Emerging drugs for age-related macular degeneration

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Age-related macular degeneration (AMD) is a leading cause of blindness that until recently had no recognised drug treatment. In wet AMD, choroidal neovascularisation (CNV) causes a profound loss of central vision. CNV is a complex process in which tissue ischaemia and/or inflammation is thought to trigger production of angiogenic signal molecules. The release of VEGF appears to be particularly important. Verteporfin photodynamic therapy was the first drug therapy to be licensed for the treatment of some types of wet AMD. Other treatments directly targeting VEGF or other aspects of angiogenesis, such as pegaptanib, ranibizumab and anecortave acetate, have either recently been licensed or are in the advanced stages of development. These and other promising treatment options such as combination strategies are reviewed.

Keywords: age-related macular degeneration, anecortave acetate, anti-inflammatory, anti-VEGF, bevacizumab, choroidal neovascularisation, combination therapy, dexamethasone, pegaptanib, photodynamic therapy, ranibizumab, reduced fluence, steroid, triamcinolone, vascular endothelial growth factor, verteporfin


1. Background

Age-related macular degeneration (AMD) causes a progressive, irreversible loss of central vision and is one of the principal causes of registered blindness among those >65 years of age in much of the world [1]. The prevalence of AMD increases with age. Due to the rapidly ageing population, the number of people having AMD in the US is estimated to increase from 1.75 million in 2000 to 2.95 million in 2020 [2]. Similar proportional increases in the worldwide prevalence of AMD can be anticipated.

People affected by vision loss due to AMD have impaired quality of life [3] and are at increased risk for depression [4]. The decreased ability to perform day-to-day activities (e.g., reading-related tasks) contributes to lower quality of life in patients with decreased visual function due to AMD. Vision loss can also result in loss of mobility, including inability to drive or walk safely, and is associated with an increased risk of falls and hip fractures [5]. The decrease in quality of life leads to an often devastating loss of independence. The depression that often results, as well as the additional care and oversight required by those with vision loss, puts a strain on healthcare systems that are already burdened.

There are two forms of the disease, dry or atrophic AMD and wet or neovascular/exudative AMD. Dry AMD is the more common form and can lead to severe vision loss due to geographic atrophy but wet AMD accounts for the majority of all blindness resulting from AMD. In wet AMD, new choroidal blood vessels are formed (choroidal neovascularisation, CNV). These vessels leak blood and fluid, resulting in fibrovascular scarring, which causes profound loss of central vision and leads to blindness.

Wet AMD is more common in white people [6] than in other races. The only clearly established risk factors for wet AMD are age [7], smoking [8] and genetic predisposition (complement H factor polymorphism [9] and susceptibility gene
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LOC 387715 [10]. High body mass index [11], systemic hypertension [12], high intake of specific types of fat [13] and hyperopia [14] may also be linked to wet AMD, but findings are inconsistent. A relationship between wet AMD and prior cataract surgery has also been demonstrated [15,16]. Recent studies have found an association between wet AMD and cytomegalovirus infection or Chlamydia pneumoniae [17,18].

Dry AMD is considered to be a natural consequence of the ageing of the retina and supporting tissues in certain individuals. The visual receptor cells of the retina are closely apposed to the underlying retinal pigment epithelium (RPE). As we age, there is a decrease in RPE cell density and both the lytic and voiding capabilities of the remaining cells appear to decline. This results in the accumulation of incompletely degraded cellular debris, termed lipofuscin granules [19]. Eventually, extruded cellular debris is thought to accumulate between Bruch’s membrane and the RPE in the form of focal aggregations called drusen [19]. Drusen are relatively common. However, the presence of soft drusen with retinal pigment abnormalities is considered to represent a risk factor for AMD progression [7].

With age, Bruch’s membrane also becomes more brittle and similar changes in the adjacent choriocapillaris reduce the size of the chorial capillaries. This process has a pronounced impact on metabolic transfer activity and can lead to some degree of hypoxia [19,20]. In fact, chorial vascular atrophy due to age-related changes and the associated inflammatory response is thought to be the principal causative event in the development of dry AMD [20]. In some cases, immunological signals, associated with acute vascular compromise, lead to the development of subretinal CNV [20,21], and so dry AMD progresses to wet (neovascular) AMD in some patients [7].

When a patient has CNV in one eye, there is an ~ 50% chance that a similar CNV lesion will develop in the second eye within 5 years [22]. In the second eye, the presence of large drusen and focal hyperpigmentation of the RPE (characteristic of dry AMD) are independent risk factors for the subsequent development of CNV [22,23].

The new vessels are accompanied by proliferation of fibrous tissue [24]. This complex of new vessels and fibrous tissue can destroy photoreceptors within 3 – 24 months. At the same time, there is degeneration of the retinal tissue, and the lesion can continue to grow throughout the macula, resulting in progressive, severe and irreversible vision loss. Without treatment, most affected eyes will lose central vision (< 20/200) within 2 years [25].

The two primary treatments available for patients with wet AMD (CNV due to AMD) were first employed in cancer treatment: photodynamic therapy (PDT), which targets the vascular component of CNV, and antiangiogenic therapy, which targets the angiogenic processes that lead to CNV. Local choroidal inflammation is another prominent target of CNV treatment, so local anti-inflammatory agents have been used to decrease the proliferation of CNV. With several treatment options now available for CNV, a trend toward combination therapy is emerging. This trend also mirrors common clinical practices in cancer treatment, as well as in HIV infection, hypertension and other diseases of complex origin and development.

