On the selectivity of photodynamic therapy of choroidal neovascularization associated with age-related macular degeneration

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INTRODUCTION

Visudyne® photodynamic therapy (PDT) in choroidal neovascularization in age-related-macular degeneration (AMD) has recently been reviewed [1-3]. Although knowledge of the etiology of the disease is as yet incomplete, one cause that is often mentioned is the decreasing ability of aging retinal pigmented epithelium (RPE) cells to digest the fragments that are shed from the neighboring photoreceptors [4]. This debris causes reduced oxygen and nutrient transport across the RPE, which in turn can provoke a biomolecular cascade leading to the formation of leaky neovascularature. It may induce scar tissue, which, particularly in the central vision region of the fovea, can result in legal blindness. This is the case in more than a quarter of a million aged persons in the USA and Western Europe every year. Visudyne® PDT, which reduces leakage of the choroidal neovascularature (CNV), thus does not treat a basic cause of the disease, but rather an effect of the disease.

This paper explores the lack of complete selectivity in the photodynamic closure of CNV. Before discussing this topic, it should be stated that a substantial number of the more than 200 000 treatments that have been dispensed so far could have resulted in stabilization of the disease for at least a number of years. Clinical observations also indicate that, in addition to the effective closure of the CNV observed 1 week after PDT, a significant closure (or at least reduced leakage) of normal choriocapillaries is observed in the treated area. Some of the concepts associated with the selectivity of Visudyne photodynamic therapy of choroidal neovascularization in age-related macular degeneration are also discussed.

Key-words: Age-related macular degeneration, choroidal neovascularization, photodynamic therapy, photosensitisers, thrombosis.
RESULTS AND DISCUSSION

Selective closure of CNV while retaining patent blood flow in the retinal capillaries

Figure 2 shows a schematic view of the central part of the retina. PDT of blood vessels most likely implies attack on endothelial cells, which finally leads to thrombosis and blood flow stasis, as described in reference [1].

In this paper, selectivity in this treatment means closure of the CNV (neovessels), while leaving the normal choriocapillaries (Chor Cap), larger choroidal blood (Chor Vess) supply, and feeder vessels (FV), as well as the retinal capillaries (Ret Cap) and larger retinal vessels (RV) with an insignificant degree of damage. In particular, the closure of the perimacular retinal capillaries must be avoided, as this was shown to lead to immediate loss of essentially all of the remaining visual acuity in these patients. Here it is interesting to note that there appears to be a degree of built-in protection in PDT of the human eye that helps to avoid photodynamic damage to the retinal capillaries in the conditions already effective for closure of the CNV: 6 mg/m² Visudyne; start of injection to therapy, 15 min; 600 mW/cm² light at 689 nm and 50 J/cm²; mostly classic CNV less than 5 mm in diameter. This remarkable and very convenient absence of photodynamic damage to the retinal capillaries at 50 J/cm² and the applied conditions can be ascribed to various factors, including decreased oxygen partial pressure [7] as well as a sturdier and less leaky endothelium. The first hypothesis appears quite reasonable, as oxygen is a major factor in PDT.

Undesirable partial closure of the normal choriocapillaries in the treated area

Also to be avoided in PDT of exudative AMD is a significant closure of the normal choriocapillaries and the consequent reduction in oxygen supply and nutrients to the fovea, which will result in an increased tendency to induce neovascularization and damage to the photoreceptors in particular, as well as to the neural part of the fovea in general. Figure 3 shows the early and late phases of fluorescein and indocyanine green (ICG) angiograms, both before and 1 week after PDT. The strongly hypofluorescent images that emanate from the PDT-treated regions 1 week after PDT are particularly noteworthy for the present discussion. The early fluorescein angiogram and the late ICG angiogram, both obtained 1 week after PDT, appear to indicate significant closure (or at least reduced leakage) of the normal choriocapillaries, in addition to the effective closure of the CNV, in the treated area.

