Pharmacotherapy of age-related macular degeneration

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Background: Age-related macular degeneration is the leading cause of blindness in the developed world. The number of persons with vision loss from age-related macular degeneration is projected to increase dramatically over the next few decades. Therefore, effective therapeutic and prophylactic agents are greatly needed. Objective: This article will discuss some of the newer treatment strategies that may help to reduce the incidence of visual loss from age-related macular degeneration. Some of these therapies and strategies can be implemented today, while many are hypothetical based on current laboratory data and ongoing clinical trials. Methods: A review of the literature and ongoing clinical trials was undertaken. Conclusion: Current therapies using antioxidants for prevention of the progression of age-related macular degeneration and anti-vascular endothelial growth factor therapies for neovascular age-related macular degeneration have given us tools for tackling this disease better and reducing the number of patients with vision loss. Combinations of some of the existing treatments and new forms of therapy may yet further decrease the treatment burden in the future.

Keywords: age-related macular degeneration, anti-VEGF, combination therapy, geographic atrophy, pharmacotherapy, photodynamic therapy

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1. Introduction

Age-related macular degeneration (AMD) is the leading cause of blindness in the developed world [1,2]. In the past decade, AMD research has improved our understanding of the pathogenesis of this condition. Accordingly, treatments for AMD have expanded from a single option, namely laser ablation of choroidal neovascularization (CNV) [3], to a multiplicity of therapies, including photodynamic therapy (PDT) with Visudyne (QLT/Novartis) [4] and anti-vascular endothelial growth factor (VEGF) treatments including intravitreal Ranibizumab (Lucentis, Genentech, Inc.) [5], intravitreal pegaptanib sodium (Macugen, OSI/Eyetech Pharmaceuticals) [6] and off-label use of intravitreal bevacizumab [5,6] (Avastin, Genentech, Inc.). Pilot studies have suggested potential benefits of combination therapy with PDT, intravitreal triamcinolone acetonide and anti-VEGF treatment and several new drugs with different modalities of therapy. Randomized clinical trials are evaluating the efficacy of some of these combination therapies.

Furthermore, several anti-angiogenic drugs are in clinical development, including VEGF trap (Regeneron Pharmaceuticals, Inc.), tyrosine kinase inhibitors, including Vatalanib (PTK-787, Novartis AG) and AG-013958 (Pfizer, Inc.) and RNA interference approaches such as Sirna-027 (Sirna Therapeutics). All promise to expand the therapeutic armamentarium for neovascular eye disease further. Aside from anti-angiogenic treatments, there are complement inhibitors, vascular occlusive drugs, polyamine analogs and radiation therapy devices in the AMD pipeline. The purpose of this article is to discuss current treatments as well as potential applications of emerging therapies in the context of the changing therapeutic landscape of AMD.
2. Prevention

In 2001 the Age-related Eye Disease Study (AREDS) research group reported that the use of high-dose vitamin and mineral supplements reduced the probability of progression to advanced AMD (CNV or central geographic atrophy) and its associated vision loss in individuals identified as being at risk for these outcomes [7].

High-risk patients are those in categories 3 (many medium-sized drusen or one or more large drusen in one or both eyes) and 4 (reduced vision in one eye due to geographic atrophy or CNV secondary to AMD). Any preparations other than the AREDS formulation should not be considered to be evidence based at the present time. Even more controversial perhaps is the recommendation of supplements, such as lutein and zeaxanthin. At the present time the evidence is limited and theoretical [8]. Another supplement, docosahexanoic acid, an ω-3 fatty acid that stabilizes the biophysiological properties of membranes, may be useful for stabilizing photoreceptor outer segments. The ongoing AREDS II, which is supported by the National Eye Institute, will investigate the utility of lutein, zeaxanthin and docosahexanoic acid in detail. Until this study is completed and the results become available, this area will remain controversial.

The role of the complement system in the development of AMD has recently attracted much study. Complement activation is an inflammatory process involving many plasma proteins, ultimately leading to cell membrane disruption through the membrane attack complex. Although activation of the complement system is an important part of the body’s immune function, inappropriate or excessive complement activation can lead to destructive consequences. In the normal eye the complement system is continuously activated at low levels and both membrane-bound and soluble intraocular complement regulatory proteins regulate this spontaneous complement activation tightly. This allows protection against pathogens without causing any damage to self-tissue and vision loss. Over the past few years independent scientific publications have strongly linked variants of genes encoding components of the complement system, namely complement factor H with a predisposition toward AMD. The histidine allele has a frequency of approximately 35% in Caucasian populations of predominantly European–American descent and confers a threefold increased risk for AMD [9-12].