Also similar to cancer treatment, early detection and treatment are essential to minimize irreversible disease effects. Early treatment to eradicate CNV and minimize retinal tissue damage can result in prevention of vision loss and even vision improvement in some patients. If fibrotic scarring is already evident, however, there is no potential for vision improvement.

2. Medical need

Substantial medical need still exists for all patients with AMD. Patients with CNV due to AMD need treatments that improve vision for all patients. There is also a need to establish therapy that requires only one or few treatment courses to achieve sustained vision improvement.

Early diagnosis and treatment is crucial for patients with wet AMD. Vision can decline rapidly, and the earlier treatment is initiated, the better the initial vision will be and the better the potential for vision improvement and good vision at the end of therapy.

Beyond wet AMD, proven treatments are needed for early AMD, both to stop vision loss from geographic atrophy and to halt progression to wet AMD. Patients who already have wet AMD in one eye, with resulting vision loss, and who show signs of early AMD in the other eye, are most at risk for progression to wet AMD in their better-seeing eye. Treatment to halt progression of early AMD in the second eye is essential to avoid bilateral low vision or blindness in these patients.

3. Existing treatment

Until verteporfin PDT became available in 2000, the only proven treatment for wet AMD was by thermal laser photocoagulation, which targets the leaky, new vessels that form the CNV lesion. Laser photocoagulation has limited applicability because it destroys the photoreceptors overlying the CNV lesion, often resulting in immediate vision loss, especially when the lesion is subfoveal and the visual acuity is ≥ 20/200 [25]. Laser photocoagulation, however, is still considered to be the standard treatment for extraretinal CNV lesions [26].

Other surgical techniques such as macular translocation [27], macular rotation [28], external beam radiation [29] and transpupillary thermotherapy [30] are still attracting attention, but are currently unproven.

This section describes AMD therapies that are established by > 1 year of clinical experience in most regions. Anti-VEGF therapies, although recently licensed for use, are still considered to be emerging treatments, so they are discussed in Section 7.

3.1 Verteporfin PDT

PDT involves the intravenous infusion of verteporfin, a light-activated drug (photosensitizer), followed by application
of continuous nonthermal laser light directed at the CNV lesion. The activated photosensitiser generates singlet oxygen and other free radicals that cause cellular damage. Because the photosensitiser accumulates predominantly in the CNV, the treatment effect is selective to the CNV, thus minimising cellular damage in surrounding tissue.

Verteporfin PDT targets the vascular component of CNV, and its mechanism of action remains unique in the field of newer, existing therapies for wet AMD. Three pivotal trials are the basis of worldwide licensing of verteporfin PDT in wet AMD. Verteporfin PDT was initially proven to reduce the risk of moderate and severe vision loss in patients with classic-containing subfoveal CNV due to AMD in two large prospective, placebo-controlled clinical trials [31]. The greatest benefit was seen in patients with predominantly classic CNV, whereas no treatment benefit was detected in patients with minimally classic CNV. An average of three treatments was required during the first year of therapy, and two were required in the second year. After the 2-year controlled study, vision was sustained through 5 years, based on patient follow-up in an open-label extension study [32].

Another trial of verteporfin PDT in patients with occult CNV showed no statistically significant benefit for the primary end point (avoiding moderate vision loss, i.e., loss of <15 letters of visual acuity score from baseline, after 12 months of follow up), but by 24 months, moderate vision loss was observed in a higher proportion of placebo patients than verteporfin PDT patients, and the difference was statistically significant [33].

Although verteporfin PDT was an important advance in treatment for patients with wet AMD, it has many shortcomings. Based on the pivotal clinical trials conducted with verteporfin PDT, its vision benefits are limited to patients with either predominantly classic CNV or occult CNV due to AMD. Results indicating vision benefit in patients with either occult CNV lesions or mixed lesions are not robust [33].

Benefit associated with verteporfin PDT is primarily reduction of vision loss, with few patients achieving vision improvement [31,33,34]. Additional verteporfin PDT courses are administered if CNV leakage recurs, based on evaluation of fluorescein angiograms, and the pivotal trials demonstrated that several treatments were necessary over 2 years to stabilise vision [31,33].

Verteporfin PDT has been calculated to be cost effective, especially when treatment is given in the early stages of disease, and considering a full spectrum of treatment and social care costs [35,36].

Recent work suggests that PDT with verteporfin may break down the blood-retinal barrier function of the RPE [37]. Treatment has also been demonstrated to induce an angiogenic response in elderly human eyes, enhancing the expression of VEGF, VEGF receptor (R)-3 and pigment epithelium-derived growth factor [38].

3.2 Triamcinolone acetonide
It has been known for some time that corticosteroids possess antiangiostatic properties. Intravitreal injection of triamcinolone acetonide, a long-acting corticosteroid, has been reported to improve or stabilise vision of patients with CNV in open studies of up to 18 months duration [39,40]. Other studies found no benefit of triamcinolone monotherapy [41]. Intravitreal use of triamcinolone has been associated with raised intraocular pressure, requiring treatment with ocular hypotensive medications, in up to 41% of eyes [42].

