ORIGINAL ARTICLE

Photodynamic Therapy for Subfoveal Choroidal Neovascularization Secondary to Age-related Macular Degeneration

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Background: To evaluate the safety and efficacy of verteporfin photodynamic therapy (PDT) in patients with subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD).

Methods: We retrospectively reviewed the chart records and fluorescein angiography of patients with subfoveal CNV who were treated with verteporfin PDT between September 2001 and March 2003 and who completed at least 1 year of follow-up. The primary efficacy outcomes were the proportions of patients whose Snellen visual acuities had more than 1 line increase, no change or more than 1 line decrease 1 year after study entry compared with their baseline examinations. The secondary efficacy outcome was the changes in the logarithm of the minimum angle of resolution visual acuities at 1-year follow-up. Complications were monitored and tabulated.

Results: Forty-eight eyes of 48 patients with subfoveal CNV secondary to AMD were enrolled in this study. The mean follow-up was 12.56 ± 1.37 months. At their last visit, 10.4% of eyes had more than 1 line improvement in Snellen visual acuity, 72.9% of eyes had no change, and 16.7% experienced more than 1 line of visual acuity loss (7 eyes lost < 3 lines of Snellen visual acuity, 1 eye lost between 3 and 6 lines). None experienced more than 6 lines of visual loss. There was no statistically significant difference between baseline and final visual acuity for eyes with predominantly classic CNV, minimally classic CNV and occult without classic CNV (Wilcoxon Signed Rank test, $p = 0.59$). There was a positive correlation between baseline visual acuity and final visual outcome (Kruskal-Wallis test, $p = 0.002$). No severe systemic and ocular adverse events were encountered.

Conclusion: Of our patients with subfoveal CNV secondary to AMD, 83.3% could maintain or improve their visual acuity 1 year after verteporfin PDT. The risk of deterioration in visual acuity due to subfoveal CNV could be reduced by verteporfin PDT. Baseline visual acuity is significantly correlated with the final proportion of visual outcome. [*J Chin Med Assoc* 2005;68(9):419–424]

Key Words: age-related macular degeneration, choroidal neovascularization, photodynamic therapy

Introduction

Age-related macular degeneration (AMD) is the leading cause of legal blindness in Caucasians over 50 years of age in the United States, with choroidal neovascularization (CNV) accounting for the majority of cases.[1–3] A population-based study estimated that 3.7% of the population over 75 years of age and 14.4% of the population over 90 years are visually impaired due to AMD, with 34% of patients being identified with neovascular AMD.[4] In Taiwan, a population-based survey of ocular diseases in residents aged over 50 years disclosed that the prevalence of AMD was 14.3% among this population with visual impairment

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(defined as best-corrected visual acuity in the better eye < 6/18).[5] A retrospective study by Chen and associates[6] revealed that only 10.5% of patients suffering from submacular hemorrhage secondary to AMD demonstrated an improvement in visual acuity 6 months after the initial presentation. Their final mean visual acuity was 0.069. Photodynamic therapy with verteporfin was designed to selectively occlude the CNV without damage to the overlying retina. The Treatment of Age-related Macular Degeneration With Photodynamic Therapy (TAP) study has shown the benefit of photodynamic therapy (PDT) with verteporfin for predominantly classic subfoveal CNV secondary to AMD,[7,8] as well as for patients complicated with occult without classic CNV and minimally classic CNV.[9–11] This retrospective study was conducted to evaluate the visual outcome and fluorescein angiographic changes after verteporfin PDT for patients with subfoveal CNV caused by AMD in Taiwan.

Methods

Patient selection

We retrospectively reviewed the chart records and fluorescein angiography (FAG) of patients who were treated with verteporfin PDT between September 2001 and March 2003, and who had completed at least 1 year of follow-up at Taipei Veterans General Hospital. Forty-eight eyes of 48 patients with subfoveal CNV secondary to AMD were enrolled. Patients were included based on their initial FAG.

CNV subtypes were classified as predominantly classic CNV, minimally classic CNV, and occult without classic CNV. Classic and occult CNV were based on the definitions from the Macular Photocoagulation Study (MPS) Group.[12] Predominantly classic CNV was defined as a lesion in which the classic CNV component accounted for more than 50% of the entire baseline lesion. If less than 50%, the lesion was graded as minimally classic CNV. For all CNV, the greatest linear dimension (GLD), including the CNV, area of leakage and areas of blocked fluorescence in the lesion, was less than 5,400 μm.

