Graefe's Arch Clin Exp Ophthalmol (2007) 245:1131–1139
DOI 10.1007/s00417-006-0532-y

CLINICAL INVESTIGATION

Chorioretinal anastomosis and photodynamic therapy: a two-year follow-up study

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Received: 30 May 2006 / Revised: 17 December 2006 / Accepted: 18 December 2006 / Published online: 17 January 2007

Abstract
Background To evaluate the two-year efficacy of photodynamic therapy with Visudyne (PDT) in neovascular age-related macular degeneration (AMD) eyes with chorioretinal anastomosis (CRA).
Methods A non-randomized, institutional, prospective study, of 28 consecutive eyes of 23 patients, with CRA, treated with PDT. Masked best corrected visual acuity (VA) and angiographic features at baseline and during the period of two years were evaluated.
Results Twenty eight eyes completed one year and 19 eyes completed two years of follow-up. The number of treatments was 3 in the first year, and 0.8 in the second year. A VA loss < 3 lines occurred in 53% of the eyes, at two years. Treated eyes lost 0.5 lines in the first year and 2.4 lines in the second ($p<0,01$). Recurrence with additional significant VA loss occurred in four eyes (21%) during the second year. Fourteen eyes (74%) showed no fluorescein leakage at two years.
Conclusion AMD eyes with chorioretinal anastomosis can benefit from PDT with Verteporfin at two years. However, during the second year significant additional VA loss occurs mainly due to recurrence. New modalities of treatment are necessary to achieve VA improvement in CRA eyes.

Keywords AMD · Chorioretinal anastomoses · PDT · Photodynamic therapy · RAL-retinal anastomosis to the lesion · RAP · Visudyne

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Introduction

Chorioretinal anastomosis, a phenotype of exudative age-related macular degeneration (AMD), may represent 5–28% of AMD exudative cases [1, 5, 8]. Different names were proposed including retinal angiomatous proliferation (RAP) [22], deep retinal vascular anomalous complex [7, 11] and more recently retinal anastomosis to the lesion (RAL) [17]. Treatment options including thermal laser photocoagulation [8], transpupillary thermotherapy [10] and surgery [2] have been tried without success. Photodynamic therapy with Verteporfin (PDT) [3, 15] and combined therapies (PDT plus intravitreous triamcinolone) [6, 18] have shown a higher efficacy at 12 months. The 2-year follow-up of CRA eyes treated with PDT is already unknown.

The purpose of this study is to evaluate, in a non-randomized, interventional, institutional, prospective study, the two-year efficacy of PDT with verteporfin in eyes with neovascular AMD and CRA.

Patients and methods

A prospective, institutional, non-randomized, non-controlled study was performed in 28 consecutive eyes, of 23

patients with exudative AMD and CRA, observed after January 2000 and treated with PDT with Verteporfin.

Patients and methods were previously described [15]. PDT treatments were performed within 3-month intervals, using the standard protocol of TAP and VIP trials [20, 21] but also including eyes with serous pigment epithelium detachment greater than 50% of the lesion. Retreatments were applied if fluorescein angiography showed any leakage from the neovascular lesion, causing VA decrease. All patients had 50 years or more of age at the time of diagnosis, and presented signs of AMD. Only patients with 12 or more months of follow-up were considered for the study.

Stereo colour, red-free fundus photographs and stereo fluorescein and digital ICG angiograms obtained with the Topcon ImageNet system were reviewed by two independent reviewers (R.M.S., J.R.F.A.) and any disagreement was resolved by a third reviewer (J.G.C.V.). The criteria for diagnosis were previously described [15] and were based on Slakter's [16] descriptions. Briefly, we considered the possibility that biomicroscopic and red-free findings suggested the presence of CRA when intraretinal or preretinal small haemorrhages and intraretinal edema (cystoid or not) were present. Fluorescein angiography (FA) and indocyanine-green video-angiography (ICG) were highly suggestive of CRA when early and/or late focal hot spots were present. Definitive CRA was only assumed when positive signs were identified on biomicroscopy and red-free photography and with at least one of the two angiographic techniques. Lesions, at the time of diagnosis were ≤5400 μm in size (greatest linear dimension) in all cases.

