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REVIEW

Bevacizumab: a new way of doing business?

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Abstract

This review highlights the history of the development of treatments for choroidal neovascularization (wct AMD). It examines how drug therapies have evolved for the management of age-related macular degeneration (AMD) and the value of randomised clinical trials in determining efficacy. Finally it examines the emerging practice of utilising bevacizumab for the treatment of choroidal neovascularization despite the lack of any phase III clinical trial data.
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The treatment of submacular choroidal neovascularisation (CNV) in all its guises is undergoing a quiet revolution. Direct laser photocoagulation of the vessels was for years the mainstay of intervention. The role of laser was carefully evaluated over many years with many large clinical trials.[1] The contraindications were established as a result of negative trial results—the wrong turns on the road and the cul de sacs became apparent through painstaking, methodical research.

Thus it was that the classic extrafoveal lesions were treated with thermal laser while the management of subfoveal lesions remained controversial.[2]

Surgical approaches to CNV were also evaluated systematically. Surgical excision of submacular vessels in age-related macular degeneration (AMD) damaged the pigment epithelium such that the net visual outcome was poor.[3] Similar surgery for inflammatory disciform lesions fared rather better.[4]

The efficacy of other surgical procedures has been evaluated, albeit with a lower standard of scientific proof. The risks and benefits of limited and 360° macular translocation and pigment epithelial transplantation are now quite well understood.[5–7]

The introduction of photodynamic therapy with verteporfin (PDT) marked a change in AMD management. Now a drug was involved, not just a device (laser) or a surgical technique, and the standards applying to drug licensing had to be met. Large-scale and expensive clinical trials demonstrated those subgroups that could benefit.[8,9]

At the same time, the marketing expertise and business disciplines of commercial pharmaceutical companies were introduced. Advertising and publicity was intense and was aimed at clinicians, regulators and the general public. The result was a rapid uptake of PDT in many parts of the world including the UK.

The discovery that vascular endothelial growth factor (VEGF) was important in modulating the behaviour of CNV marked a further turning point in treatment.[10,11] Much of the research on VEGF had been carried out in the retinal vasculature and its role in the choroidal circulation was thought to be less important.

Once a target had been identified, strategies were soon devised to block VEGF with high specificity. Pegaptanib (Macugen) has been the subject of extensive phase III trials and is set for early licensing and rapid clinical uptake.[12] Hard on its heels comes ranibizumab (Lucentis) that promises even better clinical results.[13] It too is the subject of large phase III trials and is looking likely to follow the same commercial trajectory.

All the treatments mentioned above orbit like planets around scientific orthodoxy. Bevacizumab (Avastin, Genentech Inc., South San Francisco, CA, USA) has appeared like a comet, a bright and strange phenomenon in the night sky . The parent compound to ranibizumab, it is already licensed for the management of colorectal cancer.[14] It was thought to be pharmacodynamically unsuited for the journey from the vitreous cavity to the subretinal space.[15]

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Systemic administration of bevacizumab in the management of CNV produced a significant reduction in retinal thickening and improvement in visual acuity in a small series.[16] However, the small number of reports of bevacizumab injections into the vitreous cavity[17–21] have in less than a year turned into massive widespread clinical use. In effect, a product not licensed for use in the eye has gone from the earliest phase I pilot study into a common treatment without going through any phase II or III trials.

What has driven this uptake is not so much that bevacizumab works (which does seem to be true) but that it is available and cheap.[22] The twin facts that it is licensed for cancer treatment (and therefore can be acquired through normal channels) and that it comes in the large doses necessary for its cancer role have meant that the aliquot cost per eye injection may be tens of pounds rather than hundreds or thousands of pounds.

This would seem to be excellent news for desperate patients and an overburdened health service—if it is safe. There is a reason why drugs are forced to slog down the long hard road of phased clinical trials—the process can trap serious side effects before the drug goes on general release. Even late in phase III, a drug like natalizumab can show a nasty side and be withdrawn.[23] If bevacizumab is safe, we have just witnessed a quantum leap in the management of CNV. If it is not, we might be witnessing the early stages of the largest legal case in the history of ophthalmology…and this time the pharmaceutical industry will not be picking up the tab. Therefore, as a first step there is an urgent need for a randomised clinical trial to evaluate the role of bevacizumab in the management of AMD. The economic benefit to the NHS of using such a cheap drug to prevent blindness justifies government support for such a trial.

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