Verteporfin PDT and follow-up assessment

Verteporfin PDT was administered according to the TAP study protocol. Follow-up visits were scheduled at 3-monthly intervals; measurement of best-corrected visual acuity, biomicroscopic examination and FAG were performed. Increased subretinal hemorrhage, serous detachment and lipid exudates on fundus examination were considered disease progression. Retreatment was considered at 3-monthly intervals if there was fluorescein leakage from the CNV and if no serious adverse events had resulted from prior treatment. Patients' demographic data retrieved from chart records were age, gender, Snellen visual acuity, treatment spot size, GLD, and fundus characteristics (hemorrhage, fibrosis, pigment epithelial detachment).

Outcome measurements

Patients' Snellen visual acuity was transformed to logarithm of the minimum angle of resolution (logMAR) units for statistical assessment.[13] For ease of analysis, visual acuity that was worse than Snellen visual acuity 1/60 was designated as 6/720 (logMAR = 2.1). The primary efficacy outcomes were the proportions of patients whose Snellen visual acuities had more than 1 line increase, no change or more than 1 line decrease 1 year after study entry compared with their baseline examinations. The secondary efficacy outcome was the changes in logMAR visual acuities at 1-year follow-up. Final angiographic outcomes (complete absence of leakage, leakage within the original area, progression compared with original lesion) were also recorded. The occurrence of severe adverse events (bleeding gastric ulcer, elevated blood pressure, suprachoroidal hemorrhage) and ocular adverse effects were recorded.

Statistical analysis

Patients' demographic data were summarized by descriptive statistics using SPSS version 11, Professional Statistics Release (SPSS Inc, Chicago, IL, USA). Correlations between the final proportion of visual acuity change, baseline visual acuity, CNV subtypes, GLD, and fundus characteristics were analyzed using the Wilcoxon Signed Rank test and Kruskal-Wallis test. All p values were the results of 2-tailed tests and the level of statistical significance was set at p less than 0.05.

Results

Forty-eight eyes of 48 patients were enrolled in this study. Eleven eyes were classified as predominantly classic CNV, four eyes were minimally classic CNV, and 33 eyes were occult without classic CNV. Demographic data are shown in Table 1. There were no statistically significant differences in age, follow-up profiles, retreatment or lesion size among the 3 groups. The mean initial logMAR visual acuities of eyes with predominantly classic CNV, minimally classic CNV and occult with no classic CNV were 1.78 ± 0.37,

1.25 ± 0.78 and 1.24 ± 0.65, respectively (Table 2). The mean initial logMAR visual acuity for all patients was 1.35 ± 0.64. The initial visual acuities of the 3 groups of eyes were not statistically significantly different (Kruskal-Wallis test, $p = 0.09$). The mean follow-up was 12.56 ± 1.37 months.

Visual outcomes

The final mean logMAR visual acuities of eyes with predominantly classic CNV, minimally classic CNV and occult with no classic CNV were 1.70 ± 0.45, 1.24 ± 0.71, and 1.20 ± 0.50 (Kruskal-Wallis test, $p = 0.10$). The final mean logMAR visual acuity for all eyes was 1.31 ± 0.54 (Table 2). There were no significant differences between baseline and final visual acuities in eyes with predominantly classic CNV, minimally classic CNV and occult without classic CNV (Wilcoxon Signed Rank test, $p = 0.59$). At their last visit, 10.4% of eyes showed improvement in Snellen visual acuity, 72.9% remained stable (35/48; 9 eyes with predominantly classic CNV, 3 eyes with minimally classic CNV, 23 eyes with occult without classic CNV), and 16.7% had a decrease of more than 1 line. Only 1 patient (2%) lost more than 3 lines of Snellen visual acuity. No eye lost more than 6 lines in this series (Table 3).

Table 1. Demographic data

	PC (n = 11)	MC (n = 4)	Occult (n = 33)	p*
Age (yr)	70.8	75.0	75.5	0.41
Follow-up (mo)	13.12	12.06	12.51	0.73
Retreatment	2.63	2.0	2.56	0.33
Lesion size (μm)	4,014.12	4,760.75	3,549.15	0.31

*Kruskal-Wallis test. MC = minimally classic choroidal neovascularization (CNV); Occult = occult without classic CNV; PC = predominantly classic CNV.

Table 2. Visual acuity data

	PC	MC	Occult
Baseline Snellen VA	6/20–CF/20 cm	6/12–CF/20 cm	6/12–CF/20 cm
Baseline logMAR			
Mean ± SD	1.78 ± 0.37	1.25 ± 0.78	1.24 ± 0.65
Median	1.69	1.24	1.24
Final logMAR			
Mean ± SD	1.70 ± 0.45	1.24 ± 0.71	1.20 ± 0.51
Median	1.54	1.43	1.30

CF = counting fingers; logMAR= logarithm of the minimum angle of resolution; MC = minimally classic choroidal neovascularization (CNV); Occult = occult without classic CNV; PC = predominantly classic CNV; SD = standard deviation; VA = visual acuity.