Visual acuity (VA) was tested by a masked observer using the ETDRS chart and the best-corrected VA was obtained. The neovascular lesions were classified in predominantly classic, minimally classic, and occult with no classic according to MPS, TAP and VIP protocols [12, 20, 21]. The stages of CRA were identified according to Yannuzzi criteria [22]: stage I involving proliferation of intraretinal capillaries originating from the deep retinal complex (intraretinal neovascularization); stage II characterized by the growth of retinal vessels into the subretinal space (subretinal neovascularization) with or without serous pigment epithelial detachment, and stage III when clinical and angiographic examinations clearly demonstrated the presence of choroidal neovascularization.

All the FA and ICG images were analyzed and classified according to the presence or absence of leakage and by the resolution of exudation with predominance of atrophy or fibrosis. Resolution with fibrosis was considered when ≥50% of the lesion was fibrotic; atrophy was considered when ≥50% of the lesion was atrophic.

The evolution of VA was classified in two groups: 1-VA improvement (moderate: <3 lines, and significant: ≥3 lines); and VA decrease (moderate: <3 lines, severe: ≥3<6 lines, and very severe: ≥6 lines). Optical Coherence Tomography (OCT) was performed in some patients, in a non regular basis, and only after 2003.

We considered to exist recurrence when subfoveal or juxta-foveal FA and/or ICG leakage with VA loss was observed after two periods of three months without treatment (a period greater than 6 months without treatment). The reason for choosing such an interval is related to the necessity of clearly differentiate persistence and recurrence, giving enough time for resolution of residual leakage. The eyes with incomplete resolution of leakage at the three months visit (area of leakage inferior to 50% of the lesion and not affecting VA) were not treated and were considered to have persistence. If 3 months later the leakage area was greater than 50% of the lesion (or affecting VA) this was not considered a recurrence but a persistence and PDT was performed. The lesion was only considered cured after six months without need for treatment. Any necessity of treatment after this period was classified as recurrence.

Extra-foveal leakage with no VA loss was not treated and was not considered as recurrence.

To test the statistical differences between groups (mean differences) Mann-Whitney test (for 2 groups) or Kruskall-Wallis test (for more than 2 independent groups) were chosen. For statistical differences among and between visits the Friedman and Wilcoxon tests were respectively used. For correlations between the different parameters the Chi-Square test (for categorical parameters), the Pearson and Spearman correlation coefficients (for continuous variables) were performed.

The study was approved by an internal review committee and conducted in accordance to the ethical standards laid down in the 1964 Declaration of Helsinki. Each patient signed an informed consent form after being completely instructed.

Results

Twenty eight eyes of 23 patients, 19 women and 4 men, were treated with PDT with Visudyne. Mean age of the patients was 77.3 years (SD: 4.0, var: 70–86) and mean follow-up period was 30.8 months (range 12–66). All the eyes were observed at 12 months and 19 eyes completed the 2-year follow-up (Tables 1, 2). Nine eyes (8 patients) did not complete the 2-year follow-up: five patients missed the follow-up (cases 7,10,17,19,23,24), one patient died (case 15), one was treated with combined therapy at month 12 (case 27) and one had only 21 months follow-up at the time of final evaluation (case 4).

