Pharmacotherapy for the Treatment of Choroidal Neovascularization Due to Age-Related Macular Degeneration

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Key Words

bevacizumab, choroidal neovascularization, pegaptanib, ranibizumab, verteporfin

Abstract

Age-related macular degeneration (AMD) is a progressive, degenerative disease of the macula that threatens central vision. It initially occurs in a "dry" form, and can progress to choroidal neovascularization (CNV) or geographic atrophy. It is the leading cause of blindness among European-descended people older than 65 years, with a prevalence of 1.5%. The treatment of CNV in developed nations in 2007 is substantially different than it was in 1997. Focal, photocoagulating, laser therapy was replaced by intravenous verteporfin and then by intravitreal pegaptanib, which is now being replaced by intravitreal ranibizumab and off-label use of bevacizumab. Other than a ranibizumab versus verteporfin trial, there are no published comparative studies of the three approved pharmacological treatments for CNV. Although frequent intravitreal injections are accepted as a current standard of care, their use is still far from ideal. Thus, there is an opportunity for improving therapy of CNV with respect to mechanism-targeted treatments, efficacy, and route of administration.

ANATOMY AND PATHOLOGY OF AGE-RELATED MACULAR DEGENERATION

Age-related macular degeneration (AMD): a progressive, degenerative disease of the macula

RPE: retinal pigment epithelium

Choroidal neovascularization (CNV): a pathological formation of new blood vessels in the choroid beneath the photoreceptors, causing bleeding, fluid, and ultimately scarring under the retina

The macula is an oval yellow region, approximately 1.5 mm in diameter, at the posterior pole of the primate eye. The macula has a high density of photoreceptors, and provides high-acuity vision. Age-related macular degeneration (AMD) is a progressive, degenerative disease in which the macula develops degenerative changes, resulting in a decrement in central vision.

Cells of the retinal pigment epithelium (RPE) continuously ingest photoreceptor outer segments that are shed throughout life. The residue of intracellular digestion may eventually fill the RPE cell. Drusen are extracellular lipid deposits that lie between the basement membrane of the RPE and the inner collagenous zone of Bruch's membrane. Drusen vary in size, shape, color, consistency, and distribution; however, they are often bilaterally symmetric, clustered in the macular region, and tend to increase in number with advancing age.

The mechanism of visual loss with AMD is a degeneration of photoreceptors, a result of degenerative changes in the RPE. In the early stages of AMD, there are pathological changes in the RPE cells, and drusen (lipid deposits) can be identified under the retina (dry AMD). In advanced stages of AMD, the retina produces factors that stimulate the formation of blood vessels (neovascularization) in the choroid. These vessels grow beneath the photoreceptors, causing bleeding, fluid, and ultimately scarring under the retina, thus interfering with vision. This condition, called choroidal neovascularization (CNV; wet AMD), can severely decrease central visual acuity (1).

Irrespective of the form of the disease, degeneration of the RPE precedes or accompanies death of the associated photoreceptors—both rods and cones. This degeneration is thought to be a consequence of abnormal cellular metabolism owing to imperfections in the digestive mechanisms of the cells, thereby resulting in the accumulation of abnormal material in the RPE. This accumulation increasingly interferes with normal metabolism, provoking aberrant excretions that aggregate in the form of basal laminar deposits and decay within Bruch's membrane. These abnormal extracellular deposits can be associated with neovascularization or with geographic atrophy (patches of atrophy of the RPE, the overlying retina, and the underlying choriocapillaris) (1).

PREVALENCE OF AGE-RELATED MACULAR DEGENERATION

AMD is the leading cause of blindness among European-descended people older than 65 years of age (2–7). Friedman et al. pooled several studies to calculate an overall prevalence rate of neovascular AMD and/or geographic atrophy in the U.S. population 40 years and older. They estimated the prevalence to be 1.47% (95% confidence interval, 1.38%–1.55%), with 1.75 million Americans having AMD. The prevalence of AMD increases dramatically with age, with more than 15% of white women older than 80 years having neovascular AMD and/or geographic atrophy. It

is estimated that more than 7 million individuals have drusen measuring 125 μm or larger and are, therefore, at substantial risk of developing AMD. Owing to the rapidly aging population, the number of persons having AMD is predicted to increase by 50% to 2.95 million in 2020. AMD is far more prevalent among white than among black persons (8).

