Benzoporphyrin (Verteporfin) Photodynamic Therapy for Choroidal Neovascularization in Age-Related Macular Degeneration

Terapia fotodinâmica de neovascularização de coróide por degeneração macular relacionada à idade com benzoporfirina (verteporfirina)

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SUMMARY

Purpose: **To review and discuss the available treatments for choroidal neovascularization (CNV) due to age-related macular degeneration (AMD) emphasizing to photodynamic therapy (PDT).**

Methods: **Published papers from 1974 until 1999 related to AMD, its available treatments and PDT were reviewed.**

Results: **The most used effective treatment for CNV is laser photocoagulation which does not have a major impact on the blindness due to AMD. Alternative techniques of prevention and treatment are under investigation including surgery, pharmacological antiangiogenic treatment and prevention with photocoagulation. PDT using verteporfin demonstrated effectiveness in closing CNV membranes in an experimental model. A clinical trial showed that a single course treatment could stabilize the area and extent of leakage from subfoveal CNV with classic component in the majority of patients for up to 3 months (Phase I/II). A 12-month data for quaterly treatments was recently reported and showed that vision stabilization, meaning vision improvement, no change, or loss of < 3 lines, occurred in 61.4% of the verteporfin-treated eyes and verteporfin-treated eyes are more likely to avoid a six-line or greater loss (85%) compared to placebo (76%). Another clinical trial (Phase III B) is under way to analyze the role of PDT in the occult type of CNV.**

Conclusion: **Treatment for this devastating condition remains a challenge. These clinical studies have shown an early closure of the CNV following PDT with exciting results in terms of visual acuity, although on a long-term basis these results are yet to be proven. Photodynamic therapy is one of the most promising new technologies to treat CNV.**

Keywords: Photodynamic therapy; Age-related macular degeneration; Choroidal neovascularization.

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INTRODUCTION

Age related macular degeneration (AMD) is the leading cause of severe visual impairment and legal blindness in elderly people in most industrialized countries [1-7]. This degenerative disorder is a broad-spectrum disease ranging from an early dry form with drusen and retinal pigment abnormalities and minimal or unaffected visual function to a late dry stage of geographic atrophy and marked visual loss or a wet or neovascular form characterized by choroidal neovascularization and fibrous scarring of the macula with severe vision loss.

The vast majority (79%) of patients with age-related macular degeneration usually present a slow-developing atrophic form of AMD and 5.3 % of cases of AMD have the rapidly evolving neovascular form [9]. Although the atrophic form has a higher prevalence, neovascular form accounts for 79% to 90% of legal blindness due AMD [8, 9]. It is present in 6.4 % of population between 64 and 75 years of age and in 19.7 % of the population over 75 years of age [7-9]. Furthermore, if one eye is affected and the second eye has evidence of risk factors for neovascular disease (i.e.:large soft drusen and pigmentary abnormalities), approximately 4% to 12% of patients will develop neovascular disease in the fellow eyes each year [10-12].

Choroidal neovascularization due to AMD is a pathological process in which blood vessels grow beneath the retina and leak fluid, blood and lipids. This process results in scarring, which may disrupt the integrity of the macula with associated visual loss [13]. Based on fluorescein angiogram findings and fundus photographs there are 2 types of choroidal neovascular membranes: well-demarcated areas of hyperfluorescence revealing the neovascular process itself in the early phase of the angiogram characterize the classic type. In the occult type, 2 forms of lesion are recognized: the fibrovascular pigment epithelial detachment and the late-phase leakage of undetermined source. In this occult type the neovascular complex is not demarcated but the diffuse leakage of dye derived from it in the early and late phases of the angiogram [14-16].