Table 1 Study population: the clinical characteristics

Case	Age	Follow-up	Stage	Initial VA 20/	Year 1. VA 20/	Year 2. VA 20/	Final VA. 20/	N° Treat	Classification Lesion	Lesion Size	Leakage Year 2	Serous PED Final evaluation	FA. Final evaluation	Leakage Final evaluation
1	78	42	1	32	100	320	500	3	oc1	2900			atrophy	
2	71	42	2	40	80	640	320	5	min cla	4800			fibrosis	
3	82	30	2	160	63	80	100	8	oc1	4200	Yes	Yes	fibrosis	Yes
4	84	21	2	80	125		80	2	oc1	4600		Yes	fibrosis	
5	76	24	3	800	400	320	320	3	oc1	5400			fibrosis	
6	79	56	2	200	160	640	640	5	oc1	4100		Yes	fibrosis	
7	77	12	2	200	200	.	200	1	oc1	5400			fibrosis	
8	77	38	1	40	63	100	200	3	oc2	3700			oc1	Yes
9	77	38	1	63	40	100	100	4	oc2	3700			oc2	Yes
10	75	15	2	40	40	.	50	3	oc1	2700			atrophy	
11	75	30	2	200	200	400	400	4	oc1	5400		Yes	atrophy	
12	85	30	1	63	40	63	40	1	oc2	3000			atrophy	
13	77	24	1	63	63	50	50	1	oc2	3300			atrophy	
14	77	24	1	500	400	400	400	1	oc1	5400			atrophy	
15	86	12	2	200	200	.	200	4	oc1	3000			fibrosis	Yes
16	78	51	1	25	50	50	50	11	oc1	2300	Yes		Min clas	Yes
17	72	12	2	100	250	.	250	5	oc1	4500		Yes	fibrosis	Yes
18	70	36	2	100	160	320	200	5	oc1	4300	Yes	Yes	fibrosis	
19	73	18	2	250	400	.	400	3	oc1	5400		Yes	atrophy	
20	71	58	3	80	40	160	200	12	oc1	3900	Yes		fibrosis	Yes
21	79	30	2	50	100	200	200	4	oc1	3400			fibrosis	
22	79	36	2	160	250	250	200	5	oc1	4300		Yes	fibrosis	
23	78	15	1	200	200	.	200	2	oc2	1700			atrophy	
24	78	12	2	800	400	.	400	3	oc1	4100		Yes	PED rip	
25	76	24	2	50	50	50	50	4	oc1	4300		Yes	atrophy	
26	76	54	3	200	100	100	100	6	oc1	3200			fibrosis	
27	83	12	2	80	400	.	400	3	oc2	3600			Min clas	Yes
28	74	66	3	80	100	80	400	9	oc1	5400	Yes		fibrosis	Yes

Age, duration of follow-up, stage of the lesion, initial visual acuity (ETDRS chart-20/...), VA at one and two years and at the final visit; total number of treatments, classification of the lesion in occult type one (fibrovascular pigment epithelium detachment), occult type 2 (late leakage from undetermined source) or minimally classic; size of the lesion; presence of serous pigment epithelium detachment; fluorescein angiography evolution of the lesion at the final visit; presence of leakage at the final visit.

Table 2 Age, lesion size, visual acuity evolution and number of treatments

	N	Minimum	Maximum	Mean	SD
age	28	70	86	77.3	4.1
Follow-up	28	12	66	30.8	15.7
Initial lesion size (micra)	28	1700	5400	4000	1023
Initial VA (logMar)	28	0.1	1.6	0.92	1.0
VA at year 1 (logMar)	28	0.3	1.3	1.12	0.8
Lines variation year 1	28	−7	4	−.50	2.7
N° treat. Up to 12M	28	1	4	3	1.1
VA at year 2 (logMar)	19	0.4	1.5	1.03	0.9
Lines variation up to 24M	19	−12	4	−2.4	4.3
N° treat. Up to 24M	19	1	7	3.8	2
N° treat. during 2° year	19	0	3	0.8	1.0
Final VA (logMar)	28	0.3	1.5	1.13	0.89
Lines variation final VA	28	−12	4	−2.2	3.9
N° treat. Final visit	28	1	12	4.3	2.8

Vision outcomes

The efficacy of PDT decreased during the second year of follow-up (Tables 2, 3). Treated eyes lost 0.5 lines in the first year and 2.4 lines in the second (p=0.019). There was a significant visual acuity decline between baseline and 24th month visit (p=0.002). The number of eyes with reading vision or with VA loss inferior to 3 lines decreased in the second year whereas the number of eyes with legal blindness and very severe VA loss increased (Table 3).

Treatments administered

Twenty eight eyes completed 12 months of follow-up and performed a mean number of 3 PDT sessions (SD:1.1; Var:1–4) (Table 2). Nineteen eyes completed 24 months of follow-up and performed a mean number of 3.8 PDT sessions during the two-year follow-up (SD: 1.7; var: 1–7). The mean number of treatments decreased from 3 in the first year to 0.8 in the second year (Table 2) (Fig. 1).

Angiographic evaluation

No leakage documented on FA and/or ICG was observed in 46% and 74% of the eyes at years 1 and 2, respectively. Recurrences occurred in 5 eyes (26%) during the 2-year follow-up: one case in the first year (3,6%) and 4 in the second year (25%). Four additional cases occurred after two years (Figs. 2, 3). The 4 eyes with recurrence during the second year [2, 6, 18, 20] presented a mean VA loss of 5 lines related to the recurrence, (var: 2–9 lines).

