Clinical update: new treatments for age-related macular degeneration

Age-related macular degeneration (AMD) is the leading cause of vision loss in the developed world. Until recently, this condition was believed to be largely untreatable, but developments in the past 2 years have challenged this view. A new class of drugs—based on suppression of vascular endothelial growth factor (VEGF)—has been introduced for the treatment of “wet” or neovascular AMD, the most visually disabling form (table 1).1–4

In 2006, results with an anti-VEGF agent, ranibizumab, showed that monthly intravitreal injections prevented vision loss and, in many cases, significantly improved the visual acuity of patients with neovascular AMD.3,4 Somewhat less impressive, but still effective, findings, were published 2 years earlier for another anti-VEGF agent, pegaptanib sodium.1 Both agents were recently approved for neovascular AMD by the US Food and Drug Administration (FDA) and have already been incorporated into European guidelines.5 A third agent, bevacizumab, is now increasingly used off-label for neovascular AMD. Bevacizumab was originally developed for systemic treatment of colon cancer (for which it is FDA-approved), and is related to the parent molecule of ranibizumab. Despite the lack of any randomised trial data, intravitreal injection of bevacizumab has become a popular treatment for neovascular AMD, mainly because its efficacy is perceived to be similar to ranibizumab but it is much cheaper.6

Whilst these new treatments are appropriately seen as important breakthroughs in AMD management, the long-term systemic safety of intravitreal anti-VEGF drugs remains unclear. Several concerns have not yet been addressed. First, although the drugs are administered by injection through the sclera into the vitreous cavity, systemic absorption occurs with potential for systemic adverse effects (table 1).1 In particular, human data on the pharmacokinetics of intravitreal bevacizumab are scant. Second, because anti-VEGF treatment for AMD is given monthly or every 2 months and is potentially required for years, chronic VEGF inhibition may cause adverse effects that are not immediately apparent. VEGF has many essential functions, including the formation of collateral vessels crucial for the maintenance of perfusion to ischaemic tissues, such as the myocardium, after an infarction.7 With pegaptanib, the rate of arterial thromboembolic events in treatment and sham groups was similar (table 1) and a recent pharmacokinetics study detected no evidence of systemic VEGF suppression,2 although the lack of controls makes this finding difficult to interpret. The trials for ranibizumab reported a marginally higher rate of arterial thromboembolic events in the treatment arms, which was not statistically significant. However, these trials were not powered to detect small differences in risk.

The issue is further complicated by a recent reanalysis of systemic safety outcomes with ranibizumab, which showed a significant increase in non-ocular haemorrhage in treated patients compared with controls (p=0·01), suggesting some impairment of

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<td>Pegaptanib1†</td>
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<td>Ranibizumab3,4</td>
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Table 1: Anti-VEGF drugs for neovascular AMD

VISION=VEGF Inhibition Study in Ocular Neovascularisation. MARINA=Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration. ANCHOR=Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration. FOCUS=RhuFab V2 Ocular Treatment Combining the Use of Visudyne to Evaluate Safety. *Primary endpoint of proportion of participants losing fewer than 15 letters from baseline visual acuity (treatment vs sham, all p<0·0001). †Arterial thromboembolic events (treatment vs sham, all p>0·05). ‡Mean peak serum concentration after intravitreal injection. §3 mg, ten times recommended dose.
systemic VEGF function. An interim safety analysis of another trial found that the 0.5 mg dose of ranibizumab was associated with a small but significant increased risk of stroke, compared with the 0.3 mg dose (1.2% vs 0.3%; p=0.02), although risk of myocardial infarction or vascular mortality did not differ. The full results of this trial are expected soon. Overall mortality rates were low in the anti-VEGF trials, which suggests patients with major cardiovascular disease or risk factors were under-recruited. Thus the safety of anti-VEGF treatment might not be generalisable from trial data to the wider community of AMD patients. The systemic cardiovascular effects of intravitreal bevacizumab are even more uncertain (table 1). Intravenous administration of bevacizumab increased the risk of arterial thromboembolic events in patients receiving chemotherapy for end-stage metastatic colon cancer, but the systemic safety of intravitreal administration in healthy adults remains unclear.

