Pharmacological Approaches to Age-Related Macular Degeneration

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)

2. Zinc (80 mg as zinc oxide + 2 mg copper as cupric oxide)
3. Antioxidants and zinc
4. Placebo

It is assumed that the high dosages are associated with a pharmacological effect that would not occur with normal vitamin supplementation or nutrition. Also, the doses used in this study cannot be achieved through normal dietary consumption.

This study showed an effect on AMD progression and visual acuity:

- Patients in categories 3 and 4 had a statistically significant risk reduction for progression of AMD of 25 % when taking both antioxidants and zinc (17 % and 21 %, respectively, for those taking antioxidants or zinc alone)
- The prophylactic effect of the ARED study medications was shown as a significantly reduced incidence in choroidal neovascularization in the group receiving antioxidants and zinc, while the reduction of geographic atrophy in this group was not significant
- Only participants in categories 3 and 4 assigned to antioxidants + zinc had a statistically significant reduction in the odds of a 15-letter or greater visual acuity decrease
- There was no evidence of treatment benefit in delaying the progression of AMD in participants with category 1 or 2 changes. In these groups the incidence of late stage AMD was too low to be evaluated

According to the study there were no significant side effects from the applied substances. Patients were, however, informed about the possibility of the following side effects of long-term therapy:

Vitamin E
Fatigue, muscle weakness, hypothyroidism, possible increased rate of stroke.
Vitamin C
Gastrointestinal disturbances, reflux.
Zinc
Anaemia, reduction of HDL levels, gastrointestinal discomfort, 7.5 % of patients receiving zinc complained of such symptoms as urinary tract inflammation, kidney stones, incontinence, and even prostate hyperplasia requiring hospitalization. Similar symptoms occurred in 5 % of patients not receiving zinc.
β-*Carotene*
Yellowing of the skin. From other studies, it has been shown that the consumption of higher doses of β-carotene in smokers and ex-smokers can result in an increased risk of death from lung cancer. β-*Carotene should therefore not be given to these patients.* There is no reliable data concerning the replacement of β-carotene by other carotenoids such as lutein or zeaxanthin or their side effects.

Possible side effects with other medications also cannot be ruled out. However, no negative interactions with other medications over the average evaluation time of 6.3 years were noted. Nevertheless, patients suffering from chronic disease such as cancer, heart disease, or diabetes should consult their physicians before receiving high dosage vitamins or zinc.

Up to now the ARED study has been the largest effort in determining whether or not antioxidants are beneficial in delaying the progression of AMD. Patients with bilateral late AMD were not examined in the ARED study. Furthermore, there has been some concern about the statistical analysis [92].

10.2.2 Lutein and Zeaxanthin

The antioxidative and blue light filtering effects of lutein and zeaxanthin, the two carotenoids of the macular pigment, are considered to be the most effective form of short-wavelength light protection. It is, therefore, assumed that they play an important role in the reduction of oxidative damage caused by light exposure. The highest concentration of lutein and zeaxanthin is found in the Henle fibre layer in the axonal processes of the photoreceptor inner segments, and about 25 % is found in the photoreceptor outer segments, where oxygen turnover is greatest and the amount of unsaturated fatty acids is highest [80]. The observation that reduced concentrations of macular pigment may occur with age [41] supports the hypothesis that their reduction could serve as a risk factor for AMD [6]. Lutein and zeaxanthin cannot be synthesized by the human organism. However, exogenous intake, either through diet or supplementation, can result in an increase of macular pigment density, which offers an attractive potential prophylactic tool for the prevention of AMD [80]. Particular high concentrations of lutein are found in spinach and pumpkins, and for zeaxanthin in corn. Pilot studies have shown that dietary intake as well as supplementation results in a measurable increase in both plasma levels and macular pigment density [40, 9, 62, 12]. Ten milligrams lutein intake per day over a period of 12 weeks resulted in a fivefold increase in plasma levels and an increase in macular pigment density of 20 % [9]. Retinal function determined by ERG in 30 patients with early AMD and 8 healthy volunteers could be enhanced by daily supplementation of 15 mg lutein, 20 mg vitamin E, and 18 mg nicotinamide over a period of 6 months [26]. Whereas these preliminary results are promising, large prospective randomized interventional studies to evaluate the safety and efficacy of this approach are needed.

Summary for the Clinician

- **In patients in whom advanced AMD was already present in one eye, or patients with many medium drusen, large drusen, or extrafoveal geographic atrophy, the ARED study has demonstrated a significantly reduced incidence of late-stage disease in the group receiving antioxidants and zinc**
- **These patients also had a statistically significant reduction in the odds of a 15-letter or greater visual acuity decrease**
- **Lutein and zeaxanthin supplementation results in an increase in macular pigment density and offers an attractive prophylactic strategy. However, a beneficial effect has yet to be demonstrated in randomized, placebo-controlled trials**

10.3 Antiangiogenic Therapy

Angiogenesis is defined as the growth of new blood vessels from pre-existing vasculature. It is a normal process in various physiological situations such as wound healing and the female menstrual cycle. The term angiogenic disease defines those diseases where pathological new vessel formation plays a central role. In addition to numerous extraocular diseases, there are many diseases of the eye where pathological angiogenesis plays a significant role. These include: rubeosis iridis, retinopathy of prematurity, proliferative diabetic retinopathy, and neovascular AMD.

The development of choroidal neovascularization is often associated with substantial visual loss. Choroidal neovascularization may also occur in juvenile macular degeneration so that even relatively young patients may suffer from loss of central vision [27].

The concept of antiangiogenic therapy was developed as early as the 1970s as a potential therapy for cancer. This therapeutic strategy is based on the principle that neovascularization is the result of a dysbalance between positive and negative regulators of angiogenesis. Factors which can be influenced in order to limit the growth of new vessels in AMD centre around inhibition of the positive regulators such as VEGF or administration of angiogenic inhibitors such as pigment epithelium derived factor (PEDF).

A central problem in the administration of such substances is their selective effect on tissues of interest. The injection directly into the eye is currently the preferred method of administration. Oral administration poses the danger of systemic toxicities. Newer ways of drug delivery encompass gene therapeutic approaches or transscleral administration. Additionally, concern exists as to the potential inhibition of physiological angiogenesis or wound healing during systemic delivery for substances which are capable of crossing the blood retinal barrier. This concern is of particular importance for older patients where physiological angiogenesis is thought to have beneficial effect on heart disease.

