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RETINAL DISORDERS

Combined photodynamic therapy and intravitreal triamcinolone for neovascular age-related macular degeneration: effect of initial visual acuity on treatment response

Ramin Schadlu · Steven M. Kymes · Rajendra S. Apte

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Abstract
Purpose To evaluate visual outcomes in combination therapy with photodynamic therapy (PDT) and intravitreal triamcinolone acetonide (IVTA) for subfoveal choroidal neovascularization (CNV) from age-related macular degeneration (AMD).
Methods Charts of 39 eyes from 38 patients with exudative AMD treated with PDT and 4 mg of triamcinolone acetate injected intravitreally were reviewed retrospectively. Visual data, angiographic lesion type, prior PDT exposure, number of treatments, and follow-up were recorded. Snellen visual acuities were converted to LogMAR for all calculations. Lines of vision lost or gained pertain to calculated ETDRS lines of vision (via LogMAR).
Results Twenty-two of the choroidal neovascular membranes were occult, and 17 were classified as predominantly classic. Mean follow-up was 43 weeks. The average number of treatments was 2.23. At final follow-up, 11 eyes (28.21%) experienced improved visual acuity, 8 eyes (20.51%) were stable, and 20 eyes (51.28%) had worsened. No significant difference in treatment response was found between angiographic subtypes ($p>0.59$). Lack of previous PDT exposure did not improve treatment outcomes ($p>0.77$). Pre-treatment visual acuity (PTVA) was determined as a strong predictor of treatment outcome in our study cohort. Visual acuity of 20/200 or worse was associated with a 40.9% chance of *some* improvement and a 35.75% chance of three or more lines of improvement. Visual acuity better than 20/200 was associated with an 89.4% chance of no improvement and a 58.8% chance of three or more lines of visual loss.
Conclusion Counter to previously reported results with combination therapy, the majority of our patients (72%) did not demonstrate improved vision and 51% lost vision. When PTVA was accounted for, selected patients benefitted significantly from treatment. PTVA may be a useful and simple patient selection tool for combination treatment with PDT and IVTA.

Keywords AMD · PDT · Verteporfin · Triamcinolone

R. Schadlu · S. M. Kymes · R. S. Apte (✉)
Department of Ophthalmology and Visual Sciences,
Washington University in St. Louis School of Medicine,
Barnes Retina Institute,
660 S. Euclid Avenue, Box 8096, St. Louis, MO 63110, USA
e-mail: apte@vision.wustl.edu

Introduction

Age-related macular degeneration (AMD) is the leading cause of blindness in people over 50 years of age in many industrialized nations [1]. Macular photocoagulation was the first milestone for stabilization of the neovascular form of AMD [2]. Using newer interventional therapies including photodynamic therapy (PDT) with or without triamcinolone and anti-VEGF agents such as ranibizumab, bevacizumab and pegaptanib, vision can potentially be stabilized in a majority of patients with subfoveal choroidal neovascularization (CNV) from AMD [3]. Newer strategies also improve vision in a large subset of patients [4–6].

PDT with verteporfin (Visudyne) was the first US FDA approved treatment to demonstrate stabilization of vision in subfoveal CNV from AMD [7–10].

Previous studies have reported stabilization and significant visual gain due to combination therapy with PDT and intravitreal triamcinolone acetonide (IVTA) [9–15]. Augustin et al. note in two separate studies including a prospective interventional study of 41 eyes that visual acuity improved

in the majority of patients [11, 12]. Spaide reports that combination treatment is particularly efficacious in "newly-treated" (PDT-naïve) eyes, with an average improvement of 2.5 lines of vision [14]. Another important observation was the lower than anticipated mean number of required treatments [11–13, 16, 17]. This is of theoretical advantage for multiple reasons, such as a less damaging effect to healthy choroicapillaris from repeated PDT applications. Spaide et al. report visual improvement in the majority of patients, particularly in patients who have not previously undergone PDT [13, 14]. Other studies, however, have not been able to reproduce these results [18]. To our knowledge, pre-treatment visual acuity (PTVA) has not yet been invoked as a predictor of outcome in combination treatment. We conducted a single center, single physician retrospective chart review to evaluate the results of combination therapy with PDT and IVTA for subfoveal CNV from AMD.

