# Pharmacological Approaches to Age-Related Macular Degeneration

10

N. Eter, T. Krohne, F.G. Holz

**Core Messages**

- Intravitreally delivered vascular endothelial growth factor (VEGF) inhibitors represent a novel and effective approach to treat neovascular AMD
- Treatment with parabulbar or intravitreal steroid injections was shown to have a beneficial effect on exudative AMD
- A variety of other substances with anti-inflammatory, antiangiogenic, or antiproliferative properties are potential candidates for future pharmacological interventions in AMD and are currently under investigation
- The ARED study showed that prophylactic treatment with vitamins C and E, β-carotene and zinc can reduce the risk for progression from early to late age-related macular degeneration (AMD) stages
- Macular pigment possesses antioxidant and filter effects to protect the neurosensory retina. Supplementation with lutein and zeaxanthin can result in an increase in macula pigment density. Long-term clinical trials are needed to investigate a potential prophylactic effect on AMD progression

## 10.1 Introduction

So far, only a minority of AMD patients can be treated with laser treatment, photodynamic therapy (PDT) or experimental surgical interventions such as retinal pigment epithelium (RPE) transplantation or macular translocation. In addition, these therapeutic approaches are only applicable to late stages of AMD. Due to a better understanding of the mechanisms involved in the disease process, new pharmacological interventions have become available. Antiangiogenic agents which also have an effect on the hyperpermeability of the neovascular complex have recently gained particular attention. Antioxidative strategies with supplementation of suitable compounds have also been tested for early AMD. All current pharmacological approaches will be addressed in this chapter.

## 10.2 Vitamins, Trace Elements, Zinc and Macular Pigment

Several lines of evidence indicate that oxidative damage to the retina plays an important role in the pathogenesis of AMD [5]. Light exposure enhances the production of free radicals in an environment that already has a high flux of oxygen and polyunsaturated fatty acids in the outer

layers of the retina, the RPE and Bruch's membrane [99]. Peroxidized lipids can induce new vessel growth and may contribute to the development of neovascular AMD [99]. Several endogenous systems including enzymes and compounds such as glutathione are operative in the retina to protect against oxidative damage. Nutritional compounds with antioxidative properties include vitamins C and E, β-carotenes, flavonoids, and polyphenol.

As early as 1987, Flamm and co-workers reported observations on the effect of vitamin A and E in 173 patients with age-related macular degeneration [30]. Based on visual acuity and visual field examinations, the effect of these two substances was reported as being positive. However, observation time was relatively short, a control group was missing, and patients in varying stages of the disease were included.

Some studies have also addressed a potential protective effect of zinc. Zinc is present in the human choroid-pigment epithelium-retina complex in very high concentrations and is a coenzyme of carboanhydrase, alcohol dehydrogenase, and numerous lysosomal enzymes of the RPE [55]. In a randomized double-blind study of the effect of zinc substitution in 151 patients with AMD in different stages, Newsome and co-workers found significantly reduced progression of the disease in patients who received 200 mg of zinc sulphate daily [77]. Although the authors warned of using their publication as a therapy recommendation for zinc sulphate in AMD, directly after publication numerous vitamin/zinc combinations were made available for consumption [54]. In contrast, other studies with zinc found no effect on the outcome of macular degeneration [49, 109].

### 10.2.1 ARED Study

In the Age-Related Eye Disease Study (AREDS), 4757 subjects between 55 and 80 years of age were examined over a mean of 6.3 years for the effects of antioxidative vitamins in high doses on the progression of AMD [1, 91, 106].

Four groups defined by their macular findings were compared:

*Category 1:*
Few small (<63 µm) or no drusen in a <125-µm-diameter circle in one or both eyes
*Category 2:*
Many small (<63 µm) drusen in a ≥125-µm circle, and/or few medium-sized drusen (≥63 µm but <125 µm) or pigment abnormalities in one or both eyes
*Category 3:*
Many medium-sized drusen [(63–124 µm) in a ≥360-µm-diameter circle if soft indistinct drusen were present, or in a ≥656-µm-diameter in the absence of soft indistinct drusen], and/or one or more large drusen (≥125-µm) in one or both eyes, or non-central geographic atrophy
*Category 4:*
Advanced AMD in one eye only, or vision loss due to AMD in one eye only (defined as a choroidal neovascularization, geographic atrophy involving the centre of the macula, nondrusenoid retinal pigment epithelial detachment, serous or haemorrhagic retinal detachment, haemorrhage under the retina or retinal pigment epithelium, or subretinal fibrosis)

Participants were randomly assigned to receive daily oral tablets containing:

1. Antioxidants (500 mg vitamin C, 400 IU vitamin E, 15 mg β-carotene)