Antiangiogenic therapy represents a rational approach to the treatment of neovascular AMD. Inhibition of new vessel formation is considered to be easier than the destruction of pre-formed vessels; high-risk partner eyes and early detected lesions could offer the most promise for substances capable of inhibiting angiogenesis. Occult lesions, considered to be a fibrovascular process containing a higher proportion of immature vessels, may be more susceptible to antiangiogenic therapy or steroid treatment, with the latter having both antifibrotic and antiangiogenic properties. Rather mature classic CNV membranes may benefit more from the antipermeability effects of VEGF inhibitors.

10.3.1 Anti-VEGF Therapies

As stated above, VEGF plays a central role in the development of choroidal neovascularization [69]. This molecule can induce CNV membrane formation alone [103] and its blockage can inhibit the formation of CNV membranes in experimental models [50, 33].

Pegabtanib (Macugen®) is a VEGF aptamer, i.e. an RNA molecule that binds to VEGF to block its action. It is delivered via intravitreal injection every 6 weeks. *Ranibizumab* (Lucentis®) is the antigen-binding fragment of a monoclonal antibody directed against VEGF. Like Pegabtanib it is delivered by repeated intravitreal injection. While Pegabtanib binds specifically only to $VEGF_{165}$, Ranibizumab inhibits all isoforms of VEGF.

The treatment of subfoveal CNV secondary to AMD with *Pegabtanib* has initially shown promising results in a Phase IA/IB study [109, 110]. Three months after a single intravitreal injection of the VEGF aptamer, 83 % of 22 treated patients showed stabilized or improved central vision, whereas 26 % of patients had a greater than three-line improvement of vision. In combination with PDT, 90 % of 11 patients had unchanged vision after 3 months, with 60 % having an improvement in vision of three lines or greater. This can be compared to a 44 % stabilization and a 2 % three-line improvement after PDT treatment alone. Figure 10.1 shows an example of a fundus before and 3 months after combined treat-

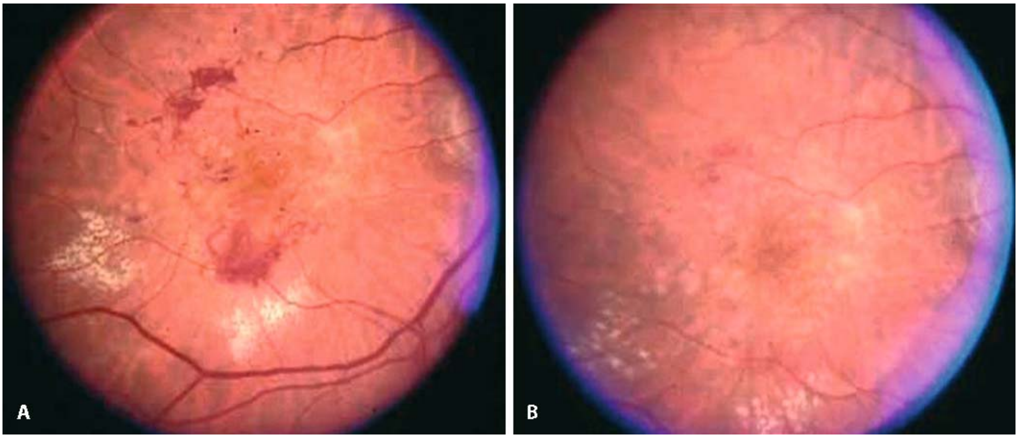

Fig. 10.1 A, B. Fundus photographs before (**A**) and after (**B**) combined treatment with PDT and an anti-VEGF aptamer (printed with permission from Eyetech Pharmaceuticals)

ment with Macugen and PDT. Of particular interest, no significant side effects were observed in these clinical trials.

In December 2004, two concurrent, prospective, randomized, double-blind, multicenter, dose-ranging, controlled phase II/III trials with a total of 1186 patients were published [36]. In these trials patients were treated with 3 different doses of Pegabtanib (0.3 mg, 1.0 mg, 3.0 mg) or sham treatment delivered *every 6 weeks* over a period of 48 weeks (9 injections). Three angiographic subtypes of lesions were included: predominantly classic, minimally classic, and purely occult. Last follow up was 54 weeks after study entry. Efficacy was demonstrated for all 3 doses of Pegaptanib and for all CNV lesion types. The proportion of patients losing fewer than 3 lines of visual acuity (15 ETDRS letters) was 70% in the 0.3 mg group, 71% in the 1.0 mg group, 65% in the 3.0 mg group, but only 55% in the placebo group. All three doses of Pegaptanib differed significantly from the sham injection. 33% of patients receiving 0.3 mg Pegaptanib maintained or gained vision compared to 23% in the placebo group ($P=0.003$). Reported side effects were mainly attributed to the injection procedure and included endophthalmitis (1.3%), retinal detachment (0.6%) and traumatic cataract (0.7%) [36, 22]. The results of these trials lead to the FDA approval of Macugen^{TM} on December 19, 2004.

Initial experiments with *ranibizumab* (Lucentis), formerly termed RhuFab V2, in an experimental primate model have shown an inhibition of CNV formation and CNV associated hyperpermeability [60]. In a phase I/II clinical trial 64 patients with predominantly classic or minimally classic exudative AMD received intravitreal injections of ranibizumab every 4 weeks. After 98 days, 32% and 21% of patients treated with 300 µg and 500 µg respectively but none of the control group patients gained 3 or more lines in ETDRS visual acuity [44, 45]. For those 40 patients in the treatment group who completed the study through day 210 this positive trend continued with an overall of 98% of patients demonstrating at least stabilized vision (change in ETDRS visual acuity of less than 15 letters) and 45% gaining 3 or more lines. The most fequently encountered side effect of treatment in this study was a mild temporary inflammatory reaction.

Results form a phase III study and a study combining Lucentis and PDT are currently pending.

10.3.2 Pigment Epithelium Derived Factor

The recently discovered cytokine pigment epithelium derived factor (PEDF) has shown antiangiogenic properties in a model of retinopathy of prematurity as well as in an animal model of laser induced CNV [105, 80, 74, 75]. As described above, the concentrations of this molecule are reduced both in patients with CNV [46] and in animal models of laser induced CNV [86]. Based on this, it was assumed that PEDF could be used to tackle choroidal neovascularization in humans. Genvec has applied to FDA for a phase I clinical study of an intravitreal injected adenovirus containing a PEDF gene construct [85].

10.3.3 Matrix Metalloproteinase Inhibitors

In the molecular cascade of angiogenesis the invasion and migration of endothelial cells through the extracellular matrix plays an important role. This process is dependent upon so-called matrix metalloproteinases (MMPs) and is modulated through tissue inhibitors of metalloproteinases (TIMPs). Numerous MMPs have been detected in CNV membranes of patients with AMD [42, 104]. *Prinonmastat* is an orally ingested inhibitor of MMPs and has shown antiangiogenic efficacy in pre-clinical studies [95]. However, this substance showed no efficacy in a phase II study in AMD patients. A second substance derived from shark cartilage, termed *Neovastat,* is also a potential MMP inhibitor possessing antiangiogenic properties and is currently being tested in a phase II study.

