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Photodynamic therapy with verteporfin in the treatment of exudative idiopathic polypoidal choroidal vasculopathy

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PURPOSE. *To determine the safety and efficacy of photodynamic therapy with verteporfin (V-PDT) in the treatment of exudative idiopathic polypoidal choroidal vasculopathy (IPCV) lesions that were not suitable for laser photocoagulation.*
METHODS. *This was a prospective, open label study in two centers involving 30 consecutive patients (31 eyes) diagnosed with exudative IPCV using fluorescein angiography (FA), indocyanine green angiography (ICGA), and optical coherence tomography (OCT). All patients underwent complete ophthalmologic examination including best-corrected visual acuity (VA) measurement, contrast sensitivity (CS) testing, FA, ICGA, and OCT. OCT was used to assess the stage of the polypoidal dilations (active or scarred) and the evolution of the signs associated with exudation. Study patients were treated with V-PDT and followed up at 6 weeks and 3, 6, and 12 months. Re-treatment was applied, at an interval of 3 months, until there was an absence of leakage on FA and hyperfluorescence on ICGA.*
RESULTS. *Thirty eyes (29 patients) completed the 12 months post-treatment visit and were retained for further analysis. The mean number of V-PDT treatments was 2.5 (SD 1.1). At 12 months post-treatment, the mean foveal thickness had significantly ($p<0.03$) decreased to 224 (SD 104) µm from the baseline 292 (SD 124) µm while the mean VA had significantly ($p<0.02$) improved to 0.50 (SD O.38) from the baseline 0.38 (SD 0.24). Serous detachment of the macula completely resolved in 83.3% of the eyes while 73.3% of the polypoidal dilations were occluded at 12 months.*
CONCLUSIONS. *The results suggest that V-PDT is effective and relatively safe in treating exudative IPCV. (Eur J Ophthalmol 2006; 16: 695-704)*

KEY WORDS. *Choroidal neovascular membrane, Idiopathic polypoidal choroidal vasculopathy, Photodynamic therapy, Verteporfin*

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INTRODUCTION

Idiopathic polypoidal choroidal vasculopathy (IPCV) is a disease of the choroidal vessels characterized by saccular choroidal dilations (SCD) that appear on funduscopy as orange, subepithelial, round, and translucent bulges that elevate the retinal pigment epithelium (RPE). Indocyanine green angiography (ICGA) shows globular, well defined, hyperfluorescent, round lesions in the venous phase and during the angiography. These lesions are mainly seen at the edge of an interconnecting vascular network. Severe and recurrent hemorrhagic detachments of the RPE and the neurosensory retina may occur in the most active stages of the disease and greatly affect visual function (1).

IPCV presents as an isolated abnormality of the posterior pole, with signs of age-related macular degeneration

The results of this study were partially presented at the Congress of the French Society of Ophthalmology (2004) and at the Association for Research in Vision and Ophthalmology Meeting (2004)

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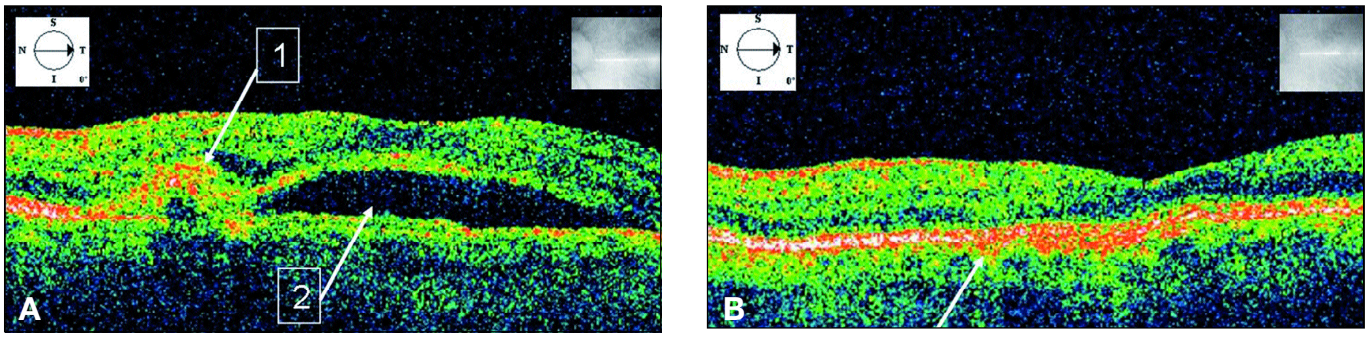