Methods

Institutional review board approval was obtained for this study. All patients underwent comprehensive dilated biomicroscopic ophthalmologic evaluation. Best-corrected Snellen visual acuity was determined and intraocular pressure (IOP) monitored at each visit. Ancillary testing such as fluorescein angiography (FA) was performed as needed for standard care. None of the patients carried a diagnosis of ocular hypertension or glaucoma. Intravitreal anti-angiogenics were not yet available at the time our patients underwent combination treatment.

Thirty-nine eyes of 38 patients with exudative AMD were treated with PDT (applied using standard Visudyne protocol) combined with 4 mg of IVTA (Kenalog-40, Bristol-Meyers Squibb, NY, USA) as part of usual care. The treatments were performed within a week of each other. Lesions measuring greater than 5,400 μm were excluded. Visual data was extracted retrospectively via chart review and included the number of PDT and IVTA applications, weeks of follow-up after PDT and IVTA, as well as pre- and post-treatment visual acuities. Indication for re-treatment was persistent leakage on fluorescein angiography with associated sub-retinal fluid on biomicroscopy.

Visual acuities were converted to their LogMAR equivalents for all calculations [19]. Visual acuity was recorded for all patients and subanalysis was performed based on angiographic lesion sub-type, such as classic and occult CNV, and on PDT-naïve and previously PDT-exposed patients. Patients were assigned to three groups depending on visual outcome. To accomplish this, visual acuity immediately before treatment was compared to vision at the final follow-up visit. "Improved visual acuity" was defined as any improvement above baseline; "worse visual acuity" was defined as any decline of acuity compared to baseline. "Unchanged visual acuity", therefore, literally indicated no increase or decrease in LogMAR score (we also refer to this as "stabilization").

Visual acuity results were evaluated to determine if the data met the assumptions of normalcy required for use of the t-test for comparison of means. Where this assumption was met the t-test was used, if not, the nonparametric Wilcoxon test was used. The proportion of individuals experiencing improvement (or decline) in visual acuity among those with a specific PTVA was calculated by dividing those with the outcome of interest by the total of those with the level of visual acuity in question. The 95% confidence intervals about this estimate are reported using the score method incorporating continuity correction [20].

Results

Fluorescein angiography allowed classification of 22 of the choroidal neovascular membranes as occult, and the remaining 17 as predominantly classic. Median PTVA for all patients was 20/200, median final acuity was 20/400. Mean follow-up was 43 weeks; 32 eyes had a follow-up of at least 6 months; 21 patients (22 eyes) were observed over 10 months. Only 7 eyes had a follow-up of less than 6 months. The average number of treatments was 2.23 for all patients, and in patients followed over 6 months, this number was 2.39.

Twenty-one of the 39 eyes (53.84%) were PDT-naïve at the time of IVTA injection. At the final follow-up visit, 11 eyes (28.21%) experienced improved visual acuity, 8 eyes (20.51%) were stable, and 20 eyes (51.28%) had worsened (Fig. 1).

Of note, there was no significant difference in treatment response between occult and predominantly classic lesions (Fig. 2).