10.3.4 Steroids

The broad anti-inflammatory properties of steroids are considered to translate into antiangiogenic activity. So-called angiostatic steroids, which have angiostatic activity independent of their glucocorticoid action, have existed for some time [17].

Anecortave acetate (Retaane®) has been shown to possess significant antiangiogenic activity in multiple models of neovascularization, potentially through upregulation of plasminogen activator inhibitor [7, 16, 67, 68, 78, 81, 84]. Interestingly, mice deficient in plasminogen activator inhibitor have a decreased incidence of laser induced CNV [61]. Additionally, anecortave acetate was found to significantly repress angiogenesis in a model of retinopathy of prematurity while not significantly affecting normal retinal vasculature [81]. This steroid compound, designed to be devoid of conventional hormonal activity, has the potentially desirable property of blocking new vessel formation without increasing intraocular pressure or accelerating cataract formation. The substance is applied juxtasclerally with the aid of a curved cannula. Recent findings have shown that anecortave acetate is significantly better at preserving vision and inhibiting lesion growth than placebo [97, 21]. In this study, 84 % of patients with predominately classic lesions maintained vision within three lines after subtenon injections, compared to 50 % of those receiving placebo. Interestingly, the efficacy was better using 15 mg than 30 mg of the drug. It should be noted, however, that only 48 % of patients completed the study while the other 52 % dropped out, many because PDT became available during the course of the study. Currently, Phase III trials are being launched in the United States and Europe to study the effects of this drug as compared to placebo or PDT treatment with Visudyne [98].

Preliminary results of another glucocorticoid, triamcinolone acetonide, are controversial. Initial studies have shown an inhibitory effect of angiogenesis in a mouse model of retinopathy of prematurity and laser induced CNV model of the rat [15, 101]. A randomized clinical study with 139 patients receiving a single 4-mg intravitreal injection of this agent has shown only a slight beneficial effect on CNV size at 3 months [35]. Additionally, two smaller studies showed promising results in the initial follow-up period after a single injection at the same concentration [72, 88]. In a pilot study on 26 patients with CNV secondary to AMD Spaide et al. used a combination of intravitreal injection of triamcinolone andPDT/verteprofin and found a beneficial effect both on the number of PDT retreatments and the visual outcomes [100].

Jonas and colleagues have used an increased dose of 25 mg delivered by repeat intravitreal injection. A recent report by this group of 71 eyes from 67 patients with predominantly or total occult CNV has shown a statistically significant but small improvement in visual acuity from 0.16±0.11 to 0.23 ±0.17 at a mean follow-up of 7.46 ±3.54 months [52]. Furthermore, this group reported that 66.2 % of their patients gained and 15.5 % lost visual acuity after injection. These higher doses of triamcinolone in AMD patients have not, to date, been tested in a randomized clinical study. It is also unclear as to which dosage should be used for optimal treatment. Furthermore, it might prove beneficial to combine intravitreal triamcinolone treatment with PDT, an approach which is currently under intensive investigation. More detailed information on the use and the current knowledge on triamcinolone are given in Chap. 9.

10.3.5 Low-Dose Chemotherapy

Results of recent experimental studies have suggested that frequent administration of certain cytotoxic agents at low doses increases the antiangiogenic activity of these drugs [34]. Daily low doses of chemotherapeutic agents might be effective in preventing CNV in high-risk fellow eyes of AMD patients or in treating patients with neovascular disease. With substantial experience in other areas such as rheumatology, low-dose chemotherapeutics have been found to have minimal side effects.

Methotrexate is a substance that combines anti-inflammatory and antiangiogenic properties, which makes it a potential therapy option for exudative AMD. An ongoing clinical trial is addressing the safety and efficacy of intravitreal injections of methotrexate (MTX) in patients with neovascular AMD [56].

10.3.6 Others

Despite preliminary findings showing efficacy of interferon-α2a in experimental and preclinical studies [13, 23, 25, 32, 63, 70, 83, 96], a large randomized trial showed no beneficial effect of this agent [82]. Patients receiving 6 million IE of this molecule were even shown to have a more rapid loss of vision than those receiving placebo.

Thalidomide has been shown to inhibit angiogenesis in experimental assays [20, 57]. However, a clinical trial of thalidomide was hampered by a high dropout rate due to side effects including peripheral neuropathy [65]. Most importantly, no angiogenic effects were seen in a small group of patients who tolerated the therapy.

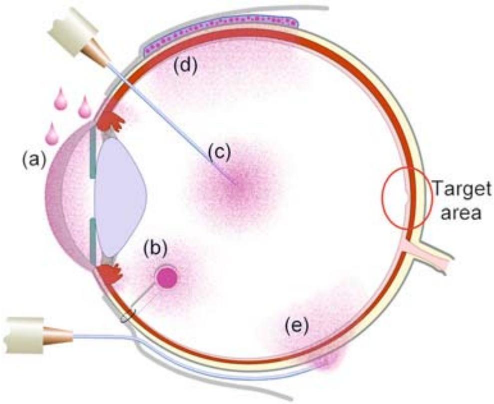

Fig. 10.2. Potential methods of drug delivery locally to achieve therapeutic concentrations in the target area and to avoid systemic side effects

Summary for the Clinician

- **In the emerging field of antiangiogenic and antihyperpermeability therapy for neovascular AMD, several substances are now subject to ongoing clinical trials, whereby efficacy has already been shown for the VEGF-inhibitor *Pegabtanib* (Macugen®)**
- **Intravitreal or parabulbar delivery is particularly attractive for such substances to achieve therapeutic levels in the target area and to avoid systemic side effects**
- **Steroids have shown promising results after both intravitreal and parabulbar delivery**
- **Antiangiogenic drugs or steroids may be applicable in combination with other therapies like PDT or surgical intervention to enhance the therapeutic effect on neovascular AMD**

10.4 Other Pharmacological Approaches

10.4.1 Statins

Statins represent a class of lipid-lowering medications that inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, which is the rate-limiting enzyme in cholesterol synthesis. Statins have been shown to reduce cardiovascular mortality, prevent progression of coronary atherosclerosis, and reduce the risk of stroke, diabetes, and dementia, perhaps by a direct antiatherosclerotic effect [114]. They also display an anti-inflammatory effect by inhibiting the activation of transcription factors such as Rho and nuclear factor κB (NF-κB), both of which mediate inflammation. This leads to a reduction of cytokine release from inflammatory cells, and a shorter macrophage survival [10, 112]. Statins can increase endothelial nitric oxide synthase, reduce apoptosis of endothelial cells, and have antioxidant properties [10, 112].

