SCIENTIFIC REPORT

Photodynamic treatment versus photodynamic treatment associated with systemic steroids for idiopathic choroidal neovascularisation

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Aim: To compare photodynamic therapy (PDT) with PDT associated with systemic steroids (SS) for the control of juxta/subfoveal idiopathic choroidal neovascularisation (ICNV).

Methods: Patients with juxta/subfoveal ICNV were randomised and then treated. Visual gain and loss were defined as improvement in or worsening for two or more lines of best-corrected visual acuity (BCVA), respectively. Choroidal neovascularisation size after treatment was classified as “increased” and “reduced” if it was increased or reduced by $>200\ \mu\text{m}^2$, respectively.

Results: 10 patients were treated with PDT, 10 with SS followed by PDT. The median follow-up time was 22 and 21 months for the “steroid+PDT group” and the “PDT group”, respectively. At 1 year, in the PDT group, five patients had stable/improved BCVA, and five became worse; the mean number of PDT was 2.3; in the steroid+PDT group, all patients were stable/improved and the mean number of PDT was 1.2. The difference between the two groups was significant ($p<0.05$). At 1 year, the ICNV size after treatment was better in the steroid+PDT group than in the PDT group ($p<0.05$).

Conclusion: The use of SS before PDT has shown better BCVA outcome than PDT alone ($p<0.05$), reducing the mean number of PDT applications (1.2 vs 2.3, respectively), with smaller scar size.

Choroidal neovascularisation (CNV) without signs of retinal scars, age-related macular degeneration lesions or high myopia is defined as idiopathic¹ CNV (ICNV).

Several papers described that indocyanine green angiography can detect choroidal abnormalities, suggesting a possible role for low-grade choroidal inflammation,^{2–4} further supported by previous publications showing CNV as its possible sequela.⁵

The use of steroids for the control of inflammation is well established, and steroids represent the preferred treatment for non-infectious choroidal inflammation.^{6,7}

Different techniques have been proposed for the management of ICNV, such as photodynamic therapy (PDT),^{8,9} surgical removal^{10,11} and thermal laser photocoagulation,¹² and even though the efficacy of local¹³ and systemic steroids¹⁴ (SS) for CNV secondary to inflammation has been described, there are, as far as we know, no publications on their use for the management of ICNV.

The aim of our study was to compare the outcome of PDT alone versus PDT with a previous course of SS.

METHODS

Patients younger than 50 years, with impairment in visual acuity, metamorphopsia and scotoma in the centre of the visual field, were referred to the Retina Unit of the Eye Clinic,

Ospedali Riuniti di Ancona, Ancona, Italy, from the casualty, the retina clinic itself and other hospitals belonging to the Italian National Health Service (table 1).

The study was designed as a prospective, consecutive, open-label, randomised control trial. The aim was to compare the efficacy of PDT versus SS with PDT in patients with ICNV. Stable/improved best-corrected visual acuity (BCVA) was the primary end point. The secondary end point was the reduction of the lesion size including the atrophic border. To detect a difference in efficacy between the two methods, we estimated that 48 patients would need to be recruited to each treatment group. This estimate was performed using a χ^2 test with a two-sided significance level of 0.05 and 80% power. CNVs without evidence of both retinal and choroidal abnormalities were included. ICNVs previously treated and patients with comorbidity were not considered. All patients were examined by AG. Two groups were created: group 1 to be treated with PDT alone, and group 2 to be treated with PDT associated with SS. Patients were randomised by casual numbers generated by SPSS software V.11.0.1. Ethics committee approval from the “Ospedali Riuniti di Ancona” was obtained. BCVA outcomes were classified according to two dichotomous predictors, defined as “stable/improved” and “worse”.

CNV size after treatment was dichotomised as “increased”, when the lesion size, including peri-lesional atrophy, was increased $\geq 200\ \mu\text{m}^2$; “stable/reduced”, if reduced $\geq 200\ \mu\text{m}^2$ or not modified by $>200\ \mu\text{m}^2$. The lesion’s size was calculated by Topcon Imagenet 2000 (Topcon, Tokyo, Japan). The Wilcoxon test was used to compare the median time of follow-up. Differences in the BCVA between groups 1 and 2 were evaluated considering the ICNV size modification after treatment, dichotomised as “stable/reduced” and “increased” as a classification criterion; the Mann–Whitney U test was used to assess any significant difference. Fluorescein angiography (FA; TRC-50 IX, Topcon) was performed. The Early Treatment of Diabetic Retinopathy Study chart was used for the visual acuity examination; a decrease or increase in visual acuity was defined as a decrease or an increase of ≥ 10 letters (two lines) of vision from the initial BCVA, respectively.

