The introduction of photodynamic therapy (PDT) in 1999 represented a major step forward in the treatment of wet age-related macular degeneration (AMD). However, the outcome of the therapy is still under discussion as reduction of vision loss and/or stabilization and re-treatment has been required in most cases. In addition, PDT has several other limitations such as lesion size and lesion composition. Moreover, since its introduction, the treatment strategy has been intensively discussed with respect to cost-effectiveness and patient convenience. A major cause of the limitations of this monotherapy procedure in terms of both the number of treatments necessary for regression and the visual outcome, may be related to the underlying photodynamic tissue effects. PDT uses a photodynamic reaction type 2 and leads to oxidative stress of the underlying tissues and inflammatory reactions, which result in an enhanced vascular endothelial growth factor (VEGF)-expression in treated areas. These photodynamic mechanisms therefore seem to enhance effects primarily associated with the pathogenesis of neovascular AMD. According to the results given and the hypothesis of AMD-pathogenesis by VEGF expression as an epiphenomenon of inflammation, an improvement of the outcome should therefore be possible when combining PDT with an anti-inflammatory and an anti-VEGF drug. At the time this hypothesis was established, the only drug available was triamcinolone. The pharmacological profile of corticosteroids has the potential to simultaneously counteract both AMD- and PDT-related inflammatory mechanisms and, to a lesser extent, VEGF-induced growth activity. Steroids inhibit angiogenesis, fibrotic proliferation and inflammatory activity by reducing the migration and activation of inflammatory cells. Uregulation of extracellular matrix protein plasminogen activator inhibitor (PAI)-1 leads to a direct angiostatic effect. Steroids downregulate intracellular adhesion molecule (ICAM) expression, which is an important stimulus in the development of choroidal neovascularisations (CNV) and an inflammatory mediator released by PDT. When using a combination of PDT and triamcinolone, researchers have achieved a dramatic reduction in the number of treatments and an increase in visual acuity in eyes with wet AMD. Moreover, all lesion types became eligible for this therapeutic approach (see Figure 1). The off-label use of PDT and triamcinolone has therefore become popular within a relatively short time. However, the adjunct intravitreal triamcinolone introduces unusual side effects which are not seen with verteporfin therapy alone - for example, an increased intraocular pressure (IOP) and progression of cataract. In clinical practice, combination therapy is already widely established.

Change of Treatment Paradigms for Wet Age-related Macular Degeneration

and is referred to as standard of care by many retinologists. Randomised trials are on-going in order to prepare a robust scientific background for data reference.

Recently, the main results of large multicentre surgical trials - the submacular surgery trials (SST) - were reported. The overall findings did not support the use of surgery in eyes exhibiting exudative AMD.8

There are also a number of pharmacotherapy options for the treatment of wet AMD. Many of these strategies directly target VEGF, which is believed to be the major factor responsible for the initiation and propagation of the disease process. The drugs showed favourable results. However, the mechanism of action is not completely understood. Firstly, it is known that VEGF is not only a growth factor but also a permeability factor. The effects therefore might not only be due to anti-angiogenesis but also to the reduction of leakage, thus explaining the anti-inflammatory effects of those drugs by reduction of inflammatory cell extravasation. To date, there has been no contradiction of the proposed effects of the combination strategy previously reported. Another approach is the extraocular application of a modified steroid with anti-angiogenic properties. There follows an update on those already approved or in the final stage of the study/approval procedure.

Pegaptanib (Macugen®) is an intravitreally administered aptamer that specifically binds with the VEGF165-isof orm. This drug has been approved by the US Food and Drug Administration (FDA) for the treatment of all lesion types. It has shown clear benefits. Seventy per cent of the patients lost fewer than 15 letters of visual acuity compared with 55% in the control group (p<0.001).9 The major disadvantage is that repeated injections - every six weeks - are necessary, and these carry a risk of endophthalmitis. This risk can be minimised with appropriate care during and following each injection. The major advantage of this approach is the eligibility of all lesion types. However, as in the combination of PDT and triamcinolone, the aim is to find a treatment leading to visual acuity increase and not only to stabilisation. Increase and stabilisation are defined with reference to the number of lines.