3.3 Triamcinolone acetonide in combination with verteporfin PDT
More recently, intravitreal injection of triamcinolone has been used in combination with verteporfin PDT. A recent large uncontrolled study in 184 patients with all types of choroidal neovascularisation due to AMD found that visual acuity improved in the majority of patients [43], and a prospective comparison of combined treatment with PDT monotherapy in 48 patients found that a significantly higher proportion of patients in the combined group did not develop moderate vision loss at 1 year (70.8% compared with 33.3%) and that significantly fewer lines of vision were lost [44]. Several case series confirm good vision results for this combination therapy [45-50].

3.4 Dry AMD: diet and dietary supplements
Because oxidative stress may be involved in the development of AMD [20], adequate dietary intake of antioxidants and antioxidant enzyme cofactors may provide protection in individuals considered to be at risk of developing AMD [51].

The use of high doses of antioxidants and zinc (an important cofactor for various antioxidant enzymes) in AMD patients was studied in the Age-Related Eye Disease Study (AREDS) [52]. A total of 3640 subjects, 55 - 80 years of age, with age-related maculopathy in one or both eyes or advanced AMD or vision loss due to AMD in one eye were randomly assigned to receive daily oral tablets containing antioxidants (vitamins C, vitamin E and β-carotene); zinc; antioxidants plus zinc; or placebo. For the group receiving antioxidants plus zinc, a statistically significant odds reduction for progression of AMD was found compared with the placebo group. A suggestive reduction was also present for zinc only, but not for antioxidants only. At 5 years, the estimated probability of progression to advanced AMD, in patients considered to be most at risk, was 28% for the placebo group, 23% for antioxidants alone, 22% for zinc alone and 20% for zinc and antioxidants.

The ophthalmic community needs to be aware that the ARED study is an intervention study and not a prevention study. Long-term results on the use of dietary supplements or vitamins for the prevention of AMD are not available.

4. Therapeutic class review
Over the next 10 years, with the ageing worldwide population, the market for AMD therapies is projected to
increase more than fourfold, from US$638 million in 2005 to US$2722 million in 2015 (Figure 1) [53]. This represents 23.5% annual growth from 2005 to 2010, and 8.2% annual growth from 2010 to 2015.

The US represents most of the market share at present, as well as in projections to 2010 (Figure 2) [53]. Germany leads the European countries in market share (the countries represented in Figure 2 were the only ones evaluated, so Australia and many Asian countries were not included).

At present, the market is focusing on VEGF inhibitors, particularly with suspected extensive worldwide off-label use of bevacizumab and the recent licensing in the US of ranibizumab (see Section 7) as therapies for all types of CNV lesions due to AMD. This focus is projected to continue. In 2010, VEGF inhibitors are predicted to take the majority of the market share (62%), with photosensitising agents taking almost all the rest (37%) (Figure 3) [53].

5. Current research goals

The current research goals in AMD therapeutics are first, vision improvement for all patients with wet AMD. Early diagnosis and treatment is an essential component of this goal, but more effective therapies are also required. So far, the best results in controlled clinical trials have been reported for the anti-VEGF therapy ranibizumab. For this new therapy, with monthly intravitreal injections, ~30% of patients had vision that improved from baseline after up to 2 years. It is not enough for only 30% of patients to have improved vision; all patients need improved vision.

Second, there must be finite treatment for all patients with wet AMD. Although ranibizumab’s results are remarkable compared with other existing therapies, controlled study results indicate that monthly intravitreal injections must continue indefinitely to ensure that vision improvement is sustained [101]. Such continued treatment increases the risk of adverse effects, not to mention the high cost and inconvenience to patients. Verteporfin PDT is a finite treatment, as 5-year follow up results have shown stabilisation of vision after a 2-year therapy course of approximately five treatments, with one additional treatment between 2 and 5 years of follow-up. Vision benefit with verteporfin PDT, however, is limited primarily to reduced vision loss, and not vision improvement.

Finally, effective combination treatment regimens, with therapies available today, need to be identified to achieve the goals above. Such a combination therapy would marry vision improvement with finite treatment, ideally with only one treatment course. As the therapies currently available have different targets (VEGF [pegaptanib, ranibizumab and bevacizumab], neovascularisation [verteporfin PDT] and inflammation [triamcinolone and other steroids]), a combination strategy is logically sound and consistent with treatment strategies in other therapeutic areas.
6. Scientific rationale

Most recent drug approvals and ongoing development focus on angiogenesis and how it leads to CNV development, progression and recurrence after therapeutic intervention. Other prominent targets include inflammatory processes and neovascularisation itself. Emerging clinical practice is combining the therapies that target these different processes, similar to standard clinical practice in cancer treatment.

6.1 Angiogenesis and choroidal neovascularisation

In pathological angiogenesis, tissue ischaemia and/or inflammation is thought to trigger production of angiogenic signal molecules. The angiogenic signal is received by vascular endothelial cells and triggers a proteolytic cascade [54]. The enzymes involved eventually produce a limited digestion of the vascular endothelium, which causes the vascular endothelial cells to leave the blood vessel, proliferate and migrate towards the angiogenic stimulus. Eventually, a new membrane is created around the vascular endothelial cell and a new blood vessel is formed. Extracellular proteolysis is a vital step in angiogenesis and occurs as the result of activation of latent matrix metalloproteases by substances such as plasmin, which itself is generated by urokinase plasminogen activator [54,55].