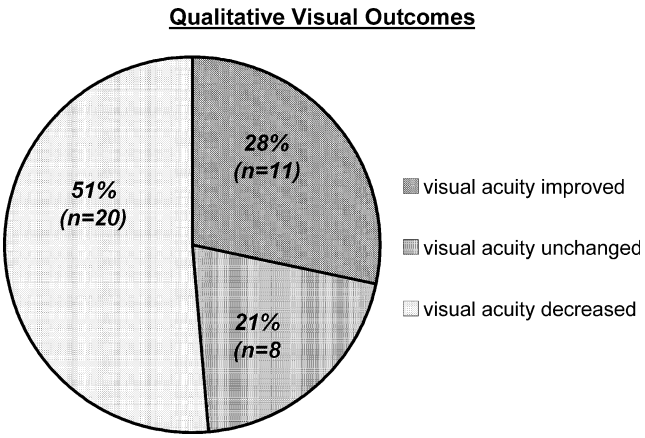

Fig. 1 Qualitative visual outcomes after combination therapy with PDT and IVTA

Lesion Type	Number of patients	Mean improvement in LogMar Units (±SEM)	Mean worsening in LogMar Units (±SEM)
Occult	22	0.30 (±0.07)	-0.64 (±.12)
Predominantly Classic	17	0.28 (±0.34)	-0.59 (±0.15)
p-value (T-Test)		0.59	0.90

Fig. 2 Visual outcomes based on fluorescein angiographic subtypes

Although previous reports have suggested that PDT-naïve patients do substantially better after combination therapy than PDT-experienced patients, analysis in our cohort of patients demonstrated that the treatment response in PDT-naïve patients was similar to PDT-experienced subjects with no statistical difference in visual gain or loss between the two groups (Fig. 3).

These results contrast earlier reports that PDT-naïve patients fare better than PDT-exposed individuals with regard to final visual outcomes after combination PDT-IVTA treatment. Although 28% of eyes had improved, the majority of eyes in this study experienced either no change or decline. This is distinctly different from the results of previously published articles [11–14, 16].

In the group of eyes that had improved vision, median pre-treatment visual acuity was 20/200 and median post-treatment visual acuity was 20/100 ($p<0.001$ using the Wilcoxon test). An average of 1.36 treatments were performed in this group. Mean follow-up was 43 weeks (Fig. 4). Patients who maintained their vision had a median pre- and post-treatment visual acuity of 20/150. On average, these patients required 2.62 treatments. Mean follow-up in this group was 39 weeks (Fig. 4). Visual loss occurred in 51% of patients. Median PTVA in these patients was 20/100. Median post-treatment visual acuity was 6/200 ($p<0.0001$ per Wilcoxon). Patients in this group had undergone an average of 2.55 interventions. Mean follow-up was 45 weeks (Fig. 4).

Patients who lost vision needed more treatments, suggesting that lesions in these patients continued to remain active. There was no statistically significant difference in the number of PDT and IVTA applications required in these patients and individuals who experienced no change in vision. These two groups of patients were therefore collectively analyzed to increase statistical power and referred to as the "no improvement group" with an average of 2.57 treatments. We compared this group to the patients who experienced vision improvement. Data analysis using the student t-test found these two groups to be statistically significantly different from each other with respect to the number of PDT and IVTA treatments as well as visual outcome ($p_{\text{treatments}}=0.02$, $p_{\text{vision}}=0.00004$). An important finding of this study is that the overwhelming majority, 72% of eyes, either had no change in vision or lost vision.

Data analysis revealed an inverse correlation between PTVAs and final outcome. Next, we calculated the proportion of people who experienced visual change at various PTVA cutoffs. At the 20/200 cutoff level (22 eyes of 22 patients), we found that 9 eyes (41%) showed improvement, 9 eyes experienced visual loss (41%), which was consistent with stabilization 59%. When PTVA was better than 20/200, a probability of 89.4% was calculated for lack of visual improvement (Fig. 5).

Visual acuity represented a good selection criterion for our patient sample. In a comparable patient sample, 40.9% of patients can be expected to respond with visual improvement if a patient's initial vision is 20/200 or worse and PDT and IVTA combination treatment are applied. When visual acuity was better than 20/200, nearly 90% of our patients could expect to experience lack of visual improvement or possible decline.

While not as stringent in assessing visual loss, the *traditional* quantifiers of moderate (>3 lines of vision) and severe (>6 lines of vision) vision loss or gain are still an important tool in assessing clinically meaningful changes (Fig. 6).