Ranibizumab (Lucentis®), a Fab fragment of the ‘mother molecule’ Bevacizumab (Avastin®) already introduced in oncology and FDA-approved for the treatment of metastatic colorectal cancer, is a drug that could lead to an increase in visual acuity in many patients (annual meeting of the American Society of Retina Specialists (ASRS), Montreal, July, 2005). It blocks all VEGF isoforms and has to be administered intravitreally every four weeks. There are several on-going phase 3 trials and the one-year results of a large trial on minimally classic and occult lesions have recently been reported. In this trial, the drug resulted in a 95% response rate and up to 33% of patients gained 15 letters or more. As in the case of the patients prescribed Macugen it is still not known how many repeat treatments will be necessary before a complete regression of the disease is achieved. These new approaches will therefore be evaluated by their effect on visual acuity, the cost per vial and the number of treatments necessary for complete regression.

Parallel to the intravitreal approach of ranibizumab, systemic bevacizumab (the Systemic Avastin for Neovascular Age-Related Macular Degeneration (SANA) study), was investigated for the treatment of patients with neovascular AMD.10 The SANA study showed the beneficial results of an off-label use of systemic bevacizumab for this disorder (exudative AMD). However, there are a number of concerns relating to a relatively high incidence of side effects associated with the systemic administration of the

Figure 1: Patient Suffering from a Minimally Classic Lesion due to Wet AMD on the Left Eye

Left: early and late phase angiogram at baseline. Only one combination treatment was necessary for complete regression. Right: early and late phase angiogram (12 months after treatment). Visual acuity increased to 20/40

drug. Those side effects include hypertension, proteinuria, gastric perforation and bleeding.

As a consequence, Dr Philip J Rosenfeld et al. from the Bascom Palmer Eye Institute in Miami (in addition to other researchers), are currently investigating intravitreal bevacizumab for neovascular AMD and macular oedema secondary to central vein occlusion.\(^\text{11,12}\) All groups report that bevacizumab has demonstrable efficacy in combating these diseases when given intravitreally. Moreover, the favourable results and cost-effectiveness (it can be easily prepared from the intravenous (IV) solution) of this approach have led to the conclusion that intravitreal bevacizumab could become the preferred first-line therapy for the treatment of neovascular AMD. It is readily available worldwide and costs much less to produce than other AMD treatments.

There could be confusion as to why a second drug, ranibizumab, was created if bevacizumab is effective. According to company reports, it was thought that the bevacizumab molecule was too large to penetrate the retina. This was concluded after testing another monoclonal antibody (trastuzumab – Herceptin\(^\text{13}\)) for permeability. Bevacizumab itself was never tested on an animal exhibiting AMD.

There are several hypotheses as to why the molecule works. The penetration rate could be higher in the aged retina or VEGF-trapping in the vitreous, rather than in the subretinal, space might be sufficient for such an approach to be effective. Recently, the American Academy of Ophthalmology (AAO) proposed comparing ranibizumab directly with bevacizumab.

Anecortave acetate (Retaane\(^\text{14}\)) is a modified antiangiogenic corticosteroid in which the side effects of corticosteroids such as elevation of intraocular pressure and cataract formation have been engineered out. It is administered every six months as a juxtascleral depot and therefore has an excellent safety profile. Promising results have been obtained in phase 1 and 2 trials. However, in a large clinical trial, the drug did not meet necessary criteria. Several factors were responsible for this – an excess of small, aggressive lesions, reflux of the drug through the incision and treatment intervals. Several studies have been performed recently confirming the importance of avoiding reflux and the necessity of keeping the treatment intervals. A counter pressure device has therefore been designed to prevent reflux during administration (see Figure 2).

Since safety data are excellent and other trials are underway, this drug could still become an option for the treatment of wet AMD. In addition, a large risk-reduction trial is underway investigating the potential of the drug in preventing progression from dry to wet AMD.

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