CNV may be initiated by a number of events. The RPE has been shown to produce a number of factors such as VEGF, fibroblast growth factor 2, pigment epithelium-derived growth factor, angiopoietins and extracellular matrix factors, which could all potentially be involved in angiogenesis [56]. Although new vessel growth and maturation are highly complex processes, VEGF signalling appears to be particularly important [56-59].

VEGF, also called VEGF-A, is a member of the cytokine group of secreted proteins that have signalling functions within the body. VEGF promotes neovascularisation in a variety of ways. It is a potent cell mitogen and sustains endothelial cell survival by inhibiting apoptosis. It also attracts endothelial cell precursors, inducing their mobilisation from the bone marrow and promoting their differentiation. VEGF increases vascular permeability and upregulates endothelial cell expression of metalloproteases. In addition, VEGF increases expression of endothelial nitric oxide synthase, which is an important mediator of VEGF-induced endothelial cell proliferation [58]. VEGF has been found to be overexpressed in RPE cells of eyes with AMD in autopsy specimens and in RPE cells from CNV membranes obtained at surgery [57,58].

Alternative splicing of the VEGF gene results in at least four major biologically active human isoforms, containing 121, 165, 189 and 208 amino acids, respectively. VEGF165 is the predominant isoform in the human eye and appears to be responsible for pathological ocular neovascularisation [57].

VEGF binds to two highly related receptor tyrosine kinases, VEGFR-1 and -2 [57]. VEGFR-1 demonstrates a weak tyrosine autophosphorylation in response to VEGF and has an essential role during embryogenesis [57]. VEGFR-2 binds VEGF with a lower affinity than VEGFR-1, but is generally considered to be the major mediator of the mitogenic, angiogenic and permeability enhancing effects of VEGF [57]. Blockade of phosphorylation VEGFR-2 has been shown to almost completely inhibit CNV in a murine model [59].

The importance of VEGF in the pathogenesis of AMD-related CNV has led to the development of a number of new treatment strategies that directly target VEGF release and activity.

6.2 Inflammation

Inflammation is mediated by the factor H protein, an important component of complement activation. Recent studies implicate a variation in the factor H gene in increasing the probability of AMD development [56], leading to the theory that AMD originates from inflammation. Inflammation is thought to be the precursor to pathological angiogenesis, triggering angiogenic signal molecules that initiate and build CNV. Inflammation, therefore, is a strong target for both AMD therapies and early diagnostic tests for AMD.

Local administration of a steroid through intravitreal injection is the primary anti-inflammatory therapy used in AMD. Steroids downregulate inflammatory stimuli, as well as stabilise the blood-retinal barrier and resorb exudation. Steroids also have angiostatic effects but these are negligible compared with their anti-inflammatory effects.

6.3 Neovascularisation

Neovascularisation is the physical, as opposed to molecular or genetic, target for stopping the deterioration of vision due to AMD. Occlusion of CNV is thought to arrest the damage to the photoreceptors of the macula caused by CNV leakage of blood and fluids, and to halt the subsequent fibrovascular scarring that leads to irreversible vision loss.

Occlusion of the CNV is thought to be the primary mechanism of action of verteporfin PDT. The verteporfin photosensitiser preferentially accumulates in CNV, and then light administered directly to the CNV selectively destroys it without damaging the overlying retinal tissue. With PDT, occlusion occurs through free radical damage to the CNV endothelial cells, causing platelet adhesion and degranulation, and thrombus formation. Reduced blood flow from the new vessels may lead to a confinement in the growth of the fibrovascular CNV lesion. In this way, PDT reduces the area of the macula affected by CNV, sparing viable photoreceptors.

Occlusion of CNV is a terminal treatment. It eradicates existing CNV. With verteporfin PDT, however, this eradication has also been shown to cause closure of the surrounding normal choroid [61], and to be followed by inflammatory and angiogenic processes [38] that result in CNV recurrence.

One way to minimise these adverse effects of PDT, which reduce the longevity of therapeutic effect and lead to the need for additional treatment courses, is to reduce the light dose for verteporfin PDT. Good rationale exists for lowering the PDT
light dose, either by reducing the light intensity or by shortening the light administration time. If the light dose is too intense or too high, then oxygen may be rate limiting in the PDT reaction. This reaction requires adequate proportions of oxygen, photosensitiser and light. If oxygen is depleted in the target tissue (CNV) because the light has caused to it be used up too quickly, then the PDT reaction will shift to tissues where oxygen is available, regardless of the preferential abundance of photosensitiser in the target tissue relative to the surrounding tissues. This shifting of the PDT reaction to the surrounding tissues leads to the damage of these tissues and resulting initiation of inflammatory processes that lead to recurrence of CNV.

With a reduced light dose, however, oxygen may remain available in the CNV for the PDT reaction to continue, selectively eradicating the CNV and leaving the surrounding normal choroid alone. Studies have shown that a reduced light dose with verteporfin PDT results in less damage to the normal choroid and good vision benefit compared with the standard verteporfin PDT light dose\(^\text{[62]}\).

Such optimisation of therapy for the disease target is central to continuing research and clinical practice in the treatment of patients with AMD.

### 6.4 Combination therapy

Combination therapy takes optimisation to a more complex, but necessary, level. There is urgent need for more effective and feasible treatment regimens for wet AMD. The therapies currently available encompass the main AMD disease targets of VEGF, inflammation and neovascularisation, leading to potential combination therapy that is complementary and synergistic. Combining two or three existing therapies could achieve the research goal of sustained vision improvement with fewer treatment courses. Optimising combination regimens has challenges, however, with variables such as the order and timing of administration of up to three different therapies.

