Pegaptanib Versus Combined Pegaptanib and Photodynamic Therapy for Neovascular Age-Related Macular Degeneration

Neovasküler Yaşa Bağlı Makula Dejenerasyonunda Pegaptanib ile Kombine Pegaptanib ve Fotodinamik Tedavinin Karşılaştırılması

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ABSTRACT Objective: The aim of this study is to review our experience with Pegaptanib in patients with neovascular age-related macular degeneration (AMD) and to determine whether outcomes would be improved by combining Pegaptanib with photodynamic therapy (PDT). **Material and Methods:** Institutional, retrospective case series. The charts of 20 patients with neovascular AMD who received Pegaptanib monotherapy or combined ocular PDT with Verteporfin were retrospectively reviewed. Main outcome measures consisted of the number of treatments applied, Snellen best-corrected visual acuity (BCVA), angiographic lesion characteristics and center field thickness (CFT) in optical coherence tomography (OCT). **Results:** Average follow-up time was 7.7 months (range, 3-12 months). Ten patients (50%) were in Pegaptanib monotherapy group (Group A) and 10 patients were in combination therapy with PDT group (Group B). Patients in both groups received 2 to 9 (mean, 5.2) Pegaptanib injections. Group B received 1 to 4 (mean, 1.8) PDT treatments. Initial BCVA ranged from 20/50 to 20/3200 (mean, 20/509), final BCVA ranged from 20/70 to 20/3200 (mean, 20/759). In group A, the mean initial and final BCVA were 20/650 and 20/617, respectively (p= 0.590). The corresponding numbers in group B were 20/398 and 20/1060, respectively (p= 0.062). Four of the 10 eyes (40%) in Group B lost three lines or more. None of the eyes in Group A lost three lines or more vision (p= 0.087). There was neither significant change in the lesion size (p= 0.513), nor in CFT (315 μm to 268 μm, p= 0.99). **Conclusion:** The results of this study suggest that combined ocular PDT and Pegaptanib treatment may not be superior to Pegaptanib alone in patients with neovascular AMD. Further studies are needed.

Key Words: Choroidal neovascularization; pegaptanib; verteporfin

ÖZET Amaç: Bu çalışmada neovasküler yaş bağımlı maküler dejenerasyon (YBMD) olgularında uyguladığımız Pegaptanib tedavisinin sonuçlarını ve kombine Pegaptanib ve fotodinamik tedavinin (FDT) olumlu etkisinin olup olmadığının araştırılması amaçlandı. **Gereç ve Yöntemler:** Retrospektif olgu serisi. Neovasküler YBMD nedeniyle tek başına veya FDT ile kombine Pegaptanib tedavisi uygulanan 20 olgunun kayıtları retrospektif olarak incelendi. Ana izlem parametreleri olarak uygulanan tedavi sayısı, Snellen en iyi düzeltilmiş görme keskinliği (EİDGK), anjiyografik lezyon özellikleri ve optik koherens tomografide santral makula kalınlığı (SMK) değerlendirildi. **Bulgular:** Ortalama izlem süresi 7.7 aydı (3-12 ay). On olguya (%50) tek başına Pegaptanib (Grup A) ve 10 olguya da FDT ile kombine tedavi (Grup B) uygulandı. Her iki grupta uygulanan Pegaptanib enjeksiyon sayısı 2 ile 9 arasında değişmekteydi (ortalama 5.2). Grup B'deki olgulara 1 ile 4 kez (ortalama 1.8) FDT uygulandı. Tedavi öncesi EİDGK 20/50 ile 20/3200 arasındaydı (ortalama 20/509). Tedavi sonrası ölçülen son EİDGK ise 20/70 ile 20/3200 arsındaydı (ortalama 20/759). Grup A'da ilk ve son EİDGK sırasıyla 20/650 ve 20/617 idi (p= 0.590). Grup B'de bu değerler sırasıyla 20/398 ve 20/1060 idi (p= 0.062). Grup B'de dört gözde (%40) üç veya daha fazla sıra görme kaybı gelişti. Grup A'da ise hiçbir olguda üç veya daha fazla sıra görme kaybı gelişmedi (p= 0.087). Ne lezyon çapında (p= 0.513), ne de SMK'da anlamlı değişiklik gerçekleşti (315 μm'ye karşın 268 μm, p= 0.99). **Sonuç:** Çalışmanın sonuçları neovasküler YBMD olgularında kombine Pegaptanib ve FDT tedavisinin tek başına Pegaptanib tedavisine üstün olmadığını düşündürmektedir. Gelecek çalışmalar daha aydınlatıcı olabilir.

