ORIGINAL ARTICLE

Photodynamic Therapy with Verteporfin in Treatment of Myopic Neovascular Choroideal Membranes

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SUMMARY

The aim of this study was to evaluate efficiency and long-term stabilization effect in patients with classic type of myopic choroidal neovascular membrane (CNV), treated with photodynamic therapy (PDT) with verteporfin (Visudyne – Novartis AG, Basel, Switzerland). We have verified the efficiency of photodynamic therapy with verteporfin in group of 51 eyes (17 men, 34 women), mean age 49,5 years with subfoveal localized predominantly classic neovascular membranes in pathologic myopia. The average follow up period was 23,7 months (± 2,3 month). Patients underwent during follow-up period 1 to 3 sessions of photodynamic therapy (PDT average number 1,25 sessions). The average best corrected visual acuity (BCVA) before treatment was 0,302 (0,65 logMAR) and the average BCVA at the end of follow up was 0,356 (0,46 log MAR). The improvement of best corrected visual acuity up to 5 letters on ETDRS (Early Treatment Diabetic Retinopathy Study) charts was observed in 23% of patients at the end of follow up.

Key words: photodynamic therapy, choroideal neovascularisation, pathologic myopia

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INTRODUCTION

Photodynamic therapy (PDT) with vertoporfin is a two-phase, non-invasive therapeutic process, which resides in intravenous application of verteporfin and subsequent intravascular activation of its molecules by diode laser. This process brings about selective occlusion of the blood vessels with a pathological vascular wall (neovascularisation). It represents a treatment used primarily in patients with the classic type of choroideal neovascular membrane (CNV) in the wet form of age-related macular degeneration (ARMD) (6, 7). Verteporfin is a photosensitizating substance, which belongs to the group of benzoporphyrin derivates. In the first phase a ten-minute intravenous infusion of verteporfin, a non-toxic, light-activated substance, is applied to the patient. 5 minutes after the end of the infusion (i.e. 15 minutes from the start of treatment) there follows a second phase, in which activation of the medicament by non-thermal diode laser with a wavelength of 698 nm takes place. The accumulation of the active substance in the neovascular tissue takes place thanks to the preferential binding of verteporfin to the receptors for low-density lipoprotein molecules (LDL) (1). These receptors in an increased concentration contain endothelial cells of neovascularisations as a result of the increased requirement of LDL receptors in rapidly dividing cells inside the neovascular tissue (1). Verteporfin, bound inside the cell to the structure of cytoplasm, is activated by laser beam and subsequently generates the formation of free radicals and singlet oxygen. These processes in their final result cause selective microthrombotisation of pathological blood vessels, whilst blood vessels with a normal wall structure remain unaffected. In general this therapeutic method should function in all ophthalmological diagnoses in connection with the formation of focal neovascular complexes. This concerns myopic CNV, post-inflammation CNV, CNV originating within the framework of macular dystrophies (e.g. Best's disease or Stargardt disease), polypoidal choroideal vasculopathy, idiopathic CNV, CNV in angioid streaks, parafoveolar teleangiectasia, choroideal hemangiomas, choroideal melanomas, choroideal metastases, retinal hamartomas etc.

Pathological myopia is a nosological unit, usually connected with progressive atrophy of the choriocapillaris. Elongation of the eye leads to alteration of the blood vessels and disorders in the area of the Bruch's membrane, with an increased risk of the occurrence of choroideal neovascularisation (CNV) (5). CNV and edemas of the neuroretina and haemorrhages connected therewith, together with central atrophy of the choroidea, are the most frequent causes of a deterioration of central visual acuity in pathological myopia. This also represents one of the most frequent causes of practical blindness in patients of productive age in developed countries.

Classic choroideal neovascular membrane (CNV) is generally an accompanying finding with a range of retinal disorders, the neovascular complex is embedded between the RPE (retinal pigment epithelium) and the neuroretina. A well-demarcated lesion is visible on FAG, staining in the early phase of angiogram, type II according to Gasse (fig. 1).