Available treatments for AMD

Laser photocoagulation is until now the most used effective treatment for CNV. For patients who have extrafoveal or juxtafoveal well-defined CNV, laser photocoagulation is better than no treatment for preventing or delaying large losses of visual acuity [17-20, 30]. Laser treatment for eligible patients with sub foveal CNV, both new and recurrent lesions may lead to severe destruction of the sensory retina with significant visual loss. Data from the Macular Photocoagulation Studies (MPS) demonstrated that laser treated eyes are less likely to suffer severe visual loss than control eyes in selected cases, but many retinal specialists are reluctant to treat subfoveal CNV because of the acute visual loss associated with the foveal photocoagulation right after the procedure [21-25]. Unfortunately, the majority of the patients, up to 87% of them, with newly diagnosed neovascular AMD accordingly to Freund et al. [26], do not meet the criteria for laser photocoagulation because the CNV is too large, occult or ill defined [14, 15, 27, 28]. Furthermore, among those patients with extrafoveal lesion treated with laser photocoagulation, up to 54% suffered recurrence (defined by leakage of fluorescein at the periphery of the laser scar later than 6 weeks after treatment) after a 5-year follow-up [18, 30, 31]. In the juxtafoveal and subfoveal groups of patients similarly recurrence occurred in 47 and 35% respectively [27, 32, 34]. Nowadays, it is becoming evident that the available techniques for laser photocoagulation of choroidal neovascular membranes due to AMD will not have a major impact on blindness due to AMD, despite early expectations [24, 27, 34, 35].

Prevention therapy with laser photocoagulation of soft drusen emerged as an alternative form of treatment, evaluated by a series of clinical trials [36-40]. Despite the initial observation that laser photocoagulation could cause large soft drusen to disappear, (which have been showed to be high risk for CNV [11, 12, 41]), a large randomized, multicenter trial (Choroidal Neovascularization Prevention Trial) revealed that laser treatment to high risk eyes may increase the short-term incidence of CNV [40, 44]. A NIH-sponsored multicenter trial is now under way to evaluate the actual role of laser treatment in the disappearance of drusen.

Submacular surgery for the removal of the CNV has been used for eyes with CNV secondary to AMD and other diseases [45-47]. CNV membrane removal in AMD patients appears to be associated with removal of native RPE cells and photoreceptors leading to loss of visual function [48]. Furthermore, there is a high-rate of recurrences (up to 46%) and complications [47, 49-51]. A large multicenter NIH-sponsored randomized trial (Submacular Surgery Trial) is currently recruiting patients in the US and will reveal the actual role of the submacular surgery in the treatment of the CNV due to AMD. Alternative modalities of surgery are being investigated including macular translocation and macular transplantation [52-57].

Radiotherapy is considered as an antiangiogenic and anti-inflammatory modality. Chakravarthy et al. were able to demonstrate in a pilot study that external beam radiation could maintain central vision and induce regression of actively growing choroidal neovascular membranes [58]. In addition, Bergiink et al. demonstrated in a well-controlled randomized study that treated patients were more unlikely to suffer severe visual loss than untreated patients (32 and 40% respectively) [59]. Similarly, Finger et al. showed relatively good results of episcleral plaque brachytherapy with palladium 103 in controlling the growth of CNV [60]. However, Spaide et al. in a nonrandomized multicenter study and Stalmans et al. reviewing 111 cases of patients submitted to radiotherapy found that external beam radiation failed to control or induce regression of active growing CNV [61, 62]. Inclusion criteria and variable follow up, different radiation types, rate of administration and doses make comparison and evaluation of the results difficult. In fact, critical analysis reveals that the efficacy of these treatments as compared to natural history remains uncertain and clinical trials are under way in the US and in the UK to investigate the efficacy of the radiation in the treatment of neovascular AMD.