Although the doses involved in intravitreal injections of anti-VEGF agents are smaller than intravenous doses, and there could be some sequestration in the eye, the plasma half-lives of these agents, except for ranibizumab, are long (table 1). Mean peak serum concentrations of pegaptanib and ranibizumab are below the levels the FDA believes to be necessary to inhibit the biological activity of VEGF-A by 50% (11–27 ng/mL), whereas the mean peak for bevacizumab is substantially above this threshold. However, intravitreal injection of all three anti-VEGF agents leads to peak serum concentrations several orders of magnitude greater than physiological levels of VEGF in adult human beings; physiological levels are usually less than 100 pg/mL. The existing pharmacokinetic data for pegaptanib are from intravitreal injections of ten times the recommended dose, while those for bevacizumab and ranibizumab have only been derived from animal models. The potential capacity of all three agents, especially bevacizumab, to saturate circulating VEGF hints at the possibility of adverse systemic effects. Thus uncertainty about the cardiovascular risk of intravitreal anti-VEGF agents will remain until additional systemic safety data become available.

The manufacturer of bevacizumab, which invested in the development of ranibizumab for AMD, has no plans for any clinical trials on intravitreal bevacizumab, and maintains that ranibizumab is the superior agent. In the absence of randomised clinical trial data, physicians have resorted to evidence from uncontrolled case series and surveys of physicians. Although these series and surveys do not suggest any increase in cardiovascular risk in treated patients, the ad-hoc reporting of uncommon adverse events is clearly incomplete. Physicians appear to have little doubt about the efficacy of intravitreal bevacizumab, with editorials in peer-reviewed journals, as well as news articles in the lay press, reporting favourably on short-term experience with this therapy and stressing its low cost. A survey of nearly 300 US retinal specialists found that more than 90% believed intravitreal bevacizumab to be better and safer than other standard FDA-approved therapies. The American Academy of Ophthalmology has even called on insurance companies to reimburse patients who receive intravitreal bevacizumab.

The issue of potential increases in cardiovascular risk with these new agents deserves scrutiny. Patients with AMD may already be at increased risk of cardiovascular disease, a point largely missed in the spate of editorials and perspectives. All of the traditional cardiovascular risk factors, except diabetes, have been linked with risk of AMD, although not always consistently. A recent prospective study of 1.4 million elderly people found that AMD increased the risk of myocardial infarction by almost 20%, with larger cardiovascular risks reported from other cohorts (table 2). These data suggest that AMD itself may be a marker of high cardiovascular risk and further reinforce the need for caution in long-term use of anti-VEGF drugs. In this context, the interim treatment guidelines from the UK Royal College of Ophthalmologists, which recommend caution and full disclosure to the patient about the lack of knowledge on long-term safety, is laudable, and the decision by the US National Institutes of Health to fund a head-to-head trial comparing the efficacy and safety of bevacizumab...
and ranibizumab will go part of the way towards clarifying uncertainties.

Anti-VEGF agents are clearly important therapeutic breakthroughs for a previously untreatable condition. However, because many patients with AMD have coexisting cardiovascular risk factors, any chronic therapy that could further increase cardiovascular risk, however small, has important public-health implications. Intravitreal bevacizumab in particular presents a new dilemma—this is an apparently effective, cheap but unlicensed drug, which is promoted by physicians rather than drug companies, and demanded by patients. However, clinical trial evidence to support its use and delineate any harms is not available. By contrast to the debate surrounding cyclo-oxygenase 2 inhibitors, which revolved around the interpretation and publication of trial data, the trial data on which to base debate about intravitreal anti-VEGF agents is sparse. There are no trial data for bevacizumab, potentially the most popular agent, yet possibly the most hazardous in view of its pharmacokinetics and greater systemic exposure after intravitreal injection. Although pegaptanib and ranibizumab appear safe in the short to intermediate term, bevacizumab cannot be assumed to have the same risk profile. This unique situation calls for prudence in prescribing anti-VEGF agents to patients with AMD, with both physicians and patients recognising that the true risks and benefits will not be known until long-term postmarketing surveillance data on pegaptanib and ranibizumab, and clinical trials for intravitreal bevacizumab, are available.

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TW and PM are on advisory boards for Pfizer and Novartis, and have received honoraria, speakers’ fees, research funding, and travel and accommodation payments from either or both companies. GL was a visual acuity examiner on several Pfizer and Genentech clinical trials involving pegaptanib sodium and ranibizumab.