Fig. 1 - *Patient 12.* (**A**) *Pretreatment optical coherence tomography (OCT) scan where the polypoidal dilation is seen as a circumscribed elevation of the retinal pigment epithelium–choriocapillaris (RPE/CC) complex (arrow 1) with an exudative serous retinal detachment (arrow 2).* (**B**) *Post-treatment OCT scan of the same eye where the circumscribed elevation of the RPE/CC complex corresponding to the polypoidal dilation is replaced by areas of RPE atrophy (arrow). Serous retinal detachment is absent.*

(ARMD), or along with central serous chorioretinopathy (CSC) and diffuse retinal pigment epitheliopathy (DRE). IPCV usually evolves through three stages: an early quiescent phase, an active exudative phase, and a late scar phase. Funduscopy, fluorescein angiography (FA), ICGA, and optical coherence tomography (OCT) confirm the presence of PCV and contribute to reliable staging of this disease. The early quiescent and late scar stages of PCV do not need any treatment (2).

In active IPCV, exudative features are more or less pronounced and the functional impact is often unpredictable. Treatment, to occlude the polypoidal lesions, has to be considered for severe exudative lesions affecting visual function. Laser photocoagulation has been proposed to occlude extrafoveal polypoidal dilations (3, 4) while photodynamic therapy with verteporfin (V-PDT) appears to be an appropriate therapeutic procedure for subfoveal lesions (5-10).

We performed a prospective open label study in two centers to determine the safety and efficacy of V-PDT in the treatment of exudative IPCV lesions that were not suitable for laser photocoagulation. An adjunctive purpose of this study was to help identify prognostic factors.

PATIENTS AND METHODS

The study patients were enrolled, treated, and followed for 12 months in two Medical Retina Centers (Lyon, France and Leuven, Belgium). The study protocol was reviewed and approved by the local Ethics Committee (CCPPRB Rhône-Alpes). Written informed consent was obtained from all the patients.

The inclusion criteria for the study patients were as follows:

- History of recent visual loss with metamorphopsia.
- Presence of a macular exudative retinal detachment with hemorrhages (± serohemorrhagic RPE detachments) on funduscopy.
- FA findings of early hyperfluorescent and late leaking, isolated, subretinal spots, associated with pinpoints, surrounding or at the borders of an irregular hyperfluorescent area corresponding to the interconnecting neovascular network (plaque).
- ICGA findings of the following:

– In the early and middle phases: a branching vascular network of dilated vessels with fluffy borders corresponding to the interconnecting abnormal neovascular network;
– In the middle phase (better visibility on the images at 3–5 minutes): typical hyperfluorescent polypoidal dilations at the border of the interconnecting abnormal neovascular network;
– In the late phase: exudative polypoidal dilations that were hyperfluorescent and/or leaking, or washed out. The interconnecting abnormal neovascular network (late plaque) could be prominent in some patients.

OCT scans

In the active phase, the polypoidal dilations were seen as circumscribed elevations of the RPE–choriocapillaris (RPE/CC) complex often filled by mildly reflective and heterogeneous material. Exudative serous retinal detachments had to be present while RPE detachments could not be present (Fig. 1A).