Pharmacological antiangiogenic treatment holds great promises. Drug therapy would enable us to avoid the deleterious effects of laser photocoagulation on the delicate macular tissue. Interferon alpha-2a has been shown to be effective as an antiangiogenic drug for several systemic disorders and experimentally caused regression of iris

neovascularization in a experimental monkey model [63-65]. However, in a multicenter randomized clinical trial with 481 patients from all over the world (Pharmacological Therapy for Macular Degeneration Group) interferon alpha-2a showed to be of no benefit for CNV secondary to AMD [65]. Further research is needed to establish the role of drugs such as thalidomide, VEGF-inhibitors, steroids, angiostatin and endostatin, which share antiangiogenic effects and have the potential to halt the progression of neovascularization [66-74].

Photodynamic Therapy

Photodynamic therapy is an attractive and innovative modality of treatment for a number of diseases. It utilizes an exogenous photosensitizing agent, which localizes the target tissue and is subsequently excited by a specific wavelength, generating highly reactive compounds that lead to cell damage and death.

The use of an exogenous sensitizer for a therapeutic effect started approximately 1500 years ago when phototherapeutic techniques for treatment of vitiligo were developed using psoralens obtained from the seeds of *Psoralia corifolia* in ancient India and from leafs of Amni majus by the Egyptians [75, 76]. Von Tappeiner and Oscar Raab in Munich developed however the use of sensitized oxygen-requiring reactions in the early 1900s in a classical example of serependity in science. While studying the toxic properties of acridine to Paramecium, a strong thunderstorm occurred during one of the experiments creating distinctly different light conditions and the exposed Paramecia died. They found that acridine even in small concentrations combined with light exposure increased the toxicity against the Paramecia. Von Tappeiner took over Raab's research and with a dermatologist named Jestoniek developed photodynamic techniques for therapy of skin diseases such as molluscum contagiosum, ptyriasis versicolor and psoriasis. Two years later skin cancer, lupus and chondylomata were been investigated using eosin as a photosensitizer [75, 76].

In its modern era, photodynamic therapy began with studies at the Mayo Clinic by R. Lipson and S. Schwartz in 1960 using hematoporphyrin as a fluorescent dye to detect cancer cells [77]. It has been proved useful for a variety of malignant and non-malignant diseases [77-81]. In 1993 PDT using Photofrin was approved by a health agency for the first time in Canada, for treatment of bladder cancer. Subsequently approvals were obtained in France, Germany, The Netherlands, Japan and USA. It is being used for treatment of early and late-stage gastrointestinal cancers, bladder cancers, lung cancers and with pending approvals for other cancers in a number of countries worldwide [80, 82, 83]. A wide variety applications are being tested such as therapy of microbial infections, skin disorders, psoriasis and ocular disorders including tumors and choroidal neovascular membranes [77, 78, 80, 81-90].

Mechanism of Action

Following the administration of the photosensitizer dye, there is a selective retention of the drug in the target tissue. Photosensitive dyes are preferentially retained in tumors or more specifically in neovascular tissue of tumors due to characteristic aspects of the photosensitize, of the cellular membrane and mechanisms of transport of macromolecules of these pathologic cells, which allows selective treatment [92-95].

The target cells are then light irradiated and the molecules of the dye gain energy passing from the ground state to an excited, highly reactive, short-lived triplet state which transfers the excess of energy by two pathways:

1) The energy absorbed from the triplet state is transferred to other molecules leading to the generation of free radicals, which instantaneously oxidize a wide variety of biomolecules - Type I mechanism.

2) The energy absorbed from the triplet state is transferred to oxygen generating high reactive short-lived oxygen - Type II mechanism which appears to play the major role in the effect seen in PDT [96].

The interactions of these highly reactive compounds cause cellular and vascular damage. Cellular membranes including plasma and nuclear membranes are severely damaged by photo-oxidation of fatty acids and cholesterol [97]. The permeability of the damaged membrane results in a rapid derangement of the cellular homeostasis. In addiction there is cross-linking of proteins responsible for the transport mechanisms and structural maintenance with release of Na^+, K^+, and Ca^{++} and direct damage to the nuclear DNA [98-100].