LASER TREATMENT

The Macular Photocoagulation Study (MPS) was a series of multicentered, controlled studies started in the late 1970s to evaluate laser treatment of CNV. These studies evaluated whether various laser treatments of CNV lesions were of benefit in preventing or delaying loss of central vision in patients with AMD or related diseases. The laser was used to coagulate the abnormal blood vessels. Laser treatment can be classified into subfoveal, juxtafoveal (1–199 μm from the center of the foveal avascular zone), and extrafoveal types (1). This study showed long-term benefit for laser photocoagulation in reducing the risk of severe visual loss in eyes with extrafoveal CNV. However, many of the juxtafoveal and extrafoveal cases will have subfoveal recurrences after laser photocoagulation treatment (9, 10). Also, the benefits of laser treatment are limited, especially for subfoveal CNV, because laser photocoagulation damages viable neurosensory retina overlaying the treated CNV (9, 10). Subfoveal treatment usually results in immediate, significant visual acuity loss, especially when visual acuity is better than 20/200. Unfortunately, most patients with subfoveal CNV will not benefit from laser photocoagulation because the lesions are too large or they have relatively good visual acuity (better than 20/200), poorly demarcated boundaries, or no evidence of classic CNV (11–13). The limitations of laser photocoagulation for subfoveal CNV stimulated researchers to find different treatment modalities with greater efficacy and safety.

CURRENT PHARMACOLOGICAL TREATMENTS

Table 1 lists pharmacological treatments for CNV currently approved in the United States. These include verteporfin (Visudyne®, QLT/Novartis Ophthalmics), pegaptanib (Macugen®, EyeTech/OSI Pharmaceuticals), and ranibizumab (Lucentis®, Genentech/Novartis). Subsequent sections describe each of these treatments in detail.

Table 1 List of approved therapies for choroidal neovascularization due to age-related macular degeneration

Treatment	Manufacturer	U.S. FDA approval	Route
Laser	Multiple	—	Laser
Verteporfin (Visudyne®)	QLT/Novartis	2000	Intravenous and laser
Pegaptanib (Macugen®)	EyeTech/OSI	2004	Intravitreal
Ranibizumab (Lucentis®)	Genentech/Novartis	2005	Intravitreal

Photodynamic Therapy

Photodynamic therapy: intravenous injection of a photosensitizer, which then is activated by laser light

One approach toward treating CNV is photodynamic therapy. This treatment involves an intravenous injection of a photosensitizer, or light-activated, drug. After infusion, the photosensitizer in the retina is activated by illumination through the pupil with light from a laser source at a wavelength that corresponds to an absorption peak of the drug. This type of laser is not a thermal laser—that is, it does not photocoagulate—but instead, activates the intravascular dye, which then is presumed to generate singlet oxygen, which in turn closes the abnormal vessel.

Verteporfin

Verteporfin is a porphyrin derivative demonstrated to be an effective photosensitizer both in vitro and in vivo (14–18). Preclinical studies showed that light-activated verteporfin selectively occludes vessels of experimentally-induced CNV in animal models with minimal effects on the surrounding and overlying retina and underlying choroid (19–21). Once excited by the laser, verteporfin is thought to generate singlet oxygen and reactive oxygen intermediates associated with damage to cellular component (22, 23). Based on Phase 1 and 2 studies (24–26), two multicenter, double-masked Phase 3 trials were conducted [the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Investigation]. Six hundred and nine patients were randomly assigned (2:1) to verteporfin (6 mg/m^2) or placebo (5% dextrose in water) administered via intravenous infusion. Fifteen minutes after the start of the infusion, the study eye received a laser light at 689 nm for 83 s. At follow-up examinations every 3 months, retreatment with the same regimen was applied if angiography showed fluorescein leakage.