The mean interval between the last treatment and the recurrence was 12 months for the recurrences up to 24 months of follow-up, and 16 months (SD:6,1; var: 9–29 months) for all 9 eyes with recurrence. Two cases showed two recurrences during the follow-up (cases 20 and 28).

At the final observation the eyes with recurrence had lost more lines of VA (5,2 lines,SD:2,4; var:−2 to−7 lines, Vs 0,6 lines, SD: 3,8; var:+4 to−12; p=0,01), had a longer follow-up (p<0.01), and received more treatments (p=0.013) than eyes without recurrence.

There was no difference between eyes with and without recurrence regarding the lesion size, presence of serous PED, mean initial or final VA.

Serous PED Ten eyes (36%) presented serous PED greater than 50% of the lesion, at the initial visit (Fig. 1). PED rip occurred only in one case. Only two of these eyes had leakage at the final visit. No difference was found between

Table 3 VA results at one and two years and at the final evaluation

	Baseline N=28	12 Months N=28	24 Months N=19	Final Observation. N=28
Mean visual acuity (logMar)	0.92	0.91	1.12	1.13
Loss < 3 lines	—	79 % n=22	53 % n=10	57 % n=16
VA equal or better	—	57 % n=16	42 % n=8	43 % n=12
Moderate VA loss	—	21 % n=6	11 % n=2	14 % n=4
Severe VA loss	—	18 % n=5	26 % n=5	21 % n=6
Very severe VA loss	—	4 % n=1	21 % n=4	21 % n=6
AV ≥20/63	36 % n=10	32 % n=9	21 % n=4	18 % n=5
AV ≤20/200	36 % n=10	39 % n=11	47 % n=9	68 % n=19