The release of all of these physiologically active ions has been associated with an immediate induction of acute inflammatory responses: Liberation of phospholipids induces arachidonic acid cascade, thromboxane, prostaglandin and leukotriene synthesis, platelet aggregation, release of histamine, serotonin and bradykinin increasing the effects of eicosanoids and activation of the complement cascade inducing response from the immune system, leading to acute inflammation and edema (vascular response) and therefore, occlusion of the feeding vessels [98, 101].

BPD-MA or verteporfin

BPD-MA or verteporfin (a benzoporphyyrin derivative) is a second generation potent photosensitizer of the tetrapyrrole group that is currently being investigated for its anti-neoplastic and anti-neovascular properties as well as for its properties regarding destruction of neovascular tissue as well as tumors in ophthalmology [90, 91]. It absorbs light at 690 nm. A longer wavelength is important because it allows deep tissue penetration, through blood, pigments and fluid which could accumulate beneath the retina. Plasma half-life ranges approximately from 5 to 6 hours and BPD-MA/Verteporfin is excreted mainly by the bile (90%). It is administered intravenously as a liposomal preparation and partitions into the LDL phase of the lipoprotein fraction of the blood [94, 102]. Endothelial cells which form the neovessels of tumors and neovascular membranes have been shown to have increased the popula-

tion of LDL receptors that play a major role in the mechanism of the uptake and therefore the selectivity of the photosensitizer in these cells [94]. It has been shown to be safe for human use and was first used in dermatology for treatment of malignant lesions of the skin [89].

Preclinical studies

PDT using verteporfin for treatment of CNV has been extensively investigated in a monkey model of choroidal neovascularization. In these studies, laser burns in the macula of the monkeys induced the CNV [103-109].

Studies have been demonstrated the in vivo localization of verteporfin in the cells relevant to CNV (i.e. RPE cells and capillary endothelial cells). Haimovici et al. were able to demonstrate the localization of BPD-MA/verteporfin in RPE and choroid within 5 minutes after the injection of the dye and in outer segments after 20 minutes in rabbit eyes [103]. Using digital quantitative analysis of fluorescence, Miller et al. were able to show the selective accumulation of verteporfin in CNV membranes of patients and in experimental CNV membranes created in the maculae of monkeys using high intensity laser burns [104].

The effectiveness, selectivity and safety of PDT using verteporfin were assessed in these models which demonstrated effective closure of the CNV membranes, documented by histopathological examinations, fundus photography and fluorescein angiography. Further evaluation on dosimetry included verteporfin dose, infusion time, light dosimetry, timing of irradiation and long-term follow up [105-109].

Clinical Trials

Based on these preclinical studies a multicenter, nonrandomized, phase I/II trial started in 1995 sponsored by QLT Phototherapeutics and CIBAVision Ophthalmics to investigate the effectiveness and dosimetry of BPD-MA [111].

Patients with subfoveal CNV with some classic component, lesion with less than 9 MPS disc areas and refracted visual acuity of 20/40 or worse were enrolled to participate in the trial. Pretreatment examination included best refracted visual acuity by protocol, standardized fluorescein angiogram and fundus photographs (when eligibility criteria were confirmed by the reading center), medical evaluation which included a medical examination, EKG, liver function tests and complete blood count and informed consent [112, 114, 115].