Modern controlled clinical studies, including TAP, use an eye chart and examination system developed in the Early Treatment of Diabetic Retinopathy Study (ETDRS) (27). The ETDRS system uses special, high-contrast, standardized visual acuity charts to facilitate quantitative use of visual acuity test results. Each line has five letters with a geometric progression in letter size from line to line. This system also allows for easy calculation of the logarithm of the minimal angle of resolution (logMAR), which is 0.1 units per line of the chart. This system thus has many improvements over the Snellen charts that are used in many clinical practices. However, for those familiar with the Snellen system, a logMAR of 0.00 is equivalent to Snellen 20/20, and a logMAR of 1.00 is equivalent to Snellen 20/200. Note that a larger logMAR indicates worse vision, as the required angle of light subtended on the retina for vision is larger. A loss of 3 lines ETDRS (15 letters) is an increase of 0.3 logMAR (0.3 is the logarithm of 5), and reflects a doubling of the visual angle (28).

In the TAP studies, at the month-12 examination, 246 (61%) of 402 eyes assigned to verteporfin, compared with 96 (46%) of 207 eyes assigned to placebo, had lost fewer than 15 letters of visual acuity from baseline. In subgroup analyses of patients with predominantly classical CNV, the visual acuity benefit (<15 letters lost) of verteporfin therapy versus placebo was clearly demonstrated (67% versus 39%). Few ocular or other systemic adverse events were associated with verteporfin

treatment compared with placebo; these included transient visual disturbances (18% versus 12%), injection-site adverse events (13% versus 3%), transient photosensitivity reactions (3% versus 0%), and infusion-related low back pain (2% versus 0%) (29). The treatment benefit continued through 24 months of treatment (30). Also, patients receiving verteporfin were advised to avoid direct sunlight for 5 days owing to possible systemic photosensitivity. Verteporfin was approved by the U.S. Federal Drug Administration (FDA) in 2000 as Visudyne® as the first pharmacotherapy for CNV. It has since gained approval in Europe, Japan, and elsewhere.

Verteporfin was also evaluated in a large, double-masked study in patients with subfoveal CNV caused by pathologic myopia [Verteporfin in Photodynamic Therapy (VIP) Study Group]. At the end of two years, 54% (121/225) of verteporfin-treated patients lost three or more lines of vision, compared with 67% (76/114) of placebo-treated patients (31).

VEGF: vascular endothelial growth factor

Vascular Endothelial Growth Factor-A

In an effort to locate a diffusible angiogenic factor postulated to be produced by ischemic retina and to lead to neovascularization of the retina, optic nerve, or iris, Miller et al. evaluated vascular endothelial growth factor-A (VEGF-A). Following the production of retinal ischemia by laser in a monkey model, VEGF-A was increased in the aqueous fluid, and the aqueous VEGF levels changed synchronously and proportionally with the severity of iris neovascularization. Based on these and other findings, the authors postulated that ocular neovascularization is regulated by a diffusible factor and identify VEGF-A as a likely candidate for a retina-derived vascular permeability and angiogenesis factor in vivo (32). In subsequent work, VEGF-A has been found to be a critical regulator of ocular angiogenesis and vascular permeability and involved in the pathogenesis of several ocular diseases involving neovascularization or increased vascular permeability, such as CNV owing to AMD, diabetic macular edema, and diabetic retinopathy (33). Hypoxia is a key regulator of VEGF-induced ocular neovascularization. Hypoxia upregulates the production of VEGF-A in a variety of retinal cells studied in vitro (34, 35). Similarly, in vivo the ischemic retina and the vitreous and aqueous humors contain higher levels of VEGF-A (32, 36–38). Inhibition of the actions of VEGF-A attenuates neovascularization in an animal model of CNV (39).

