Anti-VEGF for neovascular ARMD: visual improvement as the goal of therapy?

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There has been dramatic progress in anti-VEGF therapy, but future guidelines are needed

In the era of anti-vascular endothelial growth factor (VEGF) therapy for exudative age-related macular degeneration (ARMD), a paradigm shift has emerged. Until then, photodynamic therapy (PDT) was considered a successful therapeutic option, basically slowing down visual deterioration compared with the natural course. A milestone in drug therapy for ARMD was the introduction of pegaptanib, the first anti-VEGF drug for ocular use. For the first time, in about 10% a visual improvement in ARMD was reported.[1] Initial study data on treatment with ranibizumab showed that up to 40% of patients experienced a significant increase in visual acuity (VA) independent of the type of neovascular lesion.[2 3] Long-term data up to 2 years have been published and demonstrated that the initial positive effect could be maintained by multiple, repeated injections.

When the impressive results of ranibizumab leaked out (albeit the drug was not available outside the studies), Philip Rosenfeld reported on his impressive observations after intravitreal bevacizumab for refractive exudative ARMD (ASRS meeting, Montreal, June 2005).[4] Bevacizumab had been approved as an adjunct to therapy of metastatic colon carcinoma in 2004. Marketed as Avastin, the drug was available in most countries. The retina community received the exciting news immediately. With patients desperately waiting for more potent treatment options and ranibizumab still in the process of FDA approval and the knowledge that an effective drug is already accessible, off-label bevacizumab had become almost routine in clinical practice. By autumn 2006, the FDA approved ranibizumab for ocular use. Since then, both drugs—bevacizumab and ranibizumab—have been used for ARMD therapy. Although studies comparing bevacizumab with the other VEGF-blockers are lacking, numerous clinical case series on safety and efficacy reveal that bevacizumab seems to act in a very similar way to ranibizumab.

With ranibizumab and bevacizumab, our expectations with respect to treatment efficacy and outcomes have changed rapidly. Visual improvement in ARMD has become the goal of medical therapy. Prevention of further vision loss (stabilisation) is almost taken for granted in the era of anti-VEGF therapy.

The general effectiveness of VEGF blockers for any type of neovascular ARMD is substantiated by a considerable amount of scientific data, in particular relating to ranibizumab. In clinical practice, the individual response to therapy, however, varies considerably with respect to vision and anatomical findings. Some eyes may show dry, non-exudative lesions after just one or a few anti-VEGF administrations. Others might require continuous injections to keep the neovascular process under control, and some might not seem to respond to therapy at all. This leads to the following considerations: when to inject, how often, how long and when to stop.

In this context, the article by Lux *et al*[5] ***(see pages 1318–22)*** deserves attention. The authors report on the outcomes of bevacizumab treatment in various macular pathologies associated with choroidal neovascularisation growth. On the precondition that ''vision'' is the most important parameter for therapeutic effectiveness, they define a stringent criterion for response to treatment, namely: any improvement in VA (ETDRS letters) and/or gain in reading ability (Radner test). Conversely, non-response is described as stable or reduced vision compared with baseline. Vision was correlated with optical coherence tomography (OCT) and fluorescein angiography (FAG) findings that also served as parameters to decide upon re-injection.

The rate of ''responders'' to bevacizumab according to these definitions was 55%. The remainder were considered ''non-responders'' and remained stable or lost vision (in total 45%, 9% $\geqslant$15 letters). Parameters associated with non-response to therapy were a large initial size of lesion and a low reading ability at presentation. Interestingly, initial macular thickness and the type of lesion were of no or minor significance. The conclusion was made that the major limiting factor that prevented visual improvement with bevacizumab was pre-existing irreversible retinal/RPE-damage due to advanced or longstanding disease.

The study by Lux *et al* is an interesting contribution to defining ''success'' in ARMD therapy. In addtion, it provokes further questions: What to do with ''non-responders'', re-treatment yes/no? In view of the expected natural course of the disease, stabilisation and prevention of further visual loss can be regarded a successful treatment, in particular for eyes with initial useful vision and documented progressive disease. Provided that bevacizumab keeps the neovascular process under control and stabilises vision over some time, this can be considered a reasonable therapeutic strategy. ''Responders'' to initial anti-VEGF application as defined here describe a subgroup of neovascular ARMD with especially promising prognosis.

In this context, the role of OCT and FAG findings must be refined. From imaging techniques, it is possible to describe the type and size of the lesion, determine the activity of the neovascular process (leakage or staining?), determine the amount of intra-/subretinal fluid and help to make decisions as to whether to continue with anti-VEGF treatment. Most important in the decision-making are the patient's visual potential and the individual tissue response to the drug administration. Indicators for favourable outcomes according to the present study are therefore a good initial VA, a small lesion and recent disease progression. The amount of intra- and subretinal fluid has been shown to be less significant. In other words, the benefit of treatment for eyes with poor initial VA and exudative lesions undergoing fibrotic changes is questionable.

At present there is no general consensus on indications for initial or subsequent administration in ARMD. The study by Lux *et al* stimulates further investigations to look for parameters that allow us to define promising candidates for anti-VEGF therapy and criteria for subsequent injections. For ''responders'', according to the definition of Lux *et al*, re-treatments are indicated without question. Long-term results are needed to determine whether responders do well in the future, too. We also expect to obtain further information from a subgroup analysis of the major studies that might serve as a basis for patient selection.