The patients were followed-over 3 months with refracted visual acuity, ophthalmic examination and standardized fundus photography and fluorescein angiogram. A total of 128 patients with subfoveal CNV secondary to AMD were enrolled in dose-escalating regimens, using a verteporfin dose of 6 or 12 mg/m^2, and a light dose of 12.5 - 150 J/cm^2 and 600 mW/cm^2, with irradiation applied 10, 20 or 30 minutes after the start of verteporfin infusion. Ninety-seven patients were enrolled and received a single treatment with a planned 3-months follow-up. Additional 31 patients were enrolled in retreatment protocols, at 2- or 4-week intervals. Thirteen non-AMD patients were also enrolled and were analyzed separately. Most cases showed absence of leakage from classic CNV at 1 week of follow-up, consistent with occlusion of the CNV. Complete absence of leakage from classic CNV occurred in 52-100% of the patients at week 1, depending on the regimen. By 4 weeks of follow-up, most patients showed leakage from a part of the original area of classic CNV. At 12 weeks of follow-up, extension of the CNV beyond the original border, was seen in some cases. Increasing the verteporfin or light does did not prevent this reappearance of leakage, and non selective effects, namely retinal vessel non perfusion was seen at the highest light dose, and defined the acceptable upper limit of the light dose.

In the single treatment of AMD patients, the mean visual acuity change at 1 week was +0.7 lines. Interestingly, 18 patients (14%) showed vision improvement of > 3 lines. By week 4, the visual acuity change was +0.2, and by week 12, it was -0.5 lines. One regimen gave somewhat better results regarding visual acuity and angiographic leakage and was selected for the phase 3 trial. Multiple treatments were tolerated without any short-term loss of vision due to retreatment. Results from the phase I/II trial also showed a promising response to the treatment of patients with CNV secondary to pathologic myopia stabilizing the visual acuity and extent of the lesion [111-116].

This study showed that a single course of treatment could safely stabilize the area and extent of leakage from CNV lesions in the majority of patients for up to 3 months. Since the size and activity of the lesion has a close relation to visual acuity, these results supported the rationale for the phase III studies to evaluate the safety and efficacy of quarterly treatments of CNV stabilizing the visual acuity of such patients [115-116].

Phase IIIA trial started in December 1996 as a randomized, controlled, masked multicenter study involving approximately 18 centers (TAP study). The eligibility criteria for this study included subfoveal CNV secondary to any cause with a classic component demonstrable by fluorescein angiography and with an area of less than 9 MPS disc areas. Visual acuity had to be worse than 20/40 but equal to or better than 20/200.

Pretreatment evaluation included best-refracted visual acuity, ophthalmic examination, standardized fundus photography fluorescein angiogram and medical evaluation (EKG, laboratory tests, complete blood count and liver function tests).

By 1997, 609 patients had been enrolled by the 22 participating centers. Patients underwent refracted visual acuity, ophthalmic examination, and standardized fluorescein angiography at enrollment, and were randomly assigned (2:1) to PDT with verteporfin or PDT with D5W (placebo). Patients underwent irradiation of the macula with 690 nm laser light 15 minutes after the start of verteporfin or placebo infusion, using 50 J/cm^2 and 600 mW/cm^2. They returned at 3-month intervals and underwent protocol refraction, ophthalmic examination, and fluorescein angiography. Retreatment was per-

formed if leakage was demonstrated angiographically. The study was designed to determine whether PDT using verteporfin could reduce the risk of severe visual loss from subfoveal CNV in AMD, with the primary endpoints being of >3 lines of vision lost and > 6 lines lost. Secondary endpoints include contrast sensitivity, mean visual acuity loss, and angiographic leakage.

An interim report of the 12-month data was recently reported, showing vision improvement, no change, or loss of < 3 lines, occurred in 61.4% of the verteporfin-treated group and 45.9% of the placebo, while vision improvement of > 1 line occurred in 16% of that group compared to 7% of the placebo group. Eyes treated with verteporfin were more likely to avoid a six-line or greater loss (85%) when compared to those with placebo (76%). Based on estimates from Kaplan-Meier rates, at every follow-up examination after study entry, the proportion of eyes with > 3 line loss or > 6 line loss was less in the verteporfin-treated group. The mean number of contrast sensitivity letters lost was approximately one in the verteporfin-treated eyes compared to approximately three to five in placebo-treated eyes in every follow-up visit at the 12-month examination. Some subgroup analyses have also been performed. When the entire study population was separated by the presence or absence of occult CNV, the subgroup with no occult CNV had a substantial treatment benefit. Specifically, 23% of the verteporfin-treated eyes compared to 73% of the placebo-treated eyes had lost > 3 lines of vision. If occult CNV was present, 45% of the verteporfin-treated eyes compared to 47% of the placebo-treated eyes lost > 3 lines. A substantial treatment benefit was also seen when > 50% of the lesion area was classic CNV. Other secondary endpoints like lesion growth also favored the verteporfin-treated group. By the month 12 examination, verteporfin-treated patients received an average of 3.4 treatments per subject compared to 3.7 treatments per subject for placebo-treated patients. Treatments were well tolerated with < 2% withdrawing because of adverse events. Photosensitivity reactions occurred in 2% of the participants, and resolved within 24 hours [117].