Pegaptanib

An anti-VEGF-aptamer, pegaptanib, already in development for an oncology indication, was formulated for intravitreal delivery. Pegaptanib is selective for the 165 isoform of VEGF, and antagonism of VEGF is thought to reduce pathological angiogenesis in the retina. Pegaptanib was an effective attenuator of VEGF-mediated ocular vascular leakage in several animal models (40). Given by intravitreal injection, pegaptanib had no clinically significant safety issues in a Phase 1 trial (40), and in uncontrolled Phase 1 (single) and Phase 2 (multiple dosing) trials, most patients had stable vision and a portion had clinically significant improvements (3 or more lines by

ETDRS) (40, 41). The developers selected a combined Phase 2/3 strategy for further development (42). Two double-masked, multicenter, dose-ranging, controlled clinical trials were conducted in 1186 patients with CNV [VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group (VISION)]. Patients were randomly assigned to receive either sham injection or one of three doses of pegaptanib (0.3, 1.0, or 3.0 mg) by intravenous injection at six-week intervals. Treatment differences in favor of pegaptanib were seen as early as 6 weeks. At one year, in the group given pegaptanib at 0.3 mg, 70% of patients lost fewer than 15 letters of visual acuity, as compared with 55% among the controls. There was no dose-response in efficacy or safety. Among the adverse events that occurred, those of greatest concern were endophthalmitis (1.3% of patients), traumatic injury to the lens (0.7%), and retinal detachment (0.6%) (43). Pegaptanib, as Macugen®, was approved in 2004 by the U.S. FDA as the first intravitreal treatment for CNV owing to AMD. It has since gained approval in Europe and elsewhere. One issue brought to light in clinical use after approval was the potential for a transient mean increase in intraocular pressure of 9 mm Hg (44).

Ranibizumab

Another antagonist of VEGF, ranibizumab (Lucentis®), was also evaluated by intravitreal injection. The F_{ab} fragment of an antibody, ranibizumab binds to the receptor binding site of all active forms of VEGF-A, including the biologically active, cleaved form of this molecule, $VEGF_{110}$ (45). The safety and pilot efficacy of intravitreal ranibizumab was evaluated in several open-label, dose-escalation studies in patients with CNV (46–48).

Similar to verteporfin and pegaptanib, in large, multicenter, double-masked, randomized studies, ranibizumab was more effective than control (sham injection)—95% of treated patients lost fewer than 15 letters of visual acuity, compared with 62%–64% of sham control-treated patients. However, in contrast to the previous treatments, a substantial proportion of the patients' vision improved. In a study in minimally classic or occult with no classic CNV, patients receiving 0.5 mg of intravitreal ranibizumab on a fixed monthly schedule had a mean improvement of 7.2 letters, whereas sham-treated controls lost 10.4 letters over the course of the first year [Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA)] (49). In a study in patients with predominantly classic CNV, patients receiving 0.5 mg of intravitreal ranibizumab on a fixed monthly schedule had a mean improvement of 11.3 letters, whereas controls treated with photodynamic therapy that used verteporfin had a mean loss of 9.5 letters over the first year [Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR)] (50).

A separate open-label, noncomparative study of a population of 40 patients was conducted at one center (Prospective Optical Coherence Tomography Imaging of Patients with Neovascular AMD Treated with Intraocular Ranibizumab (PrONTO)]. Consistent with the approved labeling, these patients received monthly intravitreal doses of ranibizumab for three months. They then received subsequent doses only

when there was a clinically significant increase in macular thickness or loss of visual acuity. Over a one-year period, patients received 5.6 ± 2.3 doses, compared with the label dose of 12 doses. The mean improvement was 9.3 letters (51). As reviewed by Spaide (52), a controlled, masked-study was conducted (Phase IIIb, Multicenter, Randomized, Double-Masked, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab (PIER)] in which patients received monthly dosing with ranibizumab (0.3 mg or 0.5 mg) or sham injections once per month for the first three months followed by quarterly doses thereafter. At month three, patients treated with ranibizumab, on average, gained 2.9 letters and 4.3 letters (0.3 mg and 0.5 mg dose groups, respectively), compared with a loss of 8.7 letters among patients in the sham group. At one year, patients treated with ranibizumab lost 1.6 letters and 0.2 letters (0.3 mg and 0.5 mg), compared with a loss of 16.3 letters in the sham group. Thus, Spaide concluded that giving the patients a reduced number of injections—a therapy not based on objective factors of need—appeared to result in a less favorable outcome.

