

Management of Neovascular Age-related Macular Degeneration

a report by

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Ursula Schmidt-Erfurth is Professor and Chair of the Department of Ophthalmology at the University Eye Hospital, Vienna, Austria. Her scientific focus is the development of novel diagnostic techniques, e.g. high-resolution imaging, and new treatment strategies such as anti-angiogenic therapy. Professor Schmidt-Erfurth has received several grants and awards throughout her career, including the Carl Zeiss Award of the Fraunhofer Gesellschaft in 2000, the Research Award by the German Ophthalmological Society in 2001, the Achievement Award of the American Academy of Ophthalmology in 2002, the Johnson Award of the University of Washington in 2004 and the Rosenthal Award of the Macula Society in 2005. Professor Schmidt-Erfurth serves on the editorial board of *Spektrum der Augenheilkunde* and the *European Journal of Ophthalmology*. She has authored over 200 original articles and abstracts and is a frequent national and international speaker. Her many professional memberships include the Association for Research in Vision and Ophthalmology, Macula Society, Retina Society, Euretina and the American Academy of Ophthalmology. Professor Schmidt-Erfurth attended medical school at the Ludwig-Maximilians-University of Munich, Germany. She was a Research Fellow in Ophthalmology at Harvard Medical School and was Clinical Professor in Ophthalmology at the University Eye Hospital, Medical University of Schleswig-Holstein, Germany.

The Dilemma of Age-related Macular Degeneration

Advanced age-related macular degeneration (AMD) remains the leading cause of severe and irreversible visual loss and classified blindness throughout Europe and the US. The prevalence of advanced AMD in a European population has been reported to be as high as 1.7%, which increases strongly with age. While only 0.2% of individuals between 55 and 64 years of age are affected, 11% of the age group over 85 years experience registered blindness due to AMD. With census institutions predicting a doubling of the population aged 65 years and over by 2030, AMD and related blindness will increasingly become a substantial public health issue.

To date, the efficacy of therapeutic interventions was rather limited. No useful treatment modality was identified to treat the atrophic type of AMD characterised by progressive loss of the retinal pigment epithelium (RPE) and subsequently the overlying photoreceptors referred to as geographic atrophy. Strategies such as laser coagulation and surgical removal of the fibrovascular complex aimed at the mechanical destruction of choroidal neovascularisation (CNV) destroying RPE and retinal layers via extravasation of fluid and blood components as well as fibrovascular scarring. The non-selective nature of these procedures led to collateral damage of the adjacent sensitive neural layers and an additional iatrogenic loss in vision, strongly reducing the therapeutic benefit.

Another issue responsible for the poor prognosis of AMD is the fact that preventative measures are not available. Although early signs of the disease are easily identified (such as drusen documented in 48.2% and pigmentary abnormalities seen in 7.2% of eyes in subjects over the age of 55 years) the diagnosis of CNV development is usually made after the pertinent time and reliable strategies to prevent neovascular growth do not exist to date. If advanced AMD is found in one eye, the risk of developing sight-threatening disease in the fellow eye within the following five years is as high as 43%. Currently, a prospective, randomised trial carried out in patients

with the highest risk profile Age-Related Eye Disease Study (AREDS) categories 3 and 4, is evaluating the impact of anecortave acetate applied as a juxtasceral depot on the development of advanced AMD. Anecortave is a modified steroid, a cortisone that is devoid of side effects such as cataractogenesis and the induction of glaucoma. The substance interferes with the intracellular signal transduction of various growth factors, e.g. vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and insulin-like growth factor (IGF), and prevents matrix metalloproteinase activation and endothelial cell proliferation/migration.

The Role of Laser Therapy in Neovascular AMD

In the 1980s, photocoagulation was suggested to induce a thermal ablation of the area angiographically harbouring a CNV lesion. Despite the significant destruction of neural tissue surrounding the lesion, the macular photocoagulation study (MPS) was able to demonstrate that vision loss, although primarily enhanced by the destructive procedure itself, was significantly smaller in treated eyes than in untreated eyes undergoing the spontaneous progression of the disease during long-term follow-up. In a pioneering effort, the MPS studies provided accepted guidelines for treatment and CNV lesion classification, based on lesion location and composition. Lesions underneath the foveal avascular zone (FAZ) qualify as subfoveal CNV, while those between the FAZ and a distance of less than 200µm from the FAZ are referred to as juxtafoveal CNV. All lesions at a distance of at least 200µm and longer from the FAZ are considered extrafoveal. There is a general consensus that photocoagulation applies to juxtafoveal lesions, when the thermal damage zone will not affect the FAZ, and to extrafoveal lesions as long as the lesion composition is of the classic type. Lesion composition is defined based on angiographic features. The early detection of a vascular pattern and late leakage defines a classic component, while absence of a vascular pattern or a spotty hyperfluorescence early on followed by late leakage characterises an occult component. Dependant on the proportion of classic and occult components within an individual lesion, a CNV is

referred to as classic (composed of a classic component only), predominantly classic (more than 50% classic) or minimally classic (the classic portion covering less than 50, but more than 1% of the entire lesion) and occult only (no classic component identified angiographically).

