A prospective study on different methods for the treatment of choroidal neovascularization. The efficacy of verteporfin photodynamic therapy, intravitreal bevacizumab and transpupillary thermotherapy in patients with neovascular age-related macular degeneration

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Summary

Background: The aim of this study was to compare the efficacy of verteporfin photodynamic therapy (PDT), intravitreal injections of bevacizumab (IVB) and transpupillary thermotherapy (TTT) in patients with neovascular age-related macular degeneration (AMD).

Material/Methods: The study design was a prospective, interventional, comparative case series. Between December 2006 and March 2009, 426 eyes of 426 consecutive patients presenting with neovascular AMD were included into the study. Patients presented with subfoveal CNV predominantly classic, minimally classic, and occult with no classic component; lesion size less than 5000 µm in the greatest linear dimension, and the area of hemorrhages ⩽1/3 were randomized to receive either PDT (group I) or IVB (group II) in a 1:1 ratio. Other patients with CNV were included into the group III and received TTT.

Results: One hundred eyes were treated with PDT. Mean baseline logMAR BCVA was 0.62 and final visual acuity decreased to 0.74 (p<0.05, Wilcoxon test); 104 eyes were treated with IVB. Mean baseline BCVA was 0.82 and final visual acuity increased to 0.79 (p>0.05, Wilcoxon test); 222 patients were treated with TTT. Mean baseline BCVA was 1.10 and final visual acuity decreased to 1.15 (p>0.05, Wilcoxon test). Among all eyes the average number of treatment sessions was 2.34 (SD 1.17).

Conclusions: Our study shows that IVB injections had the best efficacy in the improvement of final BCVA. However, both IVB and TTT demonstrated good stabilization of vision. Although after PDT final BCVA was significantly worse from baseline, it may also be beneficial for some patients with neovascular age-related macular degeneration.

key words: age-related macular degeneration • intravitreal bevacizumab • verteporfin photodynamic therapy • transpupillary thermotherapy

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Med Sci Monit, 2012; 18(6): CR374-380

Nowak MS et al – The efficacy of verteporfin photodynamic therapy...

BACKGROUND

Age-related macular degeneration (AMD) is the leading cause of visual impairment and irreversible blindness in the Western world [1]. Nowadays it is also becoming an important problem in Asians and its prevalence is certain to increase substantially as the population ages [2]. "Wet AMD" contributes to the minority of cases, approximately 10% to 20%, but it is associated with 80% to 90% of visual loss. "Wet AMD" is characterized by choroidal neovascularization (CNV), the formation of which is stimulated by tissue ischemia and/or inflammation from age-related changes and is also associated with up-regulation of vascular endothelial growth factor (VEGF). Due to its multifactorial pathogenesis there is no ideal therapy for choroidal neovascularization. However, some treatments can stabilize or arrest the progression of the disease and even lead to visual improvement [3–5].

The first successful treatment of choroidal neovascularization was achieved with verteporfin photodynamic therapy (PDT) [6]. In the era of PDT, fluorescein angiography (FA) was the gold standard for monitoring the response to treatment, and classification of lesions was based on the percentage of classic CNV according to its angiographic appearance. Thus, predominantly classic lesions were defined as having 50% or more of the total lesion size comprised of classic CNV and minimally classic lesions were characterized by the classic CNV occupying less than 50% of the total lesion size. Occult CNV has been categorized as fibrovascular PED or late leakage of undetermined source. PDT has been shown to be safe and effective for treating a range of lesion types, including subfoveal predominantly classic lesions, occult with no classic lesions, and, in some cases, minimally classic lesions. Despite the demonstrated efficacy, a substantial proportion of patients still developed moderate or severe visual loss after PDT [7,8].