Whereas combination therapy with two treatments, such as verteporfin PDT and triamcinolone, has been studied and used in clinical practice for several years, the concept of triple therapy in the treatment of CNV due to AMD is new in the field. Triple therapy with antineovascular, anti-VEGF, and anti-inflammatory components has strong rationale rooted both in the pathogenesis of CNV and in the adverse molecular effects of eradicating CNV with verteporfin PDT. Inflammation, VEGF and other angiogenic factors lead to the initiation of CNV, so aiming at these targets is essential to eliminate the development and proliferation of CNV. Eradication of existing CNV with verteporfin PDT seems to be an essential part of treatment to remove the source of vision decline. This eradication, however, leads to inflammatory response and upregulation of angiogenic factors\(^\text{[38]}\), which may lead to CNV recurrence that limits vision benefit and compels further treatment courses. The addition of anti-VEGF and anti-inflammatory therapies with verteporfin PDT counteracts this adverse response to PDT. The Klinikum Karlsruhe has pioneered the use of triple therapy with verteporfin PDT, bevacizumab and dexamethasone to treat patients with CNV due to AMD. Preliminary results show vision improvement and morphological stabilisation (data on file).

Many different regimens of combination therapies for wet AMD are currently being studied. The challenges faced by retinal specialists are:

- determining the specific regimens that show good vision outcomes based primarily on case series and small studies as controlled clinical trials are not practical or feasible with so many variables for combination therapy
- selecting the specific regimen that makes sense for the specific patient to be treated

Combination therapy may lead to a more personalised therapy, based not only on a patient's disease characteristics, but also on practical considerations of time and cost.

### 7. Competitive environment

New therapies, including those recently licensed, primarily target angiogenesis. Table 1 provides information on each existing drug, as well as each drug in development, for AMD. Several currently available anti-VEGF drugs are in development for monotherapy, such as ranibizumab. Combination therapy with these drugs is also being studied.

#### 7.1 Pegaptanib

Pegaptanib is an anti-VEGF aptamer that was approved to treat all patients with wet AMD in the US in late 2004, and in Europe in early 2006. Pegaptanib is administered by intravitreal injection.

Aptamers are oligonucleotides that bind specific molecular targets. Pegaptanib sodium is a polyethylene glycol-conjugated aptamer that binds and inactivates the major soluble VEGF isoform, VEGF\(_{165}\), and blocks its interaction with VEGFR-2 on endothelial cells\(^\text{[63]}\). VEGF-induced vascular leakage and retinal neovascularisation have both been inhibited by pegaptanib in animal models\(^\text{[63]}\).

Two concurrent prospective, double-blind, dose-ranging, controlled trials are the basis of worldwide marketing approval for pegaptanib in wet AMD. In these trials, intravitreal injections were given every 6 weeks for 48 weeks\(^\text{[63]}\). The 2-year results of 133 patients who have remained on treatment with pegaptanib 0.3 mg for the full period have indicated a further improvement in the benefits of treatment compared with placebo\(^\text{[64]}\). The vision benefit with pegaptanib is primarily reduction of vision loss, as for verteporfin PDT, and not vision improvement.

As with other products that are given by intravitreal injection, the route of administration for pegaptanib represents a potential problem. Intravitreal injections carry a risk of infectious and sterile endophthalmitis, retinal detachment and cataract formation. The requirement to give pegaptanib every 6 weeks increases this risk. To overcome this problem,
<table>
<thead>
<tr>
<th>Compound</th>
<th>Company</th>
<th>Structure</th>
<th>Indication</th>
<th>Stage of development</th>
<th>Mechanism of action</th>
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<td>Novartis and QLT</td>
<td>Benzoporphyrin derivative: 1:1 mixture of two regioisomers (I and II)</td>
<td>Age-related macular degeneration</td>
<td>Launched 1999</td>
<td>Angio-occlusive photodynamic therapy</td>
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<td>Triamcinolone acetonide</td>
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<td>Launched 1969</td>
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<td>Pegaptanib</td>
<td>Eyetech and OSI</td>
<td>RNA antiangiogenic aptamer</td>
<td>Age-related macular degeneration Diabetic macular complications</td>
<td>Launched 2004</td>
<td>Selective VEGF&lt;sub&gt;165&lt;/sub&gt; inhibitor</td>
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<td>Ranibizumab</td>
<td>Genentech</td>
<td>Single-chain human–mouse chimeric monoclonal antibody fragment</td>
<td>Age-related macular degeneration Diabetic macular complications</td>
<td>Launched for wet age-related macular degeneration in June 2006</td>
<td>Anti-VEGF antibody fragment-binding domain</td>
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<td>Bevacizumab</td>
<td>Genentech</td>
<td>Humanised chimeric mouse–human antibody</td>
<td>Various tumours Age-related macular degeneration (off-label)</td>
<td>Launched 2003</td>
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<td>Regeneron and sanofi-aventis</td>
<td>Recombinant fusion protein composed of the second immunoglobulin domain of VEGFR-1 and the third immunoglobulin domain of VEGFR-2 fused to the Fc region of human IgG1</td>
<td>Age-related macular degeneration Various tumours</td>
<td>Phase II</td>
<td>Anti-VEGF</td>
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VEGFR: VEGF receptor.
### Table 1. Competitive environment, including existing and developing therapies, for age-related macular degeneration (continued)

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VEGFR: VEGF receptor.
trans-scleral delivery techniques, such as pegaptanib-encapsulated microspheres, which deliver the molecule in a sustained manner over a period of 20 days, are being developed [65].