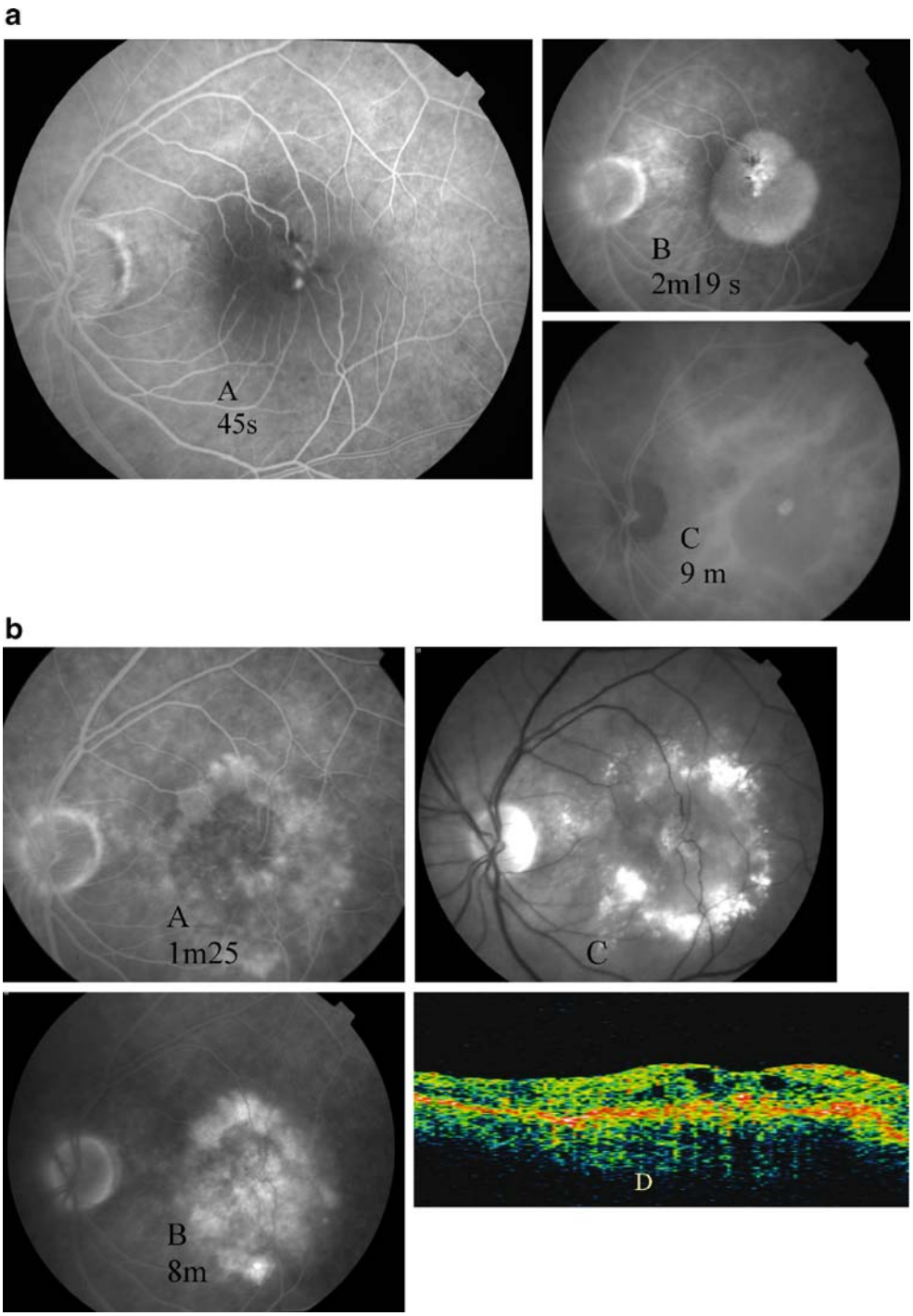

Fig. 1 **a** Case 3. Baseline. VA LE: 20/160. Fluorescein angiography (a and b) and ICG showing CRA with serous PED. A hot spot can be observed on FA and ICG. **b** Case 3 at 24 months and after 7 PDT sessions. The lesion still has leakage (FA, images a and b). A ring of lipid exudates is observed on red-free images (**c**). OCT shows flattening of PED and cystoid edema

cases with and without serous PED regarding lines of VA lost and number of treatments, at 24 months.

Stage of the lesion According to Yannuzzi's classification 8 eyes were at stage one, 16 at stage two and 4 at stage three (Table 1). The lesions of stage 1 were significantly smaller than those of stage 2 ($p<0.05$), but not than those of stage 3 ($p>0.05$). The number of treatments was 3.3 (sd:3.3); 4 (sd:1.6) and 7.5 (sd:3.9) for stages 1, 2 and 3 respectively ($p=0.03$). The eyes at stage 2, but not the eyes at stage one or three, showed a significant VA loss at 12 and 24 months ($p=0.02$).

Lesion size Lesion size correlated with initial VA ($R=0.456$. $p=0,01$). The eyes with a lesion size greater than 4 MPS disc area at baseline suffered a significant VA loss between 12 and 24 months ($p=0.03$).

FA lesion classification and outcomes Twenty seven eyes had occult CNV-21 with fibrovascular pigment epitheli-