Anahtar Kelimeler: Koroidal neovaskülarizasyon; pegaptanib; verteporfin

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Management of choroidal neovascular membrane (CNVM) secondary to age-related macular degeneration (AMD) is becoming more and more complicated with the introduction of new pharmaceuticals and photodynamic therapy.[1-11] The availability of different agents that may be given alone or in combination, and the need to determine the appropriate combination of agents make it extremely difficult to determine a standard protocol for exudative AMD. Various presentations of exudative AMD, including lesion type, location, duration, associated features such as hemorrhage, fibrous scars, and previous forms of treatment further complicate the process of determining the best treatment for each patient.[10]

Introduction of pegaptanib in December 2004 and ranibizumab in April 2006 to the retina practice has had a significant impact on the way retina specialists approach treatment of neovascular AMD.[4,7,8] Encouraged by the VEGF Inhibition Study in Ocular Neovascularisation (VISION) trial, we initiated the use of pegaptanib in every eligible patient in combination with ocular photodynamic therapy (PDT) with verteporfin with the hope of halting the progression of the lesions as effectively as possible early in the disease process. After one year we analyzed our results with pegaptanib monotherapy and with combination therapy.

MATERIAL AND METHODS

Based on preliminary data we offered combination therapy to every patient eligible for PDT and Pegaptanib since its approval. Those included patients with predominantly classical lesions with greatest linear diameter (GLD) less than 5400 microns in the fluorescein angiography (FA) and progressive occult or minimally classical lesions of less than 4 disc areas, best-corrected visual acuity (BCVA) of less than 20/40 with recent disease progression, or signs of an active CNVM. Although combination therapy was offered to every patient within these criteria, half of the patients agreed to this and the other half chose to receive only Pegaptanib. All the patients who refused PDT did so because of inconvenience since our office offered PDT only in a satellite location.

The charts of all patients who were eligible for combined pegaptanib and PDT treatment with verteporfin between January 2005 and December 2005 were reviewed. All patients received pegaptanib injections every six weeks for a maximum of nine injections. Photodynamic therapy with verteporfin was offered to every patient at the initial visit and at the 3-month follow-up visits whenever persistent leakage was documented angiographically. During follow-up we assessed the following criteria for each patient:

(1) Initial and final type and size (greatest linear diameter) of the CNVM on FA;

(2) Initial, final, and best-corrected visual acuity during follow-up;

(3) Initial and final center field thickness (CFT) in optical coherence tomography (OCT);

(4) Duration of symptoms prior to starting Pegaptanib;

(5) Number of Pegaptanib injections and PDT treatments;

(6) Follow-up time.

Retrospective analysis of the data was performed after approval was obtained from the Saint Louis University Hospital Investigational Review Board. The study conforms to the provisions of the Declaration of Helsinki. Fisher's exact test was used in order to access the visual change according to the type of the lesion and treatment. The mean initial and final BCVA, GLD and CFT were compared using Wilcoxon signed ranks test.

RESULTS

A total of 20 consecutive patients were identified for the time period of January 2005 to December of 2005. Seven patients were males and 13 were females. Eleven patients had right eye involvement and nine had left eye involvement. The mean ± standard deviation of the age was 78.7 ± 8.8 (median, 79.5). Duration of symptoms was less than one month for 16 of the 20 patients (others were 2, 3, 6 and 12 months). Ten patients were given pegaptanib monotherapy (Group A) and 10 patients received combination therapy with PDT (Group B).

