Avastin

Is intravitreal bevacizumab (Avastin) safe?

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Can a drug be safe if an FDA warning has been issued for it?

Can a drug for which a Food and Drug Administration (FDA) warning has been issued be safe? The question of safety using off-label intravitreal bevacizumab (Avastin Genentech, South San Francisco, California, USA; Roche AG, Basle, Switzerland) is a concern among ophthalmologists around the globe. This is one of the key aspects of *The international intravitreal bevacizumab safety survey: using the internet to assess drug safety worldwide* published by A Fung *et al*[1] (***see page 1344***). Why else would 70 centres from 12 countries voluntarily report on >7000 injections in >5000 patients using an internet-based questionnaire within just 6 months?

The safety survey reported no drug-related adverse events for intravitreal bevacizumab injections beyond the level of incidence rates seen in control groups of current anti-vascular endothelial growth factor (VEGF) trials in ophthalmology. No single adverse event reported was above 0.21% over a mean follow-up of 3.5 months. On the one hand, a self-reported safety survey may have the risk of underestimating adverse events, which was discussed by the authors; on the other hand, hardly any prospective clinical trial would be able to obtain safety data from such a diversity of centres, using different techniques for preparing and injecting bevacizumab and for treating a variety of exudative and neovascular ocular diseases. The safety information of this survey might bring us closer to the risks in the real world.

But let us have a look back on where safety concerns for bevacizumab come from. Bevacizumab, a monoclonal antibody designed for binding all isoforms of the VEGF, has been developed primarily for cancer treatment. It is currently approved for the treatment of metastatic colorectal cancer in combination with chemotherapy. In cancer patients, bevacizumab is typically given as a systemic infusion at 5 mg/kg every 2 weeks for months and months.[2] The FDA warning concerns this patient population and this treatment regimen, and resulted from a meta-analysis of several trials (http://www.fda.gov/medwatch/SAFETY/2005/Avastin_dearhcp.pdf). The major concern is an increased risk for thromboembolic events, which was found to increase from 1.9% to 4.4%.

Ophthalmologists commonly use a dose of 1–2.5 mg bevacizumab given intravitreally at a minimum interval of every 4 weeks. This is about 150–400 times less than the systemic dose in patients with cancer. There are basically three areas of safety concerns over using intravitreal injections as the route for delivering bevacizumab: the intravitreal injection procedure, harmful intraocular effects due to the relatively high intraocular drug dose and the potential for systemic adverse effects.

The intravitreal injection as a treatment procedure has become a commonly used procedure since the introduction of the combination treatment of verteporfin and intravitreal triamcinolone for neovascular age-related macular degeneration (AMD). Meanwhile, data on the safety of the intravitreal injection procedure have become available from large prospective clinical trials using anti-VEGF drugs. The risk for endophthalmitis was up to 0.16%/injection, for traumatic cataract up to 0.07%/injection and for retinal detachment up to 0.17%/injection.[3 4] Despite adding risks with each additional injection, the intravitreal injection procedure is considered to be safe overall.

But which toxic effects can be expected an ocular structures after an intravitreal injection of bevacizumb, as first described by Rosenfeld *et al*.[5 6] A unique effort has been made in the ophthalmological community to answer this question. Several studies have evaluated intravitreal bevacizumab for toxicity in different animal models, tissue models and cell cultures. Shahar *et al*[7] not only reported good retinal penetration of the full-length antibody bevacizumab after an intravitreal injection in a rabbit model, but also showed no evidence of toxic effects using electrophysiology. These findings are supported by no evidence for toxicity in the histological evaluation of rabbit retinae after intravitreal injections up to 5 mg/injection,[8 9] and no electrophysiological changes on isolated bovine retinae or rabbit retinae.[9 10] Cell cultures of human retinal pigment epithelial, rat neurosensory retinal or human microvascular endothelial cells showed no toxic effect at doses of bevacizumab above those in clinical use. The only dose-limiting effect reported in animals was some inflammatory reaction in the vitreous after intravitreal injections of 5 mg bevacizumab. An inflammatory reaction after an intravitreal injection of a full-length antibody has been a concern since phase I/II studies with the antibody fragment ranibizumab (Lucentis) showed an increased incidence of transient uveitis episodes. In humans, there has been no evidence for toxic ocular effects of bevacizumab in short-term follow-up. Evaluating patients with neovascular AMD treated with intravitreal bevacizumab showed improved multifocal electroretinogram macular function responses[11] and a reduction in anterior chamber cell and flare measurements, indicating potentially an anti-inflammatory effect of the drug.[12]