IPCV was considered as inactive when the circumscribed elevations of the RPE/CC complex were accom-

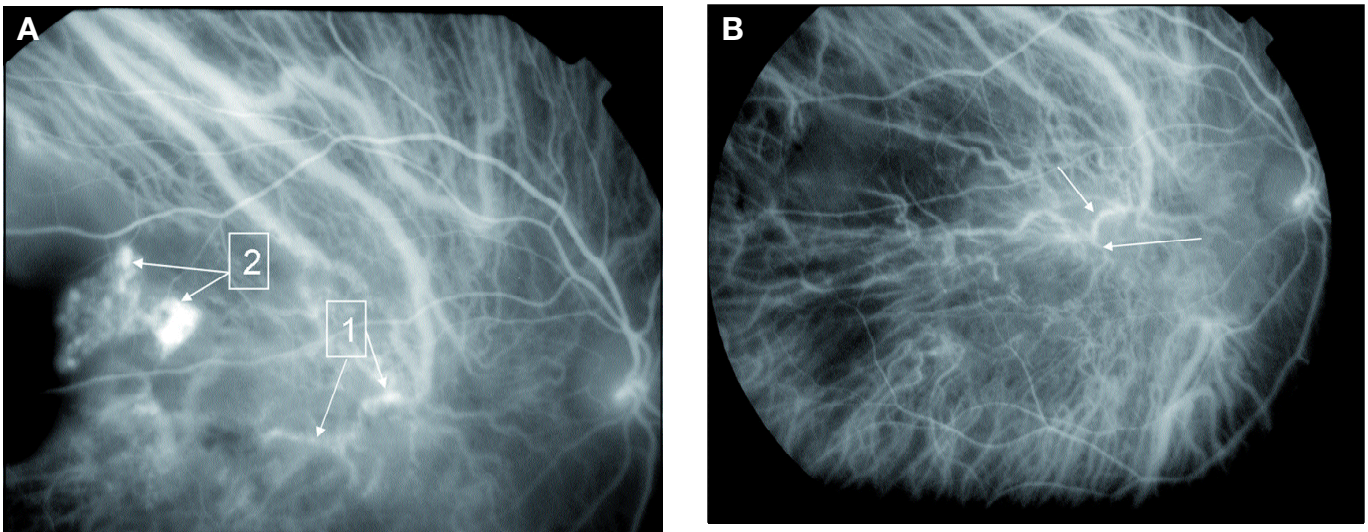

Fig. 2 - *Patient 13.* (**A**) *Pre-treatment indocyanine green angiography (ICGA) shows the branching vascular network of dilated and leaking arteries and veins derived from the choroidal circulation beneath the retinal pigment epithelium (RPE) corresponding to the interconnecting abnormal (neo)vascular network (arrow 1). Polypoidal dilations (arrow 2).* (**B**) *Post-treatment ICGA shows absence of leakage and reduction in dilation of the vessels of the interconnecting network (arrows). The polypoidal dilations have disappeared.*

panied by an optically homogeneous and hyperreflective filling or replaced by areas of RPE atrophy at the previous site of the polypoidal dilation. Serous retinal detachments, RPE detachments, and retinal edema had to be absent or demonstrate a regression (Fig. 1B).

The location of the polypoidal structure and/or of the associated abnormal neovascular network had to be subfoveal with a distance at least 200 µm from the optic nerve to be eligible for V-PDT. Exudative recurrences of an already diagnosed IPCV could be included in the study.

All the study patients underwent a complete ophthalmologic examination including best-corrected visual acuity (VA) measurement using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, contrast sensitivity using the Pelli-Robson charts, FA (Topcon 50IA, Topcon 50IX, and OIS), ICGA (Topcon 50IA, Topcon 50IX, and SLO HRA Heidelberg), and OCT. OCT3 scans (Zeiss Humphrey) were performed, after ICGA, over the area with the choroidal polypoidal dilations and across the fovea (6 mm vertical and 6 mm perpendicular) to analyze the OCT characteristics of the polypoidal structures as well as the retinal thickness and subretinal fluid in the macula. These evaluations were performed at baseline and following treatment at 6 weeks, 3 months, 6 months, and 12 months.

