with EDD use. At this time, the only consensually agreed upon contraindication against use of EDD is for patients who have already experienced NAION in one eye, since the risk for fellow eye involvement (without EDD use) is estimated to be in the range of 15–20% over 5–10 years. Other patients who are worried about their risk of developing NAION should discuss their concerns with their physicians, although their overall risk of developing NAION is low. Further investigation into these issues will provide more information about potential risk that may be helpful for future patient counselling and management.

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Age related macular degeneration

Which treatment is best for which AMD patient?

P Kroll, C H Meyer

A comparison of different treatment approaches for vascular age related macular degeneration

The treatment of choroidal neovascularisation (CNV) in age related macular degeneration (AMD) has changed enormously during the last decade.[1] While 10 years ago there was only argon laser coagulation, today we have several treatment options for classic, occult, and mixed subtypes available: classic CNV responds well to photodynamic therapy (PDT) with ''off label'' triamcinolone, while occult CNV can be treated by PDT, transpupillary thermotherapy (TTT), subretinal surgery, macular translocation, and anti-angiostatic therapy. The choice often depends on a variety of personal and environmental circumstances. Firstly, increased age and reduced health status of the patient may exclude them from surgery. Secondly, while first eyes may benefit from subretinal surgery, second eyes may be eligible for macular translocation. Thirdly, the initial visual acuity (VA) and the type of lesion often limit the success in PDT and also the financial coverage by medical insurance.

The beneficial results were initially presented by the Macular Photocoagulation Study (MPS), with laser reducing severe visual loss in extrafoveal and juxtafoveal CNV. As the mechanism of conventional photocoagulation relies on thermal damage to the neuroretina, through an estimated temperature rise to 42℃, severe central scotomas and recurrent CNV are often experienced in patients with subfoveal lesions.[2] This treatment is currently used only in selected cases with small extrafoveal lesions. This limitation of photocoagulation led to an increase in new treatments.

Transpupillary thermotherapy (TTT) is a subthreshold photocoagulation delivering moderate heat to the choroid and retinal pigment epithelium (RPE) using a diode laser (810 nm). The goal is to achieve relative sparing of the overlying neuroretina by a limited temperature elevation of approximately 10℃.[3] However, it might be difficult to deliver an appropriate irradiation in every case, as a standardised measure of the chorioretinal temperature is not available.[4] Stolba *et al* present, in this issue of the *BJO* (p 158), their own long term experience with TTT in occult CNV. Overall, 70% of patients showed an improved (14%) with unchanged (56%) visual acuity (VA) at the 24 month visit. While previous studies reported less successful data, this study gives further evidence that TTT may be the treatment of choice in occult CNV. A modification using indocyanine green mediated photothrombosis through a 810 nm laser achieved a visual stabilisation in 55%, improved VA in 33% at 12 months according to Farah *et al*.[5]

Photodynamic therapy (PDT) using a sensitising agent such as verteporfin, in conjunction with low power diode laser, achieves a selective photothrombosis of the CNV. The Treatment of AMD with PDT (TAP) Study demonstrated a decreased risk of vision loss in predominantly classic CNV.[6] In addition, the presumed selective approach in PDT has been questioned, as the binding LDL receptors for benzoporphyrin are also present in other retinal structures,[7] and possibly cause minor functional alterations after PDT.[8] An initial upregulation of vascular endothelial growth factor (VEGF),[9 10] and damage to the blood-retina barrier after PDT[11 12] seem to indicate that a combined therapy with intravitreal triamcinolone or VEGF inhibitors may reduce the recurrence and consecutive high re-treatment rate.[13] The TAP round table presented a treatment algorithm for all subtypes of vascular AMD.[14] Without any doubt PDT remains the treatment of choice in predominant classic CNV.