Probably, after an intravitreal injection some bevacizumab will reach the systemic circulation and persist in the circulation because antibodies are cleared more slowly than an antibody fragment. The essential question is whether any systemic, clinically relevant effect can be expected after intravitreal administration. Systemic bevacizumab is currently studied in patients with neovascular AMD. Despite a drug dose of 5 mg/kg, the only systemic adverse event reported was a transient, well-controllable increase in blood pressure in some patients.[13] Several retrospective clinical studies on intravitreal bevacizumab[14–17] and a recent prospective study using 2.5 mg intravitreal bevacizumab have shown an increased risk of neither ocular nor systemic adverse events.[18] *The international intravitreal bevacizumab safety survey* has further strengthened the good short-term safety profile of intravitreal bevacizumab using a novel internet approach with global input and global relevance.

So far, no definite information on long-term safety on intravitreal bevacizumab is available, but some assumptions can be drawn from other anti-VEGF drugs in ophthalmology. Compared with oncology, our goal in ophthalmology is different. We do not plan to maintain constant VEGF suppression to inhibit angiogenesis. Apparently, constant VEGF suppression is not necessary for all lesions and diseases to maintain or improve visual function and a marked individual variability is observed. As commonly performed in oncology, applying treatment cycles independent of disease activity is not necessary as new imaging modalities, such as optical coherence tomography, allow us to monitor our patients closely

for recurrences. In addition, constant VEGF suppression may contribute to an increased risk of toxicities in normal tissues.

For treating our patients with off-label bevacizumab, despite favourable short-term safety, it seems advisable to limit the number of treatments to as few as necessary.

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Retrobulbar haemodynamics

Retrobulbar haemodynamics in non-arteritic anterior ischaemic optic neuropathy

G T Feke

Clinical evaluation of the optic nerve circulation in NAION remains an elusive goal yet to be fully achieved

In this issue of the journal, Kaup *et al*[1] (***see p 1350***) report results relating to blood flow dynamics in the ophthalmic artery, the nasal and temporal short posterior ciliary arteries and the central retinal artery in patients in the acute stage of non-arteritic anterior ischaemic optic neuropathy (NAION). Although they are not the first group to conduct such a study, they are the first to compare their findings in patients with NAION with those measured in a group of age-matched controls.

Before commenting on specific results, it is instructive to consider the problem of blood flow and NAION from first principles. As initially described by Henkind *et al*,[2] and recently by Arnold[3] in his excellent review, histopathological examination shows that there is occlusive vasculopathy in the optic nerve microcirculation located primarily in the retrolaminar region of the nerve head in patients with NAION. The first question, then, is "What is the blood supply to this region?"

The answer to this question is beautifully shown in the photomicrograph published by Olver *et al*,[4] which is reproduced in fig 1. It is the paraoptic branches of the nasal and temporal short posterior ciliary arteries that supply the so-called "Circle of Zinn–Haller", which in turn supplies the retrolaminar, laminar and prelaminar regions of the optic nerve microcirculation. The second question becomes "Can the blood flow dynamics in these paraoptic branches be measured using any existing technique?"

In short, the answer is "No". In another excellent and instructive review, Hayreh[5] also describes the anatomical details of the blood supply to the optic nerve head and, in addition, proceeds to critique the various experimental methods that have been used to evaluate the optic nerve head circulation. The specific question posed is "Do colour Doppler imaging findings in posterior ciliary arteries provide information relevant to the optic nerve head microcirculation?" Hayreh points out what is quite clear from examination of fig 1—that is, it is simply impossible for colour Doppler to differentiate the individual paraoptic branches of the short posterior ciliary arteries. As Hayreh describes, "… all of them are lying jumbled and intertwined as a vascular bundle". Therefore, when users of colour Doppler imaging claim to obtain haemodynamic results from short posterior ciliary arteries, they are likely to be obtaining an averaged result from several arteries in a bundle. Furthermore, as these arteries are the primary supply to

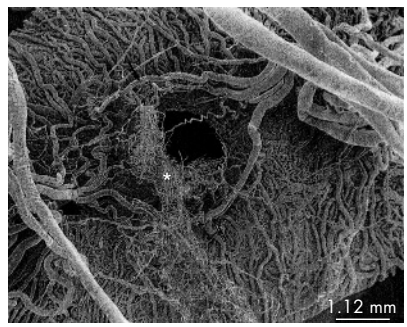

Figure 1 Scanning electron photomicrograph of the "Circle of Zinn–Haller" (centre) formed by the paraoptic branches of the temporal (upper right) and nasal (lower left) short posterior ciliary arteries. It is believed that a diminished blood supply in the Circle of Zinn–Haller is associated with non-arteritic anterior ischaemic optic neuropathy. Reproduced with permission from Olver *et al*.[4]