For group 2, the initial treatment was intravenous steroids (methylprednisolone) at a dose of 1 g daily for 3 days, followed by oral steroids (prednisone) at a dose of 1 mg/kg daily. The steroids were tapered on an individual basis. PDT was performed following the parameters indicated in the Treatment of Age-related macular degeneration with Photodynamic therapy and Verteporfin In Photodynamic therapy studies.^{9,15} The timing for PDT treatment was established according to FA leakage, CNV size reduction, and decrease and flattening of neurosensory detachment.

Abbreviations: BCVA, best-corrected visual acuity; CNV, choroidal neovascularisation; FA, fluorescein angiography; ICNV, idiopathic choroidal neovascularisation; PDT, photodynamic therapy; SS, systemic steroids

Table 1 Patient data

Patient number/age/sex	Follow-up time (months)	Eye	PDT number	BCVA			CNV size after treatment	
				Baseline (T ₀)	After 1 year	Last follow-up (T ₁)	1 year	Last follow-up
PDT								
1/14/F	28	L	3	0.40	0.32	0.20	s	i
2/39/M	26	L	2	0.20	0.20	0.32	s	s
3/31/F	24	r	1	0.63	0.63	0.8	r	r
4/38/M	22	L	4	0.32	0.20	0.1	i	i
5/38/F	21	r	1	0.40	0.40	0.50	r	r
6/26/F	20	L	2	0.63	0.63	0.8	s	s
7/37/M	18	L	4	0.32	0.20	0.2	i	i
8/28/M	16	r	3	0.08	0.08	0.05	i	i
9/34/F	16	L	2	0.1	0.063	0.063	i	i
10/24/F	15	L	1	0.32	0.05	0.05	i	i
Steroids+PDT								
11/27/M	25	L	2	0.4	0.40	0.16	s	i
12/25/F	21	L	2	0.2	0.40	0.5	s	s
13/42/M	23	L	1	0.1	0.1	0.1	s	s
14/29/M	22	L	1	0.4	0.8	0.8	r	r
15/31/M	22	L	1	0.5	0.5	0.5	r	r
16/23/F	20	L	1	0.2	0.8	0.8	r	r
17/28/M	19	r	1	0.2	0.20	0.2	s	s
18/33/M	18	L	1	0.32	0.32	0.4	r	r
19/29/F	16	r	1	0.2	0.40	0.5	r	r
20/10/M	17	L	1	0.1	0.1	0.1	s	s

BCVA, best-corrected visual acuity; CNV, choroidal neovascularisation; PDT, photodynamic therapy; F, female; M, male; L, left; R, right; r, lesion reduced $\geq 200 \mu\text{m}$, i, lesion increased $\geq 200 \mu\text{m}$; s, stable lesion.

RESULTS

A total of 20 patients were included: 11 males and 9 females. The groups showed a similar distribution of patients by sex and age (all comparisons >0.3). Mean age was 29.7 (7.3) years (range 10–44). All patients had unilateral involvement. The median follow-up was 23 months. The Wilcoxon test did not reveal statistically significant difference of the median follow-up time between the two groups. Ten patients were included in group 1; this group had a mean (SD) BCVA of 0.34 (0.19) at baseline (T₀) (table 2), with a median follow-up of 21 months.

The mean number of PDT was 2.3. At 1 year, group 1 had 5 (50%) patients with stable/improved BCVA and 5 (50%) with deteriorated BCVA; 5 (50%) patients had stable/reduced lesions. The mean (SD) BCVA at the last follow-up (T₁) was 0.31 (0.29); 4 (40%) patients were stable/improved, and 6 (60%) had deteriorated.

At the last follow-up, the analysis of the CNV size showed 4 (40%) cases with stable/reduced lesions compared with T₀ and 6 (60%) with increased lesions (fig 1).

Ten patients were included in group 2; this group had a mean (SD) T₀ BCVA of 0.26 (0.13; table 2), with a median follow-up

of 22 months. The median time between the beginning of steroid treatment and PDT was 1.5 months. The median duration of steroid treatment was 5 months. The mean number of PDT was 1.5.

After 1 year of follow-up, all patients in group 2 had stable/improved BCVA with stable/reduced lesions. At T₁, the mean (SD) BCVA was 0.41 (0.26); 9 (90%) patients had stable/improved BCVA and 1 (10%) patient had a worse BCVA. At the last follow-up, the analysis of CNV size showed 9 (90%) cases with stable/reduced CNV size (fig 1) and 1 (10%) case with increased CNV size.