Bevacizumab

The full antibody of ranibizumab is marketed in an intravenous formulation (bevacizumab, Avastin®). In combination with intravenous 5-fluorouracil-based chemotherapy, bevacizumab is approved in the United States for first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum. In combination with carboplatin and paclitaxel, it is indicated for first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic nonsquamous, nonsmall cell lung cancer. Prior to the approval and general availability of ranibizumab, Rosenfeld and others began to use it intravenously (53, 54), and then intravitreally, to treat CNV and other intraocular neovascular disorders (55–60). This is clearly an off-label use of the product. However, in a very large number of patients in open-label treatment, efficacy similar to ranibizumab was seen. Given the effective cost differential (US$50–100 for bevacizumab versus $1800 per eye per dose of ranibizumab), this is a nontrivial financial issue (61). In an editorial, Gillies pointed out the differences between ranibizumab and bevacizumab in VEGF-binding affinity, penetration into the retina, and systemic levels after intravitreal injection. He also pointed out the risk of thromboembolic events with VEGF-A antagonists, which may differ between these two molecules. Finally, he pointed out that VEGF inhibitors may eventually cause retinal atrophy by blocking the cytokine's recently discovered neuroprotective actions (62). Novack has reviewed requirements for current good manufacturing practices (cGMP) for ophthalmic products, emphasizing the special issues when dealing with liquids for application to the eye (63). He also raised concerns regarding pharmacokinetic and pharmaceutics issues in the use of drugs for off-label ophthalmic indications (64, 65). A large, randomized, controlled study is being proposed to perform a direct comparison of intravitreal ranibizumab and bevacizumab given either monthly or on an as-needed [pro re nata (PRN)] basis in patients with CNV due to AMD [Comparison of Age-Related Macular Degeneration Treatments Trial (CATT), **http://www.med.upenn.edu/cpob/studies/CATT.shtml]**. In a recent editorial, Jampol presented a rationale in favor of conducting such a study (66).

SUMMARY

Thus treatment of CNV in developed nations in 2007 is substantially different than it was in 1997. Focal, photocoagulating, laser therapy was initially replaced by intravenous verteporfin and then by intravitreal pegaptanib, which is now being replaced by intravitreal ranibizumab and bevacizumab. Other than the ranibizumab versus verteporfin trial (50), there are no comparative studies of the three approved pharmacological treatments for CNV due to wet AMD. Visual acuity results from the large, controlled trials are summarized in **Table 2**. The treatment effect (active less control) is approximately the same for laser photocoagulation, verteporfin, and pegaptanib—approximately 6 to 7 letters (mean change) or 12%–20% (proportion of patients losing 3 or more ETDRS lines of vision).

Although intravitreal injections are accepted as the current standard of care, their use is still far from ideal. Ranibizumab is labeled for monthly injection. While retina subspecialists may be comfortable with this technique, it is most likely not used by the comprehensive (or general) ophthalmologist. There is a small, but real and cumulative risk of sight-threatening endophthalmitis and retinal trauma. For this reason, for eyes requiring bilateral treatment, injections are not performed on the same day. In addition, although many patients experience an improvement in vision with ranibizumab/bevacizumab, some patients do not.

Thus, there is opportunity for improving therapy of CNV with respect to mechanism, efficacy, route of administration, and drug delivery systems. Small companies with novel ideas require venture funding, and such venture funding is difficult to obtain without proof of principle. Such proof may come from early phase studies, as conducted with verteporfin, pegaptanib, and ranibizumab. However, these

Table 2 Summary of visual acuity outcomes of approved therapies for choroidal neovascularization