Table 3. Proportion of visual acuity change* after verteporfin photodynamic therapy

	PC	MC	Occult	All eyes
Increase				
> 1 line	0	1	4	5 (10.4%)
1–3 lines	0	1	4	5 (10.4%)
> 3 lines	0	0	0	0 (0%)
No change	9	3	23	35 (72.9%)
Decrease				
> 1 line	2	0	6	8 (16.7%)
1–3 lines	2	0	5	7 (14.7%)
> 3 lines	0	0	1	1 (2.0%)
> 6 lines	0	0	0	0 (0%)

*Tested with Snellen visual chart. MC = minimally classic choroidal neovascularization (CNV); Occult = occult without classic CNV; PC = predominantly classic CNV.

The final proportion of visual acuity change was not correlated with fluorescein angiogram subtypes (Kruskal-Wallis test, $p = 0.10$) or GLD (Kruskal-Wallis test, $p = 0.40$). There was a positive correlation between baseline and final visual acuity (increase > 1 line, no change, decrease > 1 line) for all patients (Kruskal-Wallis test, $p = 0.002$). FAG showed complete absence of fluorescein leakage in 32% of eyes, leakage within the original CNV in 44% of eyes, and progression compared with the original lesion in 24% of eyes within 1 year. The mean number of retreatments was 2.40 ± 0.8.

Submacular hemorrhage was found in 24 eyes at the baseline examination and the incidence was not significantly different among eyes with predominantly classic, minimally classic and occult without classic CNV. Intravitreal injection of tissue plasminogen activator (tPA) plus sulfur hexafluoride (SF_6) was performed in 1 eye to clearly identify the CNV. The presence of submacular hemorrhage was not correlated with final change in visual acuity (Kruskal-Wallis test, $p = 0.57$) and final logMAR visual acuity (Kruskal-Wallis test, $p = 0.80$). Increased subretinal hemorrhage after treatment was noted in 7 eyes (14.6%): 6 eyes after the first course of treatment; and the last eye after the second course of treatment.

Safety and complications

No severe adverse events (bleeding gastric ulcer, elevated blood pressure, suprachoroidal hemorrhage) were noted during treatment and follow-up. Two patients complained of injection-related back pain, which resolved soon after injection. No verteporfin-related acute vision loss (defined as a decrease of at least 4 lines of visual acuity within 7 days of treatment) was noted (Table 4).

Discussion

AMD is a severe public health problem that can be complicated with subfoveal CNV leading to severe, irreversible central vision loss.[1–4,14] Patients with predominantly classic CNV may have a 60% chance of developing a 3-line loss of Snellen visual acuity in 1 year.[7] Unfortunately, use of traditional laser photocoagulation is limited to a subset of patients with juxtafoveal or extrafoveal lesions. This benefit, however, comes at the cost of indiscriminate destruction of the overlying retina at the risk of immediate and irreversible loss of vision at the site of laser light application.[12,15,16] Verteporfin PDT was designed to selectively occlude the CNV without damage to the overlying retina.[17] The TAP studies concluded that verteporfin PDT could sustain visual acuity, stabilize contrast sensitivity, and preserve quality of vision in eyes with predominantly classic CNV.[7,8,10,11] This favorable benefit for eyes with occult without classic CNV and minimally classic CNV was also disclosed in the Verteporfin In Photodynamic therapy (VIP) report[9] and Verteporfin In Minimally classic CNV (VIM) trial.[18]

Our study disclosed that 10.4% of eyes (1 with minimally classic and 4 with occult without classic CNV) could have improvement in Snellen visual acuity. Among eyes complicated with subfoveal CNV treated with verteporfin PDT, 72.9% (35/48; 9 eyes with predominantly classic CNV, 3 eyes with minimally classic CNV, 23 eyes with occult without classic CNV) could maintain their Snellen visual acuity with no change for 1 year. The treatment benefit (maintenance or improvement in Snellen visual acuity) for eyes with predominantly classic, minimally classic and occult with no classic CNV were 81.8% (9/11), 75% (3/4) and 69.7% (23/33), respectively. The estimated 1-year visual loss of less than 3 lines after verteporfin PDT in this study was 98%. The TAP study disclosed that 48% of eyes could maintain or improve their Snellen visual acuity, and the estimated visual loss of less than 3 lines was 71%.[7] In the VIP study, 23.1% of eyes could maintain or improve their Snellen visual acuity, and the estimated incidence of visual loss of less than 3 lines was 45% (Table 3).[7–11] In comparison with these carefully designed TAP and VIP studies, our study has some points that need to be addressed.

