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Photodynamic Therapy for Treatment of Subfoveal Choroidal Neovascularization in Exudative Age-Related Macular Degeneration

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Abstract

This retrospective study is designed to examine the results of photodynamic therapy (PDT) in our cases and compare our results with those of the previous studies. The data was collected from the files of 36 patients on whom PDT had been performed in the Retina Unit of the Ophthalmology Clinic of our Hospital. In the study group, gender, age, baseline best corrected visual acuity (BCVA), lesion types, mean PDT numbers, number of cases on whom multiple PDT were performed, mean visual acuity (VA) difference and the number of cases in the VA change groups were evaluated. The results were compared in themselves and with other studies. Although statistically not significant, predominantly classic and occult lesions responded to PDT better than the other one. After the estimation of all cases, a statistically significant increase was found between baseline and final VA results. Also in cases with low baseline BCVA, the benefit from the treatment was more significant than the other group. As a result of this study, it has been concluded that PDT with Verteporfin is an effective and reliable treatment that preserves visual acuity in CNV secondary to AMD. Further, for decreasing the frequency of PDT, combined therapies are also commonly preferred at present.

Keywords

Age-Related Macular Degeneration, Photodynamic Therapy, Verteporfin, Choroidal Neovascularization, Visual Acuity

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1. Introduction

Age-related macular degeneration (AMD) is the most common cause of vision loss and blindness over age 65. [1, 2] AMD was first defined by Otto Haab in 1885 as a clinical presentation characterized by pigmentary and atrophic changes in the macular region and progressive decrease in central visual acuity. [3] AMD is divided into two types as the dry type characterized by amorphous acelullar deposits called drusen in the retina and the wet type defined as choroidal neovascularization (CNV) progressing more severely. [4] AMD affects retinal pigment epithelum (RPE), Bruch membrane and choriocapillaris. The most important reason for severe vision loss in AMD is photoreceptor damage upon CNV development as well as the development of subretinal hemorrhage, RPE detachment and fibrovascular disciform scar. [3]

Population ageing prevailing in developed countries will cause a rapid increase in AMD incidence and due to the inadequacy of the current methods of treatment, AMD will continue to be a crucial public health problem. Currently, methods routinely used in the treatment of choroidal neovascular membrane (CNM) due to AMD are thermal laser

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photocoagulation (LPC), photodynamic therapy (PDT) with vetreporfin and intravitreal anti-VEGF therapy. In photodynamic therapy, a light-dose laser therapy (verteporfin PDT 689 nm, 50 J/cm² for 83 sec) applied on tissues in which light-sensitivity has been induced with medication creates photochemical effects. [5]

The Macular Photocoagulation Study defined two main angiographic types of CNV. [6] Classic and occult. In the early stages of classic CNV angiography, choroidal hyperfluo rescence with distinct borders is observed. Occult CNV is the late-stage leakage from fibrovascular pigment epithelial detachment (PED) or an unidentified source.

The TAP study identified three types of subfoveal CNVs according to their fluorescein angiography (FA) images. [7]

1. Dominant classic: Classic membrane comprises 50% or more of the lesion.
2. Minimal classic: Classic membrane exists but comprises less than 50% of the lesion.
3. Pure occult (hidden): The amount of classic component in the lesion is 0%.

The object of this study is to evaluate the treatment results of those patients on whom PDT had been performed due to AMD in the Ophthalmology Clinic of our hospital. Specifically, the conditions that necessitated retreatment and the factors that influenced the treatment process are analyzed.

2. Method

Forty-two eyes of 36 patients with subfoveal CNV secondary to AMD on whom photodynamic therapy (PDT) with verteporfin was performed were included in the study. 14 patients were female (38.8%) and 22 were male (61.1%). The patients were aged between 42 and 86 with a mean age of 71.47± 8.50. In 30 of the cases (83.3%), one eye had CNV whereas 6 patients (16.6%) had bilateral CNV. The follow-up period was at least 3 months and at most 24 months with an average of 8.56 ± 6.47 months. In ocular background, 40 eyes were phakic whereas 6 had previous history of cataract operation and pseudophakia. In the systemic inquiry of the cases, 7 had a history of diabetes (19.4%), 14 systemic hypertension (38.8%) and 15 smoking (41.6%). The pre-PDT clinic findings of the cases were recorded as logMAR visual acuity by ETDRS chart. All patients were evaluated for their fundus fluorescein angiography (FFA) characteristics.

