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Review Article

MV-6401, a potent photosensitizer in experimental animal models: a review of this agent and the current state of photosensitizing agents for the treatment of exudative age-related macular degeneration

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Abstract

Age-related macular degeneration (AMD) is the leading cause of irreversible visual loss in developed countries, but therapeutic options available for treatment of this condition are limited. Intense research oriented towards halting progression of the exudative (wet) type of AMD is being conducted, and a number of therapeutic modalities have recently reached the stage of evaluation in a clinical setting. One very promising approach is that of photodynamic therapy, which in principle allows targeted and selective destruction of aberrant blood vessels affecting the macula with minimal damage to the surrounding retina. A number of photosensitizing agents have been developed to date and some of them are currently being evaluated in clinical and preclinical studies for their safety and efficacy. The photosensitizer MV-6401 has been studied in animal ocular models of neovascularization with promising results. The outcomes of studies evaluating this and other novel photosensitizing agents, and the potential of each agent to become an effective treatment for age-related macular degeneration are reviewed in this article.

Introduction

Age-related macular degeneration (AMD) is the leading cause of irreversible visual loss in the industrialized world (1-3). Traditionally, two types of macular degeneration have been recognized: the “dry” form and the “wet” form. The “dry” or nonexudative form involves both atrophic and hypertrophic changes in the retinal pigment epithelium (RPE) underlying the central macula, as well as drusen beneath the RPE. Patients with nonexudative AMD can progress to the “wet” or exudative form of AMD, in which pathological choroidal neovascular membranes (CNVM) develop under the retina and leak fluid and blood, ultimately causing a blinding “disciform” scar in a relatively short amount of time. Approximately 10-20% of patients with nonexudative AMD eventually progress to the exudative form, which is responsible for a majority of the estimated 1.75 million cases of advanced AMD in the United States (4-6).

In 1995, the International Age-related Maculopathy (ARM) Epidemiological Study Group redefined AMD from the traditional “wet” and “dry” designations. Subsequently, the criteria for the diagnosis of AMD became stricter. Patients with minimal or moderate nonexudative age-related changes in the macula were reclassified as having ARM, and advanced atrophy (*i.e.,* “geographic atrophy”) and/or the presence of choroidal neovascularization (CNV) were determined to be required for the diagnosis of AMD. AMD was then subclassified into the nonexudative (*i.e.,* geographic atrophy) and exudative (*i.e.,* containing any CNV) forms (7). Consequently, ARM patients, comprising 85-90% of cases with age-related macular changes, exhibit only drusen and mild RPE mottling. They are typically minimally symptomatic, with mild blurred central vision, difficulty reading, color and contrast disturbances, and mild metamorphopsia. The remaining 10-15% of patients with macular changes defined as

AMD tend to describe painless, progressive, moderate to severe blurring of central vision and moderate to severe metamorphopsia, which can be acute or insidious in onset.

Although some subtypes of exudative AMD are potentially treatable, treatment efficacy is low; thus, there is great interest in delaying or stopping the progression of ARM, or more effectively treating the factors leading to vision loss once it becomes AMD. Currently, the only widely accepted method of intervention for ARM is the use of high-dose antioxidants; although this only slows progression in some patients and does not reverse any damage already present. Once AMD becomes exudative, laser photocoagulation, photodynamic therapy (PDT) with verteporfin and intravitreal pegaptanib sodium are the standard treatments to control the CNV. However, only a minority of patients with exudative AMD show well-demarcated "classic" CNV amenable to laser treatment. At least half of the patients undergoing thermal laser photocoagulation suffer persistent or recurrent CNVM formation within 2 years. In addition, since the treatment itself causes a blinding central scotoma when the CNV is located subfoveally, many clinicians do not treat subfoveal CNV with thermal laser.

Verteporfin PDT (Visudyne®; QLT/Novartis Ophthalmics) was approved by the United States Food and Drug Administration (FDA) for subfoveal CNV treatment in 2000; however, it only limits vision loss and often requires multiple retreatments. Pegaptanib sodium (Macugen®; Eyetech Pharmaceuticals), a vascular endothelial growth factor (VEGF) inhibitor, was approved by the FDA in December 2004 and became available to physicians in January 2005; however, it is an intravitreally administered medication that requires injections every 6 weeks. Because of these treatment limitations, researchers are presently developing alternative therapies for exudative AMD, including alternative types of PTD, transpupillary thermotherapy, a variety of growth factor modulators, radiation and surgical therapy. In addition, effective treatment is still limited by the lack of a true understanding of the underlying etiology of the disease.

