

Photodynamic Therapy with Verteporfin in Treatment of Wet Form ARMD – Long Term Results

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SUMMARY

Photodynamic therapy with Verteporfin (Visudyne - Novartis AG, Basel, Switzerland) is a method designed for treatment of the wet form of age-related macular degeneration. Effectiveness of photodynamic therapy with Verteporfin we approved on our department in group of 301 patients (114 males, 187 women) of average age 73.5 years with predominantly classic choroidal neovascular membrane in subfoveal localization in wet form of age-related macular degeneration. The follow up period in this group was from 6 to 36 month (mean 21 months).

Patients with predominantly classic choroidal neovascular membrane underwent during the observation period from 1 to 5 treatments (mean 1.45 treatments). Mean best corrected visual acuity was before treatment 0.708 ± 0.24 logMAR. At the end of three-year observation period was the mean best corrected visual acuity 1.016 ± 0.36 logMAR. Best corrected visual acuity dropped during this time by 3.08 lines (15.4 letters) of ETDRS (early treatment diabetic retinopathy study) visual charts.

Decrease of mean best corrected visual acuity less than 3 lines on ETDRS charts is considered as stabilisation. This goal was achieved in our group during observation period in 2/3 of patients.

Key words: age-related macular degeneration, choroidal neovascular membrane, fluorescein angiography, photodynamic therapy with verteporfin

Čes. a slov. Oftal., 68, 2012, No. 3, p. 98–101

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INTRODUCTION

Age-related macular degeneration (ARMD) is the most frequent cause of blindness in the population of patients aged over 65 years in developed countries (2). It concerns a multifactorial disorder caused by a combination of influences of environment and genetic factors (2, 3, 4). The result of the natural cause of the disorder is severe deterioration of central visual acuity (CVA), in many cases to the degree of practical blindness (4).

A significant phase in the history of treatment of ARMD was the discovery of the possibility of treatment of choroidal neovascular membranes (CNV) using photosensitising substances. The first effective photosensitiser to be used was verteporfin (Visudyne, Novartis AG, Basel, Switzerland) (3). This laid the foundation for the development of photodynamic therapy with verteporfin (PDT). Verteporfin is a photosensitising substance, which belongs to the group of benzoporphyrin derivatives (fig. 1).

The high selectivity of the effect of verteporfin molecules on neovascular tissue is due to their preferential bonding to receptors for low-density lipoprotein molecules (LDL) (1). These receptors are present mainly precisely on the surface of endothelial cells in neovascular choroidal membranes (CNV), which are highly accumulated here due to the increased requirement for the expression of receptors for LDL in rapidly dividing cells inside the neovascular tissue (1). The verteporfin molecule is bound inside the cell to the cytoplasm structures. Verteporfin, activated by laser beam, generates the formation of free radicals and singlet oxygen. There is thus a dual mechanism of the photo-chemical effect of verteporfin:

1. Free radicals react with lipids in the cellular membranes, which causes structural and functional damage to the cell.
2. Singlet oxygen reacts directly with the cellular structures, causing immediate cell death.

Damage to the endothelial cells of capillaries leads to the occurrence of

intravascular thrombosis, due to an intravascular blockage of aggregated thrombocytes, erythrocytes, leukocytes and fibrin (5). On animal models, occlusion of neovascular tissue was demonstrated as early as 24 hours following PDT with verteporfin, in which the surrounding vascular structures and large capillaries remain intact. Verteporfin is thus capable of selective vascular occlusion (cells of retina, Bruch's membrane and large vascular branches of the choroidea remain unaffected (5, 6). The main advantage of selectivity of the effect of photodynamic therapy with verteporfin is therefore the fact that important structures of the retina and choroid which are responsible for the generation of visual perception remain undamaged (unlike classic laser photocoagulation). The efficacy of PDT in the treatment of wet form ARMD has been demonstrated in two large clinical trials: TAP (Treatment of AMD with Photodynamic Therapy) and VIP (Verteporfin in Photodynamic Therapy). A total of 1236 patients were included in stages I to III of the clinical research, and the