More recently, anti-angiogenic agents have come to be at the forefront in the treatment of neovascular AMD [1]. Anti-angiogenic agents inhibit the process of angiogenesis by targeting vascular endothelial growth factor (VEGF), the main stimulus for the angiogenic cascade. At present there are 3 anti-angiogenic drugs available to treat CNV. Pegaptanib sodium (Macugen; OSI Pharmaceuticals, Melville, NY) was the first VEGF inhibitor to be approved, which targets the 165 amino-acid isoform of VEGF. The introduction of pegaptanib was followed closely by the emergence of 2 more effective VEGF inhibitors – bevacizumab (Avastin; Genentech) and bevacizumab (Avastin; Genentech) ranibizumab (Lucentis; Genentech, San Francisco, Ca) – both directed against all biologically active isoforms of VEGF-A. Ranibizumab is a humanized antigen-binding fragment (Fab) against VEGF; its efficacy and safety were confirmed by the MARINA and ANCHOR studies. It has therefore been approved for the treatment of neovascular AMD since 2006 [9,10]. Bevacizumab is a full-length antibody against VEGF, which is approved for intravenous use for the treatment of metastatic colon cancer [11]. Although bevacizumab has not been approved for ocular use in any country, there are several studies supporting the use of off-label intravitreal bevacizumab to be safe and effective in the treatment of neovascular AMD. No significant adverse events have been identified in any of these studies, and the cost of therapy is much less expensive compared to ranibizumab [5,12–15].

Transpupillary thermotherapy (TTT) with a diode laser (wavelength ẽ 810 nm) has been also used to treat choroidal neovascularization in patients with AMD. The diode laser has a number of biophysical advantages: it is poorly absorbed by hemoglobin, allowing treatment through preretinal or subretinal blood, but is well absorbed in the choroid, enabling effective treatment of choroidal lesions. Fluorescein angiography shows that TTT is effective in closing CNV. Optical coherence tomography (OCT) and clinical examination also show good stabilization of visual acuity after TTT treatment. Thus, TTT appears to be as potent in the treatment of neovascular AMD as other methods, at least in selected patients [16–18].

Since most previous studies were small and focused on a single therapy, we have not found any study comparing verteporfin photodynamic therapy (PDT), intravitreal bevacizumab (IVB) and transpupillary thermotherapy (TTT). This report on a large group of our patients fills this gap.

MATERIAL AND METHODS

Preliminary examination

The study design was a prospective, interventional, comparative case series; 426 eyes of 426 consecutive patients presenting with choroidal neovascularization (CNV) due to age-related macular degeneration were recruited into the study between December 2006 and March 2009. Patients were counseled about the prognosis for their condition and the nature and possible consequences of the study were explained. The procedures used adhered to the Declaration of Helsinki. The study was approved by the institutional review board of the Medical University of Lodz and informed consent was obtained from all included subjects.

Initial clinical examination included: best-corrected visual acuity (BCVA) using a standard Snellen chart at 6 m, intraocular pressure (IOP) measurement, a slit-lamp examination of anterior segment, mydriasis with 1% tropicamide, and funduscopy with Volk lens (80D Volk Optical, Mentor, OH, USA). Following this, the Topcon TRC-50 EX fundus camera using Imagenet 2000 software (Topcon, Tokyo, Japan) was used to perform fluorescein angiography (FA). Further analysis of retinal anatomic features was performed using optical coherence tomography (OCT) with Topcon 3D OCT-1000 (Topcon, Tokyo, Japan). Assessment of fluorescein angiograms as well as of OCT results was carried out by 2 unmasked ophthalmologists (MP and AK) and any disagreement was settled by consensus. The definitions of different types of lesions and assessments of fluorescein angiography were based on the TAP and VIP studies [19].

Patients were assigned into 3 treatment subgroups according to angiographic appearance of CNV, particularly upon the lesion size and composition as well as the angiographic leakage and the presence of retinal pigment epithelial detachment (PED), hemorrhages and fibrosis. Any previous CNV treatment was an exclusion criterion. Patients with any other ocular condition affecting vision, as well as those with history of cardiovascular event or a stroke during last year, were also excluded.

Three subgroups were distinguished based on the applied treatment: group I received verteporfin photodynamic

Table 1. The demographic structure of included patients.