7.2 Ranibizumab
Ranibizumab is an anti-VEGF antibody that was approved to treat all patients with wet AMD in the US in 2006. Ranibizumab, like pegaptanib, is administered by intravitreal injection.

Ranibizumab is a humanised monoclonal antibody fragment specifically designed to bind all forms of VEGF. It rapidly distributes to the retina after intravitreal injection [66] and has been shown to inhibit iris neovascularisation [67].

Two prospective, double-blind, sham-controlled pivotal trials are the basis of US marketing approval for ranibizumab in wet AMD. The results of these trials have not been published in a peer-reviewed medical journal so far, but they are available in the US product label, which was approved by the FDA [101], as well as in company press releases. Based on the 2-year trial results from one of these studies, in patients with minimally classic CNV or occult CNV, at least 90% of patients maintained or improved vision compared with 53% in the sham control group at 2 years. The other study, in patients with predominantly classic CNV comparing ranibizumab with verteporfin PDT, is ongoing to 2 years, but at 1 year, 96% of those on ranibizumab had maintained or improved vision compared with 64% on verteporfin PDT.

A third study with results available to 1 year appears to confirm that monthly ranibizumab intravitreal injections are necessary to maintain the vision benefits observed in the pivotal trials [101]. In this study, ranibizumab or sham was administered monthly for 3 months and then once every 3 months to patients with CNV due to AMD, with or without a classic component. After 12 months, patients treated with ranibizumab had nearly the same vision on average that they had at baseline, whereas patients receiving sham had lost an average of 16 letters of visual acuity score from baseline. Ranibizumab in this study, however, did not result in an average improvement in vision, as it had in the pivotal studies in which ranibizumab was administered monthly.

Although ranibizumab represents an extremely encouraging leap in treatment effect for patients with AMD, with most patients maintaining baseline vision and a third of patients with improved vision after 2 years of therapy, this leap is tempered by the requirement for continued, frequent intravitreal injections to sustain this vision benefit.

Effectiveness results for ranibizumab [101] are reported to be much better than for pegaptanib [63], even though both are anti-VEGF therapies. This difference may be due to the different specific targets of each treatment. Pegaptanib targets the VEGF165 isoform, which has been shown to be responsible for pathological CNV [57]. Ranibizumab, however, targets all of the biologically active isoforms [101], leading to the hypothesis that pathological CNV is caused by more complex interaction among all the biologically active isoforms, rather than an effect of only VEGF165.

7.3 Bevacizumab
Bevacizumab is an anti-VEGF humanised monoclonal antibody that is widely used as an intravitreal injection to treat all patients with wet AMD, but it is not licensed for this use. It is an antinecancer drug that is licensed for use in combination with chemotherapy for metastatic carcinoma of the colon or rectum [102]. Bevacizumab is derived from the same source antibody as ranibizumab and is suspected, but not proven, to have effects similar to ranibizumab. Retinal specialists began using bevacizumab to treat patients with CNV due to AMD in 2005 after results from ranibizumab studies were published, but ~1 year before ranibizumab became available to treat AMD patients. Several case series of bevacizumab treatment for patients with AMD and other retinal diseases have been published recently and showed an increase of mean visual acuity in treated patients [68-70].

The promise of bevacizumab in the treatment of patients with wet AMD is hampered, as for ranibizumab, by the requirement for continued, frequent intravitreal injections to sustain vision benefit. In addition, intravitreal treatment with bevacizumab has not been proved effective and safe in controlled clinical trials. Its use is based on its suspected similarity of efficacy and safety with ranibizumab.

7.4 Anecortave acetate
Anecortave acetate was approved for use in wet AMD in Australia in late 2005. The application for approval in Europe was withdrawn, and approval is pending in the US. Anecortave acetate is given as a suspension by local posterior juxtascleral administration through a special curved cannula, which positions a depot of product in the macula region. After subtenon administration, detectable retinal levels of the drug remain for ~6 months [71]. This novel administration method is intended to avoid the risks associated with intravitreal injection, and the slowly released drug should require less frequent administration than other therapies.

Anecortave acetate is a drug based on a steroid backbone, but has no glucocorticoid or mineralocorticoid activity. It has been classified as the first of a new pharmacologically active group of substances, the cortisenes. Anecortave acetate has been demonstrated to act at a number of stages in the neovascularisation process and, therefore, has the potential to block the effects of a large variety of angiogenic factors. It has been proven to block the urokinase plasminogen activator/matrix metalloprotease induction necessary for digestion of the basement membrane and the proliferation and migration of vascular endothelial cells [72]. Anecortave acetate has also been shown to block the conversion of plasminogen to fibrinolysin by decreasing the synthesis of urokinase plasminogen activator and increasing levels of the inhibitor of this enzyme [72].

