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One-year results of photodynamic therapy for small predominantly classic choroidal neovascular membranes secondary to age-related macular degeneration

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PURPOSE. *To determine the visual and angiographic outcomes of patients with small predominantly classic choroidal neovascular membranes (CNV) undergoing photodynamic therapy (PDT).*
METHODS. *The subjects were a cohort of patients with age-related predominantly classic CNV with lesion size of greatest linear diameter of 2000 µm or less treated with PDT. Lesion size and visual acuity were recorded at baseline and at 3-month intervals. Visual treatment failure was defined as either loss of at least 15 letters or visual acuity less than 35 letters on a modified Early Treatment Diabetic Retinopathy Study chart. Lesion treatment failure was defined as increase in greatest linear diameter (GLD) of at least 500 µm.*
RESULTS. *Twenty-five eyes of 25 patients were included. Visual treatment failure occurred in 16 and mean visual acuity dropped from 58 letters to 34 letters ($p<0.0001$). In 11 of these patients this occurred within the first 3 months. Lesion treatment failure occurred in 18 patients. Mean GLD increased from 1331 to 2935 µm ($p<0.0001$). Early growth of the lesion was associated with poor visual outcome with growth in GLD in the first 3 months of 310 µm in patients without eventual visual treatment failure and 1131 µm in patients with eventual visual failure ($p=0.027$).*
CONCLUSIONS. *Small predominantly classic lesions commonly cause visual deterioration if treated with PDT alone. In the first year over 50% may lose at least 15 letters or drop below 35 letters, with most visual loss occurring in the first 3 months. Visual loss is associated with early lesion growth. (Eur J Ophthalmol 2007; 17: 760-7)*

KEY WORDS. *Age-related macular degeneration, Photodynamic therapy, Outcome, Choroidal neovascular membranes*

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INTRODUCTION

Ranibizumab (Lucentis®, Novartis Pharmaceuticals) and pegaptanib (Macugen®, Pfizer Pharmaceuticals) are currently licensed, but have not yet received approval from the National Institute for Health and Clinical Excellence (NICE). Ophthalmologists in England and Wales are therefore still limited to the use of photodynamic therapy (PDT) for patients meeting the criteria for treatment under NICE guidelines, or must apply to their Primary Care Trust (PCT) to have pegaptanib, ranibizumab, or PDT funded for other lesions. However, there is evidence that newer drugs such as ranibizumab (Lucentis) targeting VEGF that require intravitreal injection may have superior results to PDT for predominantly classic lesions (1).

The Treatment of Age-related Macular Degeneration with PDT study (TAP) determined that patients with >50% classic component subfoveal choroidal neovascular membranes were statistically likely to benefit from treatment from the 1- and 2-year follow-up data (2). However,

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the subgroups were predefined and data were not presented regarding success of treatment in relation to original lesion size.

One might speculate that PDT could prevent small lesions from growing and that vision might be maintained by treating small lesions early.

We therefore examined outcomes for a subgroup of our patients with exudative age-related macular degeneration undergoing PDT presenting with small lesions. This information would help to determine the optimum follow-up protocol for such patients. It was also considered important to follow patients to the conclusion of treatment or to 1 year to overcome the shortcomings of previous reported studies.

METHODS

Data had been collected at our unit prospectively for all patients referred for assessment of choroidal neovascular membranes. This was a requirement of the Verteporfin PDT Cohort Study for the United Kingdom. Multicentre Research Ethics Committee approval had been obtained from the London Metropolitan Multicentre Research Ethics Committee and also from our Local Research Ethics Committee to collect data for this National Cohort Study.

We selected data for a subcohort of patients who had undergone treatment with PDT for choroidal neovascular membranes associated with age-related macular degeneration with lesions of greatest linear diameter (GLD) of 2000 μm or less. Additional data were obtained from analysis of case notes or digital fluorescein angiograms. Patients were excluded from our study if the lesion was minimally classic or occult, if they had undergone previous treatments for choroidal neovascular membranes in the affected eye, if they underwent injection of triamcinolone in conjunction with PDT, if they received treatments other than PDT before treatment failure, or if they had initially been observed before becoming eligible for treatment based on an angiogram at a later date. They were also excluded if they were diabetic or had any ocular comorbidity other than previous cataract surgery. Patients with cataract were included if cataract was mild (less than any LOCS III grades NO3, NC3, CO3, or P2).