At 1 year, the BCVA outcome was better in group 2 ($p=0.0147$), with a significant reduction of CNV size ($p=0.0389$). The better outcome of group 2 remained statistically significant at the last follow-up. The number of PDTs was 2.3 for group 1 versus 1.5 for group 2. After treatment, BCVA was better in patients with stable/reduced lesions ($p<0.001$, fig 2). Severe side effects have not been observed in both groups.

DISCUSSION

The pathophysiology of ICNV is still not well known. A low-grade choroidal inflammation may be a reasonable promoter, as suggested by changes of choroidal permeability in ICNV similar to choriocapillaritis/choroiditis.^{2,3} Limits of indocyanine green angiography are due to poor specificity, and we cannot prove whether these alterations are due to a low-grade non-infectious choroidal inflammation or not. However, the hypothesis that a low-grade inflammation could be the cause of pathogenesis of ICNV is supported by evidence that inflammation can be a determinant cofactor for the neovascularisation, even for those not purely due to inflammation itself.^{16,17}

The supposed role of SS for the control of CNV has been reported previously,¹⁸ but data on their use for ICNV are lacking at present. The rationale for using SS is based on the fact that recruitment of white blood cells involved in inflammation starts from bone marrow and SS are able to stop it.⁷

The natural history of subfoveal ICNV showed an association between CNV size at the onset and visual outcome: CNVs less

Table 2 Best-corrected visual acuity scores at last follow-up (Early Treatment of Diabetic Retinopathy Study chart) in the groups (n = 20)

Group	Time	Mean (SD)	Median	Min	Max
PDT (group 1, n = 10)	T ₀	0.34 (0.19)	0.32	0.08	0.63
	T ₁	0.31 (0.29)	0.2	0.05	0.80
	Diff	p>0.05, NS			
Steroids+PDT (group 2, n = 10)	T ₀	0.26 (0.13)	0.2	0.10	0.50
	T ₁	0.41 (0.26)*	0.45	0.10	0.80
	Diff	p<0.01; S			

Max, maximum; Min, minimum; PDT, photodynamic therapy; T₀, before treatments; T₁, after treatments. Diff, significance of the differences between the time points within each group. NS, difference not statistically significant; S, difference statistically significant.

*Significantly different as compared with the corresponding value of the control group, $p<0.05$.

Figure 1 Lesion size of patient 1, a 14-year-old girl, treated only with photodynamic therapy (PDT), at baseline (A) and after two applications of PDT (B). Lesion size of patient 16, a 23-year-old woman, treated with combined therapy, at baseline (C); note the regression of the lesion size after steroids and the small scar after only one PDT (D).

than one disc area had better visual prognosis than larger ones.¹ Although its natural history is not necessarily associated with severe visual loss, pilot studies on PDT for subfoveal ICNV reported promising results.⁸⁻⁹ In our trial, steroids have shown a better reduction of CNV size (fig 1) after combined treatment than after PDT alone (fig 1), with a better BCVA outcome, reducing the risk of exuberant subretinal fibrosis¹⁹ and severe pigment epithelial alterations²⁰ observed after PDT. In addition, in group 1 the mean number of PDT was 2.3, whereas that in group 2 was 1.2, suggesting that a reduction in the number of treatments could reduce oxidative damage to the retinal pigmented epithelial cells and preserve its function.

Patients in group 2, who received steroids before PDT, had a dramatic reduction of CNV size with a smaller perimetric atrophy, suggesting that steroids act as a strong control against the activation of fibroblast cells,⁷ contributing to a smaller scar

tissue, which correlates well with our results: we observed hyperplastic fibrosis only in cases treated with PDT alone.

On the basis of our results, the better strategy for the treatment of ICNV seems to be a combination of preliminary treatment with steroids, followed by PDT: intravenous methylprednisolone (1 g for 3 days), followed by oral prednisone (1 mg/kg), has produced a dramatic effect in the control of ICNV.

The timing of the PDT application was decided on the basis of FA leakage, CNV size reduction, and decrease and flattening of neurosensory detachment. Because of these criteria and also because the dose of steroids is tailored individually, it is important to proceed with short follow-ups for the first 2 months, which will help best define the correct timing for the first PDT treatment. In our experience, the median time from the beginning of steroid treatment to PDT was 1.5 months.

Considering our results, PDT preceded by SS seems to produce smaller scars and less hyperplastic fibrosis. However, this study should be interpreted with the limitation of an insufficient number of patients recruited on the basis of a power calculation, suggesting the need for multicentric trials for a larger recruitment. In addition, on the basis of our data, further case-control trials on SS alone for ICNV are strongly suggested.