Treatment/ study group	Months	Mean change			≥15 letters
		Treatment	Control	Difference	Difference
Laser (MPS) (9, 10)	24	−15.0	−22.0	7.0	20%
Verteporfin (TAP) (29)	12	−11.0	−17.5	6.5	15%
Verteporfin (TAP) (30)	24	−13.5	−19.5	6.0	15%
Verteporfin (VIP) (31)	24	−19.0	−25.5	6.5	12%
Pegaptanib (VISION) (43)	12	−8.0	−15.0	7.0	15%
Ranibizumab (MARINA) (49)	12	+6.8	−10.4	17.2	33%

Laser photocoagulation in the MPS is included for comparison with the pharmacological treatments. MPS, Macular Photocoagulation Study; TAP, Treatment of Age-Related Macular Degeneration with Photodynamic Therapy; VIP, Verteporfin in Photodynamic Therapy; VISION, VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group; ANCHOR, Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration; MARINA, Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration.

vehicle-controlled trials are challenging to conduct with an approved treatment that results in not only stabilization of vision but also improvement.

SUMMARY POINTS

1. Age-related macular degeneration (AMD) is a progressive, degenerative disease of the macula. It initially occurs in a "dry" form, and can progress to choroidal neovascularization (CNV, wet AMD) or geographic atrophy.
2. AMD is the leading cause of blindness among European descended people older than 65 years of age, with a prevalence of 1.5%.
3. In the 1970s, controlled studies showed focal photocoagulating laser to have long-term benefit for laser photocoagulation in reducing the risk of severe visual loss in eyes with extrafoveal CNV. However, laser treatment destroys viable neurosensory retina overlaying the treated CNV.
4. VEGF-A is a key signal for CNV.
5. Approved in the United States for treatment of CNV are verteporfin (Visudyne®, QLT/Novartis Ophthalmics), pegaptanib (Macugen®, EyeTech/OSI Pharmaceuticals), and ranibizumab (Lucentis®, Genentech/Novartis).
6. Verteporfin and pegaptanib stabilize vision; however, in a substantial proportion of patients treated with ranibizumab, vision improved.
7. Bevacizumab (Avastin®), an antibody analogous to ranibizumab, has been used off-label to treat CNV.
8. Future treatments may include novel agents of differing mechanisms, as well as more optimized dosing regimens and delivery systems.

FUTURE ISSUES

There are a host of novel anti-angiogenic treatments under consideration for use in ophthalmology. I have selected only those with preclinical or clinical data published in full papers as of March 2007 for this review:

1. Anecortave acetate: An anti-angiogenic steroid, devoid of corticosteroid effects, has been evaluated by posterior juxtasceral injection (67) for several intraocular neovascular conditions. In a placebo-controlled, dose-response study in patients with CNV due to AMD, anecortave acetate (15 mg) was statistically superior to the placebo for stabilization of vision (<3 logMAR line change) (68–70). Anecortave acetate has also been evaluated for retinal angiomatous proliferation (71), and idiopathic perifoveal telangiectasia (72).

2. Dexamethasone implant: An intravitreous dexamethasone drug delivery system was evaluated in patients with persistent macular edema in a six-month, masked, controlled study. Improvement in visual acuity of 2 or more lines was achieved by a greater proportion of patients treated with dexamethasone DDS, 700 μg (35%) or 350 μg (24%), than control patients (13%). As expected with chronic, intraocular corticosteroid treatment, more treated patients (11%) had clinically significant increases in intraocular pressure than control patents (11% versus 2%) (73). Although this study was for macular edema, the use of chronic intraocular anti-inflammatory therapy may be useful in CNV.
3. Lutetium texaphyrin: a synthetic water-soluble tripyrrolic pentaaza–expanded porphyrin, which exhibits strong, low-energy optical absorption in the 700–780 nm range. Given intravenously, lutetium texaphyrin was evaluated as a fluorescence imaging agent in the delineation of retinal vascular and choroidal vascular diseases (74).
4. Pigment epithelium-derived factor (PEDF): In an open-label, noncomparative study, an intravitreous injection of a modified adenoviral vector expressing human pigment epithelium-derived factor (AdPEDF.11) was administered to 28 patients with CNV due to AMD. PEDF is an endogenous compound that regulates normal blood vessel growth. Approximately one quarter of patients experienced mild, transient intraocular inflammation, and one quarter experienced elevated intraocular pressure. At six months after injection, approximately 50%–71% of patients had no clinically significant loss of visual acuity (75).
5. Polyamines: Novel polyamine analogs given by periocular injection, intravitreal injection, or by transceral iontophoresis have been reported to cause suppression and regression of laser-induced choroidal neovascularization in several murine models (76, 77).
6. RTP801: A hypoxia inducible factor (HIF)-1 responsive gene, RTP801, was induced in a murine model of retinopathy of prematurity in wild-type mice, but less so in mice genetically modified to delete that gene. This implies a role of RTP801 in the pathogenesis of retinopathy of prematurity (78). An antisense molecule for RTP801 is currently being studied.
7. Tin ethyl etiopurpurin: Tin ethyl etiopurpurin (SnET2), a synthetic purpurin with photosensitizing activity, was evaluated in rabbits as a photodynamic therapy after intravenous injection (79).
8. VEGF Trap: In an effort to attenuate VEGF at more than just VEGF-A, the VEGF Trap was evaluated. VEGF Trap is a recombinant soluble VEGF receptor protein in which the binding domains of VEGF receptor 1 (VEGF-A and placental growth factor) and receptor 2 (VEGF-A, VEGF-B,

