



# Five-year outcomes with anti-vascular endothelial growth factor in neovascular age-related macular degeneration: results of the Comparison of Age-related Macular Degeneration Treatments Trials

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*Comment on:* Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Maguire MG, Martin DF, *et al.* Five-Year Outcomes with Anti-Vascular Endothelial Growth Factor Treatment of Neovascular Age-Related Macular Degeneration: The Comparison of Age-Related Macular Degeneration Treatments Trials. *Ophthalmology* 2016;123:1751-61.

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Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in the elderly in industrialized countries (1,2). Current treatments for AMD are severely limited and only the wet form can be treated with anti-vascular endothelial growth factor (anti-VEGF). Although anti-VEGF is a palliative treatment, this drug dramatically improves the prognosis for patients with this disease (3). For example, in a population-based study in Denmark, the incidence of legal blindness from AMD was reduced by 50% after 2006 (4). Currently, all patients diagnosed with neovascular AMD are treated with intravitreal injections of one of the three drugs available in clinical practice that target VEGF: bevacizumab, the most widely used in the USA, ranibizumab and aflibercept (5).

The Comparison of Age-related macular degeneration Treatments Trials (CATT) study was the first head-to-head trial to compare 1.25 mg bevacizumab and 0.5 mg ranibizumab injected under either a monthly or as-needed regimen over a 2-year period (6). This study showed equivalent clinical functional efficacy between the two drugs at 1 and 2 years. However, in this study, the as-needed regimen seems to be associated with a slight poorer outcome regardless of the drug used. Several subsequent studies have confirmed the functional equivalence of the molecules but few investigators have addressed outcomes after 4 years or

more, and long-term results vary considerably across studies (7-10).

The CATT Research Group recently reported the clinical outcomes of participants enrolled in the CATT study at 5 years after the initiation of treatment (11). The authors contacted all patients enrolled in the original trial to schedule an appointment at a CATT clinical center or interviewed the patient and their external ophthalmologist, asking them about past care, treatment, visual acuity (VA), imaging and serious medical events. Only patients with a VA measurement between 51 months (4.3 years) and 85 months (7.1 years) were included. Finally, 647 participants were enrolled in the follow-up study out of the 914 patients still alive (71%) (1,117 patients alive at the end of the original trial) with average follow-up of 5.5 years.

At 5 years, participants lost around three letters from baseline and 11 letters from 2 years. After the end of the clinical trial, the mean number of examinations was 8 for the third year, 7 for the fourth year and 6 for the fifth year with a mean number of injections of 5, 5 and 4, respectively. Most patients still had an active neovascular lesion with persistent fluid on the OCT (83%) and a few had active leakage on the fluorescein angiography (24.5%). Moreover, out of 467 eyes with fluorescein angiography, the mean total lesion area was 12.9 mm<sup>2</sup>, a mean 4.8 mm<sup>2</sup> larger than at

2 years. In addition, geographic atrophy was present in 41% of gradable eyes at 5 years (subfoveal in 17%), compared to 21% at 2 years. These data highlight the under-dosing of patient treatment, despite the fact that 85.5% of patients were followed-up at a CATT center after the 2-year trial. Most importantly, 50% of eyes had VA of 20/40 or better and 20% VA of 20/200 or worse. This result could firstly be interpreted as normal, but it is actually remarkable when comparing VA outcomes in neovascular AMD before the anti-VEGF era during which 2 years after diagnosis, less than 10% of patients retained vision of 20/40 or better with no treatment and 15% of patients with photodynamic therapy (PDT) (12,13).

The SEVEN-UP study, another long-term follow-up study of patients from ANCHOR/MARINA (monthly ranibizumab versus sham or PDT in the study eye), and HORIZON study [open-label extension trial of patients from ANCHOR and MARINA study with patients treated with ranibizumab under a pro re nata (PRN) regimen], showed similar results or worse, with a mean change from baseline of -8.6 letters and from year 2 (end of original trial) of -19.8 letters (9). Similarly, the mean number of injections after the phase III trial was dramatically reduced between year 4 and year 7 at 6.3. These long-term studies highlight that insufficient treatment is responsible for a long-term loss of VA after the monthly injection phase.

The loading dose of three anti-VEGF injections generally dries the macula. Retaining this gain is challenging because it is difficult to propose monthly injections. A PRN regimen requires a monthly follow-up consultation with repeat visits. Despite a strict protocol, several studies have demonstrated that the gain in VA obtained at the beginning of the study is not maintained over time (IVAN, CATT, HARBOR) (6,14,15).

Pro-active regimens, such as the Treat & Extend (T&E) protocol, are an attractive alternative for patients. Rayess *et al.* used the T&E protocol to treat 212 eyes diagnosed with treatment-naïve-neovascular AMD with a mean follow-up of 1.88 years. Mean best corrected VA significantly improved in the first year of treatment and was maintained at the 2- and 3-year follow-up visits (16). Recently, the TREX-AMD study revealed the non-inferiority of the T&E regimen compared to monthly injections (17).

These long-term studies have demonstrated that anti-VEGF therapy has revolutionized the prognosis for patients with neovascular AMD. A pro-active approach adapted to each patient would appear to be a good compromise for controlling the disease and decreasing the numbers of visits

required.

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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