There are also protective haplotypes being discovered and investigated. In light of these recent discoveries of the role of the complement system in AMD, several complement inhibitors are being developed and some are entering into clinical trials [13].

Compstatin is a synthetic peptide that binds tightly to complement component C3, preventing its participation in the complement activation cascade [14,15]. As C3 is the central component of all major complement activation pathways its inhibition effectively shuts down downstream complement activation that could otherwise lead to local inflammation, tissue damage and up-regulation of angiogenic factors such as VEGF. Efforts are under way to develop an efficient ocular delivery system for Compstatin for the prevention and treatment of macular degeneration. Potentia Pharmaceutical is among this first wave with POT-4, a peptide inhibitor of complement component C3 derived from Compstatin.

Inhibition of the complement system can also be achieved with inhibition of C5. Activation of C5 is the step following activation of C3. There is an aptamer to C5 manufactured by Archemix, as well as a C5a antagonist manufactured by Jerini. In addition, there is a full-length antibody to C5, namely Eculizumab by Alexion Pharmaceuticals. Clinical trials are under way to study the potential preventive or therapeutic effects of Eculizumab and these other C5 inhibitors in AMD patients.

3. Treatment of neovascular age-related macular degeneration

3.1 Photodynamic therapy with verteporfin

Verteporfin (Visudyne, Novartis) was the first pharmacological therapy approved for the treatment of subfoveal CNV in AMD. Photodynamic therapy with verteporfin is a two-step process involving the intravenous administration of verteporfin, a drug that predominantly accumulates within the endothelial cells of blood vessels and subsequent activation of this drug by light at a wavelength of 689 nm delivered using a nonthermal (infrared diode) laser. Photostabilization of the drug generates oxygen radical species that cause localized damage to the choroidal neovascular endothelial cells, leading to platelet aggregation and occlusion of the CNV with minimal damage to the overlying retina. Photodynamic therapy has been seen to reduce the risk of moderate (a decrease of three or more lines) and severe (a decrease of six or more lines) visual acuity loss [16]. In early studies, the visual acuity benefits of PDT were greatest in the subgroup of eyes with predominantly classic CNV [16]. Furthermore, PDT was found to be beneficial for eyes with recent progression of occult with no classic CNV or minimally classic CNV in the Verteportin in Photodynamic Therapy Trial [17]. Even though PDT was an exciting treatment for CNV in an era of desperation for effective treatment, with the introduction of anti-VEGF therapies the use of PDT as a first-line treatment for CNV has dropped significantly. However, new ongoing studies have suggested potential benefits of combination therapy with PDT and anti-VEGF treatment.

3.2 Anti-angiogenesis treatments

Angiogenesis is involved in the formation of choroidal neovascularization in exudative AMD, although whether it is in response to hypoxia or inflammation is debatable. It is likely both play a part in the disease process. This dynamic process is in part regulated by VEGF (VEGF-A), of which there are several different isoforms. The VEGF 121 and 165 isoforms are proven to be upregulated in the retinal pigment epithelium (RPE), outer nuclear layers and in
CNV in hypoxic conditions [18]. Increased VEGF mRNA expression in response to hypoxia is regulated by growth factors such as epidermal growth factor, transforming growth factor-α and -β, platelet-derived growth factor and insulin-like growth factor [18]. In AMD thickening of Bruch’s membrane by lipid and induction of fibrosis from photo-sensitization leads to reduced diffusion of oxygen and nutrients across from the choroid to the RPE, hence producing relative chronic hypoxic conditions [19].