Photodynamic therapy

Photodynamic therapy (PDT) utilizes laser light and intravascular dyes (*i.e.,* photosensitizers). After intravenous injection of the photosensitizer and once sufficient time has passed for the compound to concentrate in neovascular tissue, the photosensitizer is stimulated with a specific wavelength of light to react with water and create oxygen and hydroxyl free radicals within the CNV (8). These free radicals, in turn, react with cell membranes of the pathological endothelium to induce occlusion by massive platelet activation and thrombosis, while preserving the normal choroidal vasculature and nonvascular tissue (9, 10). Ideally, the intensity of the exciting wavelength is low enough to spare the non-neovascular irradiated tissues from thermal damage. Important variables in this reaction include the intravascular concentration of dye, the photochemical behavior of the dye, as well as the interval between the injection and the onset of irradiation, the intensity and specificity of the exciting irradiation and its duration (11-13).

MV-6401

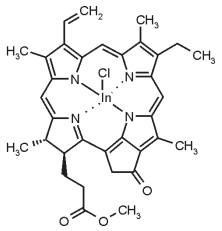
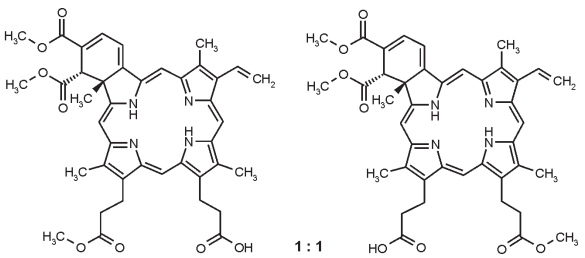
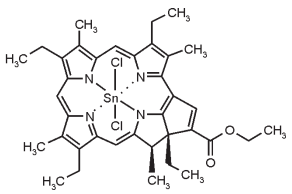
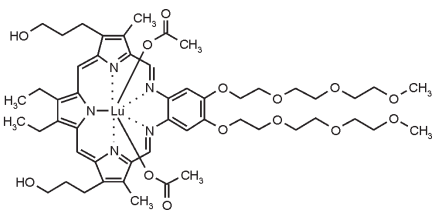
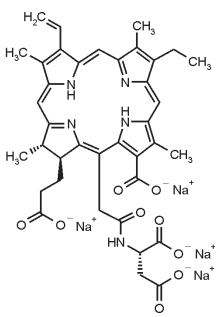
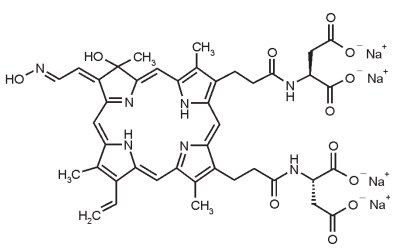
MV-6401 (indium chloride methyl pyropheophorbide) is a new photosensitizing agent manufactured by Miravant Medical Technologies (Table I). It is a pyropheophorbide with two main absorption peaks at 423 nm (molar extinction coefficient = 101,000 $M^{-1}cm^{-1}$) and 659 nm (74,000 $M^{-1}cm^{-1}$).

Pyropheophorbide-based PDT has been well studied for utilization in cancer therapy and may also have a role in ophthalmic applications. These compounds are well described chemically, hydrophobic, absorb light above 600 nm for enhanced tissue penetration, have excellent photosensitizing efficiency, and may not cause the prolonged skin photosensitivity experienced with porphyrin derivatives such as verteporfin. MV-6401-based therapy was originally studied for utilization in cancer treatment, and initial descriptions of its antivascular effects emerged in the context of tumor microvasculature. It was found to produce an effective vascular shutdown, mediated acutely by vasoconstriction and later by thrombus formation and stasis, ultimately resulting in tumor growth arrest. Further studies of the drug unveiled its selectivity, as it accumulated mainly in the abnormal, rapidly growing tumor vasculature and did not affect normal vessels at effective doses. MV-6401 was also found to be capable of extravasation and accumulation in the tumor interstitium (14).

Given that the goals of CNV treatment differ substantially from those of tumor treatment in that the main objective is to confine the disruptive effect to the vasculature and avoid any damage to surrounding tissue, the optimum therapeutic conditions for MV-6401 use as described in tumor studies cannot be directly assumed to be correct for the treatment of neovascularization in the retina. To explore a possible role for MV-6401 in the treatment of CNV, it was studied in a rat model of corneal neovascularization and in a rabbit choriocapillaris model, where it was found to effectively close the vessels. In the rabbit choriocapillaris model, a dose of 0.15 mmol/kg produced the most desirable endpoint, with a preferential effect on the choriocapillaris and choroid, along with minimal retinal toxicity. Both angiography and histology demonstrated primary closure of the choriocapillaris and moderate-sized choroidal vessels (15).

A more recent study of MV-6401 in a primate model demonstrated its effectiveness in choriocapillaris closure in the normal fundus, as well as in choroidal neovascularization induced by laser trauma. Interestingly, the damage to retinal tissue accompanying treatment was considerably more extensive when laser was applied during

Table I: Photosensitizers studied for the treatment of AMD.