Group examined	Number of subjects: n (%)	Min. age	Max. age	Mean age	Med. age	Std. dev.	Statistical analysis
PDT	100 (23.5%)	46.0	86.0	73.8	75.0	8.4	Kruskal-Wallis Test
IVB	104 (24.4%)	46.0	91.0	74.1	76.5	9.5	
TTT	222 (52.1%)	50.0	92.0	75.2	76.0	7.7	H=1.68
All	426 (100.0%)	46.0	92.0	74.6	76.0	8.4	p=0.4320

Group examined	Number of subjects: n (%)	Male n (%)	Female n (%)	Statistical analysis
PDT	100 (23.5%)	30 (30.0%)	70 (70.0%)	Chi-square χ^2 Test
IVB	104 (24.4%)	35 (33.6%)	69 (66.4%)	
TTT	222 (52.1%)	67 (30.2%)	155 (69.8%)	Ch2=0.46
All	426 (100.0%)	132 (31.0%)	294 (69.0%)	p=0.7949

therapy (PDT), group II received intravitreal injection of bevacizumab (IVB), and group III received transpupillary thermotherapy (TTT). Patients were informed of the off-label use of intravitreal bevacizumab (Avastin; Genetech, Inc.).

Patients who meet following criteria – subfoveal CNV predominantly classic, minimally classic, and occult with no classic component (occult was defined either as retinal pigment epithelium detachment-PED or as late leakage of undetermined source); lesion size less than 5000 µm in the greatest linear dimension, and the area of hemorrhages ⩽1/3 – were randomized to receive either verteporfin photodynamic therapy (PDT-group I) or intravitreal injection of bevacizumab (IVB-group II) in a 1:1 ratio.

Other patients with CNV who were not assigned to PDT or IVB groups due to the localization of membrane, its size and composition or due to area of hemorrhages and fibrosis, were included into group III and received transpupillary thermotherapy (TTT).

Treatment and evaluation

Photodynamic therapy with verteporfin was performed using a standard protocol utilized in the TAP study [6]. The area of lesion was determined using FA and the incorporated measuring software (Imaganet 2000, Topcon, Tokyo, Japan). Verteporfin (6 mg/m²) was infused intravenously for 10 min, and then diode laser treatment was performed (689 nm, 50 J/cm², 600 mW/cm²) for 83 s. Intravitreal injection of 1.25 mg of bevacizumab (Avastin) in 0.05 ml was given under aseptic condition after topical anesthesia with Alcaine. Following the injection topical antibiotic was applied and the intraocular pressure was monitored. Transpupillary thermotherapy with an 810 nm diode laser (Quantel Medical, France) was delivered through a dedicated slit lamp mounted delivery system. Patients were anaesthetized with topical Alcaine. A Volk contact lens (Volk Optical, Mentor, OH, USA) was used, giving a magnification of 1.06 × of the laser spot at the retina. Laser settings

were adjusted to give faint retinal greying following 1 min of treatment. Beam diameters varied between 800 and 3000 µm and the power range from 200 to 700 mW.

Patients were observed once each month after the treatment. The minimum follow-up period was 6 months. At each visit, best-corrected Snellen visual acuity (BCVA), intraocular pressure (IOP) and a slit-lamp examination of anterior segment and dilated fundus examination were recorded. Fluorescein angiography and OCT measurements were performed for all patients at 1-, 3- and 6-month visits and thereafter only following retreatment. In all groups retreatment was administered with "as needed" dosing to the patients who retained active membranes based on fluorescein angiography and OCT.