At present, the mainstay of treatment for exudative AMD revolves around the use of an anti-VEGF antibody (Avastin, an off-label therapy), an antibody fragment (Lucentis) or an aptamer (Macugen). Macugen was the first anti-VEGF drug for the eye (indeed it was the first drug developed specifically for retinal therapy). Macugen (pegaptanib sodium) is a 50-kDa pegylated ribonucleic acid designed for selectively binding and neutralizing the VEGF 165 isoform, a major pathologic isoform involved in angiogenesis and vascular hyperpermeability. The phase 3 VEGF Inhibition Study in Ocular Neovascularization (VISION) Trial demonstrated its efficacy in slowing the rate of visual loss in exudative AMD [20]. More recently, a subanalysis [21] of a small group of patients in the VISION Trial with ‘early’ CNV lesions, as demonstrated by various characteristics including small CNV size, lack of lipid exudates and occult lesions, suggested that initiating Macugen treatment for such early lesions may yield enhanced outcomes. Although initially used in an estimated 60000 patients in the first year of availability, Macugen monotherapy is no longer a leading treatment option. Studies with VEGF inhibitors other than Macugen have shown better visual and anatomic results in treatment of neovascular AMD.

Lucentis (Ranibizumab) is a 48-kDa humanized binding fragment of a murine full-length monoclonal antibody directed against human multiple VEGF isoforms, including VEGF 165, VEGF 121, VEGF 110 and, theoretically, all other VEGF-A isoforms [22].

These other isoforms are important in angiogenesis and this is probably why Macugen did not work as well as Lucentis. Age-related macular degeneration patients receiving Lucentis treatment showed vision stabilization and even vision improvement, as demonstrated in the results from the phase 3 MARINA (Minimally Classic/occult trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD) Trial of Lucentis in occult and minimally classic subfoveal CNV [23], together with the results from the phase 3 ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD) Trial of patients with predominantly classic CNV lesions [24]. Decreased treatment intervals have been studied. The PIER (Phase IIIb, Multicenter, Randomized, Double-Masked, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab in Subjects with Subfoveal Choroidal Neovascularization with or without Classic CNV Secondary to Age-Related Macular Degeneration) Study showed that, although stabilization of visual acuity was achieved by three initial Lucentis doses followed by quarterly dosing of Lucentis, the visual improvement of three of more lines was lost [25]. A smaller phase 1 study, the PRONTO (Prospective Optical Coherence Tomography Imaging of Patients with Neovascular AMD Treated with Intra-ocular Ranibizumab [Lucentis]) study, was performed in 40 patients. These patients underwent a ‘pro re nata’ (PRN) dosing regimen based upon clinical and optical coherence tomography (OCT) parameters. Rapid improvements in the patients’ visual acuity and OCT measurements were achieved in the PRONTO Study. The outcomes in the study were similar to the MARINA and ANCHOR results after 24 months, but with the mean frequency of dosing reduced by more than half, to about five injections per year [26]. Based on these results, OCT appears to be a useful tool for guiding re-treatment decisions for patients with neovascular AMD. Even though side effects from Lucentis therapy are very rare, they have to be considered and discussed with patients. The most common side effects of Lucentis in clinical trials have been conjunctival hemorrhage, eye pain, floaters, increased intra-ocular pressure and intra-ocular inflammation. Although there is a theoretical risk of arterial thromboembolic events in patients receiving VEGF inhibitors by intravitreal injection, the observed incidence rate was low (< 4%) and similar to that seen in patients randomized to placebo. Adverse events related to the injection procedure occurred with an incidence rate of < 1% and included endophthalmitis, retinal detachment and traumatic cataract [23,24].

Over the past couple of years the off-label use of intravitreal Avastin (bevacizumab) has gained much attention. Avastin is a full-length humanized monoclonal antibody against VEGF with a molecular weight of 149 kDa. It is an FDA-approved adjuvant intravenous therapy for the treatment of metastatic colorectal cancer [27,28] and is being widely used off-label by ophthalmologists for the treatment of neovascular AMD and other neovascular eye diseases. Improvements in visual acuity and macular thickness have been reported in uncontrolled retrospective studies [29,30]. The Comparison of Age Related Macular Degeneration Treatment Trial (CATT) Study is a prospective study comparing the safety and efficacy of Avastin with Lucentis. (There have been no prior phase 3 clinical trials performed to evaluate the efficacy and side effects of Avastin.)

Another method of blocking VEGF up-regulation is the use of treatments aimed at blocking VEGF production. Small segments of double-stranded RNA, small interfering RNA (siRNA), can degrade target mRNA and, thus, silence the production of VEGF. One such siRNA that targets VEGF is bevasiranib (OPKO Health, Miami), formerly called Cand5. The phase 2 Cand5 Anti-VEGF RNA Evaluation Study enrolled 129 patients with subfoveal CNV who were given two intravitreal injections 6 weeks apart. The study showed the drug was safe, but there was no clinically significant difference in the patient’s visual acuity outcomes [31]. A phase 3 trial, the Combining Bevasiranib and Lucentis Therapy Study,
which combines bevasiranib and Lucentis, is currently ongoing. In this study, Lucentis alone is compared with eight or 12 weekly injections of bevasiranib following three initial loading doses of Lucentis and two priming doses of bevasiranib.