There were three patients with predominantly classical membranes and seven patients with minimally classical or occult CNVM in Group A. In Group B, there were six patients with predominantly classical membranes and four patients with minimally classical or occult CNVM. Follow-up time was 7.7 ± 2.7 months (range, 3 to 11 months). Follow-up time for Group A and B were 6.6 ± 2.3 months (range, 3 to 9 months) and 8.6 ± 2.9 months (range, 5 to 12 months), respectively (p= 0.190). Patients received 2 to 9 (mean, 5.2) pegaptanib injections. The corresponding numbers in Group A and B were 2 to 7 (mean 4.1) and 4 to 9 (mean, 6.3) pegaptanib injections, respectively. Patients in Group B received 1 to 4 (mean, 1.8) PDT treatments.

Initial Snellen BCVA ranged from 20/50 to 20/3200 (mean, 20/509), and final BCVA ranged from 20/70 to 20/3200 (mean, 20/759) (Table 1). The highest BCVA score obtained during follow-up occurred three months after initiation of the treatment(s) with a mean of 0.9 line improvement (range, 0 to 4 lines). Change in the VA at the last visit ranged from 2 lines of gain to 5 lines of loss (mean= 0.9 lines loss). In group A, the mean initial and final BCVA were 20/650 and 20/617, respectively (p= 0.590). The corresponding numbers in group B were 20/398 and 20/1060, respectively (p= 0.062).

Overall, patients with minimally classical or occult CNVM did better than those with predominantly classical CNVM. Ten of the 11 eyes which were initially minimally classical or occult remained within two lines of change of vision at the end of the follow up period, and one eye lost three lines. In the predominantly classical group, three of the nine eyes lost three or more lines of vision (Fisher's exact test, p= 0.2848) (Table 2).

In the predominantly classical group, three of the six eyes which received combination therapy lost three lines or more. None of the three eyes which received pegaptanib monotherapy lost three

TABLE 1: Initial and final cracteristics of the patients (Group A: 1 to 10; Group B:11 to 20).

	Age (years)	Gender	Type of CNVM	Number of Pegaptanib Injections	Number of PDTs	Initial BCVA	Final BCVA	Initial GLD (µm)	Final GLD (µm)	Initial CFT (µm)	Final CFT (µm)	Follow-up (mo)
1	92	F	PC	4	-	20/400	20/400	2500	2000	372	279	6
2	84	M	MC	3	-	20/3200	20/3200	1500		372	218	9
3	89	F	PC	7	-	20/800	20/400	2300	2400	249	253	9
4	80	F	MC	6	-	20/100	20/100	1000	1500	328	246	9
5	78	F	O	4	-	20/200	20/800	3300	2000	387	201	6
6	69	M	O	5	-	20/100	20/200	2400	2400	403	294	7
7	89	F	O	3	-	20/100	20/70	700	0	299	236	3
8	79	M	PC	2	-	20/400	20/400	2000	2000	400	400	3
9	85	F	O	3	-	20/800	20/400	2000	3000	160	256	6
10	83	F	O	4	-	20/100	20/200	2300	1900	230	314	8
11	78	F	PC	6	1	20/200	20/3200	2000	2300	253	149	8
12	84	M	PC	5	2	20/200	20/800	600	1600	267	238	6
13	72	F	O	4	1	20/400	20/200	2100	2100	213	164	5
14	60	M	PC	7	4	20/50	20/200	400	1400	240	337	11
15	75	F	O	7	1	20/70	20/100	2000	2000	348	210	11
16	70	F	O	8	1	20/60	20/100	2700	3000	192	394	11
17	63	F	PC	9	2	20/800	20/800	1700	2000	290	321	12
18	83	M	MC	5	2	20/1600	20/1600	2800	1600	583	299	6
19	73	M	PC	8	2	20/400	20/400	1400	2300	350	212	11
20	88	F	PC	4	2	20/200	20/3200	800	1900	370	392	5

F:female; M:male; CNVM:choroidal neovascular membrane; PC: predominantly classic; MC:minimally classic; O:occult; PDT:photodynamic therapy; BCVA:best-corrected visual acuity: GLD:greatest linear diameter; CFT:central field thickness in optical coherence tomography.