Treatment was according to the TAP study protocol (2) adding 1000 μm to the GLD of the combined components of the lesion using the Zeiss Visupac software to determine the spot size. Treatment was for 83 seconds 5 minutes after the end of an infusion over 10 minutes of 6 mg/m^2 of verteporfin. Treatment was repeated at 3-month intervals if there was continued leakage irrespective of the lesion characteristics at that stage.

Data were retrieved from presentation and subsequent follow-up appointments (usually at 3-month intervals). Data included demographic data, best-corrected logMAR visual acuity on a modified Early Treatment Diabetic Retinopathy Study (ETDRS) chart at 2 or 4 meters (BSCVA), and the GLD of lesions.

The two outcome measures were visual treatment failure and lesion treatment failure. If vision worsened by 15 letters or more logMAR or if vision dropped to less than 35 letters (equivalent to 6/60 Snellen or logMAR 1.0) this was considered a vision treatment failure and if the GLD increased by at least 500 μm at any follow-up this was considered lesion failure. Final outcome was defined as the last follow-up data entry value for that patient. Differences and the pretreatment and follow-up values were tested for normality (Shapiro-Wilk test). The differences in mean GLD and BSCVA were compared using Student t test.

RESULTS

A total of 29 patients matching inclusion criteria were identified with choroidal neovascular membranes secondary to age-related macular degeneration. Of these, four patients were excluded according to the above criteria (Fig. 1). For one patient both eyes individually met the inclusion criteria. Only the eye with longer follow-up (study no. 20) was included in the study.

Baseline characteristics are shown in Table I. The age range was 60 to 89 years at first treatment. The baseline range of visual acuities was 35 to 80 letters (equivalent to logMAR 1.0 or Snellen 6/60 to logMAR 0.10 or Snellen 6/7.5).

Follow-up (Fig. 1) was completed to 1 year (18 patients) or to the point of exit from the study (7 patients) in all patients.

The reasons for exiting the study before 12 months were visual treatment failure (visual acuity less than 35 letters) and decision not to treat further at the 3-month visit (study no. 3), visual treatment failure at the 6-month visit (study nos. 7, 12, 14, 22, and 24), and refusal to undergo a second treatment at 9 months because of back pain re-

