Treatment of Subfoveal Choroidal Neovascularization Secondary to Age Related Macular Degeneration with Single Treatment of Verteporfin Photodynamic Therapy: A Safety and Short-Term Outcome

Pakitti Tayanithi MD*,
Petch Pisankosakul MD*, Prasart Laksakapuk MD*

** Department of Ophthalmology, Faculty of Medicine, Chulalongkorn University*

Objective : *To evaluate the short-term efficacy on visual outcome and safety of a single treatment of photodynamic therapy with verteporfin using the standard dosage regimen in patients with predominantly classic subfoveal choroidal neovascularization (CNV) from age related macular degeneration.*
Design : *Prospective, noncomparative, consecutive, interventional case series.*
Setting : *Department of Ophthalmology, Chulalongkorn University and Hospital, Bangkok, Thailand.*
Participants : *Patients with subfoveal CNV caused by age related macular degeneration.*
Method : *Standardized protocol refraction, visual acuity testing, complete ophthalmic examination, color photography, and fluorescein angiography were used to evaluate the effects of a single treatment of photodynamic therapy with verteporfin. Follow-up was planned through 3 months in all patients.*
Results : *A total of 39 eyes from 35 patients enrolled into the present study and have completed 3 months follow-up. The mean ± SD logMAR BCVA at baseline was 0.76 ± 0.48, equivalent to the Snellen BCVA of 20/114 (range, 20/40 to 20/1000). The mean ± SD logMAR BCVA at the final 3-month visit was 0.55 ± 0.37, which was a Snellen equivalent of 20/70 (range, 20/30 to 20/1000). The mean line of BCVA improvement was 2.1 lines. The improvement in BCVA at the 3-month follow-up was statistically significant (Wilcoxon signed-rank test, P = .043). No patient suffered moderate loss of vision or a loss of vision in 2 or more lines. None of the patients suffered severe visual threatening adverse events at the time of treatment and during the study period.*
Conclusions : *The results of short-term visual outcome is encouraging; PDT is the least invasive treatment method currently available to achieve a stable or improved vision in AMD patients. PDT with verteporfin can lead to cessation of fluorescein leakage from CNV for up to 3 months, with stabilization or improvement of vision for 12 weeks. A randomized, controlled study in the near future would be beneficial to demonstrate the long-term results and efficacy in the treatment of CNV associated with AMD.*

Keywords : *Photodynamic therapy, PDT, Verteporfin, Visudyne, Age related macular degeneration, AMD, Single treatment*

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Age related macular degeneration (AMD), especially the neovascular form of the disease, is an important cause of blindness and a serious public health challenge in older people in developed countries [1-5]. The majority of eyes suffer severe visual loss as a result of choroidal neovascularization (CNV), which is the formation of new blood vessels either between the retinal pigment epithelium and Bruch's membrane or the subretinal space [6-10]. Thermal photocoagulation is still the preferred treatment for CNV that does not involve the fovea, but it is suitable for only a small number of patients and it can lead to immediate loss or deterioration of vision. The Macular Photocoagulation Study (MPS) demonstrated that treatment of well-defined subfoveal CNV was beneficial, but most patients experienced an immediate decline in vision because of damage to the overlying neurosensory retina [11-15]. With its nonselective thermal tissue destruction, laser photocoagulation can destroy the surrounding choriocapillaries, retinal pigment epithelium (RPE), and adjacent photoreceptors, leading to an absolute scotoma at the area of treatment. Photodynamic therapy (PDT) with the use of photochemical light activation of verteporfin as a photosensitizer (verteporfin photodynamic therapy) has been shown to be effective in treating vascularized

Correspondence to : Tayanithi P. Department of Ophthalmology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

tumors [16], and its potential to treat other conditions involving neovascularization has also been suggested. Preclinical and clinical studies have indicated that verteporfin therapy can be used to treat choroidal neovascularization secondary to AMD effectively and safely [17-25]. Selective occlusion of choroidal neovasculature by this therapy causes very minimal or no damage to the overlying neurosensory retina, especially the fovea, and therefore, does not induce loss of vision when applied to the subfoveal lesion. The principle problem of PDT with verteporfin from an economy standpoint are the very high cost of the drug, the need for many and predictable number of retreatments, such as every 3 months and the continuing visual decline that most patients may experience even with treatment [26] .