It has been speculated that statins may lower the risk of CNV due to their lipid-lowering effect for two reasons: (1) studies have shown an association between serum cholesterol and CNV [108], and (2) cholesterol accumulates with age in Bruch's membrane and drusen [19]. Statins might also have an effect on CNV growth due to their anti-inflammatory and antioxidant properties.

In a cross-sectional study with 379 participants, AMD was evaluated by stereoscopic fundus photos, and the history of cardiovascular disease as well as use of drugs was recorded. AMD was less common among participants who took statins [39].

In a retrospective study on 226 veterans aged 60 years or older, the presence of CNV or dry AMD as determined by fluorescein angiography was correlated with possible risk factors such as age, gender, ethnicity, and smoking status, the presence of cardiovascular diseases, serum lipid levels, and the use of statins and/or aspirin. The authors concluded that patients with CNV were less likely to take statins, and the median time to CNV was about 8 years earlier for patients not taking statins [114]. The study population, however, underrepresented women and non-white subjects, an equal follow-up was missing, and the use of vitamins was not documented. Thus, the use of statins in the prevention or treatment of AMD cannot be recommended at this point.

10.4.2 Aspirin

It has been speculated that aspirin (acetylated salicylic acid) may have a therapeutic effect on AMD for the following reasons: (1) It is known to decrease platelet aggregation, and modifies the properties of endothelial cells [114]. Experimental studies have shown that blood flow in the choroid is impaired in patients with AMD [64]. Although controversial, a variety of epidemiologic studies also found an increased risk for AMD in patients with cardiovascular disorders, elevated blood pressure, or elevated lipid levels [14, 38, 114]. (2) Aspirin inhibits the activity of cyclooxygenase (COX) and therefore reduces the formation of prostaglandin, a proinflammatory agent [113].

In a retrospective study on 226 veterans (see above), patients with CNV were less likely to use aspirin than patients with dry AMD [114]. A randomized prospective trial to determine the relationship between aspirin intake and the development of AMD was conducted among 21,216 US physicians [14]. The follow-up was planned to be 7 years; however, the study had to be terminated after 60.2 months due to a statistically extremely reduced risk of myocardial infarction in the aspirin group. In that 5-year period men assigned to aspirin instead of placebo had a statistically non-significant 23 % reduced risk of AMD development. Similar results were obtained for the risk of AMD with reduced visual acuity to 20/30 [14]. Both studies, however, investigated subpopulations; thus, results may not be generalized, and further long-term studies are necessary to determine a protective effect of aspirin.

10.4.3 Dorzolamide

Ocular perfusion abnormalities in AMD have been demonstrated by several studies [79, 64], and are regarded as one of the possible changes that might be responsible for the development of AMD. Local administration of dorzolamide has been shown to increase macular and superficial optic nerve head capillary transit velocities [42]. In a recent pilot study 36 patients with nonexudative AMD were randomly assigned to topical dorzolamide or placebo treatment. Four months after the onset of treatment, patients with dorzolamide showed a significantly increased rapidity of choroidal filling in the superior and inferior peripapillar region as compared to the placebo group [43]. Extended studies are currently under way.

10.4.4 Cyclooxygenase Inhibitors

Endothelial cell proliferation and differentiation represent the beginning of the neovascularization cascade, and are crucial in the development of neovascular AMD. In an experimental study the effect of steroidal and non-steroidal cyclooxygenase inhibitors with varied COX-1/COX-2 selectivity was tested for inhibition of VEGF-induced bovine retinal microvascular endothelial cell proliferatin (BRMEC) and tube formation. The test compounds were: deaminated derivate of nepafenac, celecoxib, rofecoxib, diclofenac salt, ketorolac tromethamine salt, NS398, SC560, and dexamethasone. PKC inhibitor LY333531 and anecortave served as positive controls. All tested substances except dexamethasone demonstrated inhibition of VEGF-induced BRMEC proliferation, with nepafenac, anecortave, and celecoxib being the most potent. All test substances also showed inhibition of tube formation [115].

Cyclooxygenase (COX) is an enzyme that catalyses the formation of prostaglandins, which cause inflammation, swelling, pain, and fever. As inflammation is one of the possible molecular cascades in AMD, COX inhibitors might be of therapeutic value. Also, they might reduce the inflammatory response to PDT. A clinical trial is currently under way using 400 mg celecoxib or placebo over a period of 8 months starting 1 week prior to PDT [18].

10.4.5 Genistein

Genistein, an isoflavonoid, is a naturally occurring tyrosine kinase inhibitor that is found in soya beans. Along with its tyrosine kinase inhibitory properties, genistein has a variety of other biological activities including inhibition of angiogenesis, DNA synthesis, and cell cycle arrest in the S phase [66]. It has been reported to act as an antioxidant [76], and its anti-inflammatory potentials are demonstrated by the inhibition of growth-factor-stimulated migration of inflammatory cells [37]. In a diabetic animal model, oral administration of genistein led to a significant inhibition of retinal vascular leakage [76]. Cell culture experiments suggest that genistein targets only proliferative cells, leaving quiescent, non-dividing cells unaffected [31].

Compared to Europeans, the prevalence of neovascular AMD among the elderly in Asia appears rather low. It has been speculated that this may be associated with soya-intensive food. Genistein supplementation has been advised and a product containing genistein and vitamin D and E was put on the market a few years ago. Larger studies investigating the effect of supplementation on AMD have not yet been conducted.

10.4.6 Etaretin

Three studies of this substance with very similar results already exist [50, 51, 111]. Patients with stages of macular degeneration were treated with intramuscular injections of phosphates isolated from pork retina. In these studies, 'successful' therapy was defined as an improvement of vision after an undefined treatment time [111] or as a stabilizing of vision in at least one eye after 1–9 years [51]. Besides the lack of a control group, the subjectivity of the examination methods, and the heterogeneity of the treatment group, there is also no theoretical basis for an effect of this therapy in AMD.

The applied phosphates are supposed to resemble membrane components of retinal rods. There is, however, no causative evidence that a defect in photoreceptor function results in AMD. An important pathomechanism is not the lack of such substances but the accumulation of lipoid substances including phosphates and phospholipids in the retinal pigment epithelium and Bruch's membrane. Proof of the effect of these substances in AMD is still lacking.