Another method for silencing VEGF expression is by blocking the receptor. Small interfering RNA technology can also be used for blocking the production of VEGF receptor 1 (VEGFR-1) [32]. Merck is currently co-developing this molecule with Allergan. New studies have suggested that the effect of siRNA in the inhibition of CNV is a class effect and, in fact, all types of siRNA suppress CNV by activating Toll-like receptor (TLR)3, a long double-stranded viral RNA sensor on the cell surface [33].

A further method of blocking VEGF expression is to block the receptor using an antibody. Vascular endothelial growth factor trap is a fusion molecule combining part of the binding site of both VEGF receptors (VEGFR-1 and VEGFR-2). It also binds VEGF and placental growth factor. It has a very high affinity for binding to VEGF as compared to Lucentis. Although animal studies have shown impressive results for VEGF trap [34], initial human studies using intravenous VEGF trap were halted due to adverse side effects such as grade 4 hypertension and grade 2 proteinuria [35]. A phase 2 trial of intravitreal VEGF trap, the CLEAR-IT (A Randomized, Double Masked, Active Controlled Phase I Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects with Neovascular Age-Related Macular Degeneration) Study, was a multicenter randomized trial that enrolled 150 patients with five treatment arms [36]. Two groups received three doses of either 0.5 or 2.0 mg of VEGF trap over 12 weeks. The other three groups received a single dose of 0.5, 2.0 or 4.0 mg of VEGF trap. A significant reduction in central retinal thickness from baseline was seen in all groups after 12 weeks. This was associated with a significant improvement in visual acuity of 5.9 letters from baseline. Intravitreal VEGF trap was generally well tolerated with no significant adverse effects. Due to the higher affinity, the drug can achieve significant blockade even at a lower dosage, suggesting that it might have a longer duration of action, translating into less frequent injection. A phase 3 clinical trial comparison with Lucentis, the VEGF Trap: Investigation of Efficacy and Safety in Wet Age-related Macular Degeneration Study, is now under investigation.

Vascular endothelial growth factor receptor activation produces a cascade of phosphorylation of target proteins such as PI3, mitogen-activated protein kinase and protein kinase C (PKC) [37]. An increased level of β isoforms of PKC in the retina is the target for treatment of AMD. SU5416 (Pfizer) and SU11248 (Takahashi) are selective inhibitors of VEGFR-2 tyrosine kinase that have been shown to reduce CNV leakage in laser-induced CNV in animal models [38]. PKC412 (Novartis) has been shown to be effective in animal models via both oral and peri-ocular use [39]. This has also been shown to be modestly effective in diabetic macular edema. Ruboxistaurin mesilate, a PKC-β inhibitor, has now completed phase 3 trials for diabetic macular edema and may be a potential adjunctive treatment option in AMD.

Pigment epithelial-derived factor is an internal anti-angiogenic protein that promotes RPE and photoreceptor survival [40]. Theoretically, inducing its production can have protective effects against CNV. Clinical trials are ongoing to study the effect of adenoviral vector-delivered pigment epithelium-derived factor on neovascular AMD. The results of a Phase 1 of clinical trial were promising and there were no serious adverse events [41].

Vascular endothelial growth factor is alternatively spliced to form the angiogenic (VEGF_{aa}) and potentially anti-angiogenic (VEGF_{ab}) families of isoforms (where xxx denotes the amino acid number). Studies have shown that, in diabetic retinopathy, the balance between two different variants of VEGF in the vitreous has changed toward dominance of angiogenetic variants [42]. PhiloGene (Summit, NJ) is working on developing new anti-angiogenesis medications based on VEGF_{ab} isoforms. Introducing this medication to the eye can change the balance between the pro-angiogenic and anti-angiogenic forms of VEGF to control the neovascularization. Animal data have suggested that PhiloGene’s PLG101 and PLG201 are potent and specific anti-angiogenic factors that inhibit retinal neovascularization. Clinical studies are under way in order to study the safety and efficacy of this medication in humans. Potentially, this may have use in AMD.