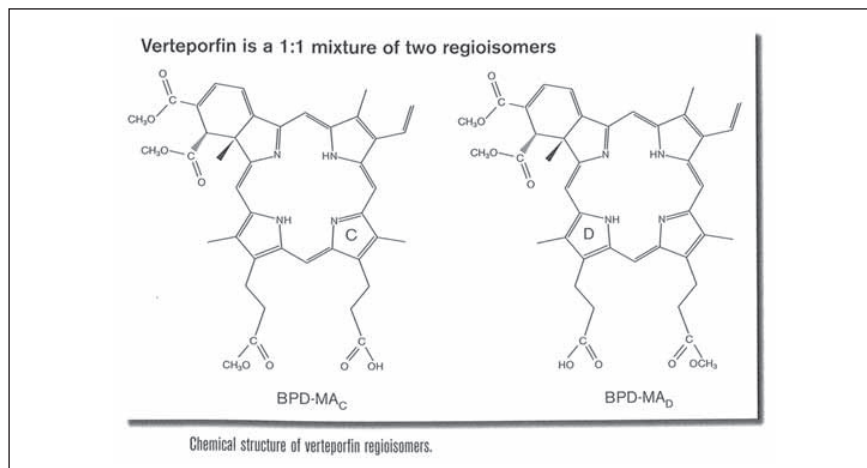


Fig. 1. Chemical structure of verteporfin – mixture of two regioisomers in ratio 1:1

efficacy of treatment was demonstrated in a comparison of patients treated with an active substance (verteporfin) as against patients treated with a placebo (8).

MATERIAL AND METHOD

This represents a retrospectively assessed group of patients after photodynamic therapy for classic or predominantly classic CNV within the framework of wet form ARMD.

The diagnosis and type of choroidal membrane was determined on the basis of performance of fluorescent angiography and OCT examination. CNV was subfoveolarly localised in all eyes. Only those patients in whom classic or predominantly classic CNV (CNV in which the proportion of the classic component was more than 50%) was diagnosed were included in the study. In all of the patients porphyria, severe malfunction of the liver and unstable angina pectoris, which are the main contraindications for performance of photodynamic therapy with verteporfin, were excluded.

All patients underwent a complex ophthalmological examination, which covered:

- Determination of visual acuity on ETDRS optotypes.
- Biomicroscopy of anterior segment on slit lamp.
- Biomicroscopy of fundus in artificial mydriasis using 78D and 60D lenses.
- OCT examination.
- Colour and red free photo of fundus.
- FAG.

We determined CVA on ETDRS optotypes. For the purposes of statistical processing, the CVA value was stated in logarithmic values (logMAR – loga-

rithm of minimum angle of resolution). The value of 0.0 logMAR corresponds to CVA of 4/4 (Snellen's equivalent 1.0). The value of 1.0 logMAR corresponds to a CVA value of 4/40 (Snellen's equivalent 0.1).

Upon performance of PDT a standard treatment protocol was used, as recommended by the TAP and VIP studies: dose of verteporfin 6 mg/m², speed of infusion 3 ml/min., duration of infusion 10 min., commencement of application of laser radiation on wavelength of 690 nm 15 min. after the start of infusion, light dose 50 J/cm², intensity 600 mW/cm², length of application of laser radiation 83 s (7, 8, 9). The size of CNV in micrometres was determined using the measurement software of the digital display system Image Net ver. 2.14 (Topcon, Japan), from images obtained in fluorescent angiography. Measurement of the size of CNV preceded every PDT session. The size of the laser pathways used was derived from the value of the largest diameter of CNV, with the addition of a collateral zone of 1000 µm.