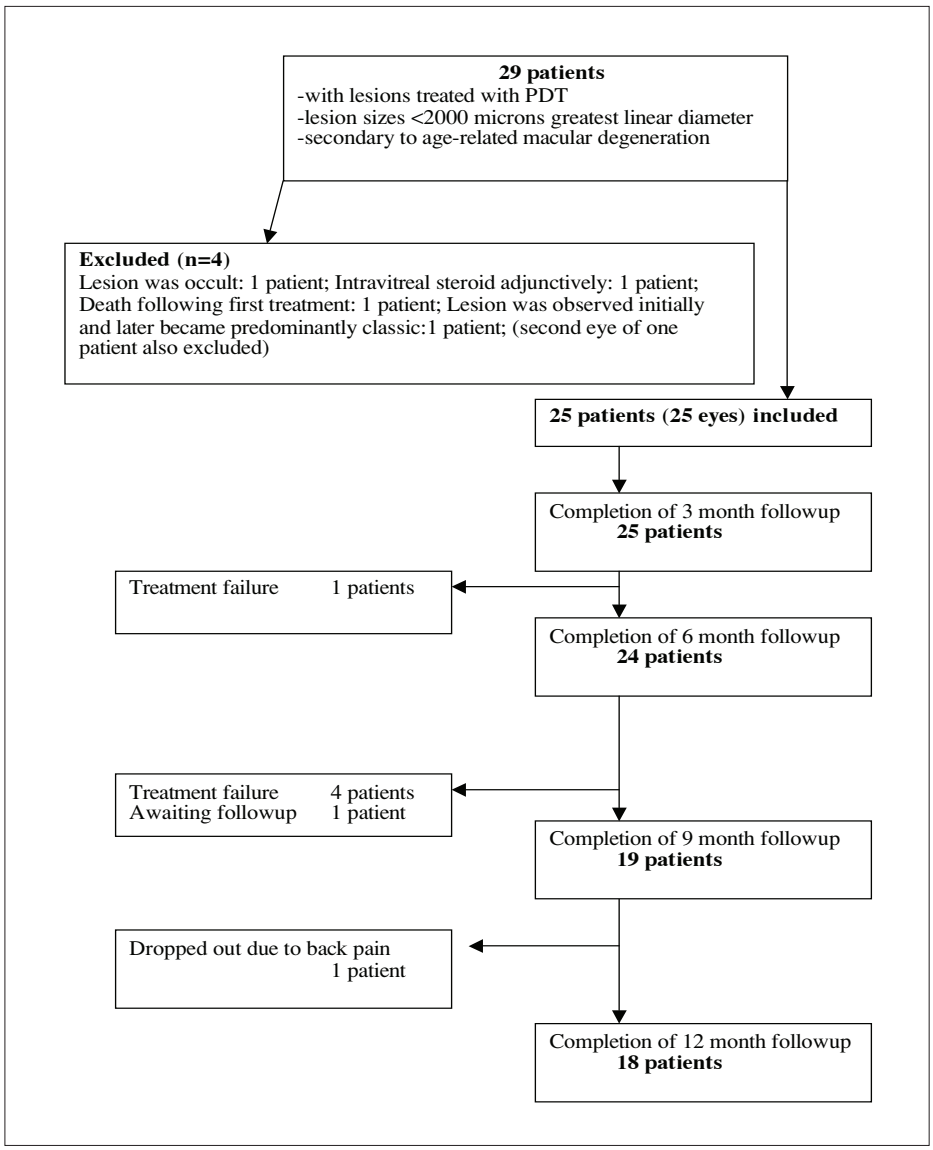

Fig. 1 - *Flow chart showing pathways of patients during the study.*

lated to the initial verteporfin infusion (study no. 5).
Patients required a range of one to five sessions of PDT (mean 2.7) in the first year.
Comparing baseline with final outcomes (Tabs. II, III, and IV), in 13 of 25 patients vision dropped to less than 35 letters and 15 or more letters were lost in 15 patients. Overall 16 eyes suffered visual treatment failure. In 4 patients vision was stable (less than 15 letters lost). In 5 patients vision improved (by 1, 2, 5, 13, and 39 letters).
In 18 patients the greatest linear lesion diameter increased by 500 µm (lesion treatment failure) or more and in 13 patients the increase was 1000 µm or more. In only one patient did lesion size decrease (by 890 µm) by final follow-up.

Timing of visual treatment failure (Tab. III)

Failure occurred in 11 by 3 months after treatment, 3 at 6 months, and 2 at 12 months.

Timing of lesion treatment failure

Twelve patients failed by the 3-month visit (52%), a further 4 failed by 6 months, 1 at 9 months, and 1 at 12 months.
Of the 12 who failed due to lesion increase at 3 months, 10 also failed visually during this period.
The reduction in mean visual acuity from 58 letters (equivalent to logMAR 0.54 or Snellen 6/21) to 34 let-