A classification based on FFA findings revealed dominant classic CNV in 31 cases (73.8%), minimal classic in 7 cases (16.6%) and occult CNV in 4 cases (9.52%). CNV was at subfoveal location in all cases. Patients with extrafoveal and juxtafoveal lesions were not included in the study.

The total number of photodynamic therapy (PDT) performed was once to 28 eyes (66.6%), 2 times to 8 eyes (19.0%), 3 times to 4 eyes (9.52%), 4 times to 1 eye (2.38%) and 5 times to 1 eye (2.38%). The lesion diameter in the first application was between 1000 µm and 6000 µm with an average of 3582 ± 3213 µm. No reactions in the infusion locations or post-PDT photosensitivity reactions were observed in any of the patients. None of the patients developed severe vision loss after the application.

The cases were divided into two groups according to baseline visual acuity (≤ 1.3 and > 1.3 logMAR). The post-PDT follow-ups were conducted quarterly and the cases were examined for best visual acuity (BVA) and fundus; and the fundus fluorescein angiographies were evaluated. Those cases with follow-up periods less than 6 months were not included in the study.

Baseline BVA was between 3.00 and 0.1 (20/20000 and 20/25) according to logMAR with a mean BVA of 1.42 ± 0.80. The baseline BVA of the cases were compared and evaluated in 2 groups having values above 1.3 and values below 1.3 respectively. Accordingly, the cases were divided into two groups comprising 21 cases (50%) in the baseline BVA group of ≤ 1.3 and 21 cases (50%) in the baseline BVA group of > 1.3 (Figure 1).

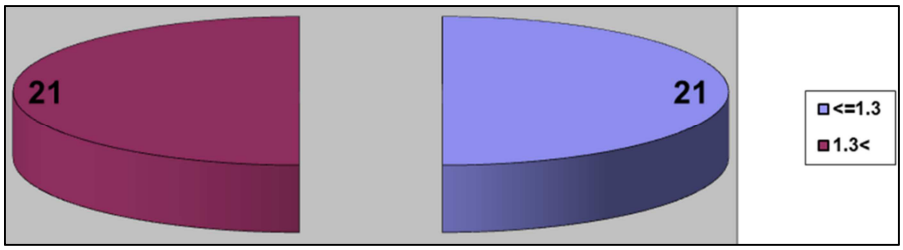

Figure 1. Number of cases according to baseline BVA (BVA: best visual acuity).

3. Result

Table 1 shows mean baseline BVA according to baseline BVA level groups.

Table 1. Average values of inter-group baseline BVA (BVA: best visual acuity, Av.: average, Min: Minimum, Max: Maximum, SD: Standard deviation).

Baseline BVA	Av.	Min.	Max.	SD	N
≤ 1.3	2.08	3.00	1.30	0.58	21
> 1.3	0.76	1.00	0.10	0.23	21
Total	1.42	3.00	0.10	0.79	42

Table 2 shows the distribution of mean baseline BVA according to lesion types.

Table 2. Distribution of average baseline BVA according to lesion types (BVA: best visual acuity, Av.: average, Min: Minimum, Max: Maximum, SD: Standard deviation).

Lesion	Av.	Min.	Max.	SD	N
Dominant classic	1.56	3.00	0.10	0.83	31
Minimal classic	0.98	2.00	0.40	0.49	7
Occult	1.05	2.00	0.60	0.64	4
Total	1.42	3.00	0.10	0.79	42

No statistically significant difference was found ($p>0.05$) in terms of baseline visual acuity values between the lesion types in the paired comparisons conducted by Mann-Whitney U and paired t tests in lesion types with mean baseline BVA measurements.

Figure 2 shows the distribution of lesion types according to FFA findings.

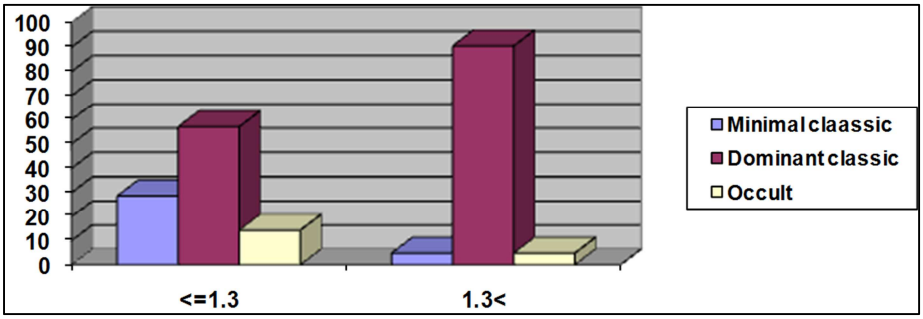

Figure 2. Distribution of lesion types in the BVA groups (BVA: best visual acuity).