Statistical analysis

Main outcome measures were visual acuity stabilization defined as no change or a gain in visual acuity and "need for retreatment" calculated as the number of applied treatment sessions required to close the CNV. For the purposes of data analyses, all vision data were converted to logMAR units (logarithm of the minimum angle of resolution). Data were entered into Microsoft Excel database and all statistical analyses were performed using STATISTICA v. 6.1 PL software. The Shapiro-Wilk test was used to determine whether the collected data were normally distributed. Non-parametric methods based on ranks were used if there was strong evidence against the assumption of normality. The Kruskal-Wallis one-way analysis of variance was used to examine the differences between all treatment subgroups. The comparison between particular subgroups was done using the Mann-Whitney U test, and the Wilcoxon signed rank test was used to examine the differences within a single subgroup. The association between applied therapy and the age and sex distributions were explored by Kruskal-Wallis test and Chi squared (χ^2) test, respectively.

Differences were considered significant at p<0.05 with a 95% confidence interval. However, in the analysis with

Table 2. Baseline best-corrected visual acuity (logMAR) measurements.

Baseline BCVA (logMAR)	PDT Group I N=100	IVB Group II N=104	TTT Group III N=222	All N=426
Minimum	0.15	0.22	0.10	0.10
Maximum	2.00	2.00	2.00	2.00
Median	0.70	1.00	1.40	1.00
Mean	0.62	0.82	1.10	0.85
Std. Dev. Confidence interval	0.31 (0.56–0.68)	0.52 (0.72–0.92)	0.45 (1.04–1.16)	0.51 (0.80–0.90)
Distribution analysis- test Shapiro-Wilk	W=0.92 p<0.0001	W=0.83 p<0.0001	W=0.53 p<0.0001	W=0.79 p<0.0001
Comparison between groups	Kruskal-Wallis Test H=116.06 p<0.0001; Mann-Whitney Test[1,2] Z=−5.02 p<0.0001; Mann-Whitney Test[1,3] Z=−10.57 p<0.0001; Mann-Whitney Test[2,3] Z=4.79 p<0.0001			

Mann-Whitney Test[1,2] comparison between PDT and IVB; Mann-Whitney Test[1,3] comparison between PDT and TTT; Mann-Whitney Test[2,3] comparison between IVB and TTT.

Table 3. Final best-corrected visual acuity (logMAR) measurements.

Final BCVA (logMAR)	PDT Group I N=100	IVB Group II N=104	TTT Group III N=222	All N=426
Minimum	0.22	0.22	0.10	0.10
Maximum	2.00	2.00	2.00	2.00
Median	0.70	1.00	1.40	1.10
Mean	0.74	0.79	1.15	0.92
Std. Dev. Confidence interval	0.34 (0.67–0.81)	0.52 (0.69–0.89)	0.41 (1.10–1.20)	0.47 (0.88–0.96)
Distribution analysis- test Shapiro-Wilk	W=0.88 p<0.0001	W=0.82 p<0.0001	W=0.59 p<0.0001	W=0.76 p<0.0001
Comparison between groups	Kruskal-Wallis Test H=95.19 p<0.0001; Mann-Whitney Test[1,2] Z=−2.79 p=0.0047 Mann-Whitney Test[1,3] Z=−9.67 p<0.0001; Mann-Whitney Test[2,3] Z=5.05 p<0.0001			

Mann-Whitney Test[1,2] comparison between PDT and IVB; Mann-Whitney Test[1,3] comparison between PDT and TTT; Mann-Whitney Test[2,3] comparison between IVB and TTT.

Mann-Whitney test combined with Kruskal-Wallis test, p value was considered significant at p<0.017 because of the Bonferroni correction.

RESULTS

Subjects

The demographic characteristics of all patients in the study are presented in Table 1. In total, 426 eyes of 426 patients were treated and none of these patients were excluded from analysis. The mean age of all patients was 74.6±8.4 years (range, 46 to 92 years). There were 132 men (31.0%) and 294 women (69.0%), divided into 3 subgroups according to the treatment given – 100 patients received verteporfin photodynamic therapy (PDT), 104 patients received intravitreal injections of bevacizumab (IVB), and the remaining 222 patients received transpupillary thermotherapy (TTT). Statistical analysis revealed that there were no statistically significant differences between the treatment subgroups in terms of age distribution (Kruskal-Wallis test p>0.05) and sex distribution (χ^2 test p>0.05).