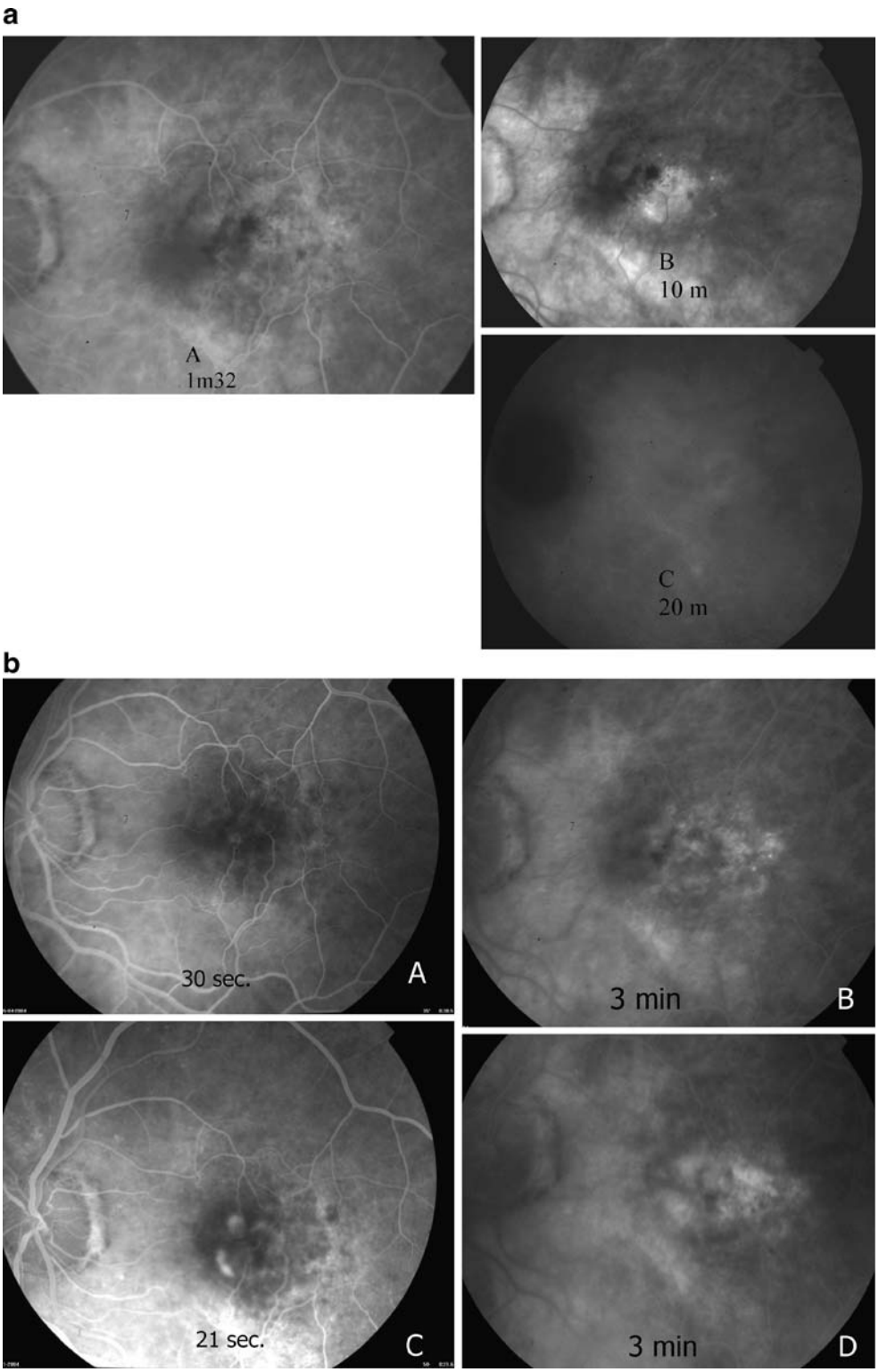

Fig. 2 **a** Case 27. CRA at baseline. Superficial retinal haemorrhages are better visualized on red_free pictures. Diffuse oedema and a small PED may be observed on FA (a and b pictures). ICG shows a barely defined hot spot. **b** Case 27 at after 1PDT session (Picture a and b). Seven months later recurrence is observed (c and d)

um detachment and 6 with late leakage from undetermined source -, one eye had a minimally classic CNV (Table 1).

At the final observation 9 eyes (32%) showed resolution of the lesion with chorioretinal atrophy and no leakage or fibrosis. Fourteen eyes (50%) showed evolution to fibrosis, and leakage was present in five (36%) of them. There was no difference between the two groups regarding initial VA, final VA, size of the lesion, number of treatments, or vision loss ($p>0.05$).