Summary for the Clinician

- **Substances already on the market for other indications including statins, aspirin, dorzolamide, and COX inhibitors are currently being investigated for efficacy in AMD. Further prospective randomized long-term studies are needed before the use of these substances can be recommended.**

10.5 Summary

Based on the results of the ARED study, a prophylactic treatment with a combination of vitamin C, vitamin E, β-carotene, and zinc is recommended for patients meeting the fundoscopic criteria described as categories 3 and 4 in the study. For all other nutritional supplementation including lutein or zeaxanthin, which increase macular pigment density, there is as yet no proven efficacy with regard to the prevention of AMD. However, many new antiangiogenic therapies are currently under investigation in large multicentre trials and hold exciting potential for patients with neovascular AMD. Further insight into the angiogenic process and its inhibition may lead to more targets that may be transferred for use in patients with neovascular AMD.

References

1. Age-Related Eye Disease Study Research Group The AREDS Study Group (2001) A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, β-carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. Arch Ophthalmol 119:1417–1436
2. Amin R, Puklin JE, Frank RN (1994) Growth factor localization in choroidal neovascular membranes of age-related macular degeneration. Invest Ophthalmol Vis Sci 35:3178–3188
3. Baird A, Walicke PA (1989) Fibroblast growth factors. Br Med Bull 45:438–452
4. Baun O, Vinding T, Krogh E (1993) Natural course in fellow eyes of patients with unilateral age-related exudative maculopathy. A fluorescein angiographic 4-year follow-up of 45 patients. Acta Ophthalmol 71:398–401
5. Beatty S, Koh H, Phil M, Henson D, Boulton M (2000) The role of oxidative stress in the pathogenesis of age-related macular degeneration. Surv Ophthalmol 45:115–134
6. Beatty S, Murray IJ, Henson DB, Carden D, Koh H, Boulton ME (2001) Macular pigment and risk for age-related macular degeneration in subjects from a Northern European population. Invest Ophthalmol Vis Sci 42:439–446
7. Ben Ezra D, Griffin BW, Maftzir G, Sharif NA, Clark AF (1997) Topical formulations of novel angiostatic steroids inhibit rabbit corneal neovascularization. Invest Ophthalmol Vis Sci38:1954–1962
8. Berendschot TT, Goldbohm RA, Klopping WA, van de Kraats J, van Norel J, van Norren D (2000) Influence of lutein supplementation on macular pigment, assessed with two objective techniques. Invest Ophthalmol Vis Sci 41: 3322–3326
9. Berendschot TT, Goldbohm RA, Klopping WA, van de Kraats J, van Norel J, van Norren D (2000) Influence of lutein supplementation on macular pigment, assessed with two objective techniques. Invest Ophthalmol Vis Sci 41:3322–3326
10. Blanco-Colio LM, Tunon J, Martin-Ventura JL, Egido J (2003) Anti-inflammatory and immunomodulatory effects of statins. Kidney Int 63:12–23
11. Blodi BA, AG3340 Study Group (2001) Effects of prinomastat (AG3340), an angiogenesis inhibitor, in patients with subfoveal choroidal neovascularization associated with age-related macular degeneration. Invest Ophthalmol Vis Sci 42:(4, ARVO Suppl):S311
12. Bone RA, Landrum JT, Guerra LH, Ruiz C (2003) Lutein and zeaxanthin dietary supplements raise macular pigment density and serum concentrations of these carotenoids in humans. J Nutr 133:992–998

13. Brouta-Boyé D, Zetter BR (1980) Inhibition of cell motility by interferon. Science 208:516–518
14. Christen WG, Glynn RJ, Ajani UA, Schaumberg DA, Chew EY, Buring JE, Manson JE, Hennekens CH (2001) Age-related maculopathy in a randomized trial of low-dose aspirin among physicians. Arch Ophthalmol 119:1143–1149
15. Ciulla TA, Criswell MH, Danis RP, Hill TE (2001) Intravitreal triamcinolone acetonide inhibits choroidal neovascularization in a laser-treated rat model. Arch Ophthalmol 119: 399–404
16. Clark AF, Mellon J, Li XY, Ma D, Leher H, Apte R, Alizadeh H, Hegde S, McLenaghan A, Mayhew E, D'Orazio TJ, Niederkorn JY (1999) Inhibition of intraocular tumor growth by topical application of the angiostatic steroid anecortave acetate. Invest Ophthalmol Vis Sci 40: 2158–2162
17. Crum R, Szabo S, Folkman J (1985) A new class of steroids inhibits angiogenesis in the presence of heparin or a heparin fragment. Science 230:1375–1378
18. Csaky KG, C-PDT Study Group (2004) Phase II trial of celebrex in photodynamic therapy (C-PDT) for neovascular age-related macular degeneration (AMD): rationale and baseline characteristics. Invest Ophthalmol Vis Sci 45 (Suppl): E-Abstract 1186
19. Curcio CA, Millican CL, Bailey T, Kruth HS (2001) Accumulation of cholesterol with age in human Bruch's membrane. Invest Ophthalmol Vis Sci 42:265–274
20. D'Amato RJ, Loughnan MS, Flynn E, Folkman J (1994) Thalidomide is an inhibitor of angiogenesis. Proc Natl Acad Sci U S A 91:4082–4085
21. D'Amico DJ, Goldberg MF, Hudson H, Jerdan JA, Krueger DS, Luna SP, Robertson SM, Russell S, Singerman L, Slakter JS, Yannuzzi L, Zilliox P (2003) Anecortave Acetate Clinical Study Group. Anecortave acetate as monotherapy for treatment of subfoveal neovascularization in age-related macular degeneration: twelve-month clinical outcomes. Ophthalmology 110: 2372–2382
22. D'Amico DJ, Bird AC (2004) VEGF Inhibition Study in Ocular Neovascularization-1 (VISION-1): Safety Evaluation from the Pivotal Macugen (Pegaptanib Sodium) Clinical Trials. Invest Ophthalmol Vis Sci 45:E-Abstract 2363
23. Engler CB, Sander B, Koefoed P, Larsen M, Vinding R, Lund-Anderson H (1993) Interferon alpha-2a treatment of patients with subfoveal neovascular macular degeneration. A pilot investigation. Acta Ophthalmol 71:27–31
24. Eto M, Kozai T, Cosentino F, Joch H, Lüscher T (2002) Statin prevents tissue factor expression in human endothelial cells. Circulation 105: 1756–1759
25. Ezekowitz RAB, Mulliken JB, Folkman J (1992) Interferon alfa-2a therapy for life-threatening hemangiomas of infancy. N Engl J Med 326: 1456–1463
26. Falsini B, Piccardi M, Iarossi G, Fadda A, Merendino E, Valentini P (2003) Influence of short-term antioxidant supplementation on macular function in age-related maculopathy: a pilot study including electrophysiologic assessment. Ophthalmology 110:51–60
27. Ferris F, Fine SL, Hyman L (1984) Age-related macular degeneration and blindness due to neovascular maculopathy. Arch Ophthalmol 102:1640–1642
28. Fett JW, Bethune JL, Vallee BL (1987) Induction of angiogenesis by mixtures of two angiogenic proteins, angiogenin and acidic fibroblast growth factor, in the chick chorioallantoic membrane. Biochem Biophys Res Commun 146:1122–1131
29. Fischer D, Pavlidis M, Thanos S (2000) Cataractogenic lens injury prevents traumatic ganglion cell death and promotes axonal regeneration both in vivo and in culture. Invest Ophthalmol Vis Sci 41:3943–3954
30. Flamm P (1987) Zur Therapie der degenerativen Makulopathie mit Cosaldon A+E. Klin Monatsbl Augenheilkd 190:59–66
31. Fotsis T, Pepper M, Adlercreutz H, Hase T, Montesano R, Schweigerer L (1995) Genistein, a dietary ingested isoflavonoid, inhibits cell proliferation and in vitro angiogenesis. J Nutr 125 (Suppl):790–797
32. Fung WE (1991) Interferon alpha 2a for treatment of age-related macular degeneration. Am J Ophthalmol 112:349–350
33. Garrett KL, Shen WY, Rakoczy PE (2001) In vivo use of oligonucleotides to inhibit choroidal neovascularization in the eye. J Gene Med 3:373–383
34. Gasparini G (2001) Metronomic scheduling: the future of chemotherapy? Lancet Oncol 2:733–740
35. Gillies MC, Chua W, Mitchell P, Billson F, Hunyour A, Penfold P, Simpson J (2002) Photographic and fluorescein angiographic outcomes from the Intravitreal Triamcinolone Study For Neovascular ARMD. Invest Ophthalmol Vis Sci 43:E-Abstract 290