It can therefore be concluded that there is only partial therapeutic selectivity. Importantly, there also appears to be little CNV leakage both at short times and at longer times after PDT. The hyperfluorescence that can be seen in the fluorescein angiogram is interpreted as being mostly due to staining of the tissue in the macular region after PDT. Unfortunately, the late-stage ICG angiogram shows some hyperfluorescence around the macular region, which may be due to PDT damage to the deeper-lying larger choroidal vessels.
Selective uptake of Visudyne in the region of neovascular growth

Selectivity in Visudyne PDT of CNV in AMD has also been demonstrated in the clinical fluorescence pharmacokinetic studies that we did with this compound. These experiments were carried out with a modified fundus camera in order to measure the time dependence of the fluorescence angiograms of Visudyne itself. The compound underwent excitation near 680 nm and emission around 700 nm. The results shown in figure 4 suggest an interesting degree of Visudyne...
fluorescence contrast, in particular between 10 and 20 min after the injection, which is when, clinically, PDT takes place. This molecular fluorescence selectivity is not easy to interpret, as the optical properties inside and outside the macula responsible for transmission of the excitation and emission wavelengths are not the same. Nevertheless, the observed fluorescence signal from Visudyne — as shown by the solid line for the main retinal vessels, and the dotted line for the choroidal vessels — indicates that time dependence plays an essentially identical role as Visudyne concentration. The latter was independently measured in blood plasma, and these data are represented by the dots in figure 4. The similarity between the Visudyne fluorescence kinetics and the concentration of this compound measured in the blood plasma is taken here as a strong indication, but not absolute proof, that the observed fluorescence pharmacokinetics is closely related to the local presence of the drug. The reason for the type of fluorescence selectivity observed here is the subject of much speculation. Arguments put forward to explain this include:

1) A larger activity of, for instance, LDL receptors in the neovessels.
2) Slower blood flow in the more tortuous neovessels, inducing a slower wash out.
3) Enhanced neovessel leakage, or sticking of the drug to inter- or subendothelial tissue.

Selective confinement of Visudyne to the vasculature

In the present approach to Visudyne PDT of CNV in AMD, it is undesirable that a significant amount of the Visudyne leaks out of the vasculature on the time scale up to and including the light application. Leakage on this time scale could lead to photodynamic damage to parts of the retina such as the photoreceptors and the RPE, both of which are in the immediate vicinity of the leaky CNV. In particular, the macrophage-like RPE cells could well take up leaked Visudyne on a very short time scale and hence be considerably damaged upon irradiation. The apparent selective retention within the vasculature of the Visudyne as indicated by its fluorescence (fig. 4) may be due to this compound being mostly bound to blood lipoproteins, which are large enough not to leak significantly on the time scale of interest here.

At this point, one might speculate that a different approach to PDT of AMD could be to use a highly water soluble photosensitizer, which would leak out of the vasculature rapidly, and be selectively taken up by the RPE cells on a short time scale. This type of photosensitizer could then be partially destroyed by PDT in order to try to regenerate RPE cells in the subsequent repair process.

CONCLUSION

A small selection of rather typical results of PDT on CNV related to AMD have been shown and are discussed in terms of various types of therapeutic and drug-concentration selectivity. We observe that the essential therapeutic selectivity between closure of CNV and non-closure of retinal capillaries is present in this therapy as it is carried out today. The undesirable closure of normal choriocapillaries in the treated area is one area of possible improvement for the next generation of drugs. Nevertheless, one should note that the present therapy has brought significant benefits to date to nearly a quarter of a million patients. Novel approaches to improve the selectivity may include attaching a photosensitizer to a targeting moiety such as a monoclonal antibody or a peptide [8, 9]. A small peptide termed RGD could be taken as an example of this idea. It will selectively target an integrin surface receptor identified as \( \alpha \beta \), which is reputed to be more expressed on the endothelial cells of neovascular than on normal endothelium.

RÉFÉRENCES