Nowadays, the most common application of photodynamic therapy (PDT) in ophthalmology is the treatment of specific types of age-related macular degeneration (AMD). PDT aims the selective occlusion of the abnormal choroidal neovasculature (CNV) proliferating behind the retina, which is responsible for the critical loss of central vision in neovascular forms of AMD. During PDT, the photosensitizer verteporfin encapsulated in liposomes (Visudyne®) is injected systemically and preferentially accumulates in the CNV; it is then activated by mild laser excitement to liberate cytotoxic reactive oxygen species that partially selectively occlude the choroidal neovessels. PDT with verteporfin reduces the risk of moderate and severe vision loss and stabilizes the development of the disease in many patients; nevertheless vision improvement is a rather rare event (1). Limitations associated with PDT using verteporfin include high recurrence rate of CNV leading to the repetition of the treatment, and lack of complete selectivity, which may result in both photodynamic damage of normal tissues surrounding the CNV, and temporary skin photosensitivity.

In order to improve vision outcome, intravitreally administered antibodies against vascular endothelial growth factor (VEGF) –the major stimulus for abnormal vessel growth– have recently been approved for clinical practice. Anti-VEGF agents, such as pegaptanib (Macugen®), and ranibizumab (Lucentis®), offer a significant chance of an increase in visual acuity to patients affected with neovascular AMD (1). Furthermore, combining the anti-VEGF approach with PDT may have a synergetic long-term effect potentially reducing the frequency of treatments.

The lack of complete selectivity of verteporfin might result in the closure of some normal choriocapillaries, and some damage to the retinal pigment epithelium (RPE) and outer retina. This effect is probably due to the rapid early localization of verteporfin in CNV neighboring tissues following verteporfin leakage from CNV and/or choriocapillaries. Due to the flexible nature of liposomes, they can potentially cross the discontinuous endothelium of CNV. In contrast, polymeric nanoparticles, another type of colloidal drug carriers, are solid and non-deformable. Nanoparticles able to stay inside the CNV would increase the photosensitizer dose at the target site while protecting surrounding tissues of the undesirable photodynamic damage.

Nanoparticles are colloidal systems (diameter < 1 µm) made of solid polymers in which drugs can be either encapsulated within the nanoparticle core or adsorbed at the nanoparticle surface. Encapsulation of photosensitizers into polymeric nanoparticles has shown promising results for PDT of cancer in terms of tumor targeting improvement and reduction of skin photosensitivity (2). Furthermore, photosensitizer delivery mediated by nanoparticles can take advantage of natural processes, such as the enhanced uptake of nanomaterials by cells of particular tissues and the size-dependent passage of nanoparticles through biological barriers, to increase the drug concentration in target tissues and to reduce adverse effects.

The potential use of photosensitizer-loaded nanoparticles for AMD treatment has been assessed preclinically using the chorioallantoic membrane (CAM) of the developing chick embryo (3-6). The CAM is a highly vascularized membrane that was demonstrated to be of clinical relevance for the
screening of new photosensitizers intended for AMD treatment (7). Furthermore, intravenous administration is feasible in this model thus mimicking conditions used in clinics.

Considering a future clinical application, nanoparticles made of biodegradable polymers accepted by the FDA, either poly(D,L-lactic acid) (PLA) (3,6) or poly(D,L-lactide-co-glycolide) (PLGA) (4,5) have been investigated so far. The possibility of encapsulating photosensitizers with different physicochemical and photochemical properties into nanoparticles was assessed by Pegaz et al. (3). Four different photosensitizers differing in their hydrophilic/lipophilic balance were incorporated into PLA nanoparticles. The most lipophilic photosensitizer, the meso-tetraphenylporphyrin, led to the highest extent of vascular occlusion of CAM vessels.

The increased retention of nanoparticles inside CAM vessels compared to photosensitizer in solution was demonstrated using the meso-tetra(p-hydroxyphenyl)porphyrin (m-THPP) encapsulated into PLGA nanoparticles (4). After intravenous administration, nanoparticles remained intravascular for at least 25 min, whereas the non-encapsulated m-THPP leaked rapidly out of the blood vessels. Furthermore, the incorporation of m-THPP in nanoparticles significantly enhanced its phototoxic effect on blood vessels, thus allowing a decrease of photosensitizer dose. This study points out that for achieving a selective destruction of vasculature (while protecting surrounding tissues), an increase in the residence time of the photosensitizer in blood vessels during light activation is mandatory.

The size of colloidal drug carriers is one of the parameters governing their passage through physiological barriers and their extravasation. Hence, medium or large sized nanoparticles, which do not cross the discontinuous endothelium of CNV, would be useful to increase the selectivity of PDT. m-THPP encapsulated in PLGA nanoparticles of diameters around 100 nm, 300 nm and 600 nm were demonstrated to stay intravascular for at least 25 min after administration to chick embryos (5). However, vascular occlusion decreased with the increase in nanoparticle diameter. The same trend was observed with meso-tetra-(carboxyphenyl)porphyrin encapsulated in PLA nanoparticles of diameters up to around 350 nm (6).

Although increasing the size of the photosensitizer carrier might be useful for avoiding its passage through abnormal choroidal neovessels, and the subsequent damage of neighboring tissues, experiments with the CAM model demonstrated that the photodynamic activity of large nanoparticles was poor. PDT using nanoparticles is a relatively new application, and the extent at which the photochemical properties of photosensitizers are affected by incorporation into nanoparticles remains to be determined. Preliminary data from our laboratory suggest that the photodynamic efficiency of nanoparticles is influenced by the aggregation state and distribution of the photosensitizer inside the nanoparticle core, as well as by the photosensitizer release rate. Additionally, the tight packaging of the photosensitizer inside the nanoparticle matrix seems to be deleterious for the activity. Therefore, some strategies to increase the activity of large nanoparticles would be (i) the photosensitizer adsorption at the nanoparticle surface instead of its incorporation within the nanoparticle core; and (ii) a decrease in the amount of photosensitizer encapsulated.

Even though PDT has been more investigated for the treatment of neovascular AMD, its application in ophthalmology is expanding to the treatment of CNV secondary to various vascular retinochoroidal diseases or CNV associated with macular dystrophy, idiopathic CNV, as well as to diseases without CNV, such as ocular tumors (8). While further investigation is needed to optimize nanoparticles for the photodynamic treatment of eye diseases, nanoparticles exhibit attractive properties, such as the modulation of the photodynamic effect, the possibility of variation of drug release patterns, and good in vivo tolerability. Moreover, they allow the administration of hydrophobic photosensitizers in aqueous media. Further development of nanoparticles for PDT would be to coat the particles surface with recognition moieties, as it is proposed for cancer therapy, to increase distribution selectivity by a so called active targeting (9). It is thus likely that nanoparticles will become a valuable tool for the controlled photosensitizer delivery in the eye.

REFERENCES