Another phase 3 trial using verteporfin PDT for CNV was initiated in 1998, enrolling patients with subfoveal CNV secondary to AMD with occult-only components, and subfoveal CNV secondary to pathologic myopia. Known as VIP (**V**erteporfin **I**n **P**hotodynamic therapy), the study had over 400 patients enrolled as of September, 1998, and follows the same treatment protocol as TAP.

These clinical studies have shown an early closure of the CNV following PDT with exciting results in terms of visual acuity, although on a long-term basis these results are yet to be proven. Reopening of the lesion with leakage of dye in the angiogram was very common and required reapplication. At the present, photodynamic therapy is the most effective and less damaging treatment for neovascular CNV. New dyes and lasers have been tested in a number of experimental trials including tin-ethyl etiopurpurin (Purlytin) and lutetium texaphrin (Lu-Tex), and further research is needed to determine the most appropriate photosensitizer and laser for PDT in ophthalmology. In the very near future the approach to the treatment of this blinding disease is going to be changed dramatically with improvement of Photodynamic Therapy which could be used in a multifaceted aspect of treatment associated with pharmacologic inhibition of angiogenesis, conventional laser, ocular surgery and other modalities of treatments.

RESUMO

Objetivo: *Rever e discutir os tratamentos disponíveis para neovascularização subrretiniana (CNV) secundária a degeneração macular relacionada a idade (DMRI) com ênfase especial a terapia fotodinâmica (PDT).*

Métodos: *Revisamos artigos publicados a partir de 1974 até 1999 relacionados a DMRI, seus tratamentos disponíveis e PDT.*

Resultados: *O tratamento provadamente efetivo mais utilizado para CNV é fotocoagulação com laser o qual não apresenta um impacto expressivo na deficiência visual causada pela DMRI. Técnicas alternativas de prevenção e tratamento estão sob investigação incluindo cirurgias, tratamento farmacológico antiangiogênico e prevenção com fotocoagulação. PDT com Verteporfina demonstrou ser efetiva no fechamento de CNV em nosso modelo experimental. Um estudo clínico inicial demonstrou que uma aplicação única poderia estabilizar a área de CNV subfoveal com componente clássico na maioria dos pacientes por até 3 meses. Dados de 12 meses em tratamentos quadrimestrais revelaram que a estabilização da visão, significando melhora, não alteração ou perda de até 3 linhas ocorreu em 61,4% dos pacientes tratados e que estes eram menos susceptíveis a perda visual de 6 ou mais linhas (85%) quando comparados com placebo (76%). Outro estudo clínico está em andamento para analisar o PDT em CNV do tipo oculto.*

Conclusão: *O tratamento para esta devastadora patologia continua desafiador. Estes estudos clínicos demonstraram fechamento inicial do CNV com PDT e interessantes resultados em termos de acuidade visual, embora estes resultados necessitem de comprovação clínica a longo prazo. A terapia fotodinâmica é uma das mais promissoras novas tecnologias para o tratamento de CNV.*

Palavras-chave: *Terapia fotodinâmica; Degeneração macular relacionada a idade; Neovascularização de coróide.*

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