The primary end point (noninferiority as compared with PDT) was not reached in the major study in patients with wet
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AMD [73]. Treatment intervals and reflux have been identified as the major issues that might have influenced the outcome of this study. However, because anecortave acetate appeared to be safe in the major study, and the product only needs to be administered every 6 months, it is being evaluated in a clinical trial as a preventive treatment in patients with a high risk of developing AMD (Anecortave Acetate Risk Reduction Trial – AART) [74]. Patients enrolled in this study have already lost vision due to membrane development in one eye and have high-risk drusen in the other. Because anecortave acetate leads to the downregulation of the fibrinolysin pathway, leading to reduced activation of VEGF, it is considered that this could reduce the rate of conversion of these second-at-risk eyes to wet AMD. The study, which involves ~2500 patients at ~100 study centres, compares anecortave acetate 15 and 30 mg/ml with placebo and is planned to last for 4 years.

7.5 Combination therapy with available and future drugs

Combination therapy is gaining prominence in the treatment of wet AMD, especially now that anti-VEGF therapies are available in some regions. Various combination therapies have been studied and reported, with many combination regimens under study and evaluation.

As noted in Section 3, the first combination therapies evaluated for AMD were with verteporfin PDT and triamcinolone. Clinical trials have also evaluated verteporfin PDT administered in conjunction with the intravitreal anti-VEGF therapies pegaptanib, ranibizumab and bevacizumab. The pivotal trials for pegaptanib included treatment with verteporfin PDT for patients with predominantly classic CNV, and no safety issues were reported for the combination [63]. The efficacy of multiple intravitreal injections of pegaptanib with or without verteporfin PDT was studied in 21 patients with AMD-related subfoveal CNV [75]. After 3 months, 87.5% of the patients who received pegaptanib alone had stable or improved vision, a three-line or greater gain in visual acuity was seen in 25% of the patients who received the combined therapy. A small, prospective, pilot study demonstrated improved vision and reduced CNV leakage with triple therapy, including verteporfin PDT, triamcinolone and pegaptanib [76]. A single masked study comparing ranibizumab in combination with verteporfin PDT compared with PDT alone in 162 patients with predominantly classic wet AMD (RhuFab V2 Ocular Treatment Combining the Use of Visudyne™ to Evaluate Safety – FOCUS), found that >90% of patients on the combined therapy maintained or improved vision at 12 months compared with ~68% on PDT alone [77]. In another study (PROTECT), in which patients were treated with verteporfin PDT and ranibizumab on the same day, preliminary results show good vision outcomes, a low rate of retreatment and no new safety issues [78]. Reduced lesion size, improved central macular function and reduced CNV leakage and retinal thickness have been shown in other small clinical studies of verteporfin PDT in combination with ranibizumab [78-80]. At Klinikum Karlsruhe, it has been observed that intravitreal bevazucumab treatment, administered after combination therapy with verteporfin PDT and triamcinolone, reduced remaining CNV activity, resolved oedema and improved vision [81].

7.6 VEGF-Trap

VEGF-Trap represents a new treatment approach based on the principle that, in many cases, for cytokine molecules to bind tightly to the target cell surface they need to engage two distinct receptor components. Trap technology basically combines these two receptor components in a single, soluble entity. VEGF-Trap is a high-affinity recombinant fusion protein, which consists of the immunoglobulin domain 2 of VEGFR-1 and domain 3 of VEGFR-2 fused to the crystallisable fragment of human IgG. This antigen selectively binds and neutralises all exogenous VEGF molecular isoforms as well as placentral growth factor. VEGF-Trap was found to inhibit CNV formation, preretinal neovascularisation and retinal vascular leakage as well as reducing blood-retinal barrier breakdown [82]. A single intravitreal injection also induced rapid and complete regression of established, active CNV in a primate model [83]. This new technology offers a second promising anti-VEGF approach and might become a more potent and longer-lasting candidate for the treatment of both neovascular AMD and neovascular diseases of other origin, such as diabetic retinopathy and vein occlusions.

7.7 Squalamine lactate

Squalamine lactate, a novel aminosterol with antiangiogenic properties, has also been shown to inhibit the development of CNV in the rat [84]. In small-scale clinical studies, it has been shown to maintain or improve visual acuity in patients with wet AMD when given by intravenous infusion as monotherapy [85] and to be safe when used in combination with verteporfin PDT [86].

7.8 Modulation of VEGF-receptors (siRNA)

RNA interference is a method of post-transcriptional gene silencing, which uses double-stranded RNA to target a specific mRNA transcript. Small interfering RNA (siRNA) destroys targeted mRNAs, thereby silencing the expression of the target gene. siRNA can be designed to specifically target a pathological mRNA, such as VEGF mRNA, and completely stop VEGF production. An siRNA has recently been shown to silence VEGF mRNA in murine models of VEGF upregulation [87] and to inhibit choroidal neovascularisation in murine and rat models with no signs of toxicity [87].

7.9 PKC inhibitors

PKC activation is a critical step in the pathway leading to angiogenesis [88]. VEGF can activate several PKC isozymes on endothelial cells, but mediates its mitogenic effects and
induces intracellular signalling predominantly through the activation of the PKC-β isoform [89]. PKC inhibition has been considered as a strategy to decrease retinal neovascularisation in diabetic retinopathy and AMD [90].

A number of orally administered PKC inhibitors with good gastrointestinal absorption have been developed for possible use in cancer therapy [90]. Because PKC has many activities in the body, most are unlikely to be of value in the treatment of retinal neovascularisation [91]. However, PKC inhibitors that are relatively specific for the β-isoform of PKC, such as ruboxistaurin, appear to be well tolerated and have demonstrated positive activity in patients with diabetic retinopathy [92]. These therapies have not yet been studied in AMD.