Visual acuity

Overall stabilized visual acuity occurred in 329 patients (77.2%) at the final follow-up. This was defined as no change or an improvement in visual acuity. Sixty-four patients (15.0%) had an improvement in visual acuity and 97

Table 4. Comparison of baseline and final best-corrected visual acuity (logMAR) according to applied therapy – Wilcoxon signed rank test.

Treatment subgroup	Number of patients	T	Z	Statistical analysis
PDT	100	155.50	3.70	p=0.0002
IVB	104	391.50	0.25	p=0.8036
TTT	222	1357.00	1.09	p=0.2758

Table 5. Analysis of the number of applied treatment sessions in different subgroups.

Number of therapies	PDT N=100 (%)		IVB N=104 (%)		TTT N=222 (%)		All N=426 (%)	
One therapy	39	(39.0%)	34	(32.7%)	51	(23.0%)	124	(29.1%)
Two therapies	31	(31.0%)	30	(28.9%)	57	(25.7%)	118	(27.7%)
Three therapies	13	(13.0%)	25	(24.0%)	84	(37.8%)	122	(28.6%)
Four therapies	9	(9.0%)	13	(12.5%)	24	(10.8%)	46	(10.8%)
Five or more therapies	8	(8.0%)	2	(1.9%)	6	(2.7%)	16	(3.8%)
Comparison between groups	Kruskal-Wallis Test H=9.06 p=0.0108 Mann-Whitney Test[1,2] Z=−0.80 p=0.4017 Mann-Whitney Test[1,3] Z=−2.71 p = 0.0049 Mann-Whitney Test[2,3] Z=1.83 p = 0.0675							

Mann-Whitney Test[1,2] comparison between PDT and IVB; Mann-Whitney Test[1,3] comparison between PDT and TTT; Mann-Whitney Test[2,3] comparison between IVB and TTT.

(22.8%) patients had loss of vision. Baseline and final visual acuity measurements are summarized in Tables 2 and 3. Among all eyes, the mean logMAR baseline best-corrected visual acuity (BCVA) was 0.85 (Snellen equivalent in decimal 0.14). The study revealed that the differences in baseline BCVA were statistically significant among all treatment subgroups (Kruskal-Wallis test p<0.05). Patients included into the TTT subgroup had significantly worse visual acuity as well as more advanced retinal changes at baseline than patients included into the PDT and IVB subgroups. However, statistical analysis revealed that between the PDT and IVB treatment subgroups the differences in baseline BCVA were also statistically significant (Mann-Whitney test p<0.017). In the PDT subgroup the mean baseline BCVA was 0.62 (Snellen equivalent in decimal, 0.24). After the treatment, visual acuity was unchanged in 58 (58.0%) patients. Ten patients (10.0%) had an improvement and 32 (32.0%) patients had loss of vision. The final mean BCVA in the PDT subgroup decreased to 0.74 (Snellen equivalent in decimal, 0.18). In the IVB subgroup the mean baseline BCVA was 0.82 (Snellen equivalent in decimal, 0.15). After the treatment, visual acuity was unchanged in 64 (61.5%) patients. Twenty-one patients (20.2%) had an improvement and 19 (18.3%) patients had loss of vision. The final mean BCVA in the IVB subgroup increased to 0.79 (Snellen equivalent in decimal, 0.16). In the TTT subgroup the mean baseline BCVA was 1.10 (Snellen equivalent in decimal, 0.08). After the treatment, visual acuity was unchanged in 143 (64.4%) patients. Thirty-three patients (14.9%) had improvement and 46 (20.7%) patients had loss of vision. The final mean BCVA in the TTT subgroup slightly decreased to 1.15

(Snellen equivalent in decimal, 0.07) compared to baseline. Among all eyes, the mean logMAR final BCVA decreased to 0.92 (Snellen equivalent in decimal, 0.12). Differences of final BCVA were statistically significant either among all treatment subgroups or between them (Kruskal-Wallis test p<0.05 and Mann-Whitney test p<0.017, respectively).