TABLE 2: Change in Snellen best-corrected visual acuity (BCVA) in eyes with predominantly classical (PC) choroidal neovascular membranes (CNVM) versus minimally classical or occult (MC+O) CNVM after treatment with either pegaptanib monotherapy or combination therapy.

BCVA	PC CNVM	MC + O CNVM
Same	6	10
Worse (three lines or more)	3	1

Fisher's exact test, p= 0.2848.

lines or more vision. This difference was not significant (Fisher's exact test, p= 0.4643) (Table 3). In the minimally classical or occult group, one of the four eyes which received combination therapy lost three lines or more, while none of the seven eyes which received pegaptanib monotherapy lost three lines or more vision. The difference was not significant (Fisher's exact test, p= 0.3636) (Table 4). At the conclusion of the study, four of the on eyes (40%) which received combination therapy lost three lines or more but none of the ten eyes which received pegaptanib monotherapy lost three lines or more vision. The difference between the groups did not reach the significant level (Fisher's exact test, p= 0.0867) (Table 5).

The GLD between the initial and final visit was unchanged (mean initial GLD of 1825 ± 799 μm and mean final GLD of 1925 ± 642 μm, p= 0.513). The baseline GLD (2000 ± 761 μm) was not different than that of the final visit (1911 ± 111 μm) in Group A (p= 0.590) and in Group B (1650 ± 838 μm versus 2020 ± 456 μm, p= 0.159).

Mean center field thickness in OCT (315 ± 97 μm) was not significantly different than that of final CFT (268 ± 67 μm, p= 0.099). The initial mean CFT in Group A and B were 320 ± 83 and 310 ± 112 μm, respectively (p= 0.393). The mean CFT did not change at the final visit (269 ± 56 μm) neither in Group A (p= 0.173), nor in Group B (271 ± 89 μm, p= 0.333).

One eye which initially demonstrated occult CNVM and two eyes which initially demonstrated minimally classical CNVM converted to predominantly classical CNVM during the follow up and treatment(s).

CASE REPORTS

CASE 1

A 60-year-old man presented with smaller than one disc area subfoveal predominantly classical CNVM of one month duration in his right eye. His initial BCVA was 20/50. FA is seen in Figure 1A. In January 2005, he was started on combination therapy. His lesion continued to progress in the following 11 months despite 4 additional PDT and 7 pegaptanib injections. In his last examination, his BCVA was 20/200 and FA was as seen in Figure 1B.

CASE 2

An 80-year-old woman presented with subfoveal minimally classical CNVM of one month duration. The CNVM was approximately one disc area in size in her

TABLE 3: Change in Snellen best-corrected visual acuity (BCVA) in eyes with predominantly classical choroidal neovascular membranes undergoing treatment with either pegaptanib monotherapy (Group A) or combination therapy (Group B).

BCVA	Group A	Group B
Same	3	3
Worse (three lines or more)	0	3

Fisher's exact test, p= 0.4643.

TABLE 4: Change in Snellen best-corrected visual acuity (BCVA) in eyes with minimally classical or occult choroidal neovascular membranes (CNVM) undergoing treatment with either Pegaptanib monotherapy (Group A) or combination therapy (Group B).