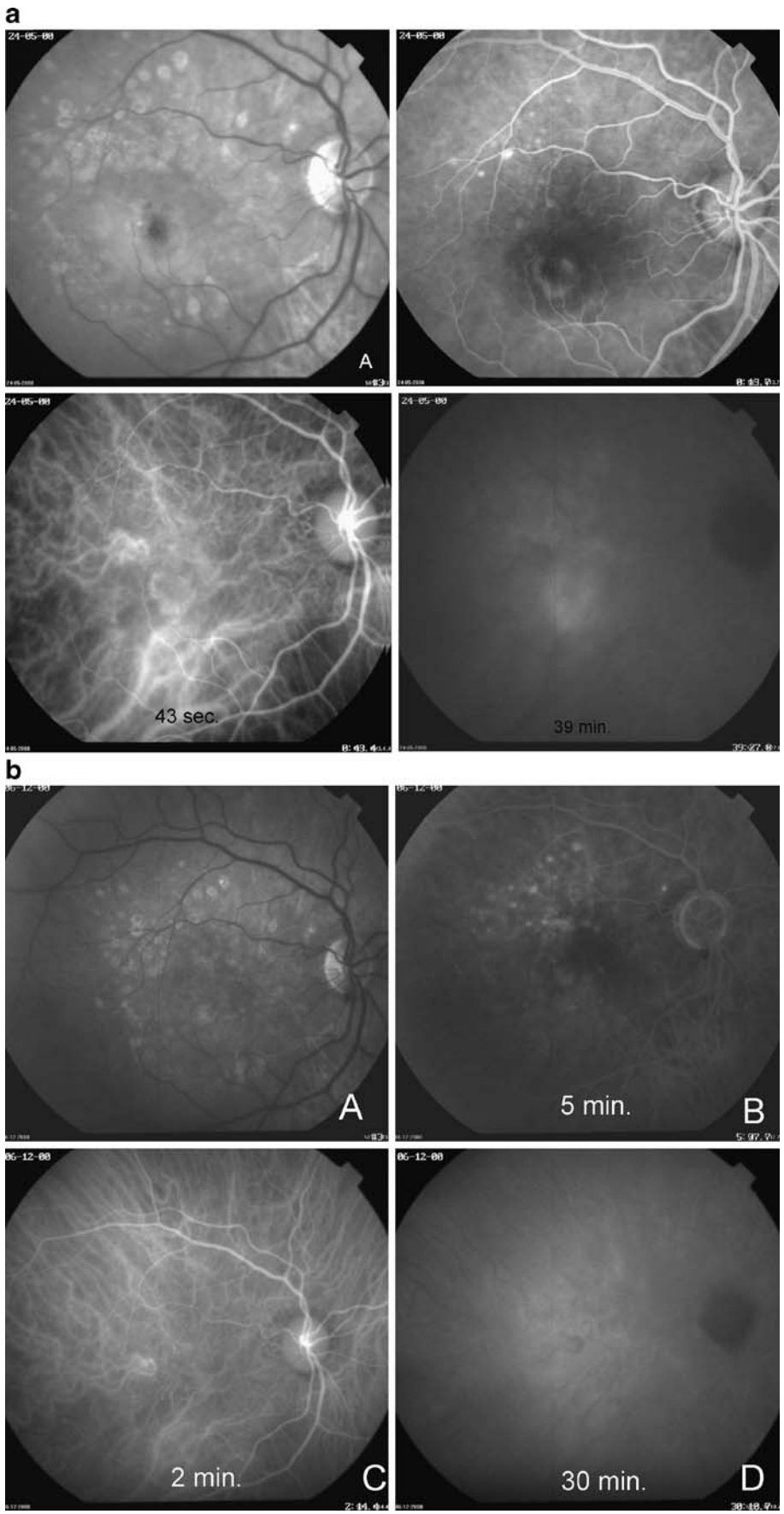

Fig. 3 **a** Case 23. Baseline. Red-free picture (a) with superficial retinal haemorrhages. FA shows a focal hot spot at 43 seconds. A focal hot spot is also observed in ICG early and late phases. **b** Case 23. At six months and after 2 PDT sessions. Red-free picture (a): No retinal haemorrhages are visualized. FA and ICG show resolution of exudation

Discussion

Our study evaluates the two-year efficacy of PDT in AMD eyes with CRA. We have found a significant VA decline between baseline and the 2-year visit. The more severe VA prognosis, during the second year, was related to the presence of recurrences. Apparently CRA has a particular outcome different from other eyes with choroidal neovascularization. Recurrences are frequent and associated with significant VA loss. The four cases with recurrence during the second year were responsible for 47% of the lines lost in the same period. The rate of recurrences increased with longer follow-up. Possible reasons for recurrences may include, according to Criswell [4]: 1-relatively higher retinal blood flow rate in the proximal retina; 2-sustained arterial pressure of retinal blood vessels resulting in distension of both retinal and anastomotic trunks, after PDT occlusion; 3-PDT, although effective in occluding smaller diameter new vessels of choroidal origin (up to approximately 5 μm diameter), may not be effective in blocking larger diameter blood vessels (5 μm diameter and larger). CRA is a particular form of neovascular AMD. It has two foci of neovascularisation, one at the retinal level and the other at the choroidal level. We may speculate that despite the apparent occlusion of CRA with Visudyne, a connexion between retinal circulation and CRA may persist. Viable anastomotic vessels could contribute to the subsequent long-term revascularization of treated CRA and to continued angiogenesis.