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Figure 2 Box-plot of the best-corrected visual acuity (BCVA) gain after treatment in patients showing a stable/reduced and an increased choroidal neovascularisation CNV size.

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REFERENCES

- 1 Allen CH, Yannuzzi LA, Pisicano K, *et al*. The natural history of idiopathic choroidal neovascularization. *Ophthalmology* 1995;**102**:782–9.
- 2 Giovannini A, Scassellati-Sforzolini B, Mariotti C, *et al*. Indocyanine green angiography findings in idiopathic choroidal neovascularization. *Int Ophthalmol*, 1996–97, **20**:171–9.
- 3 Gharbiya M, Pantaleoni FB, Grandinetti F, *et al*. Indocyanine green angiographic findings in idiopathic choroidal neovascularization. *Eye* 1999;**13**(Pt 5):621–8.
- 4 Parvan PR, Margo CE. Submacular neovascular membrane and focal granulomatous inflammation. *Ophthalmology* 1996;**103**:586–9.
- 5 Forrester JV, Liversidge J, Dua HS, *et al*. Comparison of clinical experimental uveitis. *Curr Eye Res* 1990;**9**:75–84.
- 6 Gordon DM. Prednisone and prednisolone in ocular disease. *Am J Ophthalmol* 1956;**41**:593–600.
- 7 Vitale AT, Foster CS. Corticosteroids. *Diagnosis and treatment of uveitis*. Philadelphia: WB Saunders, 2002:142–58.
- 8 Spaide RF, Martin ML, Slakter J, *et al*. Treatment of idiopathic subfoveal choroidal neovascularization lesions using photodynamic therapy with verteporfin. *Am J Ophthalmol* 2002;**134**:62–8.
- 9 Chan WM, Lam DS, Wong TH, *et al*. Photodynamic therapy with verteporfin for subfoveal idiopathic choroidal neovascularization: one-year results from a prospective case series. *Ophthalmology* 2003;**110**:2395–402.
- 10 Sears J, Capone A Jr, Aaberg T Sr, *et al*. Surgical management of subfoveal neovascularization in children. *Ophthalmology* 1999;**106**:920–4.
- 11 Lit ES, Kim RY, Damico DJ. Surgical removal of subfoveal choroidal neovascularization without removal of posterior hyaloid: a consecutive series in younger patients. *Retina* 2001;**21**:317–23.
- 12 Macular Photocoagulation Study Group. Laser photocoagulation for neovascular lesion nasal to the fovea. Results from clinical trials for lesions secondary to ocular histoplasmosis or idiopathic causes. *Arch Ophthalmol* 1995;**113**:56–61.
- 13 Okada AA, Wakabayashi T, Kojima E, *et al*. Trans-tenon's retrobulbar triamcinolone infusion for small choroidal neovascularization. *Br J Ophthalmol* 2004;**88**:1097–8.
- 14 Flaxel CJ, Owens SL, Mulholland B, *et al*. The use of corticosteroids for choroidal neovascularization in young patients. *Eye* 1998;**12**(Pt 2):266–72.
- 15 Treatment of Age-related macular degeneration with Photodynamic therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin. One year results of 2 randomized clinical trial-TAP report 1. *Arch Ophthalmol* 1999;**117**:1329–45.
- 16 Espinosa-Heidmann D, Suner IJ, Hernandez EP, *et al*. Macrophage depletion diminishes lesion size and severity in experimental choroidal neovascularization. *Invest Ophthalmol Vis Sci* 2003;**44**:3586–92.
- 17 Reddy VM, Zamora RL, Kaplan HJ. Distribution of growth factors in subfoveal neovascular membranes in age related macular degeneration and presumed ocular histoplasmosis syndrome. *Am J Ophthalmol* 1995;**120**:291–301.
- 18 Levy J, Shneck M, Klemperer I, *et al*. Punctate inner choroidopathy: resolution after oral steroid treatment and review of the literature. *Can J Ophthalmol* 2005;**40**:605–8.
- 19 Puliafito CA, Rogers AH, Martidis A, *et al*. Ophthalmic complications of photodynamic therapy for choroidal neovascularization. In: *Ocular photodynamic therapy*. Thorofare, NJ: SLACK Inc, 2002:109–16.
- 20 Postelmans L, Pasteels B, Coquelet P, *et al*. Severe pigment epithelial alterations in the treatment area following photodynamic therapy for classic choroidal neovascularization in young females. *Am J Ophthalmol* 2004;**138**:803–8.

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