TABLE I - BASELINE CHARACTERISTICS OF 25 PATIENTS (25 eyes) INCLUDED IN THE STUDY

					Fluorescein angiogram characteristics			
Study no.	**Age, yr**	**Lesion characteristics**	**Lesion size**	**VA treated (letters on modified ETDRS chart)**	**FFA % classic**	**FFA late leak***	**Hemorrhage**	**Exudates**
1	77	Pr	1570	54	50	N	Y	Y
2	77	Cl	1010	64	100	N	N	N
3	81	Cl	540	70	100	N	N	N
4	89	Cl	1800	60	100	N	Y	N
5	77	Cl	1920	58	100	N	Y	N
6	79	Pr	1730	51	53	Y	N	N
7	75	Cl	1350	70	100	N	N	N
8	83	Cl	1790	35	100	N	N	N
9	82	Cl	1750	54	100	N	N	N
10	73	Cl	1200	35	100	N	N	N
11	73	Cl	310	60	100	N	Y	N
12	84	Cl	1500	69	100	N	N	N
13	84	Cl	570	59	100	N	N	N
14	78	Cl	1270	58	100	N	N	N
15	60	Cl	1940	69	100	N	N	N
16	82	Pr	1960	53	55	Y	Y	Y
17	83	Cl	650	54	100	N	N	N
18	79	Cl	1220	80	100	N	N	N
19	77	Cl	1480	69	100	N	N	N
20	76	Pr	970	54	94	N	Y	N
21	84	Cl	1170	65	100	N	N	N
22	84	Pr	1370	35	50	Y	Y	N
23	81	Pr	1080	44	71	N	Y	N
24	85	Cl	1690	50	100	N	Y	N
25	71	Cl	1440	70	100	N	N	N

*None of the patients had pigment epithelial detachment as a component of the lesion
VA = Visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; FFA = Fundus fluorescein angiography; Pr = Predominantly classic; Cl = 100% classic

ters (equivalent to logMAR 1.01 or Snellen 6/61) and the increase in mean lesion size from 1331 µm to 2935 µm from baseline to final follow-up were both highly statistically significant (Tab. IV).

Data of differences between baseline and 3 months lesion size were normally distributed (Shapiro-Wilk p=0.195). There was a significant increase in mean lesion size (p<0.001) in the 3-month time interval. The mean increase was 835 (95% CI: 460, 1210).

By final follow-up mean increase was 1604 (95% CI 916, 2353, p<0.001) µm.

Difference between baseline and 3 months VA data were normally distributed (Shapiro-Wilk p=0.5889). There was a significant deterioration in VA (p=0.0023) during this time interval. The deterioration was 11.2 letters (95% CI: 4.4 to 17.9).

By final follow-up mean deterioration was 23.6 letters (11.6, 33.6, p=0.003).

For the 9 eyes with 6/18 or better vision at initial treatment all lost 15 or more letters with a mean number of letters lost of 40 (range 15 to 65; SD 15.0). The mean final visual acuity for this group was 29 letters (range 4 to 65; SD 18.2) which is equivalent to logMAR 1.1 or Snellen 6/79 with a range of logMAR 0.4 to 1.62. Only one of these nine patients (Patient 18) retained a visual acuity equivalent to 6/18, having started 12 months earlier with 6/7.5 vision.

A univariate analysis found no association between growth of the lesion by 3 months and each of the following baseline angiogram characteristics: baseline lesion size (GLD), pigment surrounding the lesion, or hemorrhage associated with the lesion.

TABLE II - COMPARISON OF BASELINE VISUAL ACUITY (VA) AND BASELINE LESION SIZE WITH FINAL VA AND FINAL LESION SIZE

Study no.	Age, yr	Lesion characteristics	Baseline lesion size (µm greatest linear diameter)	Baseline VA (no. of letters on modified ETDRS chart)	Final VA	Final lesion size	Increase in lesion size (µm)	No. of letters lost
1	77	Pr	1570	54	55	1620	50	–1
2	77	Cl	1010	64	20	4840	3830	44
3	81	Cl	540	70	30	2230	1690	40
4	89	Cl	1800	60	4	4300	2500	56
5	77	Cl	1920	58	50	1030	–890	8
6	79	Pr	1730	51	40	2460	730	11
7	75	Cl	1350	70	20			50
8	83	Cl	1790	35	37	2490	700	–2
9	82	Cl	1750	54	59	2110	360	–5
10	73	Cl	1200	35	74	1280	80	–39
11	73	Cl	310	60	73	330	20	–13
12	84	Cl	1500	69	15	5060	3560	54
13	84	Cl	570	59	29	1000	430	30
14	78	Cl	1270	58	55	4690	3420	3
15	60	Cl	1940	69	25	4020	2080	44
16	82	Pr	1960	53	40	2580	620	13
17	83	Cl	650	54	24	2900	2250	30
18	79	Cl	1220	80	65	2080	860	15
19	77	Cl	1480	69	4	3350	1870	65
20	76	Pr	970	54	4	4770	3800	50
21	84	Cl	1170	65	40	2580	1410	25
22	84	Pr	1370	35	25	2250	880	10
23	81	Pr	1080	44	15	5940	4860	29
24	85	Cl	1690	50	4	3370	1680	46
25	71	Cl	1440	70	44	3160	1720	26