Table 4. Side effects and complications

	All patients (n = 48)	VIP	TAP
Verteporfin-related acute visual acuity loss (%)	0	4.4	0.7
Injection site adverse reaction (%)	0	6.7	14.4
Infusion-related back pain (%)	4.2 (2/48)	2.2	2.5
Allergic reactions (%)	0	0	0
Photosensitivity reactions (%)	0	0.4	3.0

TAP = treatment of age-related macular degeneration with photodynamic therapy study; VIP = verteporfin in photodynamic therapy report.

First, our series included patients complicated with predominantly classic CNV, minimally classic CNV or occult without classic CNV, which is different from the TAP (reported on predominantly classic lesions) and VIP (reported on fully occult lesions) studies.[7–11] Second, the baseline visual acuity in our series (logMAR, 1.35; approximate Snellen equivalent, 3/60) was much worse than that in the TAP study (mean, 20/80; range, 20/40 to 20/200).[7,8] It was also worse than the median visual score in the Japanese Age-related Macular Degeneration Trial (JAT).[19] That could be the reason for the much larger proportion of estimated 1-year visual loss of less than 3 lines in our series. Third, our series was a non-randomized study, in contrast with the randomized, double-masked, multicenter TAP and VIP studies.

Our study also disclosed that baseline visual acuity was positively correlated with the final visual acuity change 1 year after study entry. However, the TAP studies did not show that the baseline visual acuity of eyes with predominantly classic CNV influenced outcomes. Axer-Siegel and associates reported that the better visual outcome in eyes that presented with better visual acuity was probably due to the poor natural history of predominantly classic CNV.[20–23] This result may reflect the benefit of early therapeutic intervention.[20] For patients with occult without classic CNV, the VIP trial showed more benefit from treatment in patients with either smaller lesions (< 4 MPS disc diameter) or lower levels of visual acuity (Snellen equivalent worse than 20/50).[9] That could explain why patients with occult without classic CNV might have a lower mean baseline logMAR visual acuity of 1.24 (Snellen equivalent < 20/200), and a smaller mean lesion size of 3,549.15 μm (< 4 MPS disc diameter).

There was no statistically significant difference in the initial logMAR visual acuity among predominantly classic, minimally classic and occult without classic CNV. Previous studies disclosed that the different natural histories of predominantly classic CNV and occult without classic CNV could result in different changes in visual acuity.[20–23] Patients complicated with predominantly classic CNV usually suffer from a severe and rapid central vision loss in contrast with the slowly deteriorating visual acuity in patients complicated with occult CNV. However, our series could not make such a conclusion, perhaps due to the unequal sample distribution (predominantly classic, 11; minimally classic, 4; occult without classic, 34) and patient selection. A large sample size and randomized study are mandatory for further evaluation.

Baseline examination found submacular hemorrhage in 24 eyes before treatment, which was not correlated to final visual acuity. However, increased hemorrhage was noted after PDT in 7 eyes, causing rapid decline in visual acuity. While visual deterioration and hemorrhage are part of the natural history of CNV-related conditions, the latter usually occurs 2–3 months after initiation of therapy instead of acutely within 1 week. This massive submacular hemorrhage could result in a median 8.5 lines decrease compared with pretreatment acuity.[24] The TAP and VIP studies reported that increased hemorrhage after verteporfin PDT occurred mostly in eyes with occult without classic CNV.[7–11] In our series, it occurred in 7 eyes after verteporfin PDT, 2 eyes had predominantly classic CNV and the other 5 eyes had occult with no classic CNV. Intravitreal injection of tPA and SF_6 was performed in 2 eyes. After the hemorrhage was displaced, 1 eye received 1 verteporfin PDT retreatment 3 months after the first treatment, and the other eye received 1 session of transpupillary thermotherapy (TTT) 3 months later. Baseline Snellen visual acuity was 6/60 for the first patient and 2/60 for the second patient. Final Snellen visual acuity was 3/60 for the first patient and 4/60 for the second patient. Flat retinal scar without fluorescein leakage was noted in their final visits. The submacular hemorrhage was not severe enough to interfere with verteporfin therapy in the other 5 eyes. There was no statistical difference between baseline and final logMAR visual acuity in these 7 eyes (Kruskal-Wallis test, $p = 0.25$).

No severe adverse events were noted in our study except for injection-related back pain, and there was no acute severe vision loss after treatment. This showed that verteporfin PDT was tolerated well in Chinese patients with AMD complicated with subfoveal CNV.

Conclusion

Our study disclosed that 83.3% of patients with subfoveal CNV secondary to AMD could maintain or improve their visual acuity 1 year after verteporfin PDT to reduce the risk of visual deterioration. Baseline visual acuity was correlated with the final proportion of visual acuity change. A large population-based study is necessary to explore if there are any racial differences in the natural course of the disease and the poor initial visual acuity. Early detection of the disease and proper management to reduce the risk of central vision loss are mandatory for the treatment of patients with AMD complicated with subfoveal CNV.

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