Reperfusion of CNV most often occurs within 3 months of the performance of PDT with verteporfin. For this reason a complete ophthalmological examination, biomicroscopy of the fundus and OCT examination were indicated again within this interval, and upon demonstration of intraretinal fluid on OCT and also control FAG. If reperfusion of CNV was demonstrated, a further PDT session with verteporfin was performed, until the finding in the macula was stabilised.

The instrument Visulas 690s (Zeiss, Germany) was used for the performance of the laser procedure. The laser pathway was applied using the contact lens Equator Plus (Volk Optical

Inc., USA), which provides very good visualisation of the macular area even through a more narrow cornea or dense lens capsule upon pseudofakia.

OBSERVED PATIENTS

The group comprises 301 eyes of 301 patients (114 men, 187 women), with an average age of 73.5 years. The observation period of the subjects included in the study was 6-36 months (on average 21 months). The patients were treated in the period from 12/2002–06/2010 (see table 1).

In all patients only one eye was treated in the stated period. In the other eye there was dry form ARMD or a terminal finding of wet form ARMD (disciform scar). There were 65 cases of practical monocularis.

RESULTS

At the beginning of the observation period, CVA was within the range of 0,708 ± 0,24 logMAR. Median CVA before the commencement of therapy was on the level of 0.7 logMAR. Therefore, before the commencement of therapy, the patients most frequently distinguished 4 rows of ETDRS optotypes – 20 letters.

The average size of CNV before the commencement of the first PDT session was 4563 ± 1375 micrometres. During the course of the observation period, the patients underwent 1-5 sessions of PDT with verteporfin (on average 1.8 sessions). Repetition of PDT was indicated on the basis of demonstrated activity of CNV on OCT and FAG.

One year results

The one year observation period was completed by 261 patients from the group (87 %), whose CVA value was within the range of 0.75 logMAR ± 0.16 logMAR. The median CVA after one year was on the level of 0.8 logMAR.

In the first year of observation we used an average of 1.9 PDT sessions for stabilisation.

Two year results

The two year observation period was completed by 157 patients (52 %). CVA was within the range of 0.745 logMAR ± 0.22 logMAR. The median CVA after two years was on the level of 0.82 logMAR. In the second year of observation it was necessary to use only 0.42 PDT sessions for stabilisation.

Number of eyes	301
Age	73.5 ± 9.5 years
Sex	114 men 187 women
Size of lesion	4563 ± 1375 µm
Observation period	6-36 months (N21 months)
Type of CNV	100% classic and predominantly classic CNV

Table 1. Characteristics of sample

Three year results

The two year observation period was completed by 122 patients (41 %). CVA was within the range of 1.016 logMAR ± 0.36 logMAR. The median CVA after three years was on the level of 0.96 logMAR.

In the third year of observation it was necessary to use 0.26 PDT sessions for stabilisation.

DISCUSSION

A loss of less than 3 rows of ETDRS optotypes was considered to represent stabilisation of the condition. This loss represents a doubling of the minimum angle of resolution. The average CVA before the commencement of therapy was on the value of 0.708 0.24 logMAR. At the end of the three year observation period average visual acuity was 1.016 0.36 logMAR. There was thus a decrease of CVA by 2.92 rows of ETDRS optotypes and stabilisation of CVA was thus attained in 52% of patients in the group.

A loss of less than 6 rows of ETDRS optotypes was attained in 78% of patients in the group. The development of CVA of our patients (for comparability of data only within the two year period) and a comparison thereof with the results of the TAP study is illustrated in graph 1.

The group comprised patients with classic or predominantly classic CNV in subfoveolar localisation. This data is very closely connected with the degree of aggression of CNV, which is high in this type of CNV. This is caused by the position of the neovascular complex of CNV. In classic CNV the complex is situated between the cells of the pigment epithelium (PE) of the retina and the photoreceptors. The photoreceptors are therefore far more easily afflicted than in occult CNV, in which the neovascular complex is situated in the choriocapillaris beneath the PE cells. In this case there is only a secondary influence on the photoreceptors by means of edema and dysfunction of the PE cells (5, 8).

