.4 letters). A recent meta-analysis of comparative trials showed no difference between these drugs in mean change in VA at 1 year (bevacizumab vs ranibizumab, 0.5 letters; 95% confidence interval, 1.6 to 0.6).(3)

After 2 years, patients were released from their assigned treatment groups and subsequently, all treatments were administered according to best medical judgment. All CATT patients who were alive at the end of the trial were targeted for the CATT 5-year Follow-up Study. Participation rate was good, with VA obtained for 647 of 914 (71%) living patients with average follow-up of 5.5 years. Given the

trial's elderly patient demographic, the CATT investigators should be commended for their thoroughness with a large proportion with follow up data. Non-participants were generally 2.5 years older and had slightly poorer VA (3 letters worse at baseline and 5 letters worse at 2 years) compared to those who returned to participate.

After trial cessation, over the course of 3 years, patients had an average of 25 examinations for AMD, and an average of 15 treatments (mean of 5 treatments/year). Most (60%) patients were treated with a drug other than their initial assigned drug and 15% received no treatment.

At the 5-year visit, only 50% of eyes had VA of 20/40 or better and 20% had VA of 20/200 or worse, with a mean worsening in VA of 3 letters from baseline and 11 letters from 2 years. The major cause of this significant visual decline appears to have been under-treatment, once released from the trial regime, between years 2 to 5. There are several threads that support this hypothesis. In 467 eyes with fluorescein angiography (FA) at 5 years, mean total lesion area was a 4.8 mm^2 larger than at 2 years, with activity in 25%. The mean lesion size increased by more than 50% over the 3.5-year follow up period. A fibrotic scar was present at the fovea in 20% and non-fibrotic scar was present in an additional 5% of eyes. Among 555 eyes with spectral-domain OCT, majority of patients (83%) had fluid (61% were intra-retinal, 38% sub-retinal, and 36% sub-retinal pigment epithelium). There were more eyes with intra-retinal fluid at year 5 compared to year 2 (61% vs 50%), suggesting under-treatment once released from trial protocol. Despite this, there was an increase in geographic atrophy (GA) which was present in 213 of 515 (41%) gradable eyes, with subfoveal GA in 85 eyes (17%). At year 5, the mean foveal total thickness was 278 mm, a decrease of 182 mm from baseline and 20 mm from 2 years, with the retina abnormally thin (<120 mm) in 36% of eyes.

The cause of drop in VA was multiple, related to an increase in patients with 1) atrophic changes: an abnormally thin retina (<120 mm), and an increase in

prevalence of GA, which is noteworthy, and 2) a substantial increase in CNV lesion size. It is unclear if anti-VEGF treatment has directly resulted in atrophy due to excessive VEGF blockage needed for normal retinal health, or it has simply unmasked a natural process in the pathogenesis of CNV due to the abnormal feeding vasculature when neovascularisation has halted. We also know that more frequent treatment, both in the initial 2 years and in later years, seems to be associated with better long-term outcomes, and many patients require treatment through 5 years and beyond to limit CNV enlargement.

In the CATT 2-year study, more eyes that received monthly treatment developed GA than PRN treatment (24% vs. 15%; P 0.003).(2) This difference in GA rates between monthly vs PRN treatment was also found in IVAN(4) and HARBOR studies(5). Evaluating the 5-year data for residual effect of drug/dosing, the CATT investigators found a higher proportion (44%) of eyes originally assigned to ranibizumab with GA than eyes assigned to bevacizumab (38%) and a higher proportion (47%) assigned to monthly treatment for 2 years with GA than PRN treatment (40%), but they were not statistically significant. Correspondingly, at the end of year 2, the proportion with no fluid on OCT ranged from 45.5% in the ranibizumab monthly group to 13.9% in the bevacizumab PRN group.

The location and quantification of persistent fluid and its relation to GA, CNV and VA needs to be further evaluated. Intra-retinal fluid has been associated with worse VA, whereas the presence of sub-retinal fluid was associated with better VA during anti-VEGF treatment.(6, 7)

Clearly, further comparative studies evaluating the optimum Anti-VEGF dosing regimen to maximise gain (decrease GA and control CNV development) and minimise cost (through drug choice and reduction in injection frequency) are needed. These studies need should: 1) quantify the role of fluid as a surrogate for VEGF control, 2) find other markers that help identify whether GA or CNV is likely to develop with Anti-VEGF treatments, 3) investigate anti-VEGF dosing regimens

including treat and extend protocols (which may allow a period of Anti-VEGF dilution that may normalise physiological levels of intra-ocular VEGF to limit GA development).

We know from the CATT follow up study that PRN treatment outside of stringent monthly assessments resulted in poorer visual outcomes, and although monthly anti-VEGF treatment was associated with the best visual outcomes in the short term, it still carries a high follow up burden and also the risk of increased atrophic changes in the medium to long term, which can worsen VA. Given these limitations, the inject and extend protocol(8) is a good compromise of the above two regimes. In a recent systematic review, the injection and extend protocol was shown to have better VA outcomes compared to PRN treatment.(9) Inject and extend generally involves anti-VEGF injections every 4 weeks until the macular is dry, followed by a slow extension of the injection interval by 2 weeks. This usually means approximately 7-8 injections in the first year to stabilise the disease, which provides patients with a more realistic clinical follow-up plan that helps to minimise recurrences. Treatment burden can subsequently be as few as 4 treatments annually once the disease stabilises. The role of anti-VEGF treatment in AMD is unequivocal as evidenced by its superior VA outcomes compared to the natural history of AMD(10), it is the optimization of the regimen that is now under scrutiny. At this stage, the treat and extend protocol seems to be the logical treatment regimen.

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