36. Gragoudas ES, Adamis AP, Cunningham ET, Feinsand M, Guyer DR for the VEGF inhibition study in ocular neovascularization clinical trial group (2004) Pegabtanib for neovascular age-related macular degeneration. N Engl J Med 351:2805–2816
37. Gruber BL, Marchese MJ, Kew R (1995) Angiogenic factors stimulate mast-cell migration. Blood 86:2488–2493
38. Goldberg J, Flowerdew G, Smith E, Brody JA, Tso MO (1988) Factors associated with age-related macular degeneration: an analysis of data from the First National Health and Nutrition Examination Survey. Am J Epidemiol 128:700–710
39. Hall NF, Gale CR, Syddall H, Phillips DIW, Martyn CN (2001) Risk of macular degeneration in users of statins: cross sectional study. Br Med J 323:375–376
40. Hammond BR, Johnson EJ, Russel RM, Krinsky NI, Yeum K-J, Edwards RB, Snodderly DM (1997) Dietary modification of human macular pigment density. Invest Ophthalmol Vis Sci 38:1795–1801
41. Hammond BR Jr, Caruso-Avery M (2000) Macular pigment optical density in a Southwestern sample. Invest Ophthalmol Vis Sci 41:1492–1497
42. Harris A, Arend O, Arend S, et al. (1996) Effect of topical dorzolamide on retinal and retrobulbar hemodynamics. Acta Ophthalmol Scand 74:569–572
43. Harris A, Ciulla TA, Pratt LM, Rechtmann E, Piper HC, Garzozi HJ (2003) The effect of dorzolamide on choroidal and retinal perfusion in non-exudative age-related macular degeneration. Br J Ophthalmol 87:753–757
44. Heier JS, Sy JR, McCluskey ER, rhuFab V2 Study Group (2003) RhuFab V2 in Wet AMD – 6 Month Continued Improvement Following Multiple Intravitreal Injections. Invest Ophthalmol Vis Sci 44:E-Abstract 292
45. Heier JS, Sy JP, McCuskey ER (2002) ruhFab V2 (anti-VEGF antibody) for treatment of exudative AMD. Retina Society Annual Meating
46. Holekamp (2001) Deficiency of anti-angiogenic pigment epithelial-derived factor in the vitreous of patients with wet age-related macular degeneration. Retina Society Annual Meeting, Chicago
47. Holz FG, Miller D (2003) Pharmacologic therapy for age-related macular degeneration. Ophthalmologe 100:97–103
48. Holz FG, Schutt F, Kopitz J, Eldred GE, Kruse FE, Volcker HE, Cantz M (1999) Inhibition of lysosomal degradative functions in RPE cells by a retinoid component of lipofuscin. Invest Ophthalmol Vis Sci 40:737–743
49. Holz FG, Wolfensberger TJ, Piguet B, Gross-Jendroska M, Arden GB, Bird AC (1993) Oral zinc-therapy in age-related macular degeneration: a double blind study. Germ J Ophthalmol 2:391(Suppl)
50. Hruby K (1977) Aussichten und Grenzen der Behandlung seniler Makulopathien mit Phosphatiden. Wien Klin Wochenschr 89:439–442
51. Hruby K, Wiesflecker J (1983) Trockene senile Makulopathie. Prophylaxe und Therapie in Risikofallen. Klin Monatsbl Augenheilkd 182: 570–575
52. Jonas JB, Kreissig I, Hugger P, Sauder G, Panda-Jones S, Degenring R (2003) Intravitreal triamcinolone acetonide for exudative age-related macular degeneration. Br J Ophthalmol 87: 462–468
53. Kadonosono K, Yazama F, Itoh N, Sawada H, Ohno S (1999) Expression of matrix metalloproteinase-7 in choroidal neovascular membranes in age-related macular degeneration. Am J Ophthalmol 128:382–384
54. Kaminski MS, Yolton DP, Jordan WT, Yolton RL (1993) Evaluation of dietary antioxidant levels and supplementation with ICAPS-Plus and Ocuvite. J Am Optom Assoc 64:862–870
55. Karciouglu ZA (1982) Zinc in the eye. Surv Ophthalmol 27:114
56. Karl SE, Bindewald A, Roth F, Krohne T U, Eter N, Holz FG (2004) Intravitreale Methotrexat-Injektionen bei chorioidalen Neovaskularisationen im Rahmen der altersabhängigen Makuladegeneration (AMD). German Society of Ophthalmology (DOG), Annual Meeting 2004, Poster 158
57. Kaven C, Spraul CW, Zavazava N, Lang GK, Lang GE (2001) Thalidomide and prednisolone inhibit growth factor-induced human retinal pigment epithelium cell proliferation in vitro. Ophthalmologica 215:284–289
58. Klein R, Klein BE, Linton KL, De Mets DL (1993) The Beaver Dam Eye Study: the relation of age-related maculopathy to smoking. Am J Epidemiol 137:190–200
59. Knighton DR, Phillips GD, Fiegel VD (1990) Wound healing angiogenesis: indirect stimulation by basic fibroblast growth factor. J Trauma 30(Suppl):134–144