The main result measurements at the end of the study were mean final BVA, number of PDT, number of cases on whom PDT was performed once or multiple times, mean VA difference and number of cases with VA difference.

In the study group, the final BVA was between 3.00 and 0.10 with an average of 1.25 ± 0.66. Table 3 shows the distribution of mean final BVA according to lesion types in all cases.

Table 3. Distribution of final BVA in all treatment groups according to lesion types. (BVA: best visual acuity, Av.: average, Min: Minimum, Max: Maximum, SD: Standard deviation).

Lesion	Av.	Min.	Max.	SD	N
Dominant classic	1.37	3.00	0.10	0.69	31
Minimal classic	1.02	2.00	0.40	0.50	7
Occult	0.75	1.30	0.40	0.40	4
Total	1.25	3.00	0.10	0.66	42

Tables 4, 5 and 6 show mean final BVA in baseline BVA level groups and its distribution according to lesion types.

Table 4. Average final BVA values in both BVA groups. (BVA: best visual acuity, Av.: average, Min: Minimum, Max: Maximum, SD: Standard deviation).

Final BVA	Av.	Min.	Max.	SD	N
≤ 1.3	1.61	3.00	0.80	0.71	21
> 1.3	0.89	1.60	0.10	0.35	21
Total	1.25	3.00	0.10	0.10	42

Table 5. Distribution of average final BVA according to lesion types in BVA≤ 1.3 ones (BVA: best visual acuity, Av.: average, Min: Minimum, Max: Maximum, SD: Standard deviation).

Lesion	Av.	Min.	Max.	SD	N
Dominant classic	1.61	3.00	0.80	0.74	19
Minimal classic	2.00	2.00	2.00	-	1
Occult	1.30	1.30	1.30	-	1
Total	1.61	3.00	0.80	0.71	21

Table 6. Distribution of average final BVA according to lesion types in those with a BVA of > 1.3 (BVA: best visual acuity, Av.: average, Min: Minimum, Max: Maximum, SD: Standard deviation).

Lesion	Av.	Min.	Max.	SD	N
Dominant classic	0.99	1.60	0.10	0.38	12
Minimal classic	0.86	1.30	0.40	0.29	6
Occult	0.56	0.80	0.40	0.20	3
Total	0.89	1.60	0.10	0.35	21

In paired comparisons by paired t test, no statistically significant differences were detected ($p>0.05$) in terms of final BVA values among lesion types.

No statistically significant difference was observed ($p> 0.05$) between mean baseline visual acuity and final visual acuity in any of the groups.

In the BVA ≤ 1.3 group, no significant changes were observed in the final BVA values in comparison to the baseline BVA values ($p> 0.05$). In the BVA > 1.3 group, a statistically significant decrease was observed in the final BVA values in comparison to the baseline BVA values ($p<0.05$).

An overall evaluation of the eyes revealed the mean VA change as 0.16 ± 0.70 lines of visual acuity increase. Tables 7, 8, 9 and 10 show the distribution of BV difference according to baseline groups and lesion types.

Table 7. Distribution of VA difference according to BVA groups. (BVA: best visual acuity, VA: Visual acuity, Av.: average, Min: Minimum, Max: Maximum, SD: Standard deviation).

Baseline BVA	Av.	Min.	Max.	SD	N
≤ 1.3	0.46	-1.00	2.00	0.85	21
> 1.3	-0.13	-0.90	0.20	0.30	21
Total	0.16	-1.00	2.00	0.70	42

Table 8. Distribution of BV difference according to lesion types. (VA: visual acuity, Av.: average, Min: Minimum, Max: Maximum, SD: Standard deviation).

Lesion type	Av.	Min.	Max.	SD	N
Dominant classic	0.19	-1.00	2.00	0.80	31
Minimal classic	-4.29	-0.60	0.20	0.25	7
Occult	0.30	0.10	0.70	0.27	4
Total	0.16	-1.00	2.00	0.70	42

Table 9. Average VA difference values in the BVA ≤ 1.3 group (BVA: best visual acuity, VA: Visual acuity, Av.: average, Min: Minimum, Max: Maximum, SD: Standard deviation).