Along with hyperfluorescence and leakage from the polypoidal dilations, the ICGA features of the branching vascular network were evaluated at baseline and at 12 months post-PDT (Figs. 2A, 2B, 3A, and 3B). At baseline, the status of the other eye of each patient was classified into three categories: no drusen, early stage of ARMD, and intermediate and advanced stage of ARMD according to the Age-Related Eye Disease Study (AREDS) classification (11).

Verteporfin photodynamic therapy

V-PDT was performed in all patients following the standard TAP protocol (12). We used a treatment spot that covered not only the area with the choroidal dilation but also the whole abnormal choroidal network as visualized on ICGA and the blood overlying the lesion. The size of the PDT spot was 1000 µm larger than the greatest linear diameter of the polypoidal/plaque lesion.

All the treated patients were scheduled to return 6–8 weeks after the first V-PDT and every 3 months thereafter. Retreatment was applied until there was an absence of leakage on FA (disappearance of pinpoints), occlusion or reduction of the polypoidal dilations on ICG, and signs of scarring on OCT associated with a partial or total regression of exudative serous retinal detachment.

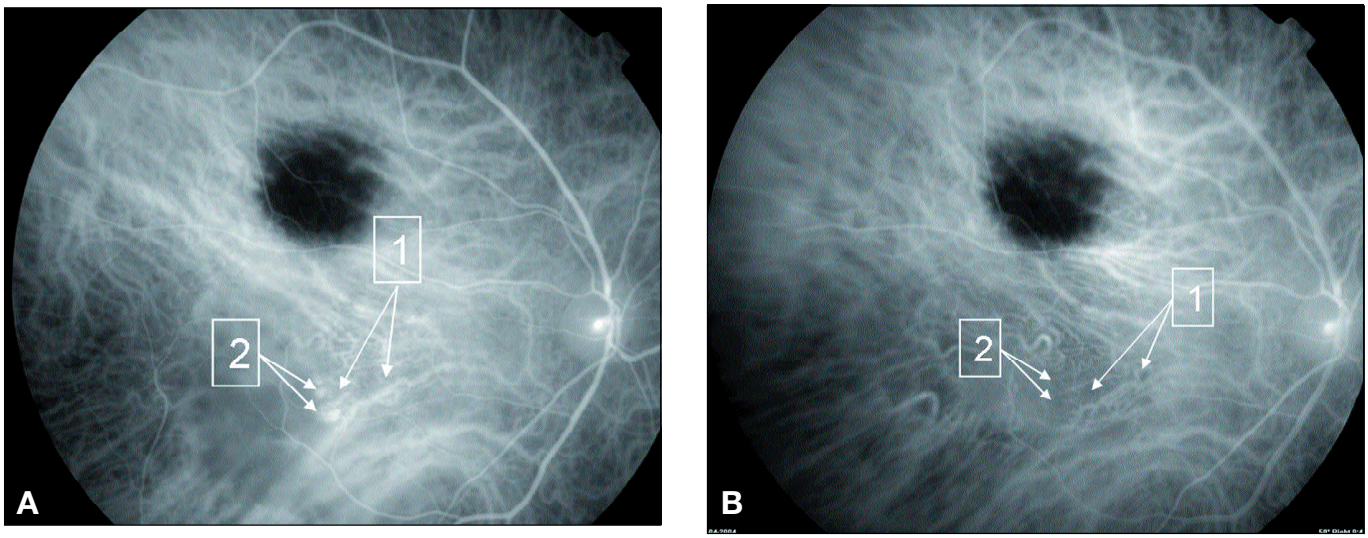

Fig. 3 - *Patient 18.* (**A**) *Pretreatment indocyanine green angiography (ICGA) shows the branching vascular network of dilated and leaking arteries and veins derived from the choroidal circulation (arrow 1). Polypoidal dilations are seen at the border (arrow 2).* (**B**) *Post-treatment ICGA shows narrowing and absence of leakage of the vessels of the interconnecting network (arrow 1). The polypoidal dilations have disappeared (arrow 2).*