In our treatment cohort the following results were extracted: 8 of 39 (20.51%) eyes experienced moderate visual gain (>3 lines), and 2 of 39 eyes (5.12%) recorded a visual gain of >6 lines of vision. Interestingly, all but one eye that gained at least a moderate amount of vision had pre-treatment acuities of 20/200 or worse, and the two eyes that gained 6 or more lines of vision had very poor vision of 1/200 and 2/200. Six out of the 8 eyes (75%) with at least moderate visual gain were classified as occult lesions, two were predominantly classic. One of the two eyes that gained at least 6 lines of vision were PDT naïve. The minority of the eyes (3 out of 8) that experienced at least moderate visual gain were PDT naïve. This stands in stark contrast to previous studies concluding that newly treated patients fare better [13, 14]. Fifteen out of 39 eyes (38.4%) sustained at least moderate visual loss (>3 lines), and 9 eyes (23.1%) suffered severe visual loss (≥6 lines). Nine (60%) lesions with at least moderate visual loss were occult, six (40%) were predominantly classic. Seven of these 15 eyes (46.7%) were PDT naïve. Finally, severe vision loss was observed in 9 cases (23.1%). Eight (88.9%) of these cases occurred in patients whose PTVA was better than 20/200.

Previous PDT Exposure	Number of patients	Mean improvement in LogMar Units (±SEM)	Mean worsening in LogMar Units (±SEM)
PDT naïve	21	0.438 (±0.15)	0.53 (±0.14)
Previously PDT-exposed	18	0.444 (±0.10)	0.59 (±0.11)
p-value (T-Test)		0.98	0.77

Fig. 3 Visual outcomes in PDT-naïve versus previously PDT-exposed patients

Fig. 4 Quantitative treatment outcomes after combination therapy

Outcome	Incidence	Median PTVA)	Median final acuity)	Average number of treatments (±SEM)	Mean follow-up in weeks
Visual Gain n=11	28 %	20/200 (20/50-3/200)	20/100 (20/40-20/800)	1.36 (±0.15)	43
No change n=8	21 %	20/150 (20/40-1/200)	20/150 (20/40-1/200)	2.62 (±0.5)	39
Visual Loss n=20	51 %	20/100 (20/60-1/200)	6/200 (20/150-2/200)	2.55 (±0.62)	45

Only one case with visual acuity of 20/200 or worse experienced severe visual loss (Fig. 6).

In summary, angiographic classification did not appear to affect treatment outcomes in any well-defined manner. Occult lesions may have a tendency to respond more favorably. We were unable to reproduce the previous finding that PDT naïve patients were more treatment-responsive. The factor most related to outcomes was pre-treatment visual acuity (Fig. 6). We determined predictive values to assess how useful this variable is as a risk stratification tool (Fig. 6). We utilized the above-mentioned two categories: visual acuity better than 20/200 and visual acuity equal to or worse than 20/200. In the latter group we calculated a 35.75% chance for improvement of three or more lines, and a 9.1% chance for improvement of at least six lines. For patients with PTVA better than 20/200, we determined a 58.8% chance of worsening three or more lines and a 47.1% chance of worsening more than six lines (Fig. 6).

Figure 7 depicts an overview of the collected patient data.

In order to minimize the risk that our favorable findings in legally blind patients was confounded by shorter follow-up, we conducted a subgroup analysis excluding patients with follow-up of less than 6 months. This group was comprised of 32 patients. Seven of the 23 patients (30.4%) with initial visual acuity of 20/200 or worse improved their visual acuity by three or more lines of vision. Only one of the 9 patients (11.1%) with initial acuity better than 20/200 experienced a similar improvement. The only three patients with a 5-line visual improvement were found in the group of patients with visual acuity of 20/200 or below. Average improvement in this group was 0.58 LogMAR units (nearly 6 ETDRS lines). These findings confirm our impression that lower levels of initial visual acuity may be a good predictor of visual outcome.