Lesion type	Av.	Min.	Max.	SD	N
Dominant classic	0.47	-1.00	2.00	0.89	19
Minimal classic	0.00	0.00	0.00	-	1
Occult	0.70	0.70	0.70	-	1
Total	0.46	-1.00	2.00	0.85	21

Table 10. Average VA difference values in the BVA > 1.3 group (BVA: best visual acuity, VA: Visual acuity, Av.: average, Min: Minimum, Max: Maximum, SD: Standard deviation).

Lesion type	Av.	MIN.	MAX.	SD	N
Dominant classic	-0.25	-0.90	0.10	0.29	12
Minimal classic	-0.05	-0.60	0.20	0.28	6
Occult	0.16	0.10	0.20	0.05	3
Total	-0.13	-0.90	0.20	0.30	21

The baseline BVA level was analyzed in two different groups and showed the mean VA change in the BVA ≤ 1.3 group as 0.46±0.85 lines of increase. On the other hand, the mean VA change in the baseline BVA > 1.3 group was 0.13±0.30 lines of VA loss.

As a result of the follow-ups, in the separate comparisons according to lesion types by Wilcoxon Sign Test and paired t Test, no significant changes were observed in any of the three lesion types (dominant classic, minimal classic, occult) between baseline BVA and final BVA ($p>0.05$).

A comparison of the VA of our cases at the time of referral and the post-treatment final VA values revealed that there were 14 eyes with no change in VA (33.3%), 7 eyes with a VA increase less than 3 lines (16.6%) and 10 eyes with a VA increase of 3 lines or more (23.8%). As for VA decrease, mild vision loss less than 3 lines was detected in 3 eyes (7.14%), moderate vision loss of 3-6 lines was detected in 5 eyes (11.9%) and severe vision loss of 6 lines or more was detected in only 3 eyes (7.14%) (Table 11).

Table 11. Distribution of the post-treatment VA difference in the lesion groups. (VA: Visual acuity).

Lesion type	Severe VA loss	Moderate VA loss	Mild VA loss	Unchanged VA	<3 Lines Increase	≥3 Lines Increase	Total
Dominant Classic	2 (4.76%)	5 (11.9%)	3 (7.14%)	10 (23.8%)	4 (9.52%)	7 (16.6%)	31
Minimal Classic	1 (2.38%)	0	0	4 (9.52%)	2 (4.76%)	0	7
Occult	0	0	0	0	1 (2.38%)	3 (7.14%)	4
Total	3 (7.14%)	5 (11.9%)	3 (7.14%)	14 (33.3%)	7 (16.6%)	10 (23.8%)	42

After the application of PDT, quarterly FFA were taken to evaluate the status of the membrane according to the FFA classification of TAP. Those with no or minimal leakage and with no VA change were followed. Those with moderate leakage or progression were given another PDT. Accordingly, there was disciform scar in 22 eyes (52.3%), moderate leakage in 8 eyes (19.0%), minimal leakage in 10 eyes (23.8%) and progression in 2 eyes (4.76%).

4. Discussion

In today's world, there is a desire for extending quality of life and labor force into advanced age, however AMD has been reported as the primary cause of decreased quality of vision among the elderly. CNV that develops in neovascular (wet) type AMD is the primary reason for vision loss due to this illness. Irreversible vision loss occurs as these membranes progress beneath the foveal avascular zone. [8]

PDT with verteporfin is an important development in the treatment of neovascular AMD. In PDT, a non-toxic light-sensitive substance converts light energy into chemical energy which is transported into the target tissue, and the resulting changes in the tissue are used for therapeutic purposes. It is considered that verteporfin concentrates in CNV and upon stimulation with laser energy, causes thrombus formation and occlusion in CNV vessels. This therapy can be repeated quarterly for 2 years. [9] As a result of PDT, the neurosensory retina is protected and selective damage is caused in CNV.