This report presents a series of patients with predominantly classic subfoveal CNV secondary to AMD who have been treated with a single treatment of verteporfin PDT.

Designs

The study was a prospective, noncomparative, consecutive, open-label, interventional study aimed at investigating the short-term efficacy on visual outcome and safety of a single treatment of PDT with verteporfin (Visudyne, Novartis AG, B lach, Switzerland) on patients with predominantly classic subfoveal CNV secondary to AMD.

Patients and Method

Patient selection

Patients were enrolled from a tertiary ophthalmic center in Bangkok (Chulalongkorn University and Hospital). Informed consent was obtained from all patients after thorough discussion and full understanding of the potential benefits and risks of PDT and other alternative treatment modalities including observation.

Inclusion Criteria

1. Clinical signs of CNV secondary to AMD
2. CNV under the geometric center of the foveal avascular zone (subfoveal)
3. Predominantly classic CNV pattern on the fundus fluorescein angiograms (defined as a lesion in which classic CNV accounted for ≥50% of the area of the entire lesion at baseline [27])
4. Greatest linear dimension of entire CNV less than 5400 m in diameter
5. Nasal side of CNV at least 500 m from temporal border of optic nerve
6. Best-corrected visual acuity (BCVA) of 20/40 or worse
7. 50 years of age or older

Exclusion Criteria

1. Substantial hepatic or renal disease
2. History of previous treatment for CNV, including laser or submacular surgery
3. Additional retinovascular diseases compromising visual acuity of the study eye
4. Porphyria, porphyrin sensitivity, any systemic contraindications for verteporfin or angiographic dyes
5. Ocular surgery within 2 months before treatment
6. Any acute illness during screening or fever on the day of treatment before verteporfin infusion
7. Any other significant concurrent ocular diseases in the treated eye with disease that has compromised or could compromise vision.

All patients received comprehensive ocular examinations prior to baseline including BCVA, dilated fundoscopic and macular examinations with a contact lens or a Volk Superfield noncontact lens, color fundus photography and fundus fluorescein angiography (FFA). BCVA was measured by using a standard Snellen chart. To quantify the change in vision, all Snellen visual acuity were converted to logarithm of the minimum angle of resolution (logMAR) BCVA for statistical analysis. Each 0.1 logMAR unit represents 1 line of Snellen visual acuity [28]. Visual acuity of counting fingers was assigned a value of 20/1000 for statistical purposes. The proportion of classic CNV in the lesion was determined by FFA as defined in the treatment of AMD with PDT (TAP) study [27].

Verteporfin therapy and follow-up assessment

PDT with verteporfin was performed according to the TAP study [27]. All patients received 6 mg/m^2 infusion of verteporfin (Visudyne, Novartis AG, B lach, Switzerland) in 10 minutes followed by delivery of diode laser at 689 nm (Opal, Coherent Inc., Santa Clara, California, USA) to the CNV 15 minutes after commencement of infusion. A total light energy of 50 J/cm^2 and light dose rate of 600 mW/cm^2 for 83 seconds was used to cover the whole lesion with an additional 500 mm covering the borders on each side of the lesion. After treatment, protective spectacles were given, and patients were prohibited from total body and eye exposure to direct sunlight or strong light for 48 hours.

Patients were scheduled to have follow-up visits at 1 week, 1 month and 3 months after treatment

with the BCVA, fundoscopic examination, color fundus photography were performed at each follow-up visit in the same fashion as the baseline examination. Patients who had completed the 3-month follow-up would be analyzed.

Short-term efficacy and safety parameters

The short-term efficacy outcome was the changes in the mean logMAR BCVA at the final 3-month visit compared with baseline examination and the proportion of eyes that had moderate loss of vision (loss of 3 or more lines or doubling of the visual angle). Safety was assessed by recording any ocular or systemic adverse effects due to the treatment.

Statistical analysis

Demographic characteristics of the patients, including the angiographic findings, were summarized by descriptive statistics using a statistical software (SPSS for Windows, version 10.1.0, SPSS Inc., Chicago, Illinois, USA). Snellen BCVA was converted to logMAR BCVA and its corresponding line number for statistical analysis. Nonparametric analysis for paired continuous variables was compared using the Wilcoxon signed-rank test. The *P* value of 0.05 or less was considered to be statistically significant.