Drug	Chemical structure	Class	Source	Development phase
MV-6401		Pyropheophorbide	Miravant Medical Technologies	Preclinical
Verteporfin (Visudyne®)		Chlorin	QLT/Novartis Ophthalmics	Launched
Rostaporfin (Photrex®)		Purpurin	Miravant Medical Technologies	Phase III
Motexafin lutetium (Optrin™)		Texaphyrin	Pharmacyclics	Phase II (on hold)
Talaporfin sodium		Chlorin	Light Sciences	Phase I
ATX-S10(Na)		Chlorin	Allergan/ Photochemical	Preclinical

the first hour after MV-6401 injection as compared to activation after 60 min (16). This could be attributable to rapid extravasation of drug through the imperfect walls of the CNV, resulting in the presence of MV-6401 in the adjacent retina and its activation by light treatment. Presumably, once the interstitial drug is cleared, damage to nonvascular tissues in response to photosensitizer activation would diminish. Even though this has not been corroborated, it finds some support in studies of tumors treated with MV-6401, where drug extravasation and accumulation in surrounding tissues have been demonstrated and pathologically correlated with interstitial damage after laser activation (17).

Photodynamic therapy with MV-6401 yielded selective closure of choriocapillaris and CNVM, and after optimization of light dosage and activation times, this was achieved with minimal injury to the overlying retina. These results suggest that MV-6401 could potentially be used for the treatment of subfoveal CNV. Further study of this compound, including refinement of light dosage parameters within different portions of the macula, is thus warranted.

Verteporfin

The FDA approved verteporfin (Table I) in 2000 for patients with "predominantly classic" subfoveal CNV caused by AMD, which demonstrates a characteristic early and well-defined RSFA (rapid sequence fluorescein angiography) stain to over 50% of the CNV complex. Similarly, marketing approval was granted in Europe in July 2000, and it is currently commercially available in over 70 countries for predominantly classic CNV. Verteporfin is a modified porphyrin with an absorption peak near 689 nm that is delivered intravenously for 10 min. After a 5-min delay, the CNV complex is irradiated through the pupil with a large spot diode laser at 689 nm for 83 sec. The laser energy activates the intravascular compound and stimulates the photodynamic action within the CNV. Verteporfin is cleared rapidly from the body, resulting in minimal skin sensitivity after 5 days.

In 1999 and 2001, respectively, the 1- and 2-year results from the Treatment of AMD with PDT (TAP) study were published. TAP consisted of two randomized, prospective, double-blind, placebo-controlled phase III trials in 609 subjects. First-year data reported that the proportion of eyes with less than 15 letters of visual acuity loss on a standardized eye chart was 67% in the treated group *versus* 39% in the control group ($p < 0.001$) when the CNV was predominantly classic; however, no significant differences in visual acuity were demonstrated when the area of classic CNV was less than 50% of the entire complex. Also, researchers noted that 90% of the subjects required retreatment at 3 months and an average of more than 3 retreatments over the first year (18). Second-year follow-up data reported that 59% of treated eyes had a favorable visual outcome *versus* 31% of control eyes when the lesion was predominantly classic (19). The TAP trial was unmasked at 2 years of follow-up. Subsequently, an open-label extension to 36 months in 124 of the 159 original TAP participants with predominantly classic CNV revealed that visual acuity remained nearly constant and required fewer retreatments (20).

Based on the success of the TAP trial, the Verteporfin in Photodynamic Therapy (VIP) trial, another randomized, prospective, double-blind, placebo-controlled clinical trial, was designed to examine many of the patients who fell outside the inclusion guidelines set by TAP. VIP evaluated the efficacy of PDT in 339 subjects with total occult subfoveal CNV, classic CNV with a visual acuity better than 20/40, or CNV secondary to pathological myopia. One-year results of the occult AMD arm showed no significant difference in visual acuity outcomes in exudative AMD patients treated with verteporfin or placebo (51% of PDT- and 54% of placebo-treated had unfavorable visual outcomes). However, 2-year follow-up data revealed that 55% of the treated subjects with occult CNV had an unfavorable outcome *versus* 68% of the placebo-treated patients ($p = 0.023$). On average, the verteporfin-treated patients received 5 treatments over 24 months of follow-up. Based on these findings, the study group recommended verteporfin for purely occult subfoveal CNV demonstrating recent disease progression in all patients except those with large lesions and good visual acuity (21). Because the FDA requested additional data before approving verteporfin for occult CNV, the Visudyne in Occult (VIO) trial was designed as a 24-month study to analyze patients with only occult CNV. Enrollment of 364 subjects was completed in September 2003 and the trial is currently in the second year of follow-up as recommended by the data and safety monitoring committee (22).