Discussion

This article is one of the largest retrospective reviews of PDT and IVTA combination treatments. Our study contains all the limitations of a retrospective review such as selection bias. Although some of our results are consistent with previous reports such as the lower than expected number of PDT re-treatments with combination therapy, several of our findings are significantly different [11–13, 16]. Some of the visual loss detected in our study may be due to cataract formation. No attempt was made to pinpoint these patients due to the fact that current anti-angiogenic interventions only have a minimal risk of cataract formation. In order to see how the combination of PDT and IVTA performs compared to these treatments, we did not exclude or separate cataract formation from our analysis of visual outcomes.

The overwhelming majority, 72% of our patients treated with combination therapy, did not demonstrate improved vision. On the contrary, 51% of patients lost vision. This

Fig. 5 Visual outcomes (presence or absence of *any* amount of visual gain at final follow-up)

Outcome	Pre-treatment acuity *equal or worse than 20/200*	Pre-treatment acuity *better than 20/200*	Pre-treatment acuity of *equal or worse than 20/200* predictive of improvement (in percent)	Pre-treatment acuity *better than 20/200* predictive of no improvement (in percent)
Visual gain (any)	n=9	n=2	40.9%	n/a
No visual gain	n=13	n=17	n/a	89.4%

Fig. 6 Visual outcomes (traditional criteria for moderate and severe visual change in AMD) related to pre-treatment acuity and PDT exposure

Outcome	Pre-treatment acuity of *equal or worse than 20/200*	Pre-treatment acuity *better than 20/200*	PDT naïve	Previously PDT-exposed	Total	Pre-treatment acuity of *equal or worse than 20/200* predictive of improvement (in percent)	Pre-treatment acuity *better than 20/200* predictive of worsening (in percent)	95% Confidence Interval
Improvement of ≥ 3 lines	n=7	n=1	N=3	n=5	n=8	35.75%	n/a	9.3%-71.4%
Improvement of ≥ 6 lines	n=2	n=1	n=1	n=1	n=2	9.1%	n/a	1.6%-71.3%
Visual loss ≥ 3 lines	n=5	n=10	n=7	n=8	n=15	n/a	58.8%	31.8%-82.1%
Visual loss ≥ 6 lines	n=1	n=8	n=4	n=5	n=9	n/a	47.1%	17.0%-78.9%

stands in contrast to previous publications [11–14, 16], which claim improvement in most patients. Furthermore, some reports conclude that PDT-naïve patients respond more favorably to combination therapy [13, 14]. We did not find such a relationship in our cohort of patients. The majority of our patients with significant improvement in central vision were PDT-experienced (Fig. 6). There was no statistically significant difference in treatment response

Fig. 7 Comprehensive patient data. "Active lesion" defined as neovascular complex with leakage on fluorescein angiography. V_A=visual acuity