ETDRS = Early Treatment Diabetic Retinopathy Study; Pr = Predominantly classic; Cl = 100% classic

TABLE III - SUMMARY OF OUTCOMES (FOR ALL PATIENTS N=25)

	No. of patients at 3 months (%), n=25	No. at 6 months (%)	No. at final follow-up (%)
Loss of 15 or more letters	10 (40)	13 (52)	13 (52)
Vision drop to <35 letters	4 (16)	10 (40)	15 (60)
Visual treatment failure*	11 (44)	14 (56)	16 (64)
Lesion treatment failure†	12 (48)	16 (64)	18 (72)

*Loss of 15 or more letters or drop in vision to less than 35 letters; †Growth in the lesion by 500 µm or more

TABLE IV - SUMMARY OF RESULTS

	Initial	Final	Two-tailed paired t-test p value
Mean visual acuity (letters) ± SD	57.6±11.8	34.0±21.5	≤0.0001
Range of visual acuity (letters)	35 to 80	4 to 74	
Mean lesion size (µm)	1331±465	2935±1456	≤0.0001
Range of lesion size (µm)	310 to 1960	330 to 5940	

There was a significant association between growth of the lesion in the first 3 months and visual failure at final follow-up. The mean increase in lesion size was 310 in the group that did not fail visually (n=9) compared to 1131 µm in the visual failure group (n=16) (p=0.027).

DISCUSSION

The results suggest that the majority of patients with good initial visual acuity and/or small lesion size will lose significant visual acuity if treated with PDT-verteporfin alone. All patients with initial visual acuity of 6/18 or better would be classified as visual treatment failures by our criteria (loss of 15 letters or visual acuity falling below 35 letters on a modified ETDRS chart). Treatment may modify the natural history of the disease to create a dry fibrotic scar after which further deterioration is less likely. However, late growth of fibrotic scars with visual deterioration has been described (3). The criterion for visual treatment failure used in most other studies has been loss of 15 letters or more (4), which in patients with already poor vision is unlikely to occur whether the treatment is effective or not, thus overestimating the success of treatment. The absolute visual acuities are often not mentioned, and studies investigating smaller lesion size outcomes are also limited by short or unclear follow-up (5). These two factors may explain why our results cast the results of PDT for small lesions in a relatively darker light. Another possibility is that the success of treatment is operator dependent, as a result of the technique for administering the PDT or interpretation of the angiograms.

A subgroup analysis of patients from the TAP study (4) found no lesion size-dependent effect on outcome for predominantly classic lesions. Patients with predominantly classic lesions with lesion size less than 4 MPS disc areas (equivalent to around 3000 µm GLD) had a mean loss of 15.7 letters with PDT vs 25.9 letters with placebo at 24 months. As with our study most vision was lost in the first 3 months.

Such disappointing results have led others to alter the PDT treatment regime or to combine PDT with intravitreal triamcinolone injection but with the attendant risks and side effects. The rationale is that steroids can limit the resulting inflammation that may stimulate further vessel growth. Nonetheless 44% of patients with predominantly classic lesions will lose 3 or more lines on ETDRS by 1 year (6). The effect for small lesions has not been separately investigated but in our practice we now routinely co-administer PDT with 4 mg intravitreal triamcinolone for predominantly classic lesions when patients cannot afford the costs of anti-VEGF treatments.