60. Krzystolik MG, Afshari MA, Adamis AP, Gaudreault J, Gragoudas ES, Michaud NA, Li W, Connolly E, O'Neill CA, Miller JW (2002) Prevention of experimental choroidal neovascularization with intravitreal anti-vascular endothelial growth factor antibody fragment. Arch Ophthalmol 120:338–346
61. Lambert V, Munaut C, Noel A, Frankenne F, Bajou K, Gerard R, Carmeliet P, Defresne MP, Foidart JM, Rakic JM (2001) Influence of plasminogen activator inhibitor type 1 on choroidal neovascularization. FASEB J 15:1021–1027
62. Landrum JT, Bone RA, Joa H, Kilburn MD, Moore LL, Sprague KE (1997) A one year study of the macular pigment: the effect of 140 days of a lutein supplement. Exp Eye Res 65:57–62
63. Loughnan MS, Heriot WJ, O'Day J (1992) Treatment of subfoveal choroidal neovascular membranes with systemic interferon-alpha 2a. Aust N Z J Ophthalmol 20:173–175
64. Lutty G, Grunwald J, Majji AB, Uyama M, Yoneya S (1999) Changes in choriocapillaris and retinal pigment epithelium (RPE) in age-related macular degeneration. Mol Vision 5:35
65. Maguire MG, Fine SL, Maguire AM, D'Amato RJ, Singerman LJ (2001) AMDATS Research Group: Results of the age-related macular degeneration and thalidomide study (AMDATS). Invest Ophthalmol Vis Sci 42:233
66. Majji AB, Hayashi A, Kim HC, Grebe RR, de Juan E (1999) Inhibition of choriocapillaris regeneration with genistein. Invest Ophthalmol Vis Sci 40:1477–1486
67. McNatt LG, Lane D, Clark AF (1992) Angiostatic activity and metabolism of cortisol in the chorioallantoic membrane (CAM) of the chick embryo. J Steroid Biochem Mol Biol 42:687–693
68. McNatt LG, Weimer L, Yanni J, Clark AF (1999) Angiostatic activity of steroids in the chick embryo CAM and rabbit cornea models of neovascularization. J Ocul Pharmacol Ther 15:413–423
69. Miller JW, Shima DT, Tolentino M, Gragoudas ES, Ferrara N, Connolly EJ, Folkman J, D'Amore PA, Adamis AP (1995) Inhibition of VEGF prevents ocular neovascularization in a monkey model. Invest Ophthalmol Vis Sci 36:401
70. Miller JW, Stinson WG, Folkman J (1993) Regression of experimental iris neovascularization with systemic alpha-interferon. Ophthalmology 100:9–14
71. Montesano R, Vassalli JD, Baird A, Guillemin R, Orci L (1986) Basic fibroblast growth factor induces angiogenesis in vitro. Proc Natl Acad Sci U S A 83:7297–7301
72. Moon SJ, Mieler WF, Holz ER (2002) Pilot Study of Intravitreal Injection of Triamcinolone Acetonide in Exudative Age-Related Macular Degeneration. Invest Ophthalmol Vis Sci 43:E-Abstract 1220
73. Mori K, Duh E, Gehlbach P, Ando A, Takahashi K, Pearlman J, Yang HS, Zack DJ, Ettyreddy D, Brough DE, Wei LL, Campochiaro PA (2001) Pigment epithelium-derived factor inhibits retinal and choroidal neovascularization. J Cell Physiol 188:253–263
74. Mori K, Gehlbach P, Ando A, McVey D, Wei L, Campochiaro PA (2002) Regression of ocular neovascularization in response to increased expression of pigment epithelium-derived factor. Invest Ophthalmol Vis Sci 43:2428–2434
75. Mori K, Gehlbach P, Yamamoto S, Duh E, Zack DJ, Li Q, Berns KI, Raisler BJ, Hauswirth WW, Campochiaro PA (2002) AAV-mediated gene transfer of pigment epithelium-derived factor inhibits choroidal neovascularization. Invest Ophthalmol Vis Sci 43:1994–2000
76. Nakajima M, Cooney MJ, Tu AH, Chang KY, Cao J, Ando A, An G, Melia M, de Juan E (2001) Normalization of retinal vascular permeability in experimental diabetes with genistein. Invest Ophthalmol Vis Sci 42:2110–2114
77. Newsome DA, Swartz M, Leone NC, Elston RC, Miller E (1988) Oral zinc in macular degeneration. Arch Ophthalmol 106:192–198
78. Oikawa T, Hiragun A, Yoshida Y, Ashino-Fuse H, Tominaga T, Iwaguchi T (1988) Angiogenic activity of rat mammary carcinomas induced by 7,12-dimethylbenz[a]anthracene and its inhibition by medroxyprogesterone acetate: possible involvement of antiangiogenic action of medroxyprogesterone acetate in its tumor growth inhibition. Cancer Lett 43:85–92
79. Pauleikhoff D, Chen JC, Chisholm IH, Bird AC (1990) Choroidal perfusion abnormality with age-related Bruch's membrane change. Am J Ophthalmol 109:211–217
80. Pauleikhoff D, van Kuijk FJ, Bird AC (2001) Makulapigment und altersabhängige Makuladegeneration. Ophthalmologe 98:511–519
81. Penn JS, Rajaratnam VS, Collier RJ, Clark AF (2001) The effect of an angiostatic steroid on neovascularization in a rat model of retinopathy of prematurity. Invest Ophthalmol Vis Sci 42:283–290