Patient	Fluorescein subtype	PDT naïve	Number of Treatments	follow-up (weeks)	Initial V_A	V_A at 6 months	6-month change (LogMAR)	Final V_A	Final V_A change (LogMAR)	Active lesion at 12 months	
Patient 1	occult	no	3	72	20/400	20/800	0.30	6/200	0.22	yes	
Patient 2	occult	yes	1	48	3/200	3/200	0	2/200	0.18	n/a	
Patient 3	occult	yes	1	12	20/60	n/a	n/a	20/400	0.82	n/a	
Patient 4	classic	yes	4	33	20/400	20/400	0	20/400	0	n/a	
Patient 5	occult	yes	1	14	20/40	n/a	n/a	2/200	1.70	n/a	
Patient 6	occult	yes	1	28	5/200	4/200	0.10	4/200	0.10	n/a	
Patient 7	classic	no	2	14	20/100	n/a	n/a	20/150	0.18	n/a	
Patient 8	occult	no	8	52	20/80	20/200	0.40	8/200	0.80	yes	
Patient 9	occult	no	1	24	20/80	20/400	0.70	20/400	0.70	n/a	
Patient 10	classic	no	1	12	20/150	n/a	n/a	20/150	0	n/a	
Patient 11	occult	yes	1	30	20/400	20/800	0.30	20/800	0.30	n/a	
Patient 12	occult	yes	6	24	20/70	5/200	1.06	5/200	1.06	n/a	
Patient 13	classic	yes	1	44	20/60	20/40	-0.18	20/40	-0.18	n/a	
Patient 14	occult	yes	1	12	20/200	n/a	n/a	20/100	-0.30	n/a	
Patient 15	classic	no	1	63	1/200	1/200	0	20/800	-0.70	no	
Patient 16	occult	no	2	12	2/200	n/a	n/a	1/200	0.30	n/a	
Patient 17	classic	yes	2	44	1/200	1/200	0	1/200	0	n/a	
Patient 18	occult	yes	1	36	20/200	20/400	0.30	20/400	0.30	n/a	
Patient 19	classic	no	5	76	20/70	20/80	0.06	20/200	0.46	yes	
Patient 20	classic	no	2	82	20/80	20/200	0.40	20/800	1.00	no	
Patient 21	occult	yes	2	45	20/80	20/30	-0.43	20/40	-0.30	n/a	
Patient 22	occult	no	3	96	20/100	20/100	0	20/200	0.30	yes	
Patient 23	occult	no	2	54	3/200	20/200	-0.82	20/400	-0.52	yes	
Patient 24	classic	no	1	61	20/200	20/60	-0.52	20/80	-0.40	no	
Patient 25	classic	no	2	51	20/200	20/100	-0.30	20/200	0	n/a	
Patient 26	classic	no	2	48	20/400	20/800	0.30	2/200	0.70	n/a	
Patient 27	occult	yes	1	40	20/200	20/150	-0.12	20/150	-0.12	n/a	
Patient 28	occult	yes	1	44	20/60	20/80	0.12	20/60	0	n/a	
Patient 29	occult	yes	3	32	20/40	20/40	0	20/40	0	n/a	
Patient 30	classic	yes	3	51	20/100	20/100	0	20/100	0.18	yes	
Patient 31	classic	yes	3	52	3/200	3/200	0	2/200	0.18	no	
Patient 32	occult	yes	1	56	20/200	20/200	0	20/150	-0.12	no	
Patient 33	classic	no	6	90	20/50	20/100	0.30	5/200	1.20	yes	
Patient 34 OD	classic	no	5	48	20/400	20/200	-0.30	20/400	0	n/a	
Patient 34 OS	occult	yes	1	48	20/80	20/100	0.10	20/400	0.70	n/a	
Patient 35	classic	yes	1	36	2/200	20/40	-1.70	20/50	-1.60	n/a	
Patient 36	occult	no	2	47	20/200	20/100	-0.30	20/100	-0.30	n/a	
Patient 37	classic	yes	1	32	20/200	20/400	0.30	20/400	0.30	n/a	
Patient 38	occult	no	2	12	20/200	n/a	n/a	20/100	-0.30	n/a	

between classic and occult lesions. There was however a trend for occult lesions to fare better.

PTVA appears to be a useful parameter in predicting treatment outcomes. The incidence of visual improvement in our sample increases to 40.9% when 20/200 is chosen as the cutoff level of vision for analysis. Our study data suggests that when used in patients whose vision is better than 20/200, combination treatment with PDT and IVTA has an 89.4% chance of no improvement or visual decline. More specifically, there is a 58.8% risk of losing three or more lines and a 47.1% risk of losing six lines or more. In the current era of anti-VEGF therapy and the recent interest in using PDT with anti-VEGF agents as combination therapy, this study highlights the need to perform controlled randomized trials in order to truly assess the efficacy of various combinations in treatment of neovascular AMD.

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