Studies have combined anti-VEGF agents with PDT with good results (7, 8). Addition of steroid and bevacizumab to PDT may offer the best chance of visual improvement with a mean improvement of 1.8 lines in

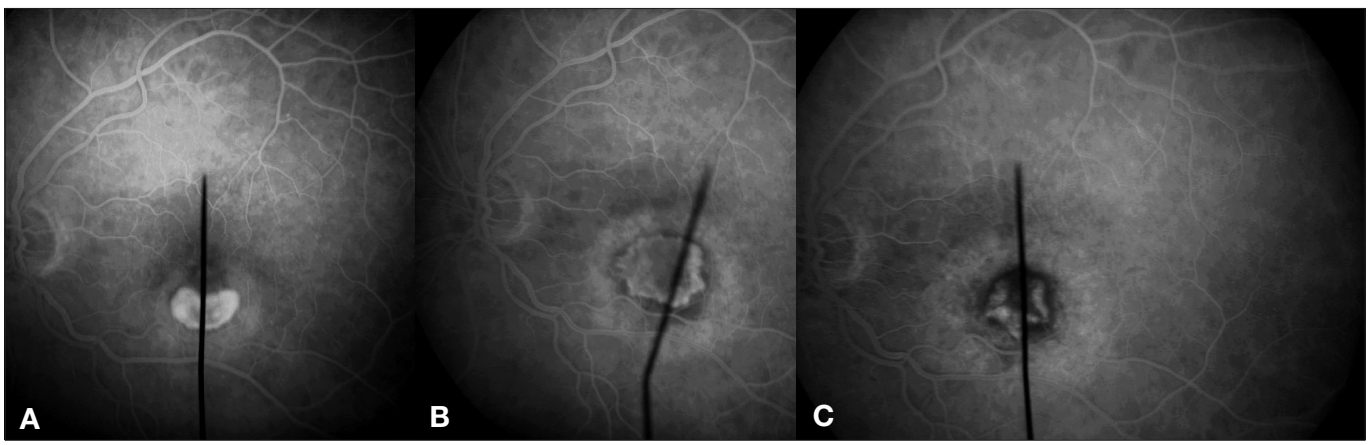

Fig. 2 - *Second eye of Patient 20.* **(A)** *Initial lesion size was 1710 µm greatest linear diameter with visual acuity of 80 letters.* **(B)** *After treatment with photodynamic therapy the lesion grew to 2820 µm with a drop to 43 letters at 3 months.* **(C)** *One month after intravitreal bevacizumab treatment the vision recovered to 61 letters corresponding with shrinkage of the lesion to 980 µm.*

one study (n=104) (9). However, the justification for continued inclusion of PDT in such regimens when anti-VEGF agents alone may be effective is questionable and requires further research.

Interestingly, when Patient 20 developed a classic choroidal neovascular membrane in her second eye she again underwent PDT. Vision had dropped from 80 to 43 letters by 3 months and the lesion size had increased from 1710 to 2820 µm. She then opted for intravitreal treatment with bevacizumab which resulted in a recovery of vision to 61 letters and lesion size reduction to 980 µm (Fig. 2).

More frequent follow-up may be another option and one study has shown a significant improvement for small (<2000 µm GLD) lesions with more frequent follow-up and retreatment (2-month angiogram-dependent retreatment for the first 6 months as opposed to the standard 3-month intervals) (10). In this large study the standard protocol resulted in a steady decline in visual acuity over 1 year with a mean loss of 10 letters from 51 to 42 letters. A total of 21% lost 30 or more letters. In contrast the 2-month protocol resulted in stabilization of visual acuity with only a 1-letter mean drop in vision.

Possible drawbacks of our study are that we discharged patients with treatment failure without continuing to follow patients in case there might be subsequent improvement again. However it is widely accepted that visual improvement in such patients is unlikely either spontaneously or with further PDT. Also this was a small, uncontrolled observational study.

In conclusion, small predominantly classic lesions should be considered to be potentially aggressive lesions that will cause visual deterioration when treated with PDT alone, and not as mild or early lesions that therefore might be expected to respond well by virtue of being caught early. Commissioning bodies may use the evidence of randomized trials to continue to recommend the use of PDT-verteporfin for small classic lesions in spite of the indication that ranibizumab offers a significant advantage. Patients should be counseled about the better results that may be achieved for these lesions treated with bevacizumab or ranibizumab and close follow-up is recommended so that anti-VEGF treatment can be instituted early if PDT fails.

Proprietary interest: None.

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