Results

Baseline characteristics

A total of 39 eyes from 35 patients enrolled into the study and had completed 3 months of follow-up. 54% (19/35) of the patients were male, and 46% (16/35) were female. The mean ± standard deviation (SD) of age of patients was 65.58 ± 9.67 years (range, 50–87 years). 57% (20/35) of patients received PDT in the right eye, 32% (11/35) in the left eye and 11% (4/35) received PDT in both eyes. 62% (24/39) were right eyes and 38% (15/39) were left eyes. The mean ± SD logMAR BCVA at baseline was 0.76 ± 0.48, equivalent to the Snellen BCVA of 20/114 (range, 20/40 to 20/1000).

Visual outcomes at 3 months

The mean ± SD logMAR BCVA at the final 3-month visit was 0.55 ± 0.37, which was a Snellen equivalent of 20/70 (range, 20/30 to 20/1000). The mean line of BCVA improvement was 2.1 lines. The improvement in BCVA at the 3-month follow-up was statistically significant (Wilcoxon signed-rank test, $P = .043$). The mean BCVA in Snellen equivalent at the final 3-month follow-up had improved from 20/114 to 20/70. No patient suffered moderate loss of vision or a loss in vision of 2 or more lines.

Safety and complications

Photodynamic therapy was well tolerated by all patients, and none of the patients suffered severe visual threatening adverse events at the time of treatment and during the study period. None of the patients in the series developed acute severe vision loss with PDT, skin complications secondary to intravenous infusion, photosensitivity reaction, or treatment-related systemic adverse events. Only 3% (1/35) of the patients complained of low back pain at the treatment which resolved completely the next day.

Discussion

PDT is a treatment modality in which a non-toxic light-sensitive compound called a *Photosensitizer* is administered and subsequently activated by light exposure to produce photochemical effects in the target area [29, 30]. PDT has the potential advantage of dual selectivity: firstly, there is a preferential concentration of the photosensitizer in the target tissue, and secondly, the light irradiation is directed toward and confined to the specific target area. PDT is currently used to treat various types of solid tumors. However, recent improvements in the understanding of the mechanisms of action, light sources, and light delivery systems, and the development of specific photosensitizing agents with improved selectivity and activity, such as verteporfin (benzoporphyrin derivative monoacid A, BPD-MA), have expanded the possible therapeutic uses of PDT to nononcologic applications [31]. In the field of ophthalmology, PDT with verteporfin (Visudyne) was licensed for use in predominantly classic wet AMD in 2000. However, PDT is merely a symptomatic treatment of CNV which does not eliminate the angiogenic stimulus in neovascular AMD and is well tolerated in a clinical setting and minimizes visual loss in patients with CNV due to AMD. Recurrent leakage after a single PDT treatment was significantly reduced for as long as 3 months in the majority of eyes, suggesting satisfactory prevention of CNV growth and stabilization of visual acuity. Since PDT may be performed in CNV eyes without impairing retinal integrity and function, the treatment can be repeated as soon as a decline in visual acuity due to progressive leakage occurs.

Conclusion

In the present series, the mean improvement in BCVA was 2.1 lines. The procedure is quite safe.

None of the patients developed a loss of BCVA by 2 or more lines. There were some limitations of the study. The main limitation of the study was the short duration of follow-up, with a follow-up period of 3 months. There is also a lack of control group for comparison.However, the results of early visual outcome are encouraging; PDT is the least invasive treatment method currently available to achieve a stable or improved vision in this group of patients. A randomized, controlled study in the near future would be beneficial to demonstrate the long-term results and efficacy compared with observation or submacular surgery in the treatment of CNV associated with AMD. PDT with verteporfin can lead to cessation of fluorescein leakage from CNV for up to 3 months, with stabilization or improvement of vision for 12 weeks.