Currently, there are exciting clinical trails under way studying the effects of a few new investigational medications on neovascular AMD. CGC-11047 (Cellgate) is a polyamine analog that induces apoptosis by preventing cell replication. Theoretically this effect can cause fibrosis and suppression of CNV [43]. ATG3 (mecamylamine hydrochloric acid) is a nicotinic acetylcholine receptor antagonist. This nicotinic acetylcholine pathway has recently been shown to be involved in angiogenesis. ATG3 presumably has an anti-angiogenic effect by blocking this acetylcholine pathway [44]. Finally, mammalian target of rapamycin is a substance that plays a critical role in regulating basic cellular functions, including cell proliferation, survival, mobility and angiogenesis [45]. As such, inhibitors of mammalian target of rapamycin (such as Sirolimus) are expected to show a therapeutic effect in treating the pathological angiogenesis of the CNV associated with wet AMD [46].

### 3.3 Combination therapy

Combination therapy is attractive in principle. Synergistic effects may arise from direct CNV closure via initial PDT, together with suppression of CNV recurrence and leakage via intravitreal anti-VEGF drugs. Photodynamic therapy is currently the only modality that has been shown to result in occlusion of blood vessels within a few minutes on fluorescein angiography in a chick allantoic model [47]. In humans, closure of the CNV and choriocapillaris underlying the retina is seen after successful PDT and appears as a hypofluorescent area on a post-treatment angiogram [48]. In contrast, anti-VEGF drugs inhibit CNV growth and leakage and work to cause
regression and not physical occlusion of the CNV. Furthermore, VEGF expression is up-regulated after PDT, providing a further rationale for concomitant VEGF inhibition \cite{49,50}. Multiple clinical trials have been conducted in order to evaluate various combination therapies in AMD.

The first trial that combined PDT and Ranibizumab was the FOCUS (The RhuFab V2 Ocular Treatment Combining the Use of Visudyne to Evaluate Safety) trial, which was designed to investigate whether monthly Ranibizumab decreased the need for additional courses of PDT. The study showed that 90.5\% of the subjects treated with PDT and Ranibizumab and 67.9\% of the PDT control subjects lost fewer than 15 letters of visual acuity at 1 year. With respect to visual gain, 23.8\% of subjects in the PDT/Ranibizumab group and 5.4\% of the PDT control subjects gained at least 15 ETDRS (Early Treatment Diabetic Retinopathy Study) letters of visual acuity. Patients who received Ranibizumab with PDT needed fewer PDT re-treatments than those who received PDT alone \cite{51}.

The VERITAS (Verteoparin intravitreal Triamcinolone Acetonide Study) Trial was designed for comparing PDT with verteporfin with two different doses of intravitreal triamcinolone acetonide versus intravitreal pegaptanib in patients with neovascular AMD. Patients were randomized into three arms to receive PDT with either 1 or 4 mg of intravitreal triamcinolone or PDT with intravitreal pegaptanib. The patients were supposed to be treated for 12 months with the primary outcome being the proportion of patients who lost less than 15 letters in their visual acuity score at 12 months. This study had to be terminated early since the results in all groups were significantly lower compared to the results reported from Lucentis treatment \cite{52}.

The Reduced Fluence Visudyne—Anti-VEGF-Dexamethasone in Combination for AMD Lesions Study is an ongoing multicenter randomized clinical trial comparing the effect of Ranibizumab alone versus Ranibizumab with PDT versus Ranibizumab with PDT and intravitreal dexamethasone. This clinical trial is currently completing the recruiting phase.

4. Dry age-related macular degeneration

With the available new treatments for neovascular AMD and many other treatments on the horizon, as discussed earlier, new hopes have been raised for treatment of the severe form of dry AMD, namely geographic atrophy. There are ongoing clinical trials into the protective effect of antioxidants (Othera Pharmaceutical) and synthetic retinoids such as lenretinide (Sirion Therapeutics). The rational for using lenretinide is that it will slow the visual cycle, leading to less accumulation of lipofuscin.

Researchers are working on RPE cell transplantation, hoping that these new RPE cells may secrete protective factors that preserve the native RPE and photoreceptors.

Neurotech is conducting a phase 2 clinical trial of implantable capsules containing ciliary neurotrophic factor-producing cells in the hope that this factor will slow the process of macular degeneration.