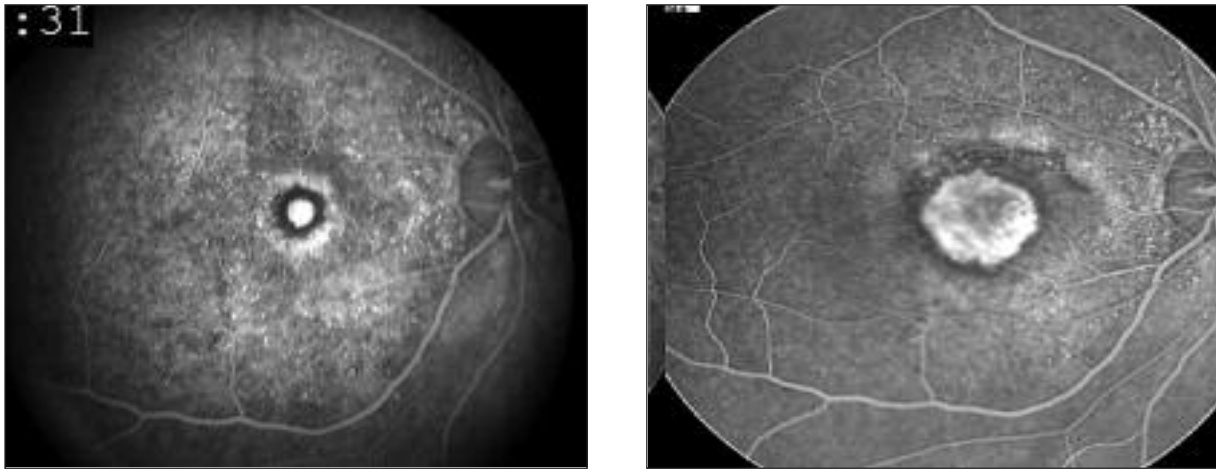
BCVA	Group A	Group B
Same	7	3
Worse (three lines or more)	0	1

Fisher's exact test, p= 0.3636.

TABLE 5: Change in Snellen best-corrected visual acuity (BCVA) in all eyes (predominantly classical, minimally classical and occult choroidal neovascular membranes combined) undergoing treatment with either pegaptanib monotherapy (Group A) or combination therapy (Group B).

BCVA	Group A	Group B
Same	10	6
Worse (three lines or more)	0	4

Fisher's exact test, p= 0.0867.



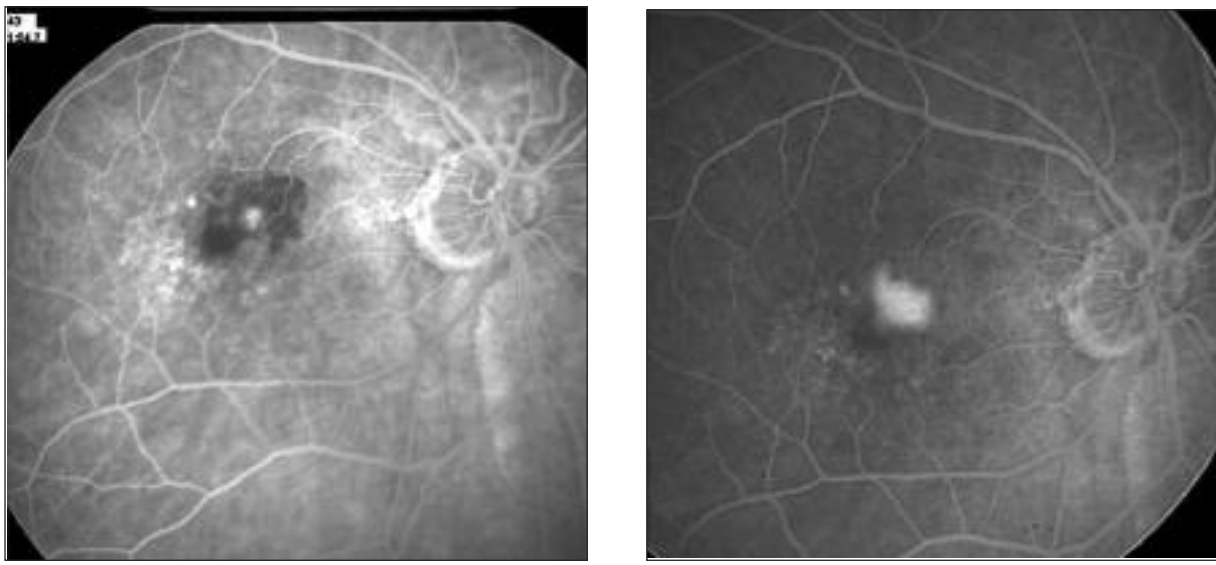
A B

FIGURE 1: Case 1. Initial **(A)** fluorescein angiogram shows predominantly classical lesion. **(B)** Corresponding photograph obtained after 11 months show progression of the lesion despite the combination therapy.

right eye (Figure 2A). The BCVA was 20/100. She received a total of 6 Pegaptanib injections over 6 months follow-up. Six months after the beginning of treatment, the occult component of the CNVM resolved and the classical component persisted as juxtafoveal CNVM (Figure 2B). The BCVA was 20/100.