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การรักษาเส้นเลือดเกิดใหม่ที่อยู่ใต้ต่อจุดภาพชัดในผู้ป่วยโรคจอตาเสื่อมเหตุอายุโดยใช้เวอร์เตพอฟินโฟโต้ไดนามิคเพียงครั้งเดียว : ความปลอดภัยและประสิทธิผลในระยะสั้น

ปกิตติ ทยานิธิ, เพชร พิศาลก่อสกุล, ประศาสน์ ลักษณะพุกก์

วัตถุประสงค์ *: เพื่อศึกษาประสิทธิผลในระยะสั้นและความปลอดภัยของการรักษาเส้นเลือดเกิดใหม่ที่อยู่ใต้ต่อจุดภาพชัดในผู้ป่วยโรคจอตาเสื่อมเหตุอายุ โดยใช้เวอร์เตพอฟินโฟโต้ไดนามิคเพียงครั้งเดียว*

รูปแบบการศึกษา *: แบบไปข้างหน้า, ไม่สุ่มตัวอย่าง, consecutive, interventional case series.*

สถานที่ *: ภาควิชาจักษุวิทยา, คณะแพทยศาสตร์, จุฬาลงกรณ์มหาวิทยาลัย, กรุงเทพ 10330*

ผู้ป่วย *: ผู้ป่วยโรคจอตาเสื่อมเหตุอายุที่มีเส้นเลือดเกิดใหม่อยู่ใต้ต่อจุดภาพชัด*

วิธีศึกษา *: ก่อนการรักษาผู้ป่วยทุกคนจะได้รับการตรวจวัดสายตา วัดการมองเห็นตรวจตาอย่างละเอียดถ่ายภาพจอตาและถ่ายภาพเส้นเลือดที่จอตาร่วมกับการฉีดสีเข้าเส้นเลือดดำตามวิธีมาตรฐานเพื่อใช้พิจารณาในการรักษาเวอร์เตพอฟินโฟโต้ไดนามิคเพียงครั้งเดียวและติดตามผลการรักษาครั้งสุดท้ายที่ 3 เดือนหลังการรักษาครั้งแรกเปรียบเทียบกับก่อนการรักษา*

ผลการศึกษา *: มี 39 ตาจากผู้ป่วยทั้งหมด 35 คนเข้าร่วมในการศึกษานี้และสามารถติดตามผลการรักษาได้ตลอด 3 เดือน มีค่าเฉลี่ย ± ค่าเบี่ยงเบนมาตรฐานของ logMAR BCVA ก่อนการรักษาเท่ากับ 0.76 ± 0.48, ซึ่งเทียบเท่ากับ Snellen BCVA ที่ 20/114 (ช่วงระหว่าง 20/40 ถึง 20/1000) มีค่าเฉลี่ย ± ค่าเบี่ยงเบนมาตรฐานของ logMAR BCVA 3 เดือน หลังการรักษาเท่ากับ 0.55 ± 0.37, ซึ่งเทียบเท่ากับ Snellen BCVA ที่ 20/70 (ช่วงระหว่าง 20/30 ถึง 20/1000) มีจำนวนแถวของการมองเห็นที่ดีขึ้นเฉลี่ย 2.1 แถว BCVA ที่ 3 เดือนหลังการรักษาดีขึ้นอย่างมีนัยสำคัญทางสถิติ (Wilcoxon signed-rank test, P = .043) ไม่มีผู้ป่วยรายใดเลยมีการมองเห็นลดลง 2 แถวหรือมากกว่า และไม่มีผู้ป่วยรายใดที่มีอาการไม่พึงประสงค์ของการรักษาทั้งผลต่อการมองเห็นและผลทางร่างกายทั่วไปตลอดตั้งแต่เวลาที่ให้การรักษา*

สรุป *: ประสิทธิผลในระยะสั้นของการศึกษาได้ผลดีเป็นที่น่าพอใจ การรักษาเวอร์เตพอฟินโฟโต้ไดนามิคน่าจะเป็นการรักษาโรคจอตาเสื่อมเหตุอายุที่มีเส้นเลือดเกิดใหม่อยู่ใต้ต่อจุดภาพชัดที่ได้ผล มีความปลอดภัยและเกิดผลเสียน้อยที่สุดในปัจจุบัน การรักษาด้วยเวอร์เตพอฟินโฟโต้ไดนามิคเพียงครั้งเดียวสามารถคงสภาพการมองเห็นหรือทำให้การมองเห็นดีขึ้นได้อย่างน้อยเป็นระยะเวลา 3 เดือน*