> With increasing life expectancy we will face more patients with vascular AMD searching for cost effective approaches

The goal of ''subretinal surgery'' was to remove the CNV after a pars plana vitrectomy (PPV) through a small retinotomy to reduce the progression of the disease, yielding a long term stabilisation of the visual function.[15] However, the surgical benefits are limited by the removal of adjacent RPE adherent to the removed CNV, frequently extending the preoperative size of the CNV itself.[16] Although the results of the Submacular Surgery Trial (SST) indicated no benefit from this treatment,[17] we think that patients with massive subretinal haemorrhages[18] or of a short duration in the first eye and a preferably extrafoveal location of the CNV may benefit from subretinal surgery. We performed subretinal surgery in 50 eyes and determined decreased VA in 44%, a stabilised VA in 24%, and improved VA in 32% after a long term follow up of 4 years.[19]

RPE cell suspension,[20] or the free autologous transplantation of a full thickness graft ''patch'' from the mid-peripheral

RPE, with the adjacent Bruch's membrane and choriocapillaris is a novel modification of subretinal surgery.[21] The normalised autofluorescence of the transplanted RPE sheet indicates an ongoing interaction between photoreceptors and autologous graft, which corresponds with a central fixation of the foveal photoreceptors over the graft. However, during the follow up RPE cells seem to lose their pigmentation, possibly limiting the duration of the supply. The future of this experimental approach will show, by valid long term data, which patients will benefit from this intriguing approach.

Macular translocation with 360° retinectomy remains the most invasive and consequential approach to treating vascular AMD by moving the intact central photoreceptors away from the damaged underlying layers onto intact RPE choriocapillaris. While most intraoperative complications could be compensated by advanced surgical techniques, some side effects, including cystoid macular oedema, PVR, small persisting subretinal fluorocarbon bubbles, diplopia, or consecutive asthenopic problems remain.[22] However, long term results demonstrated significantly improved near VA from 20/70 to 20/50 at 12 months postoperatively.[23] More than half of the patients achieved reading speeds of 70 words/minute. A remaining problem in macular translocation is the high recurrence rate of CNV, which becomes more evident with a prolonged follow up. Within a follow up of 2 years we experienced a recurrence in approximately 10%.[24] Today we consider postoperative additive antiangiogenic treatment in selected patients. However, it is our opinion that macular translocation remains currently the only procedure for patients with subfoveal CNV to regain a final vision of 20/30 in selected cases.

Antiangiogenic treatment approaches are currently being investigated in numerous studies. Three anti-VEGF agents are now clinically available—pegaptanib (Macugen; Eyetech/Pfizer), bevacizumab (Avastin; Genentech), and ranibizumab (Lucentis; Genentech/ Novartis).[25]

Pegaptanib sodium is to date the only therapy approved by the Food and Drug Administration to treat all vascular AMD.[26] The antiangiogenic agent belongs to a new class of so called ''aptamers'' (from the Latin *aptus*, ''to fit,'' and the Greek *meros*, ''part or region''). Pegaptanib is synthesised by polymerase chain reaction for a specific inhibition of VEGF 165, the isoform mainly responsible for ocular CNV. The VEGF Inhibition Study demonstrated with nine intravitreal injections at 6 week intervals significantly reduced VA loss by approximately 50% regardless the angiographic subtype. As the CNV tends to progress, longer term data are required to characterise the efficacy.

Bevacizumab, a recombinant humanised, full length, anti-VEGF monoclonal antibody that binds all isoforms of VEGF-A, has been approved for colorectal cancer. Additional controlled clinical trials will investigate its effect on the angiogenesis in AMD. However, Nguyen *et al* recently reported the effect of intravenous infusions of 5 mg/kg bevacizumab in CNV secondary to pathological myopia.[27] A reduced leakage was accompanied by improved VA in active subfoveal CNV at baseline. Bevacizumab, with a molecular weight of 150 kD, is possibly too large to penetrate the entire retina. However, Rosenfeld *et al* described the favourable intravitreal ''off label'' application of bevacizumab in CNV secondary to AMD.[28] Approximately 1.0 mg of bevacizumab was intravitreally injected. Using 100 mg bevacizumab vials (cost $550), the price of a 1 mg intravitreal dose is only $5.5.

Ranibizumab, a 48 kDa humanised Fab fragment of a monoclonal anti-VEGF antibody, binds non-specifically to all VEGF isoforms. The efficacy of intravitreal injections with ranibizumab in combination with PDT is currently being investigated in controlled clinical trials. Previous results of experimental CNV in monkey eyes demonstrated no leakage if the monkeys were treated with ranibizumab and PDT, rather than with PDT alone.[29]

In the future we will face a change from current monotreatments in a variety of combinations.[30] The combination of PDT with triamcinolone seems to be logical first step, and intravitreal applications of avastin or macugen will shortly be available as an adjunctive after laser or surgical approaches. With increasing life expectancy we will face more patients with vascular AMD searching for cost effective approaches as shown by Farah *et al*,[5] Rosenfeld *et al*,[28] Spaide *et al*,[13] and Stolpa *et al* (this issue). Limited financial resources will force us to select the best, most effective and most cost effective treatment for our patients. Each monotherapy has demonstrated its benefit in terms of numeric gain by ETDRS lines. However, we should not be too euphoric about these scientific results as the overall satisfaction of our patients mainly relies on restoring quality central vision to read and watch TV on a long term basis. It seems that this major goal has not yet been achieved, making further research necessary.