GROUP OF PATIENTS AND METHODS

In the group of patients with myopic CNV were included 51 subjects (51 eyes), 34 women and 17 men with an average age of 49.5 years. The average size of the lesion was 1888

micrometres (± 750 µm). In 5 cases (10%) it concerned a patient with the last functional eye. The observation period was on average 23.7 months (± 2.3 months). All patients completed an observation period with a minimum duration of 18 months. All lesions were characterised as subfoveolarly localised, predominantly classic and therapeutically naive. In all 51 eyes (100%) the finding was accompanied by neuroretinal edema and a varying degree of collateral haemorrhage (maximum 40% of the total extent of the lesion).
The average spherical equivalent was -10.7 (± 4.8 Dpt) (table 1).

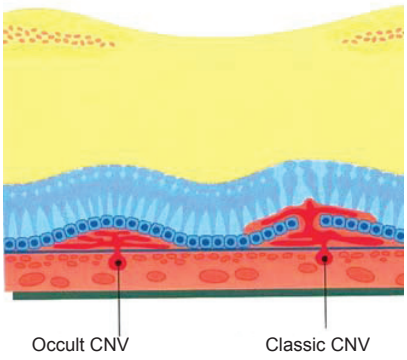


Fig. 1 Types of choroideal neovascular membranes according to Gasse

Before the procedure a complex ophthalmological examination was performed on all subjects, which covered:

- Determination of the value of best corrected visual acuity (best CDVA) on ETDRS optotypes by a certified person,
- Measurement of intraocular pressure by applanation tonometry
- Biomicroscopy of anterior segment on Zeiss SL120 slit lamp,
- Biomicroscopy of posterior segment in artificial mydriasis on Zeiss SL120 slit lamp using lens Ocular Instruments +78 and +60 D
- Determination of central retinal thickness using OCT examination on Zeiss Stratus III instrument (Fast Macular Map Scan, 6mm Cross Hair Scan),
- Fluorescent angiography on Topcon IX instrument using display system ImageNet 2000.

The size of laser beam was determined by individual measurement of the lesion using software of the display system ImageNet 2000 with the addition of a collateral zone of 1000 µm. The protocol of performance of PDT was standard, without reduction. Upon all checks the examination scheme was identical. FAG was repeated if it was necessary to conduct another PDT session or in the case of contentious clinical and OCT finding.
The intervals of the follow-up examinations were 3, 6, 12, 18 and 24 months.
The statistical processing of the results was performed by means of a Wilcoxon test, for statistical processing the decimal values of Best CDVA were converted to log MAR values.

Table 1

Observation period	Ø 23.7 months
Group of patients	51 subjects (51 eyes)
Sex	34 women, 17 men
Size of lesion	Ø 1888 µm
Number of PDT = photodynamic therapy	Ø 1.25
Initial Best CDVA	Ø 0.302 (0.65 log MAR)
Best CDVA at end of observation period	Ø 0.356 (0.46 log MAR)
Initial CCT	Ø 371 µm
CCT at end of observation period	Ø 211 µm
Spherical equivalent	Ø -10.7 D

RESULTS

Best CDVA expressed in a decimal value was on average 0.302 (0.65 log MAR) before the performance of PDT, and at the end of the observation period on average 0.356 (0.46 log MAR). This represents a statistically significant increase in the values of Best CDVA ($p > 0.005$).
In a section of the patients (23%) a gain