The PrONTO study,[6] which investigated whether reduced injections according to need are sufficient to maintain functional results, suggests the following criteria for evaluation: visual loss, OCT alterations

(persistent or increased intra- and subretinal fluid, retinal thickness), FAG findings (active leakage, lesion growth) and ophthalmoscopic symptoms, such as a new haemorrhage. The choice of these parameters seems logical, as they hint at a continuing active neovascular process. If previous treatments have been shown to improve or at least stabilise the eye condition, further treatments would be justified.

National and international retina societies are intensively working on guidelines for anti-VEGF therapy. Recommendations from the view of the retina specialists might differ from indications that insurances will be ready to cover due to of the economic pressure on healthcare systems. Furthermore, studies on vision-specific quality of life indicate that ARMD that affects either the first or the other eye has a different impact on quality of life. Future guidelines could include the patient's binocular condition as well.

At present, ranibizumab and bevazicumab are the most powerful weapons against neovascular ARMD and definitely more efficacious than PDT and pegaptanib. Meanwhile, ranibizumab is available in many countries, but retina specialists continue to use intravitreal bevacizumab as a low-cost alternative for treatment of neovascular maculopathy. Alternative treatment regimes are under investigation to reduce the total number of injections and to individualise therapy based on the need for follow-up injections (PIER, PrONTO) as well as studies on combination therapies (PROTECT, SAILOR). All these investigations are aimed at improving the efficacy of therapy, minimising the number of follow-up injections, decreasing the cumulative risk of injection-related endophthalmitis and reducing the enormous economic burden of a (possibly lifelong) therapy.

Br J Ophthalmol 2007;**91**:1259–1260.
doi: 10.1136/bjo.2007.120303

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REFERENCES

1 **Chakravarthy U**, Adamis AP, Cunningham ET Jr, (VISION Clinical Trial Group). VEGF Inhibition Study in Ocular Neovascularization. Year 2 efficacy results of 2 randomized controlled clinical trials of pegaptanib for neovascular age-related macular degeneration. *Ophthalmology* 2006;**113**:1508.
2 **Rosenfeld PJ**, Brown DM, Heier JS, (MARINA Study Group), *et al*. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006;**355**:1419–31.
3 **Brown DM**, Kaiser PK, Michels M, (ANCHOR Study Group), *et al*. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006;**355**:1432–44.
4 **Rosenfeld PJ**, Moshfeghi AA, Puliafio CA. Optical coherence tomography findings after an intravitreal injection of bevacizumab (Avastin) for neovascular age-related macular degeneration. *Ophthalmic Surg Lasers Imaging* 2005;**36**:331–*5*.
5 **Lux A**, Llacer H, Heussen FMA, *et al*. Non-responders to bevacizumab (Avastin) therapy of choroidal neovascular lesions. *Br J Ophthalmol* 2007;**91**:1318–22.
6 **Fung AE**, Lalwani GA, Rosenfeld PJ, *et al*. An optical coherence tomography-guided, variable dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration. *Am J Ophthalmol* 2007;**143**:566–83.

Corneal transplant surgery

"Small bubble technique" helps "big bubble technique"

Francis W Price Jr

Surgeons will increasingly use big bubble technique

Corneal transplant surgery has recently seen rapid and exciting changes on multiple fronts, following several previous decades of only minimal change after introduction of the operating microscope and monofilament sutures. New transplantation techniques are primarily taking off on three fronts: endothelial keratoplasty (EK), femtosecond laser assisted penetrating keratoplasty (PK), and anterior lamellar keratoplasty (ALK). All three of these procedures address one of the primary limitations of traditional PK—that is, poor wound healing.

The increasing use of EK to treat dysfunctional corneal endothelium is a prime example of how rapidly a new technique may be adopted once it evolves to the point that it produces superior outcomes and can be reliably performed. For example, the first EK technique not requiring corneal sutures to hold the graft in place was introduced about nine years ago.[1] Subsequent improvements, including methods to reduce the incision length and amount of tissue removed from the recipient eye, resulted in the iteration known as Descemet's stripping with endothelial keratoplasty (DSEK), introduced in late 2003.[2–4] At that time the number of EK procedures was so low that they were not even tracked by the Eye Bank Association of America (EBAA). By the time the EBAA began tracking use of EK procedures in 2005, they represented 4.5% of the grafts performed in the United States. By 2006, EK procedures represented 18% of US grafts (2006 Eye Banking Statistical Report, Eye Bank Association of America), and based on current levels of demand for donor tissue, the number of EK procedures is expected to further double in 2007.

Femtosecond laser contoured PK is still quite young—the first procedure was performed at our centre in late 2005. Early results suggest that interlocking incisions created with a femtosecond laser may result in faster wound healing with less induced astigmatism than standard PK. As the hardware and software to perform this procedure are introduced at more centres around the world, we expect the number of procedures performed this way to dramatically increase.

ALK has been performed for many years using various methods. Most have involved the use of metal blades to perform hand dissections of varying depth on both the donor and recipient corneas. The major problem with these techniques has been difficulties with visual recovery because of irregularities in the dissection planes. Manual dissections by necessity introduce some irregularities, so the donor and recipient interfaces seldom match up perfectly.

> An elegant method of using a small secondary bubble in the anterior chamber to help determine if a successful big bubble has been achieved

Microkeratomes have been used to help create smoother dissection planes, but even with a microkeratome it can be difficult to precisely match the dissection depths in the donor and recipient corneas. Limitations with hand and microkeratome dissection techniques have led surgeons to develop methods for removing all, or most, of the corneal stroma in the recipient with transplantation of all but the donor endothelium and Descemet's membrane, a technique known as deep anterior lamellar keratoplasty (DALK). Melles *et al* introduced a method of filling the anterior chamber with air to help the surgeon more