The efficacy of PDT in eyes with CRA has been questioned by some authors [4, 9]. No data are available from randomized, multicentre clinical trials like TAP, VIP or VISION because ICG was not used and CRA was not identified as clinical entity. Patients with CRA were included and classified as occult, minimally classic or predominantly classic lesions. A retrospective analysis of TAP and VIP studies has shown that the presence of CRA (also called "associated retinal anastomosis to the lesion-RAL") should not influence Verteporfin treatment recommendations at 2 years [17]. Treated eyes compared with placebo eyes, had a reduced risk of losing 3 or more lines of visual acuity, a reduced risk of having visual acuity worse than 20/200, and had a reduced mean visual acuity loss from baseline [17]. Limitations of this analysis are related to two facts: first, it was retrospective and second, ICG was not used for the diagnosis. Accepting these limitations we may consider that the results are, likewise in our work, in favour of benefit of treating CRA with PDT.

We know the natural history of CRA at one year [15] but not at two years. PDT has shown benefit at one year when compared with natural evolution. Sixty nine percent of the untreated eyes loose more than three lines at one year, [15], compared to 21% of the eyes treated with PDT. Natural evolution of CRA has not shown cases with VA improvement at 12 months [14], compared to 18% of cases in the PDT group.

A comparison at two years can be done with VIP trial results [21] considering that our membranes were occult in 96% of the cases: 45% of treated eyes in the VIP study lost less than 3 lines at two years, comparing with 53% in our study. However this comparison needs to be cautiously looked at since our study has limitations such as being an open, interventional, institutional and nonrandomized study with a relatively small sample.

The importance of classifying lesions in stage 1, 2 and 3 is an interesting issue. Stages 2 and 3 are assumed to have a more severe prognosis without treatment. We have found no difference between stages 1, 2 and 3 regarding initial VA, VA at 12 and 24 months. The eyes in stage 2 showed a significant VA loss at 24 months. The reduced number of eyes with 24 months of follow-up in stage 1 or 3 prevents us to further conclude about the importance of Yannuzzi's stages for VA outcome in eyes treated with PDT.

The presence of serous PED greater than 50% of the lesion is assumed to be a sign of bad prognosis and a potential counterindication for PDT [3, 14]. These lesions were not included in TAP and VIP studies [19–21]. We have treated 10 eyes with CRA and serous PED greater than 50% of the lesion. The lesions with serous PED were larger (Student t test, $p<0.05$) and we found no differences between eyes with and without serous PED regarding lines of VA lost and number of treatments at two years ($p>0.05$, student t test). A PED rip occurred in one case (17%). In our study serous PED seems not to change the VA prognosis of treated lesions. However, these conclusions are limited by the reduced number of eyes with serous PED at 2 years of follow-up (six cases).

Treating CRA with PDT may stabilize vision in a high percentage of eyes but the number of eyes with VA improvement is small. New treatment modalities using single or combined therapies including antiangiogenic agents or PDT with intravitreous triamcinolone (IVT) may probably offer more benefits [13, 18]. At the moment there are no available data regarding the efficacy of antiangiogenic or angiostatic agents in the treatment of CRA. However, combining PDT with IVT seems to be more effective than PDT alone at 12 months [6]. Complete resolution of the angiographic leakage has been achieved in 89% of eyes, visual acuity improvement in 37% and VA stabilization in 52% of eyes. Thirty percent of the cases presented recurrent leakage after 3 to 11 months [6]. These results are clearly better that PDT alone at one year. The rate of recurrences is higher than in our study. This may be due to two reasons: one, more cases may have been closed with combined therapy during the first year, and second, Freund and col., considered any retreatment as a recurrence,

whereas we considered recurrences only after an interval greater than six months had elapsed.

In conclusion, eyes with CRA may benefit with PDT up to two years of follow-up. However, during the second year a significant VA decline may occur mainly due to recurrence. New treatment modalities are necessary to achieve VA improvement in CRA eyes.

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