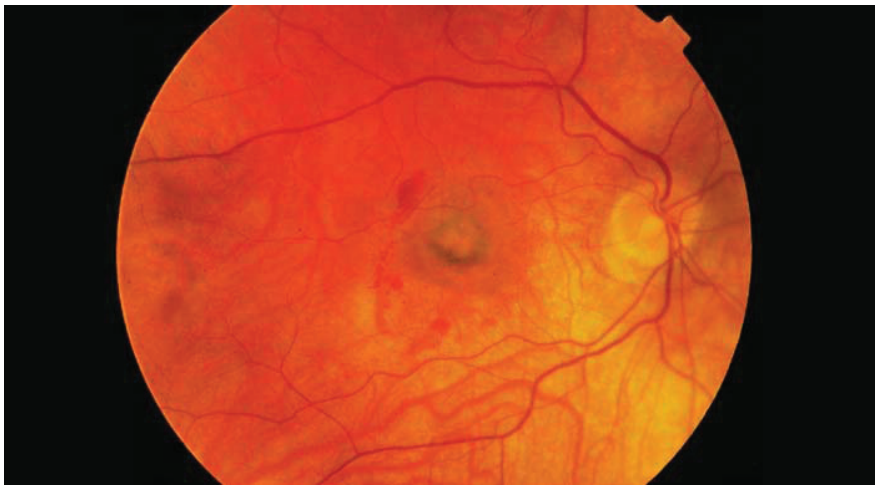


Fig. 2 Classic myopic subfoveolar CNV before PDT

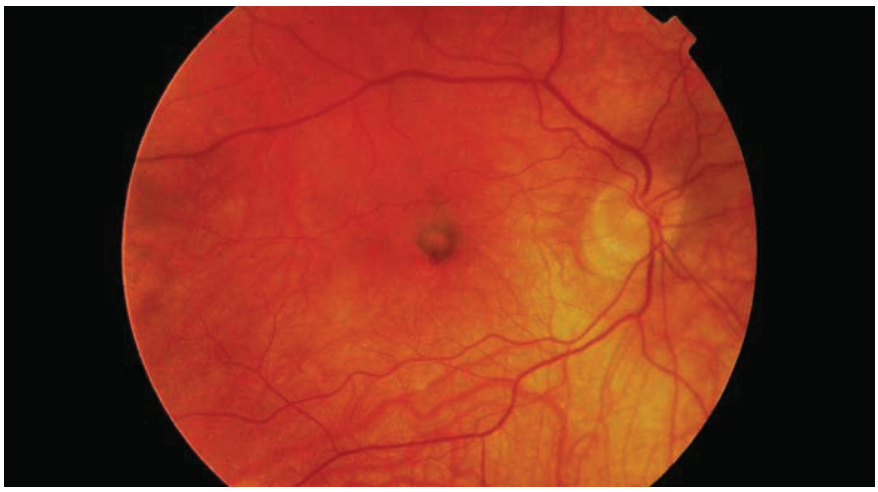


Fig. 3 Classic myopic subfoveolar CNV after PDT

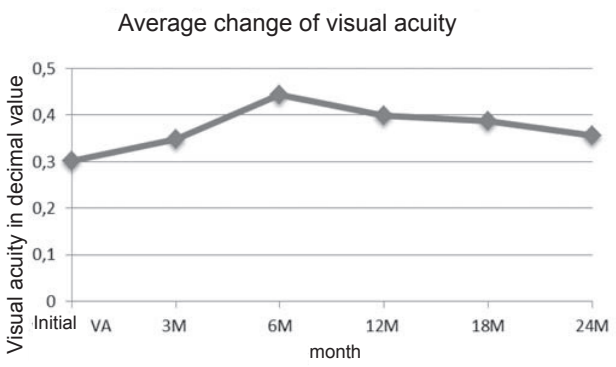
of minimally 6.3 of a letter of ETDRS optotypes persisted at the end of the observation period (graph 1).
The average thickness of the central area of the macula measured on the OCT Stratus III instrument was 371 microns before the beginning of treatment, at the end of the observation period it was on average 211 microns. This difference is highly statistically significant ($p > 0.001$).
The clearance of intraretinal edema or ablation of the neuroretina, which was achieved in all eyes at the end of the observation period, was considered to represent stabilisation of the finding.
For stabilisation of the finding it was necessary to use an average of 1.4 PDT sessions, 91% of necessary retreatments were performed in the first year of observation (fig. 2, 3).
Figs 2 and 3 show a finding of a patient before PDT and after stabilisation of the finding.
We did not record any serious local or general effects of treatment in our study group. In 1 patient (2%) back pain occurred during intravenous application of verteporfin, in 13 patients (26%) we measured increased systemic blood pressure before commencement of application of the infusion (maximum value of systolic pressure 155 mmHg and diastolic pressure 90 mmHg). Local complications were observed in 14 patients (29%), in whom progression of central atrophy of RPE occurred.