Statistical analysis with Wilcoxon signed rank test of differences of baseline and final best-corrected visual acuity (BCVA) measurements within treatment subgroups is presented in Table 4. It revealed that the differences were statistically significant only in the PDT subgroup (p<0.05). However after PDT therapy, final BCVA was significantly worse from baseline, and the mean final BCVA was still best in the PDT subgroup. In both IVB and TTT subgroups we observed stabilization of vision after the treatment.

Treatment and safety

Among all eyes, the follow-up period ranged from 6 to 24 months and the mean follow-up was 12.3 (SD 2.6) months. The average number of treatment sessions was 2.34 (SD 1.17). Analysis of the number of applied treatment sessions in different subgroups is presented in Table 5. The highest number of patients (39.0%) who required only 1 treatment session for closing the CNV was in the PDT subgroup. The average number of treatment sessions in the PDT subgroup was 2.22 (SD 1.42). The smallest number of patients (1.9%) who required 5 or more treatment sessions for closing the CNV was in the IVB subgroup. The average number of treatment sessions in the IVB subgroup was 2.23 (SD

Med Sci Monit, 2012; 18(6): CR374-380

Nowak MS et al – The efficacy of verteporfin photodynamic therapy...

1.12). In the TTT subgroup the average number of treatment sessions needed for closing the CNV was 2.45 (SD 1.06). The study revealed that the differences in the number of treatment sessions between the particular subgroups were statistically significant only between the PDT and TTT subgroups (Mann-Whitney test p<0.017).

During the follow-up of patients in this study no thromboembolic events or deaths occurred. None of the patients developed serious ocular complications such as endophthalmitis, retinal detachment or post-treatment hemorrhage. Only transient increases in intra-ocular pressure were observed after IVB injections, and all resolved with topical medication.

DISCUSSION

Overall, the results of our study show good stabilization of vision in the majority of treated individuals. However, the subgroup analysis revealed that only in patients treated with intravitreal injections of bevacizumab was there a significant improvement in BCVA between the initial and final examinations. Stabilization of vision was achieved in 81.7% of patients after bevacizumab treatment. A direct comparison of our results to the results obtained in other studies conducted either with bevacizumab or ranibizumab is difficult to make due to the different inclusion criteria of the various studies. Another limitation is that other studies had different follow-up periods; however, the improvement of visual acuity in our study was in general agreement with the results of other recently published studies conducted on anti-angiogenic drugs [14,20–24]. In those studies intravitreal bevacizumab resulted in a statistically significant improvement in both visual acuity and anatomic outcome of the retina (decrease in foveal thickness). There were no statistically significant differences regarding BCVA between intravitreal bevacizumab at 1.25 mg or 2.5 mg doses; however, patients who received bevacizumab repeatedly every month obtained better results than patients treated with "as needed" dosage [21,25]. In our study bevacizumab was administered "as needed" after the first injection due to cost considerations. When the study was being conducted none of the anti-VEGF therapies were refundable by health insurance in Poland. Cost considerations aside, patients and clinicians might be encouraged to use bevacizumab because of its therapeutic properties. In our study off-label intravitreal bevacizumab has been shown to be effective in management of exudative AMD and appears to be a potential alternative to ranibizumab.

In our research, patients who met the same inclusion criteria were randomized to receive either intravitreal injection of bevacizumab or verteporfin photodynamic therapy (PDT) in a 1:1 ratio. Our results showed that after PDT treatment the final visual acuity measurements were significantly worse compared to baseline. The statistical analysis revealed that the number of patients with substantial loss of vision after therapy was much higher in the PDT subgroup than in the intravitreal bevacizumab subgroup (32.0% and 18.3%, respectively). We are not able to explain why the rate of patients with vision loss was so high in the PDT subgroup. Previously published studies showed a significant correlation between PDT outcomes and lesion size for minimally classic and occult with no classic lesions, but not for predominantly classic lesions. [5] Smaller lesions (≤4 disc areas) were associated with less loss of visual acuity, regardless of lesion

composition. However, we also found that the mean best-corrected visual acuity (BCVA) was the best in the PDT subgroup either before or after the treatment, and stabilization of vision was achieved in 68.0% of patients. Taking this into account, our study showed that photodynamic therapy with verteporfin may also be beneficial in selected patients with neovascular AMD. The preservation of vision-related functions after PDT had been also reported by other authors [4].