82. Pharmacological Therapy for Macular Degeneration Study Group (1997) Interferon alfa-2a is ineffective for patients with choroidal neovascularization secondary to age-related macular degeneration: results of a prospective randomized clinical trial. Arch Ophthalmol 115: 865–872
83. Poliner LS, Tornambe PE, Michelson PE, Heitzmann GJ (1993) Interferon alpha-2a for subfoveal neovascularization in age-related macular degeneration. Ophthalmology 100:1417–1424
84. Proia AD, Hirakata A, McInnes JS, Scroggs MW, Parikh I (1993) The effect of angiostatic steroids and beta-cyclodextrin tetradecasulfate on corneal neovascularization in the rat. Exp Eye Res 57:693–698
85. Rasmussen H, Chu KW, Campochiaro P, Gehlbach PL, Haller JA, Handa JT, Nguyen QD, Sung JU (2001) Clinical protocol, an open-label, phase I, single administration, dose-escalation study of ADGVPEDF.11D (ADPEDF) in neovascular age-related macular degeneration (AMD). Hum Gene Ther 12:2029–2032
86. Renno RZ, Youssri AI, Michaud N, Gragoudas ES, Miller JW (2002) Expression of pigment epithelium-derived factor in experimental choroidal neovascularization. Invest Ophthalmol Vis Sci 43:1574–1580
87. Risau W (1990) Angiogenic growth factors. Prog Growth Factor Res 2:71–79
88. Roth DB, Spirn M, Yarian DL, Green SN, Leff SR, Friedman ES, Keyser BJ, Wheatly MH (2002) Intravitreal triamcinolone injection for the treatment of occult choriodal neovascularization associated with age-related macular degeneration. Invest Ophthalmol Vis Sci 43:E-Abstract 2500
89. Scheider A, Neuhauser L (1992) Fluorescence characteristics of drusen during indocyanine-green angiography and their possible correlation with choroidal perfusion. Ger J Ophthalmol 1:328–334
90. Schütt F, Davies S, Kopitz J, Holz FG, Boulton ME (2000) Photodamage to human RPE cells by A2-E, a retinoid component of lipofuscin. Invest Ophthalmol Vis Sci 41:2303–2308
91. Schütt F, Pauleikhoff D, Holz FG (2002) Vitamine und Spurenelemente bei der altersabhängigen Makuladegeneration. Ophthalmologe: 99:301–303
92. Schweigerer L (1988) Basic fibroblast growth factor and its relation to angiogenesis in normal and neoplastic tissue. Klin Wochenschr 66:340–345
93. Seddon JM, Ajani UA, Sperduto RD, Hiller R, Blair N, Burton T, Farber MD, Gragoudas ES, Haller J, Miller DT, Yannuzzi LA, Willett W (1994) Dietary carotenoids, vitamins A, C, and E, and advanced age-related macular degeneration. Eye Disease Case-Control Study Group. JAMA 272:1413–1420
94. Seigel D (2002) AREDS investigators distort findings. Arch Ophthalmol 120:100–101
95. Shalinsky DR, Brekken J, Zou H, McDermott CD, Forsyth P, Edwards D, Margosiak S, Bender S, Truitt G, Wood A, Varki NM, Appelt K (1999) Broad antitumor and antiangiogenic activities of AG3340, a potent and selective MMP inhibitor undergoing advanced oncology clinical trials. Ann NY Acad Sci 878:236–270
96. Sidky YA, Borden EC (1987) Inhibition of angiogenesis by interferon: effects on tumor- and lymphocyte-induced vascular responses. Cancer Res 47:5155–5161
97. Slater JS, Singerman LJ, Russell SR, Hudson HL, D'Amico DJ, Jerdan J, Zillox P, Robertson SM, Anecortave Study Group (2002) Anecortave acetate administered as a posterior juxtascleral injection for subfoveal CNV in age-related macular degeneration (AMD) – clinical results. Retina Society Annual Meeting
98. Slakter JS (2004) Anecortave Acetate in the treatment of Age-Related Macular Degeneration (AMD). Invest Ophthalmol Vis Sci 45:E-Abstract 1110
99. Spaide RF, Ho-Spaide WC, Browne R, Armstrong D (1999) Characterization of lipid peroxides in Bruch's membrane. Retina 19:141–147
100. Spaide RF, Sorenson J, Maranan L (2003) Combined photodynamic therapy with verteporfin and intravitreal triamcinolone acetonide for choroidal neovascularization. Ophthalmology 110:1517–1525
101. Spandau UM, Sauder G, Jonas JB, Hammes HP (2002) Angiostatic effect of crystalline triamcinolone acetonide on ocular neovascularization in vivo. Invest Ophthalmol Vis Sci 43:E-Abstract 2497

102. Spencer B, Agarwala S, Gentry L, Brandt CR (2001) HSV-1 vector-delivered FGF2 to the retina is neuroprotective but does not preserve functional responses. Mol Ther 3:746–756
103. Spilsbury K, Garrett KL, Shen WY, Constable IJ, Rakoczy PE (2000) Overexpression of vascular endothelial growth factor (VEGF) in the retinal pigment epithelium leads to the development of choroidal neovascularization. Am J Pathol 157:135–144
104. Steen B, Sejersen S, Berglin L, Seregard S, Kvanta A (1998) Matrix metalloproteinases and metalloproteinase inhibitors in choroidal neovascular membranes. Invest Ophthalmol Vis Sci 39:2194–2200
105. Stellmach V, Crawford SE, Zhou W, Bouck N (2001) Prevention of ischemia-induced retinopathy by the natural ocular antiangiogenic agent pigment epithelium-derived factor. Proc Natl Acad Sci U S A 98:2593–2597
106. Stokes CL, Rupnick MA, Williams SK, Lauffenburger DA (1990) Chemotaxis of human microvessel endothelial cells in response to acidic fibroblast growth factor. Lab Invest 63:657–668
107. Stur M, Tittl M, Reitner A, Meisinger V (1996) Oral zinc and the second eye in age-related macular degeneration. Invest Ophthalmol Vis Sci 37:1225–1235
108. The Eye Disease Case-Control Study Group (1992) Risk factors for neovascular age-related macular degeneration. Arch Ophthalmol 110:1701–1708
109. Singerman LJThe Eyetech Study Group (2002) Anti-VEGF therapy for subfoveal choroidal neovascularization secondary to age-related macular degeneration: phase IB results. Invest Ophthalmol Vis Sci 43:E-Abstract 2908
110. The Eyetech Study Group (2002) Preclinical and phase IA clinical evaluation of an anti-VEGF pegylated aptamer (EYE 001) for the treatment of exudative age-related macular degeneration. Retina 22:143–152
111. Varga M, Gabriel I, Follmann P (1986) Behandlung der senilen Makulopathie mit Etaretin. Klin Monatsbl Augenheilkd 188:622–624
112. Veillard NR, Mach F (2002) Statins: the new aspirin? Cell Mol Life Sci 51:1771–1786
113. Vane JR, Botting RM (2003) The mechanism of action of aspirin. Thromb Res 110:255–258
114. Wilson HL, Schwartz DM, Bhatt HR, McCulloch CE, Duncan JL (2004) Statin and aspirin therapy are associated with the rates of choroidal neovascularization among patients with age-related macular degeneration. Am J Ophthalmol 137:615–624
115. Yang R, McCollum GW, Bingaman DP, Penn JS (2004) Inhibition of VEGF-induced endothelial cell proliferation and differentiation by steroidal and non-steroidal COX inhibitors with variable COX-1/COX-2 selectivity. Invest Ophthalmol Vis Sci 45 (Suppl):E-Abstract 1914