5. Conclusion

Age-related macular degeneration is the current leading cause of blindness in the developed world. Over the past decade of AMD research, we have developed a clearer idea of the pathogenesis of AMD and we are at a turning point in the development of AMD treatment strategies. Although anti-VEGF therapies combined with early detection techniques such as OCT have changed the landscape of this blinding disease and raised hopes of a significant reduction in blindness, significant visual loss and poor reading ability remains a problem in patients who have been treated for neovascular AMD or those with the severe dry form of the disease. Like any other major public health problems, prevention is the key for the future management of AMD.

6. Expert opinion

At present, most specialists use an anti-VEGF therapy as the first line of treatment for neovascular AMD. Retinal specialists use Lucentis, Avastin and sometimes a combination of anti-VEGF therapy and steroids or PDT. One of the author’s (Dr Lim) current regimens is to begin with an anti-VEGF as monotherapy. This author uses combination therapy only in the context of clinical trials, since combination therapy, although theoretically sound, has not been proven to improve visual acuity outcomes as compared to monotherapy, nor to result in a decreased number of treatments required compared to PRN dosing. The author strongly encourages patients who are contemplating their treatment options to enroll into these clinical trials. The idea of combining treatments with different mechanisms of action in order to achieve synergy is a reasonable one. The possibility of decreasing treatment frequency is also attractive. However, until there is solid evidence of the efficacy and safety of these various modes of combination therapy, the author does not recommend their usage outside of clinical trials. The author realizes there are varying opinions on this matter.

Currently the author uses a PRN dosing regimen for Lucentis. Usually two or three doses (with doses spaced 1 month apart) are given followed by true PRN dosing. The decision to treat or to hold treatment is based upon the presence or absence of evidence of active neovascular leakage and the absence of subfoveal scar formation. If there is subretinal fluid, an OCT measurement is performed and the patient continued on therapy. If there is no evidence or subretinal fluid, an OCT is performed in order to document its absence. However, if the OCT shows the presence of fluid then fluorescein angiography follows and treatment is given. The author usually recommends a fluorescein angiography for detecting the presence of active CNV. If the fluorescein angiography shows no leakage, then treatment is held. The
patient is asked to return 1 month later. If there is still no subretinal fluid clinically and their visual acuity is stable, then treatment is again held. The patient is asked to return in 1 month later. Continued absence of leakage results in gradually lengthening the treatment evaluation intervals until 6 months is reached. When a patient has had no leakage and their visual acuity is better than 20/200, the author recommends resumption of the AREDS vitamins although there is no phase 3 clinical evidence for its use in this situation (after successful control of neovascular AMD).

Avastin therapy is a viable treatment option. There is no robust clinical trial evidence at the present time to say whether Avastin is equivalent, better or worse than Lucentis with regards to efficacy and safety. However, in the anecdotal literature there does not appear to be a large discrepancy between the results attainable with Avastin. The author usually informs patients that there is robust clinical trial data showing benefit with Ranibizumab but not yet for bevacizumab and, therefore, informs them of the accepted usage of bevacizumab amongst retina specialists and the non-FDA-approved nature of the drug. The author also informs them that the trial comparing these two drugs is the ongoing CATT Study.

As for future therapies, there is an abundance of emerging new treatment strategies. Of these, it seems logical to use natural existing anti-angiogenic agents, such as pigment epithelium-derived factor, in conjunction with VEGF-blocking medications. This combination of treatment for neovascular AMD may prove to be able to reset the balance between angiogenesis and anti-angiogenesis to that which is naturally present in patients without neovascularization. It is also logical to use combinations of drugs with different mechanisms of action in order to close CNV and suppress the formation and, perhaps, enhance the presence of naturally existing anti-angiogenic substances. The creation of preventative therapies and, perhaps, gene-tailored treatments will be a welcome addition to the AMD treatment armamentarium.

As far as new and emerging treatments are concerned, whether these new forms of therapy will be clinically useful depends upon several factors: these include efficacy, the route of treatment, the frequency of therapy and safety. Of course, the efficacy of the drug, as compared to Ranibizumab and the safety profiles are crucial. However, if the new drugs are equal in these areas to Ranibizumab, then the frequency and route of dosing will come into play. A therapy may be deemed to be more user friendly if fewer treatments are required: these characteristics may make it more apt to be chosen as the treatment of choice.

**Declaration of interest**

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