Management of Wet Age-related Macular Degeneration

a report by
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Age-related macular degeneration (AMD) is the most frequent cause of blindness in people over 65 years of age in developed countries.[1] Its pathogenesis is multifactorial, involving a complex interaction of metabolic, functional, genetic and environmental factors, and remains largely unclear. For a long time age and smoking were the only identified factors that definitely increased the risk. More recently, genetic risk factors for AMD were characterised as well. In addition to these significant advances in our understanding of the pathophysiological processes underlying the disease, treatment of the neovascular form of AMD has improved markedly over recent years. The aim of this review is to summarise the current treatment options for neovascular AMD and provide an outlook for future choices that are under investigation.

Treatment Strategies

Laser Photocoagulation

The first therapy for wet AMD was conventional laser treatment, which began in the 1980s. Several clinical trials have shown that the mid- and long-term success of this treatment is superior to no intervention in patients with subfoveal AMD. However, it has also been shown that laser photocoagulation is associated with an increased risk of early vision loss related to the collateral damage of the photoreceptors, leading to an absolute scotoma.[2,3] Taking into account the newer pharmacological treatment options for wet AMD, photocoagulation is no longer recommended as a first-line treatment in subfoveal or juxtafoveal lesions.

Photodynamic Therapy

Photodynamic therapy (PDT) using verteporfin (Visudyne®) as an intravenously infused photosensitising dye for subfoveal choroidal neovascularisation (CNV) due to AMD offers the possibility of avoiding non-selective tissue damage. A diode laser in the red wavelength spectrum (689nm) activates the sensitiser, which in turn leads to a release of radicals that cause endothelial damage and vascular thrombosis of the neovascular vessels. This results in a selective ablation of the membrane, maintaining photoreceptor integrity and retinal function. Several randomised clinical trials have proved the efficacy of this intervention in patients with CNV. In the Treatment of AMD with PDT (TAP) study, enrolling patients with subfoveal lesions with any classic component PDT symptoms reduced the risk of moderate vision loss – defined as losing more than 15 letters (three lines) on the Snellen chart – from 62% in the sham-treated group to 47% in the PDT-treated group over two years. The largest benefit was found for predominantly classic lesions with 59% of treated eyes compared with 31% of placebo-treated eyes losing fewer than 15 letters.[4] In the Verteporfin in PDT (VIP) trials, 45% of PDT-treated eyes compared with 32% of sham-treated eyes lost fewer than 15 letters.[5] The subgroup of patients with a smaller lesion size showed more pronounced treatment success. Most patients need three to five treatments over a two-year period.[6] Although PDT has been shown to slow down the visual field loss in wet AMD, an improvement of visual acuity following PDT treatment is only rarely found. The most important prognostic factors for visual outcome are the lesion size[7] and the number of treatments applied.[8] In patients with serous detachment of the retinal pigment epithelium (RPE), accompanying occult CNV PDT therapy includes the risk of mechanical rips.[9] Due to the mean decrease in vision following the treatment, PDT monotherapy is not considered to be a recommended treatment and is almost universally applied in combination with pharmacological adjuncts.

Photodynamic Therapy Combined with Intravitreal Triamcinolone

Corticosteroids have an inhibitory effect on vascular permeability, inflammation and expression of vascular endothelial growth factor (VEGF). Corticosteroids have been used in combination with PDT, because after application of PDT VEGF expression is increased in the adjacent choriocapillaries.[10] In various clinical trials it has been shown that the combination of PDT and intravitreal steroids has a beneficial additive effect on visual acuity, rate of recurrence, re-treatment frequency, reduction of lesion size and foveal thickness.[11–13] Using this treatment regimen, the well-known side effects of corticosteroids need to be taken into consideration. For triamcinolone, secondary glaucoma (25.8%) and cataract progression (32%) were found in a significant proportion of the treated patients.[13]

Anti-antiangiogenic Treatments

VEGF is an important cytokine for the development of choroidal neovascularisation, increasing vascular permeability and leading to angiogenesis. Numerous experimental and clinical studies have indicated that VEGF plays a key role in the development from dry to exudative AMD.

Pegaptanib (Macugen®)

Macugen is a highly selective blocker of VEGF 165, which has been found to play a pivotal role in blood–retina barrier breakdown.[14] It inhibits angiogenesis and pathological leakage and was chosen based on the idea of eliminating the pathogenical stimulus of CNV – where the VEGF 165 isoform plays a key role – and preserving all physiological structures of the macular area so that the photoreceptor function may recover.[15] A phase I trial showed a promising perspective,[16] and the results of the Ventavis

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Inhalation with Sildenafil to Improve and Optimise Pulmonary Arterial Hypertension (VISION) trial confirmed some therapeutic efficacy of the drug, although the results were less promising than expected. However, patients treated with Macugen lost a mean of nine letters during the observation period of one year compared with a loss of 14 letters in the control group. After two years, 59% of eyes treated with a dose of 0.3mg pegaptanib lost fewer than 15 letters compared with 45% of sham-treated eyes.[17] Based on these results, Macugen was approved in the US for all lesion types in neovascular AMD in December 2004; approval in the EU followed in January 2006. The therapeutic benefit of Macugen does not significantly exceed the effect of PDT monotherapy, but requires a more frequent re-treatment regimen, with re-injections every six weeks for at least two years.