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Glaucoma

The rising cost of glaucoma drugs

A Azuara-Blanco, J Burr

Are we wasting precious resources of our healthcare budgets?

In the recent past glaucoma care has experienced a revolution led by new technologies and treatments. As Knox *et al* describe in this issue of the *BJO* (p 00), new glaucoma medications have caused profound changes in glaucoma treatment in Ireland. It is highly likely that these trends are occurring throughout the Western world.[1–4] We would like to comment on several of the findings reported in their compelling and solid analysis.

There is an overall increase in the number of prescriptions for glaucoma that is not justified by an increased prevalence of the disease

Among several possible explanations, it would seem that physicians may be (a) trying to reach lower intraocular pressure (IOP) in existing glaucoma subjects, and/or (b) recommending treatment to patients who would not be treated in previous years (for example, patients with ocular hypertension, OHT). Considering the available scientific evidence, maximising IOP lowering in patients with advanced glaucoma should not be contested. However, we should question the benefit of treating patients with OHT or pre-perimetric glaucoma (that is, incipient optic nerve damage with normal visual field) and challenge this trend. From the health provider point of view, this is a most important problem as the prevalence of OHT and early glaucoma is much higher than the prevalence of manifest disease. According to the Ocular Hypertension Treatment Study, the number needed to treat to prevent conversion to early visual field loss in patients with OHT is 42.[5] From the patients' perspective, a deterioration of their condition to reach an incipient visual field loss in one eye would not affect their quality of life (QoL).[6] How many patients with OHT converting to early glaucomatous visual field loss in one eye will end up with severe visual disability? With current medical and surgical standards the number could be zero. If the number were not zero, we would still need to know whether such visual disability would be avoidable by treating them earlier.

The use of β blockers is decreasing and prostaglandins are becoming the mainstay of medical treatment. Other new treatments (topical carbonic anhydrase inhibitors and α-2 adrenergics) have been successfully introduced in the market and the overall cost of medical treatment is escalating

Considering the IOP lowering efficacy and safety profile, it is not surprising to see prostaglandins displacing β blockers as the most commonly used drug. However, prostaglandins cost three to four times more than β blockers, the difference in efficacy is small (5% reduction of baseline IOP, or 1.6 mm Hg),[7] and β blockers are well tolerated by the majority of patients without respiratory or heart disease. Other new medications are also more expensive than β blockers but with similar or less IOP lowering efficacy. It is remarkable that the cost of glaucoma treatment in the Republic of Ireland has increased 227%. Will this increase in cost be translated in a reduction of visual disability—that is, what is the cost/effectiveness or cost/utility of new antiglaucoma medications?

The frequency of glaucoma surgery is decreasing. Laser trabeculoplasty for treating open angle glaucoma continues to be rarely used

In spite of apparent improvements in surgical techniques and outcomes (for example, releasable and adjustable sutures, antimetabolites, etc), the frequency of glaucoma surgery has decreased considerably. It seems that the majority of patients and doctors choose to avoid surgery when glaucoma can be controlled medically. This trend would be supported by a recently published Cochrane review that did not find any substantial difference in glaucoma control and QoL between these two options.[8] However, it is interesting to see that laser trabeculoplasty is ignored as a treatment option, in spite of scientific evidence supporting its role.[9 10] In an environment of evidence based medicine, the lack of use of laser trabeculoplasty is a good example of how difficult it is to change physicians' attitudes and practices.

Glaucoma management is also being influenced by new diagnostic technology. Primary and secondary healthcare providers are increasingly using new diagnostic tools that may detect glaucoma at early stages (for example, frequency doubling perimetry, confocal scanning laser tomography, scanning laser polarimetry, and optical coherence tomography). This technology is further increasing the cost of glaucoma care although there may not be scientific evidence to support its use in clinical practice.[11 12] In addition, it is unclear