DISCUSSION

In this study, we reviewed our first year experience with pegaptanib. It is known from the natural history and the treatment response data from previous studies of the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group comparing the effectiveness of PDT with vertoporfin to placebo and the VISION which compared the effectiveness of Pegaptanib to placebo that the fastest loss of vision occurs in the first year of CNVM and the initiation of the treatment.[4,12-14] Retrospective analysis of the VISION trial data, although it was not statistically significant, suggested that combination therapy with Pegaptanib and PDT with verteporfin might be more



A B

FIGURE 2: Case 2. **(A)** Initially minimally classical lesion converted to a **(B)** classical lesion located juxtafoveally after 4 sessions of pegaptanib monotherapy.

effective than pegaptanib alone.[4] The outcomes of the combination therapy are being studied in a randomized trial.

The number of patients in our study was limited to show significant strength in the results. The minimally classical and occult CNVM did better than predominantly classical CNVM with either pegaptanib monotherapy or with the combination therapy, consistent with findings reported in other studies and as anticipated from their natural history. On the other hand, patients receiving monotherapy did better than the patients in combination therapy both for the minimally classical or occult group and the predominantly classical group. There are several possible explanations for the discrepancy in our findings:

(1) This may have been due to the method of combination therapy used in our patients.

(2) The possibility of excessive insult to the retinal neurosensorial, pigment epithelial cells, choroidal cells, or their blood vessels by the PDT.

(3) PDT counteracting vascular endothelial growth factor inhibition by Pegaptanib

(4) The small sample size and the retrospective nature of our study.

Recently, Calvo-Gonzales et al. have reported poor response to combined therapy using PDT and Pegaptanib in their seven cases of predominantly classic juxtafoveal CNVM due to AMD.[15] This was also the case in our cases with predominantly classical CNVM. Many studies have reported better visual results and less retreatment need in cases receiving combined FDT and either ranibizumab or bevacizumab compared to cases treated with monotherapy alone.[16-18] It is known that PDT increases the VEGF levels in CNVM.[19,20] Ranibizumab and bevacizumab inhibit all isoforms of vascular endothelial growth factor.[10,11,16-18] However, pegaptanib is an aptameric molecule which inhibits only the 165 isoform of VEGF.[4] Inhibition of only the 165 isoform of VEGF might not be enough to suppress the total pathologic effect of VEGF. Photodynamic therapy induced VEGF secretion and its insufficient inhibition by pegaptanib might be responsible for the worse visual prognosis and high retreatment rate in our patients received combined PDT and Pegaptanib. Joeres et al. have reported that intravitreal bevacizumab leads to better functional and anatomical improvement than intravitreal pegaptanib in cases of neovascular AMD.[21] Similarly, Smith et al. have reported that 11 of 40 eyes (%48) received combined bevacizumab and PDT required only a single combined treatment for CNVM resolution at the 12-month follow-up.[22] These findings and our high retreatment rate show that combined pagaptanib and ocular PDT does not seem to be the current treatment of choice in CNVM due to AMD. Another possible factor that may influence the treatment response is the order of combined treatment. Ju et al. have shown that simultaneous but not prior inhibition of 165 isoform of VEGF with pegaptanib enhances the efficacy of PDT in multiple models of ocular neovascularisation.[23] The fact that the combined treatment was not simultaneous in our study might help explain the unfavourable response to treatment in our combined group.

In conclusion, our results suggest that combined ocular PDT and pegaptanib treatment may not be superior to pegaptanib alone in patients with neovascular AMD. Therefore, until prospective controlled multicenter randomized trials show significant benefit, this combination therapy should be employed with caution and awareness in the treatment of neovascular AMD.

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