Transpupillary-thermotherapy (TTT) was another treatment method evaluated in our study for efficacy. The results obtained in the TTT subgroup showed good stabilization of vision in 79.3% of patients. Surprisingly, statistical analysis revealed no statistically significant differences between final and baseline best-corrected visual acuity measurements in this treatment subgroup. Although the mechanism of action with TTT is still unclear, the low retinal irradiance and low temperature increase is potentially a therapeutic advantage. In our study, both intravitreal bevacizumab and transpupillary thermotherapy showed good stabilization of vision. Direct comparison of TTT with other treatment methods is impossible because of the different eligibility criteria used. Patients included into the TTT subgroup had significantly worse visual acuity and more advanced retinal changes at baseline than patients included into the bevacizumab subgroup. However, the stabilization of vision demonstrated after transpupillary thermotherapy in our research is in the agreement with the results obtained in other studies. Previously published data showed stabilization of vision in 75% of patients with neovascular AMD with predominantly classic or occult lesions [17,18].

Another outcome of our study was the "need of retreatment", calculated as the number of treatment sessions needed to close the CNV. Overall, the average number of treatment sessions among all patients was 2.34 (SD 1.17). Statistical analysis revealed no statistically significant differences between patients randomized to receive either PDT or intravitreal injections of bevacizumab. Low retreatment rates were also observed in other studies evaluating intravitreal bevacizumab, PDT and TTT [8,17,26,27]. The incidence of complications in our study was low, and no serious adverse events were observed during the follow-up. A much larger randomized study is necessary to document the incidence of both ocular and systemic adverse effects.

Despite advances, each of the treatments reported in our study concentrates mainly on a single mechanism of choroidal neovascularization in AMD. With that in mind, different combinations of CNV therapy have been investigated, such as combination therapy with PDT and bevacizumab or with PDT and intravitreal triamcinolone and a "triple therapy" (combining bevacizumab, PDT and the steroid dexamethasone) [3,8,26–28]. All combinations led to vision benefit for most patients and the number of retreatments was lower than after treatment delivered as monotherapy. However, we do not have an algorithm to inform us of which patient may respond best to a particular combination, or whether a patient may respond better to more of 1 agent, and less of another.

Our study has limitations, including the lack of a control group. It would be interesting to compare the efficacy of different treatment methods with a natural history of the disease. Another possible limitation was the use of the Snellen chart to assess visual acuity. Converting visual acuity data to

logMAR units was carried out, but did not represent a true ETDRS rigor. Supplementary information of central retinal thickness (CRT) would be also useful to show the extent and effect of therapy in the reduction of macular edema. A comparative study with CRT measurements would be helpful to provide further information on the best treatment regimen.

The results of our study showed that current methods for treatment of age-related macular degeneration each have their own limitations, and many patients often experience rapid loss of central vision with profound impact on everyday life. Although their further improvement is still possible, it is also reasonable and necessary to look for more successful and definitive alternatives. The new perspective of CNV therapy is the use of gene therapy, and a future focus will be identification of specific gene, gene products, metabolic pathways and metabolites related to the disease. This information, in addition to being suitable for gene- and target-specific therapies, will also allow the development of new procedures to improve diagnosis and/or prognostic evaluation of the disease [29–32].

Conclusions

Based on our observations we conclude that intravitreal injections of bevacizumab had the best efficacy in the improvement of final BCVA; however, both intravitreal bevacizumab and TTT demonstrated good stabilization of vision. Although after PDT final BCVA was significantly worse from baseline, it may also be beneficial for some patients with neovascular age-related macular degeneration.

Acknowledgments

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