7.10 VEGFR inhibitors
Although PKC inhibitors may not be sufficiently specific to be of value in the treatment of wet AMD, other molecules that are specific inhibitors of VEGFR kinases have been developed and have shown activity in various rodent models of CNV [93].

7.11 Gene transfer therapy
Gene transfer therapy for CNV is also being considered. A gene transfer vector containing the transgene for human pigment epithelium-derived growth factor, one of the most potent angiogenic proteins found in human, has been shown to be active in murine models of CNV and retinopathy [94]. Other gene transfer vectors are also under investigation [95].

8. Potential development issues

The goal of vision improvement with one treatment course confronts several challenges.

A definitive effective combination treatment strategy will be difficult to identify, given the wide range of treatment variables, including the order of treatments given, the time between the treatments, the actual treatments used, and the use of rescue or back-up treatment. Large-scale, controlled clinical trials cannot encompass all the required variables and still be run practically.

Variability in patient and disease characteristics also contributes to a potential lack of definitive answers about treatment comparisons. The pivotal trials for the treatments available today were conducted in different patient populations (e.g., eligibility criteria specified different vision, lesion type, disease progression and morphological characteristics), which leads to questionable comparisons among treatment outcomes. As knowledge of AMD and treatments grows, eligibility criteria for clinical trials may grow more specific and be tailored to show effect in the investigational drug, depending on its characteristics.

Furthermore, although the population of patients with AMD is predicted to increase, these patients now have good treatment options and may not be willing to participate in clinical trials that test unknown investigational drugs and include placebo or sham or treatments that are perceived to be less effective than the current standard. Clinical trials may be more difficult to conduct based on patient recruitment alone.

These issues lead to the concept of personalised medicine, which grew out of genetic research and is gaining momentum in practice. Informed by the available evidence on treatments from clinical trials, as well as by individual patient data, retinal specialists may best treat future patients on a case-by-case basis with drug development becoming more specialised as well.

9. Expert opinion and conclusion

9.1 Wet AMD

At the present time, treatment of AMD is still unsatisfactory. Verteporfin PDT provides a significant benefit for a proportion of patients, but efficacy is only moderate and treatment is expensive, time consuming and inconvenient. Approaches directed at inhibiting the activity of VEGF, particularly with pegaptanib (VEGF-aptamer) and ranibizumab (VEGF-anti-body fragment) appear promising and have wider applicability. However, both of these treatments suffer from the need to give the therapy repeatedly by intravitreal injection. This procedure again makes therapy time consuming and inconvenient and carries with it the risk of endophthalmitis and retinal detachment. New formulations, such as the presentation of the active ingredient in the form of sustained-release microspheres, could help to overcome this issue.

Newer treatments directed against VEGF, such as VEGF-Trap and siRNA, are still too early in their development to draw firm conclusions concerning their potential. However, these targeted approaches appear to have more promise than the less specific approach offered by orally administered PKC inhibitors. The development of kinases directed specifically against VEGFR-2 stimulation could be of more significance.

In most cases, the addition of other chemical therapy to PDT has produced a better result than PDT alone. This seems reasonable as the physical effects of PDT combined with the biochemical effects of signalling inhibition appear likely to be complementary. PDT has also been shown to stimulate an angiogenic response, and so pharmacological suppression of this response should be of benefit. At the present time, therefore, a combination of PDT with an angiostatic agent, such as corticosteroids, and/or a specific VEGF inhibitor, may well provide the best approach to treatment. There is evidence that inflammation plays an important role in CNV pathogenesis. If VEGF expression is an epiphenomenon of inflammation, a more finite approach would be the combination of PDT, an anti-inflammatory drug and an anti-VEGF drug. This approach is currently being investigated by Augustin’s group.

9.2 Prevention of AMD progression

AMD is an insidious disease that leads, in most cases, to a slow, progressive loss of central vision and a much more rapid
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deterioration in cases that progress to wet AMD. As current treatment options are limited, prevention or delaying progression is an important consideration. Greater education about the risk factors associated with the disease, particularly smoking, obesity and inheritance, is essential, and the general importance of a healthy diet needs to be emphasised. Although still relatively controversial, there is now evidence from AREDS to indicate that the use of dietary supplements, containing high doses of zinc and antioxidants, may be of some value in individuals considered to be at particular risk of developing the condition.

The current study of the use of anecortave acetate as a prophylactic approach in the second eye of patients with existing monocular wet AMD is of great interest, as it could represent the best current means of preserving relatively good vision in those at high risk. This would have significant implications for the alleviation of much of the social and economic impact of this condition.

9.3 Final remarks
Wet AMD is primarily a disease of the elderly and, with an ageing population, the impact of this disease will increase.

In the past two decades, our knowledge of the pathogenesis of the condition has increased greatly and as a result of this, together with new approaches to drug development, the first effective chemical treatments, which specifically target the angiogenic process, have become available. However, the ubiquitous nature of angiogenesis throughout the body means that currently envisaged treatment options are best given by the local intravitreal route. This makes therapy expensive, difficult and inconvenient and is likely to limit its applicability, particularly as present therapy appears to delay disease progression rather than affect a cure.

Because AMD is a progressive disease with a clear genetic component, identification of those at risk and early preventative treatment is probably the best option for reducing the incidence of severe vision loss. However, this has significant implications for healthcare budgets until simpler therapies become available.

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