DISCUSSION

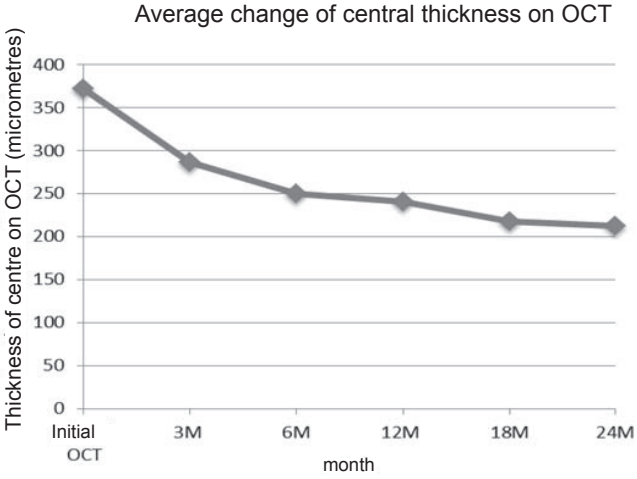
The occurrence of central classic myopic CNV, together with the progression of central choroideal atrophy, is the main cause of decreased of central visual acuity in pathological myopia (8).
The VIP study demonstrated a stabilising effect of photodynamic therapy (loss of less than 15 letters of ETDRS optotypes) in classic subfoveolar CNV as against a placebo within a 24-month observation period (3). In our study group of patients a satisfactory stabilising effect of PDT on the Best CDVA value was also demonstrated at the end of the observation period.
During the observation period the largest increase in the Best CDVA values occurred between the initial value and the 3rd month of observation (on average +0.05) ($p > 0.001$) and between the initial value and the 6th month of observation (on average +0.14) ($p > 0.001$). Also between the 3rd and 6th month the trend of improvement of Best CDVA continued (on average +0.09) ($p > 0.001$).
In the 12th month there was a slight decline in the values of Best CDVA against the best attained values in the 6th month, but the Best CDVA value continued to be stable until the end of the observation period ($p > 0.005$).
In 23% of patients an average gain of 6.3 letters of ETDRS optotypes persisted at the end of the observation period.
The decline of the average values of central retinal thickness measured on OCT in the centre of the fovea as against the initial measurement was statistically significant in the 3rd, 6th, 12th and 18th month ($p > 0.001$) and also if applicable in the 24th month of observation ($p > 0.005$). Retinal thickness in the centre of the fovea practically declined in a linear progression during the observation period. We observed the greatest decline between the initial examination and the first check in the 3rd month.
91% of retreatments of PDT were indicated in the first year of observation, which corresponds with the results of Bandell et al. (2), that the frequency of reperfusions of CNV in the second year of treatment drops dramatically down.
Better functional results were achieved in younger patients, smaller lesions and patients with better initial Best CDVA.
We did not record any complications during the performance of photodynamic therapy, such as photosensitive reaction, extravasation of substance, dyspnoea, pruritis or nausea, in 1 patient (2%) back pain occurred during intravenous application, but about this undesirable side effect is written in the informed leaflet of the product.
In 13 patients (26%) we measured increased systemic blood pressure before commencement of application of the infusion, which we attribute to psychological stress before the procedure. Local complications were observed in 14 patients (29%), this concerned progression of central atrophy of RPE. However, there is a question here as to whether it is possible to attribute atrophisation of RPE in this group of patients to the therapeutic procedure, or whether this concerns a natural course of the disease. Rupture of RPE did not occur in our group.

CONCLUSION

In our experience, photodynamic therapy with verteporfin is an effective mini-invasive method of treatment of classic myopic neovascular choroideal membranes. It has the potential to stabilise and in a quarter of patients even to improve visual acuity. Photodynamic therapy is not conne-



Graph 1



Graph 2

cted with the risk of complications ensuing from the process of intraocular intervention, which is another indisputable advantage, especially in the group of patients who have a high percentage of e.g. peripheral degeneration of the retina. Even today, when photodynamic therapy is on the decline in comparison with intravitreal applications of anti-VEGF preparations, with regard to its good stabilising effect, minimal necessity of retreatment and last but not least also its lower financial costs (for both the patient and the health insurance company), it continues to have its significant place in the treatment of classic myopic CNV.

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