Treatment of age-related macular degeneration

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Age-related macular degeneration is the leading cause of blindness in developed countries. Since the mid-2000s, intraocular injections of agents inhibiting vascular endothelial growth factor (VEGF) have become the mainstay of treatment for neovascular (wet) age-related macular degeneration. Emerging data from national registries show that blindness related to age-related macular degeneration started to fall when anti-VEGF treatment was introduced. However, three key questions remain unanswered for physicians, their patients, and policy makers. First, what is the most cost-effective drug? Two anti-VEGF agents are available: ranibizumab, which was approved by the US Food and Drug Administration, and bevacizumab, which is a cancer drug widely used off label. Bevacizumab costs a fraction of ranibizumab, and is the main drug used in many non-reimbursed settings, such as in US practice. A report suggested that US Medicare could save more than US$1 billion within 2 years if bevacizumab replaced ranibizumab. Second, how often should injections be given? Initial clinical trials suggested that ranibizumab should be given monthly for the best visual outcome. In clinical practice, physicians and patients would obviously prefer injections with intervals of longer than 1 month, and alternative regimens (eg, as needed) have been proposed. However, whether such alternative regimens have acceptable results is unclear. Third, does long-term treatment have safety issues? Although anti-VEGF agents are injected in small quantities into the eye, concerns about systemic safety have been raised, including possible risk of stroke.

In The Lancet, Usha Chakravarthy and colleagues report 2-year findings of the IVAN randomised controlled trial. This trial, along with the US CATT trial, attempts to answer these questions. In IVAN, adults with untreated neovascular age-related macular degeneration were randomly assigned to receive intravitreal injections of ranibizumab or bevacizumab in continuous (monthly) or discontinuous (as needed) regimens. Unfortunately, the results have not clarified the situation. For best corrected distance visual acuity—the primary outcome—bevacizumab was neither non-inferior nor inferior to ranibizumab (mean difference −1.37 letters in favour of ranibizumab, 95% CI −3.75 to 1.01; prespecified non-inferiority limit 3.5 letters). Similarly, discontinuous treatment was neither non-inferior nor inferior to continuous treatment (−1.63 letters in favour of continuous treatment, −4.01 to 0.75). Can the three questions now be answered?

Can the cheaper drug (bevacizumab) achieve results that are similar to those of the approved treatment (ranibizumab)? Chakravarthy and colleagues suggest the answer is yes. Although the 2-
year IVAN results were inconclusive, the meta-analysis of pooled IVAN and CATT data \(^9\) suggests the difference in mean visual acuity between drugs is only −1·15 letters in favour of ranibizumab (95% CI −2·82 to 0·51).

Can injections be given less frequently than every month and yet achieve similar outcomes? The answer is possibly not. CATT showed that the as-needed dosing regimen saved nine injections in 2 years, but resulted in a small but significant reduction in vision (−2·4 letters) compared with monthly treatment. \(^11\) Chakravarthy and colleagues’ meta-analysis confirmed that injections given as needed led to a small loss of efficacy (−2·23 letters, −3·93 to −0·53). \(^9\) Importantly, patients in both trials assigned to discontinuous treatment still attended monthly monitoring visits, which is often not the case in practice. Therefore, although these studies had reasonable results with injections given as needed, monthly physician visits and monitoring were still necessary, and actual clinical outcomes seem to be progressively worse as monthly monitoring and treatment are lost. \(^13\), \(^14\)

Finally, are there systemic safety concerns? The answer is unclear. Age-related macular degeneration has long been suggested to have similar developmental characteristics to cardiovascular diseases, and studies \(^15\), \(^16\) have shown that patients with age-related macular degeneration have an increased risk of stroke. An observational study based on US Medicare \(^7\) showed significantly lower risk of all-cause mortality, incident myocardial infarction, and stroke with ranibizumab than with bevacizumab. In Chakravarthy and colleagues’ report, \(^9\) no difference was recorded in frequency of death (odds ratio 0·96, 95% CI 0·46–2·02) or of an arterial thrombotic event or hospital admission for heart failure (1·69, 0·80–3·57) between drugs. In CATT, however, more serious adverse events were reported in the bevacizumab group than the ranibizumab group, although this risk was not dose dependent. \(^10\), \(^11\) Intriguingly, systemic safety seemed to be worse when treatment was given as needed rather than monthly in IVAN: there were fewer deaths (odds ratio 0·47, 0·22–1·03) and fewer arterial thrombotic events (0·42, 0·17–1·03) with continuous than with discontinuous treatment. \(^9\) This finding raises possible new mechanisms of systemic interaction—e.g., instead of the intuitive dose-dependent link, fluctuation in serum VEGF concentrations might be detrimental to systemic vascular health. Another explanation that has been suggested is the potential protective effect of continuous anti-VEGF therapy, perhaps by suppressing early malignancy. Examination of serum VEGF concentrations and systemic effects in oncology patients could be a way to study this association further. A limitation of Chakravarthy and colleagues’ meta-analysis is that only 1-year data from CATT were included for comparison between regimens. Because of the small number of events at 1 year (24 deaths and 27 arterial thrombotic events), \(^10\) incorporation of the 2-year CATT data (68 deaths and 57 arterial thrombotic events) \(^11\) would be important.

Thus, the ultimate importance of the IVAN trial remains to be established. Despite the similar efficacy between treatments, the uncertainty about safety (particularly systemic events) means ranibizumab users are unlikely to switch to bevacizumab and policy makers are unlikely to mandate
such a switch. A reduction in injection frequency also seems to come at the price of a proportionate reduction in efficacy.

Chakravarthy and colleagues’ results do not address the newest treatment options. Aflibercept, a VEGF-binding fusion protein given every 2 months after loading, was approved by the US Food and Drug Administration after clinical trials showed its results were non-inferior to those of ranibizumab monotherapy. Fovista, an aptamer against platelet-derived growth factor, has better outcomes than ranibizumab monotherapy when used in combination with ranibizumab. With increasingly complex treatment options, more research will be needed to study combination and sequential treatment—used widely in oncology. Both the IVAN and CATT studies have advanced our understanding of the treatment of age-related macular degeneration. Whether these data can significantly impact on clinical management and eventually lead to adoption of bevacizumab for public health funding remains to be seen. The search for a cheaper, better, and safer treatment continues.

CMGC is on advisory boards for Bayer, Novartis, and Roche; and has received honoraria for travel and service on advisory boards, and research support from these companies. TYW is on advisory boards for Abbott, Allergan, Bayer, Novartis, Roche, and Pfizer; has received honoraria for travel and service on advisory boards, and research support from these companies; and has provided expert testimony to Novartis.

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