Deterioration of central visual acuity by 3 rows of ETDRS optotypes represents a doubling of the minimum angle of resolution, which in practice means that the patient distinguishes only double sized characters on the optotype. As a result, in the large clinical trials dealing with therapy of ARMD, deterioration of CVA by less than 3 rows of ETDRS optotypes is considered to constitute stabilisation of the finding.

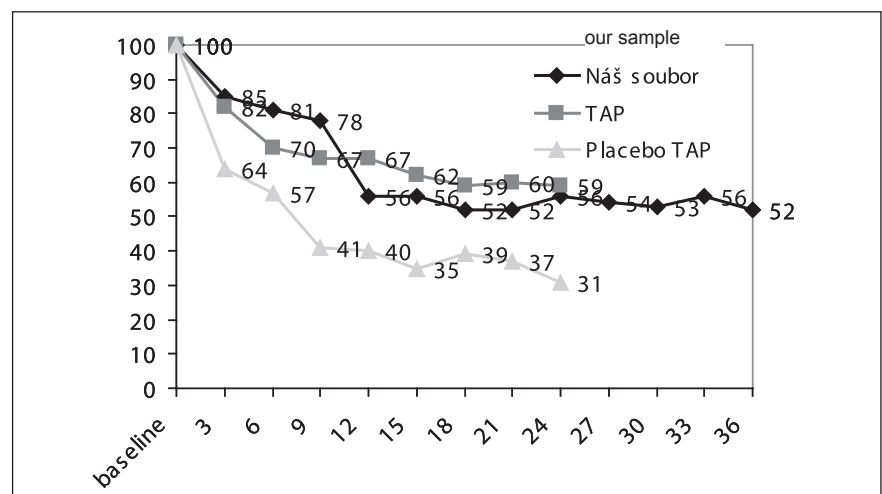
In our group of patients there was a decrease of CVA by 2.92 rows of ETDRS optotypes over the course of the three year observation period. Stabilisation of CVA within the three year observation period was attained in 56% of patients. In the TAP study stabilisation was attained in 59% of patients treated by PDT with Visudyn over a two year observation period. Stabilisation was attained in only 31% of patients treated within the same study by PDT with a placebo. This means that in 2/3 of patients treated with a placebo there is a substantial deterioration of CVA over the course of a two year observation period. The results of the TAP study and our results in preventing severe deterioration of CVA (i.e. decrease by more than 6 rows of ETDRS optotypes) are similarly comparable. In

our sample severe deterioration of vision at the end of the observation period was prevented in 78% of patients.

CONCLUSION

The data on the patients who were observed for a minimum of 24 months was compared with the results of the TAP and VIP clinical trials. In the sense of stabilisation of CVA our results were fully comparable with the results of the above-named large clinical trials and demonstrate stabilisation of CVA also in the patients who were observed for 36 months.

Stabilisation of CVA brings the treated patients preservation of usable visual acuity. This fact takes on an extensive significance also with regard to the fact that in advanced age patients deal with the loss of usable CVA only with great difficulty, regardless of the frequent occurrence of other comorbidities in this age group. Even in the present age of antiVEGF preparations, it is possible to use PDT as an effective monotherapy in the treatment of classic type CNV, especially in the case of smaller lesions, with regard to the overall condition of health of the patient etc., thus with an individually chosen therapeutic approach to each patient. Another significant fact is the saving on financial resources from the social security budget which are otherwise provided to partially sighted patients on the basis of legal norms. Based on our experience, even at present, when other alternative treatments of ARMD are available, PDT with Visudyn remains an effective mini-invasive therapy, which has the potential to stabilise usable CVA and prevent the onset of practical blindness in 2/3 of patients afflicted with wet form ARMD.



Graph 1. Graphic illustration of development of CV in observation period in the case of predominantly classic CNV (our sample, TAP – sample of patients in TAP study treated with Visudyn, placebo – sample of patients in TAP study treated with placebo)

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