and VEGF-C) are combined with the F_c portion of immunoglobulin G. The safety, pharmacokinetics, and biological activity of VEGF Trap given by intravenous administration was assessed in 25 patients with neovascular AMD in a randomized, multicenter, placebo-controlled clinical trial. Patients were randomized to receive a placebo or 0.3-, 1.0-, or 3.0-mg/kg VEGF Trap—a single IV dose followed by a four-week observation period and then three doses two weeks apart. Dose-limiting systemic toxicity with the 3.0 mg/kg dose suggests that 1.0 mg/kg is the maximally tolerated dose. The mean percent decreases in excess retinal thickness as measured by optical coherence tomography (as possible surrogate of CNV treatment) were 12%, 10%, 66%, and 60%, respectively, for the placebo and 0.3-, 1.0-, and 3.0-mg/kg groups at day 15 (80). In a small pilot study of a quantitative analysis of CNV by fluorescein angiography, VEGF Trap resulted in a decrease in CNV (81).

9. As ranibizumab improves not only vision, but also the edema associated with CNV, optical coherence tomography (OCT), a noninvasive retinal imaging technique, may be used to help guide the need for additional treatment, as used in the PrONTO study (51). In an assessment of angiogenesis, cancer therapy, and inflammation as they may pertain to choroidal neovascularization, Spaide developed a conceptual framework in which therapies for choroidal neovascularization could be evaluated alone or in combination. He proposed a two-compartment model with a vascular component of choroidal neovascularization comprised of vascular endothelial cells, endothelial cell precursors, and pericytes, and an extravascular component, which by histopathology appears to be both the source of angiogenic stimuli and often the largest component volumetrically, comprised of inflammatory, glial, and retinal pigment epithelial cells and fibroblasts. He proposes that combination therapies offer the possibility of attacking one component in more than one way or by attacking both components simultaneously (82). Many feel that the future of treatment of CNV due to AMD lies in combination therapy. One combination, available today, is the use of photodynamic therapy with verteporfin in combination with intravitreal injection of VEGF-antagonists (83). Challenges abound. There are ethical issues in conducting placebo- or sham-controlled trials to evaluate the efficacy of the novel molecule at a time when an approved treatment, albeit a relatively costly one, exists that may improve vision (ranibizumab). It may be challenging to truly double-mask trials where one treatment is given intravenously, one by intravitreal injection, one by eye drops, and one by intravitreal implant. Finally, the size of such trials may be substantial, requiring extensive resources.

DISCLOSURE STATEMENT

The author owns stock in Inspire Pharmaceuticals, Inc. and King Pharmaceuticals, and serves as a consultant to numerous ophthalmic pharmaceutical and medical device firms, including several firms developing treatments for choroidal neovascularization. There were no outside sources of funding for this report.

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Contents

Indexes

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