Ranibizumab (Lucentis®)

Ranibizumab is a small, recombinant, humanised anti-VEGF-A neutralising antibody fragment targeting all VEGF isoforms. It offers a short half-life of two to four days, resulting in rapid clearance and high systemic safety. Many large multicentre trials were performed to investigate efficacy and safety concerns with this drug. To summarise, ranibizumab leads to a maintenance of vision within three lines in approximately 95% of treated eyes. Improvement of visual acuity by ≥15 letters was found in 34–42% of treated eyes, and the benefit was maintained throughout observation periods of one to two years.[18–21] These significant benefits formed the basis for the approval of ranibizumab by the US Food and Drug Administration (FDA) for the treatment of all lesion types in neovascular AMD at a dose of 0.5mg in July 2006. EU approval followed in January 2007. Anti-VEGF substances were the first to achieve a formidable and consistent improvement of visual acuity due to their selective strategy to eliminate the pathogenical stimulus of the CNV and spare all physiological structures of the macular area. Therefore, ranibizumab is recommended as a first-line therapy in AMD by the expert committees in most countries.[22] The rapid effect on CNV leakage is illustrated precisely with optic coherence tomography (OCT) images. Consequently, this non-invasive imaging method gained relevance for treatment indication and follow-up and has been proposed to replace fluorescein angiography in the guidance of re-treatment. Clinical studies are under way to support the correlation of morphological and functional changes of the retinal layers.

Bevacizumab (Avastin®)

Bevacizumab is a full-length recombinant humanised antibody binding to all VEGF isoforms. Originally, it was approved systemically for the treatment of metastatic colorectal cancer. The drug is used off-label due to the low costs, but prospective randomised clinical trials are not yet available that evaluate efficacy and safety in a reliable way. Like ranibizumab, bevacizumab reduces vascular permeability and angiogenesis. Although there have been no randomised multicentre trials comparing the use of bevacizumab with the approved therapy, ranibizumab, the results of smaller interventional series appear promising. Both intravenous and intravitreal administration have been reported to treat neovascular AMD. Intravitreal administration of bevacizumab was reported in a retrospective analysis of data in a population of patients who were mostly non-responders to other treatments. Intravitreal use was shown to be safe and well tolerated, and within three months of treatment visual acuity improved significantly and retinal thickness decreased when measured with OCT.[23] A total of 94% of eyes presented with stable or improved visual acuity.[24] In conclusion, bevacizumab may offer an effective and cheap treatment for neovascular AMD, but direct comparisons with other treatments are required to finally elucidate the therapeutic value of this approach.

Combination Therapy of Antiangiogenic Treatment and Photodynamic Therapy

The combination therapy of anti-VEGF therapy with verteporfin therapy was proved to be safe and effective. The prognosis with regard to improvement of visual acuity appears to be comparable to anti-VEGF monotherapy. The potential benefit of a combined treatment is the reduced need for re-treatments, providing a less time- and cost-intensive alternative. The RhuFab V2 Ocular Treatment Combining the Use of Visudyne® to Evaluate Safety (FOCUS)[21,25] trial demonstrated a substantial visual improvement of at least three lines in one-third of treated patients with a combination of standard PDT with intravitreal ranibizumab. The Prophylaxis of Thromboembolism in Critical Care Trial (PROTECT)[26] study demonstrated a mean visual improvement of one line in the entire study population and an extremely low need for re-treatment. Further studies, MONTBLANC and DENALI, are ongoing to demonstrate the same benefit as antiangiogenic monotherapy at a reduced re-treatment regimen.

Surgical Treatment Approach

A recently published meta-analysis did not find any relevant evidence for a beneficial outcome of surgical procedures such as removal of subfoveal CNV, macular translocation, transplantation of pigment epithelium or removal of subretinal haemorrhage.[27]

Future Directions

Recently, there has been a significant improvement in therapeutic approaches to treat exudative AMD.[28] Nevertheless, it has to borne in mind that with current technologies the symptoms of wet AMD only are targeted. In order to intervene earlier in the disease progression or even to prevent the sight-threatening forms of AMD, a more complete understanding of the processes that lead to AMD and end-stage neovascularisation is required. Recent studies have proved that AMD is also partially a genetic disease. More specifically, the complement Factor H gene that encodes the inhibitor of the complement alternate pathway was identified as the first gene that confers a significant genetic risk for the development of AMD.[29] While this finding may be important for identifying individuals who are at a particularly high risk of the development of AMD, it may also offer a new pathway for the treatment of the disease. ■

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