Photodynamic therapy (PDT) was developed to avoid thermal damage to sensitive neural structures. In PDT a light-activable chromophore, e.g. verteporfin, is administered intravenously (IV) and preferentially accumulates within a neovascular lesion. Exposure to monochromatic light within the absorption peak of the dye molecules induces a chemical process involving the production of singlet oxygen and other highly toxic oxidative species leading to endothelial cell damage followed by vasothrombosis. Verteporfin therapy was therefore suggested as an ideal treatment modality for subfoveal lesions or those juxtafoveal lesions, whereas thermal damage to the FAZ was likely to occur with photocoagulation.

Prospective clinical trials clearly demonstrated that in predominantly classic lesions, a stabilisation of visual acuity (defined as less than three lines of vision loss) was achieved in 69% of eyes treated with PDT using verteporfin compared with 41% in untreated eyes. Subsequent trials performed in occult CNV revealed a significant benefit for lesion sizes smaller than four disk areas (DAs) or an initial visual acuity of less than 20/50 with 75% of PDT-treated eyes maintaining stable vision, compared with 49% of eyes in the sham group. The Treatment of Age-related Macular Degeneration with Photodynamic Therapy (TAP) and the Verteporfin in Photodynamic Therapy (VIP) trials were designed as phase III trials and were used for the US Food and Drug Administration (FDA) approval of verteporfin therapy in 1999 and 2003 for the treatment of subfoveal lesions with a predominantly classic lesion composition of any lesion size and occult CNV smaller than four DAs. In contrast, if occult lesions were larger than four DAs and higher levels of visual acuity were documented, verteporfin therapy had a negative impact with 72% of eyes losing at least three lines when treated with PDT, while only 52% did so in the sham arm. For minimally classic lesions, phase II trials support the hypothesis that a benefit may be expected for lesions smaller than six DAs. In general, PDT monotherapy is able to reduce the risk of future visual loss significantly by a factor of approximately two, compared with the untreated condition. However, treatment is effective even in terms of a stabilisation, accepting a three-line loss in two-thirds of all patients; the remaining one-third will continue to decline. A mean loss of visual acuity between two and four lines for classic only and occult lesions, respectively, will occur in the overall population of treated patients and the chance for an improvement in visual acuity is minimal with approximately 5% to 10%.

Retinal Pharmacotherapy using Anti-VEGF Strategies

VEGF has been known for years as a vascular permeability factor (VPF) in different disease entities. In ocular neovascular disease, VEGF appears to be the major stimulus of neovascular growth originating from retinal as well as choroidal vasculature. VEGF is released following hypoxia due to choriocapillary loss, structural alteration of Bruch's membrane, oxidative stress from lipid degradation within photoreceptors and RPE and local inflammatory processes – all factors that play a major role in the pathogenesis of AMD. VEGF induces a decomposition of basal membranes, endothelial cell proliferation and migration. VEGF alone may therefore be responsible for the two key features of neovascular symptoms representing leakage and fibrovascular growth.

Macugen™ (pegaptanib) was the first compound with anti-VEGF activity to have been evaluated in clinical trials. The drug represents an aptamer (a nucleotide), which offers a high affinity to VEGF165 (a subtype of VEGF). Macugen is administered intravitreally at intervals of six weeks and has an inhibitory effect on leakage from CNV. The VEGF Inhibition Study in Ocular Neovascularization (VISION) trial included patients with all lesion types in neovascular AMD and evaluated treatment effects during two years of follow-up and continuous re-injection. In the dose group of 0.3mg that was found to be most effective, 70% of eyes remained stable within three lines in the Macugen group, while 55% of eyes in the sham group maintained stability. A mean loss of two lines was observed in the overall population and vision improvement occurred in 22% with Macugen compared with 12% with sham treatment – a difference of only 10%. Although the VISION trial led to the approval of the therapy in 2004, because it provided proof of principle of a novel approach in the treatment of neovascular AMD, outcomes are very similar to those previously obtained with verteporfin therapy. Although the benefit in terms of visual acuity was maintained throughout the second year with 59% stable vision in the Macugen and 45% in the sham group, a cross-over of verum and placebo groups revealed that treatments had to be repeated continuously throughout the second year in six-week intervals to preserve the effect. A total number of 15 intravitreal interventions carries a significant risk of intraocular contamination and infectious endophthalmitis. Repeated visits and interventions, as well as a significant amount of drug supply, also represent a significant burden for patients, ophthalmologists and healthcare budgets. ■

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