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Vascular-targeted photodynamic therapy in the treatment of neovascular age-related macular degeneration: Clinical perspectives

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Abstract Vascular targeted photodynamic therapy (VTP), with use of verteporfin as a photosensitizer is one of the few therapies, which has been shown to effectively slow the progression of the ''wet'' form of age-related macular degeneration (AMD), and even to stabilize visual acuity over many years. Although, due to considerable advance of AMD treatment, it is currently not recommended in monotherapy of AMD, however, its combination with steroids and anti-angiogenic biologic drugs may reveal high therapeutic potential in the treatment of

Abbreviations: AMD, age-related macular degeneration; ANCHOR, ANti-VEGF Antibody for the Treatment of Predominantly Classic CHORoidal Neovascularisation in AMD; BCVA, best corrected visual acuity; CAVE, Canadian Study of Avastin® and Visudyne® in Exudative AMD; CHF, Swiss franc; CNV, choroidal neovascularisation; CMT, central macular thickness; COX-2, cyclooxygenase-2; DA, disk area; DMSO, dimethyl sulfoxide; EMA, European Medicines Agency; EMBASE, Excerpta Medica database; ETDRS, Early Treatment Diabetic Retinopathy Study; FDA, Food and Drug Administration; GBP, pound sterling; LDL, low density lipoproteins; MAR, minimum angle of resolution; MPS, Macular Photocoagulation Study; NPe6, N-aspartyl chlorin e6; PBS, phosphate buffer saline; PCV, polypoidal choroidal vasculopathy; PDT, photodynamic therapy; QALY, quality adjusted life-year; PRN, as needed regimen (from Latin: *pro re nata*); RADICAL, Reduced Fluence Visudyne®-Anti-VEGF-Dexamethasone In Combination for AMD Lesions; RF, reduced fluence; ROS, reactive oxygen species; RPE, retinal pigment epithelium; SnEt2, tin etiopurpurin; SF, standard fluence; TAP, Treatment of Age-related Macular Degeneration with Photodynamic Therapy; TPE, two-photon excitation; TPE-VTP, vascular targeted photodynamic therapy with two-photon excitation; USD, United States dollar; VEGF, vascular endothelial growth factor; VEGF-A, vascular endothelial growth factor-A; VIA, Visudyne® and Avastin®; VIM, Verteporfin in Minimally Classic CNV due to AMD; VIP, Verteporfin in Photodynamic Therapy; VIO, Visudyne® in Occult; VTP, vascular targeted photodynamic therapy.

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neovascular AMD. The future of VTP as a method of AMD treatment is development of new selective and targeted photosensitizer and combination of this method with other therapeutic strategies targeting cellular structures or pathways involved in AMD progression.

Contents

Introduction

Age related macular degeneration (AMD) is a progressive chronic disease of the central retina which is a major cause of vision loss in the World. In the developed countries more than 20% of ageing population may suffer from this disorder [1]. Most visual loss occurs in the late stages of the disease due to neovascular (''wet'') AMD in which subfoveal choroidal neovascularization (CNV) breaks through to the neural retina, leaking fluid, lipids, and blood, and leading to fibrous scarring [2]. ''Wet'' AMD is divided into ''classic'' and ''occult''. The classic form is well defined and involves substantial loss of visual acuity (between 20/250 and 20/400, but it may be worse than 20/800). In the occult form, visual acuity is better (between 20/80 and 20/200), the lesions are not well delineated and have less leakage than in the classic one [3]. Several therapeutic strategies, introduced during past decade, changed substantially management of AMD [1,4,5]. One of these strategies is vascular-targeted photodynamic therapy (VTP).

Vascular targeted photodynamic therapy as a method of AMD treatment

In general, photodynamic therapy (PDT) is a minimally invasive treatment modality, involving light, oxygen, and light-sensitizing dye, called photosensitizer. The PDT action is based on light activation of photosensitizer localized in target tissue producing reactive oxygen species (ROS) which destroy target cells though direct cytotoxicity, vascular shutdown and activation of an immune response [6,7]. Current clinical applications of PDT include the treatment of numerous solid tumors as well as of and noncancerous hyperproliferative conditions, such as macular degeneration [6—8].

For successful treatment of diseases involving neovascularization, the destruction of functional vasculature is essential. This observation led to the concept of vascular targeted PDT (VTP). Following photosensitizer accumulation and irradiation, the damage of sensitive sites within the microvasculature causes increase in vascular permeability and vessel constriction thus resulting in destruction of target tissue by vascular collapse, blood flow stasis and tissue hemorrhages [9]. Comparing to conventional PDT, VTP is characterized by a short drug to light interval (usually 0—30 min), when photosensitizer is confined within the vasculature of target tissue.

VTP is effective in the selective destruction of CNV to confine the lesion from growing and thereby reduce the risk of progressive visual damage without causing significant destruction to viable neurosensory retina overlying the CNV [10,11]. The effects of VTP on vascular lesions consist of damage to the vascular endothelium, exudation due to vascular leakage, photothrombosis within the vessels, recanalization and reproliferation due to activation of angiogenic factors, such as vascular endothelial growth factor (VEGF) and, finally, fibrosis and deactivation following retreatments [12].

Vascular effects of VTP strongly depends on used photosensitizer and drug-light interval. Many dyes, such as tin ethyl etiopurpurin (SnEt2, Photrex®), lutetium texaphyrin (Lu-tex) or N-aspartyl chlorin e6 (NPe6, Talaporfin) have been under investigation as potential photosensitizers in neovascular AMD treatment [13,14]. However, verteporfin is the only photosensitizer currently approved for clinical use in clinical ophthalmology, because of its selectivity for neovasculature lesions and of its pharmacokinetic profile (Table 1). VTP with use of verteporfin as a photosensitizer, was the first therapy approved by the Food and Drug Administration (FDA) in 2000, for treatment of subfoveal lesions [2].

Verteporfin as photosensitizer in VTP

Verteporfin (benzoporphyrine derivative monoacid ring A, BPD-MA), is a chlorin derivative which is largely used as a photosensitizer in PDT. Its molecule has two absorption maxima at 400 and 692 nm (water/ethanol mixture), however, to avoid adverse phototoxic effect due to excitation of natural chromophores in adjacent tissues, which absorbs light in the same region [15,16], in VTP is used only the absorption maximum at 692 nm, lying in near infrared region (800—2500 nm),