In the TAP study, at the end of 1 year, the rate of those patients who had vision loss less than 15 letters in the eyes treated with verteporfin was 61% whereas the rate was 46% in the placebo group. [7] As a result of the subgroup analysis, it was revealed that the greatest benefit was observed in the dominant classic CNV eyes. In our study, in the group with baseline BVA >1.3, out of the 12 eyes with dominant classic membrane, 4 had VA maintained or increased (%33.3) whereas 1 eye had mild vision loss (8.33%), 5 had moderate VA loss (41.6%) and 2 had severe VA loss (16.6%). A comparison of these results with the TAP study shows that in the TAP study, no severe vision loss was observed in dominant classic lesions whereas in our study, severe VA loss developed in 16.6% of the dominant classic lesions. As for moderate VA loss, in the TAP study, it was 33% at the end of 12 months whereas it was 41.6% in our study. The fact that our study shows higher visual loss in dominant classic lesions compared to the TAP study has been attributed to the fact that sufficient number of PDT according to lesion sizes had not been performed. In minimal classic lesions, the TAP study showed moderate VA loss at 44% whereas in our study no moderate VA loss was detected but severe VA loss formed in only 1 eye (16.6%). In this group, VA was maintained or increased in a total of 5 eyes (83.3%). VA increased in all of the occult eyes. As a result, a combined evaluation of all lesions in our study shows that there was no significant change in the final VA in the baseline BVA > 1.3 group ($p>0.05$). On the other hand, in the baseline BVA ≤ 1.3 group, none of the 19 eyes with dominant classic lesions had moderate or severe VA loss. Moderate VA loss developed in 2 eyes (10.5%) whereas in 17 eyes (89.4%) VA was maintained or increased. In minimal classic and occult lesions, VA was also maintained or increased in all cases. In this group, significant changes were observed in final BVA values in comparison to baseline VA values in all lesions ($p< 0.05$).

As for the VIP study, moderate vision loss in those eyes with subfoveal occult CNV at the end of 2 years was 54% in the treatment group whereas this rate was 67% in the control group. That is, while PDT could prevent severe vision loss, increase in visual acuity only rarely occurred. [10] In our study, none of the 4 cases with occult CNV developed visual loss. A VA increase of less than 3 lines was observed in 1 eye (25.0%) whereas a VA increase of more than 3 lines was detected in 3 eyes (75.0%). It is observed that our VA results are better than those of the VIP study. An evaluation of our cases according to lesion types reveals that the intergroup VA changes were not statistically significant but our occult lesions responded to treatment better (VA increase of 0.30 lines in occult lesions and VA increase of 0.19 lines in dominant classic lesions). A comparison of the cases included in the VA change groups shows that the rate of those cases with VA increase was higher in occult lesions whereas the rate of those cases with mild, moderate and severe VA loss was higher in dominant classic lesions. It is also significant that in occult lesions, no cases with VA loss were present. These findings show that occult lesions respond to PDT better. In the dominant classic lesions, the BVA≤ 1.3 group revealed better results than the other group. Thus, it may be deduced that especially in dominant classic and occult lesions, even if there is an advanced VA decrease, PDT can still be useful.

In the TAP and VIP reports, it is reported that the visual results of PDT are effective on the baseline lesion sizes rather than the membrane properties of CNV. In classic CNVs, lesions smaller than 4 MPS, and in occult and minimal classic lesions, lesions bigger than 4 MPS presented worse results. [11] On the other hand, our study did not reveal any statistically significant difference in terms of final VA values and the average number of PDT performed between the groups with lesion diameters of < 4 MPS and ≥ 4 MPS ($p>0.05$).

In the histopathological examination of the eyes with CNV, inflammatory cells and neovascularization were detected. In the subfoveal membrane sections removed surgically, VEGF which is the key mediator of angiogenesis was found at a rate proportional to the inflammatory cell number. [12] Owing to its anti-angiogenic and anti-permeability properties, intravitreal anti-VEGF treatment is used together with PDT in the combined treatment of AMD. VEGF-A which is one of the many isoforms in the VEGF family, is the main culprit for exudative AMD pathogenesis. With the discovery of the role of VEGF in AMD, intravitreal application of anti-VEGF agents has become the most important therapeutic method in the treatment of AMD and this way, vision loss due to exudative AMD can be significantly prevented. [13, 4] Intravitreal anti-VEGF use as an alternative to PDT has become popular in such patients. Intravitreal steroid injections have also been used in CNV cases as they alleviate retinal edema and subretinal fibrosis. Steroids with anti-angiogenic and anti-inflammatory properties inhibit vascular proliferation and permeability, thereby decreasing leakage from the membrane and edema. [15, 16] Due to the fact that PDT requires frequent repetition and causes angiogenic stimulation and increase in vascular permeability as side effects in the treatment of AMD, various combination therapies are currently the most preferred methods, as PDT, steroids and anti-VEGF drugs target different mechanisms in the pathogenesis.

5. Conclusion

In our cases, the best response was obtained in occult lesions in both groups and it was observed that PDT was effective in all three lesion types. In conclusion, we are of the opinion that the use of PDT alone or in combined therapy is useful in the treatment of exudative AMD.

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Competing Interest

All authors declare that they have no competing interests.

Consent for Publication

Written consent was obtained from the patients shown in the figures.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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