Several other trials have evaluated the efficacy of verteporfin in a variety of clinical situations previously lacking sufficient data. Retrospective TAP and VIP data suggested some treatment benefit for smaller, minimally classic lesions. The Visudyne in Minimally Classic Trial (VIM) was thus initiated as a randomized, prospective, double-blind, placebo-controlled phase II clinical trial designed to study the use of verteporfin in patients with minimally classic CNV. One-year data on 117 patients suggest that small, recently progressive, minimally classic CNV might benefit from verteporfin therapy (23, 24). Two-year follow-up data revealed that, compared to placebo, fewer verteporfin-treated eyes lost 3 or more lines of vision on a standard visual acuity chart or converted to a predominantly classic lesion (25). Consequently, a phase III study (the VMC Trial) was started in late 2003 to further evaluate verteporfin in minimally classic CNV (26).

Based on evidence that 80% of vision loss in verteporfin-treated patients occurs within 6 months of developing CNV, the phase III Verteporfin Early Retreatment (VER) trial was conducted in 323 patients to compare the benefit of retreatment at 6-week intervals *versus* the standard 3 months (27). Twelve-month interim results of the 2-year trial did not show improved outcomes when compared to the standard treatment (28). Additionally, the Verteporfin with Altered (Delayed) Light

in Occult (VALIO) study was designed to evaluate whether delaying the light application to 30 min after the initiation of verteporfin infusion (*versus* the standard 15 min) would improve outcomes in occult CNV. Phase II data at 6 months of follow-up show that the group treated at 30 min postinfusion lost 1.3 lines of vision while the standard 15 min postinfusion treatment group lost 2-3 lines, which was not statistically significant (27, 29). One-year data substantiated the 6-month findings (30).

At present, verteporfin is the only approved PDT agent, although additional photosensitizing products are under development.

Rostaporfin

Rostaporfin (SnET2, Photrex®; Miravant Medical Technologies) (Table I) is a purpurin with a structure similar to chlorophyll that absorbs maximally at 664 nm. Like verteporfin, the preconstituted solution is intravenously infused over 10-20 min (31). In December 2001, enrollment for a placebo-controlled, double-masked phase III clinical trial involving 920 patients was completed. Two-year follow-up data revealed that 58% of patients receiving a dose of 0.5 mg/kg of SnET2 lost less than 15 letters compared to 42% of placebo patients (p = 0.0045). Rostaporfin was well tolerated and demonstrated an acceptable safety profile (32). In September 2004, the FDA requested an additional confirmatory clinical trial before final marketing approval, which is scheduled to begin before the end of 2005.

Other photosensitizing agents

Motexafin lutetium (Optrin™; Pharmacyclics) (Table I), which is activated by 732-nm light, can be utilized as both an imaging and a photosensitizing agent. It had shown promise for the treatment of AMD in phase II trials involving 75 patients; however, 77% of subjects receiving therapeutic doses developed peripheral extremity paresthesias (33). Due to these side effects, further development of this drug is currently on hold (27). Other drugs in early stages of development include talaporfin sodium (LS-11; Light Sciences) (Table I), which is currently in the stage of patient recruitment for a phase I study to be completed by late 2006, and ATX-S10(Na) (Allergan/Photochemical) (Table I), which has demonstrated the ability to occlude choroidal vessels in nonhuman primates (34).

Receptor-targeted PDT

Receptor-targeted PDT is currently in preclinical stages of development. Instead of a nonspecific vaso-occlusion based on generalized high intravascular concentrations of photosensitizer, it is presumed that a conjugated photosensitizer can be effectively concentrated in neovascular tissue by binding to receptors expressed preferentially in CNV. Conjugating verteporfin to a VEGF receptor 2 antagonist and then performing PDT resulted in 100% angiographic closure in rat laser injury models of CNV. Histological examination revealed minimal collateral damage to the surrounding retinal structures as compared to verteporfin controls (35).

Conclusions

Although standard PDT with verteporfin has shown promise in treating some forms of CNV, it often requires numerous retreatments, is expensive and typically slows vision loss rather than improving it. In addition, PDT can also damage adjacent normal tissue containing the photosensitizer (36). Immunohistopathological examination suggests that PDT with verteporfin causes only short-term damage to the CNV, which recovers to normal in a matter of weeks (37). Therefore, other pharmacological interventions are being pursued to treat subfoveal CNV.

In summary, many exciting management options are on the horizon and will undoubtedly become an integral part of AMD treatment soon. Until the pathophysiology of AMD is better understood, treatment will likely depend on a combination of approaches to limit the underlying CNV often associated with severe vision loss. The millions of current and future AMD patients and the eye care community eagerly await the results of future large-scale studies evaluating many of the initially promising findings detailed here.

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