RESULTS

Patient characteristics

Thirty-one eyes of 30 consecutive IPCV patients were included in this study between September 2003 and September 2004; 29 patients (30 eyes) completed the 12-month follow-up visit and were retained for further analysis. There were 13 women (43%) and 17 men (57%). The mean age at presentation was 67.0 (standard deviation [SD] 8.5) years with a range of 52 to 80 years. The mean age for men was 63.1 (SD 6.9) years with a range of 52 to 74 years. The mean age for women was 72.1 (SD 7.8) years with a range of 53 to 80 years. All the study patients were white. Twenty-eight patients had unilateral presentation while two patients had bilateral involvement but only one patient was treated bilaterally (Cases 27 and 28). The mean duration of visual complaints before V-PDT treatment was 3.8 (SD 2.5) months.

Status of the other eye

Nine patients (10 eyes; 32.3%) had no drusen. In this group, two eyes had clear signs of diffuse RPE changes similar to those seen in diffuse retinal epitheliopathy (DRE) or in former PCV scars and four eyes had small areas of regressed CSC; two of the latter eyes had a vitelliform deposit. Seventeen patients (17 eyes; 54.8%) had signs of early ARMD. In this group, two eyes also had signs of diffuse RPE changes. One patient (1 eye; 3.2%) had signs of intermediate ARMD. The 3 (9.7%) remaining patients had advanced stages of ARMD.

Number of V-PDT sessions

The mean number of treatment sessions in this study was 2.5 (SD 1.1). The 13 female patients (mean 2.9, SD 1.1) required more treatments than the 17 male patients (mean 2.1, SD 1.0); analysis of variance (ANOVA), $p<0.03$. The mean number of treatments according to the status of the other eye was as follows: group with no drusen 2.50 (SD 1.08); group with early ARMD 2.24 (SD 1.03); and group with intermediate and advanced ARMD 3.25 (SD 1.25). There was no statistically significant difference between the treated eyes, in the number of treatments required, when categorized according to age or the ARMD status of the fellow eye.

Visual acuity outcomes

The mean VA at baseline was 0.38 (SD 0.24) and improved to 0.44 (SD O.24) at 6 weeks following treatment (Tab. I). At this time, only 5 eyes experienced a decrease in VA while 15 eyes experienced an increase and 11 were stable. Generally, this improvement continued, resulting in a mean VA of 0.50 (SD 0.34) at 12 months. The final improvement in VA was statistically significant compared with the pretreatment VA ($p<0.02$; paired Student t-test). The VA at 12 months was significantly better in younger patients ($p<0.03$; Student t-test), patients who required only one or two PDT treatments ($p<0.02$; paired Student t-test), and males ($p<0.03$; ANOVA).

Contrast sensitivity

The mean CS at baseline was 1.23 (SD 0.36) and improved at 6 weeks to a mean of 1.29 (SD 0.30). CS remained quite stable during the whole follow-up (Tab. I) and was 1.28 (SD 0.33) at 12 months. These results were not statistically significant.

Clinical, angiographic, and OCT outcomes

The frequency of retinal hemorrhages progressively decreased from 67.7% (n=21) at baseline to 20% (n=6) at 12 months (Tab. II). The frequency of retinal haemorrhages at 12 months post-treatment was significantly ($p<0.001$; chi-square test) less than that at baseline.

The frequency of eyes with leakage on FA in the treated area generally decreased during post-treatment follow-up (Tab. II). Eleven eyes (36.7%) continued to show angiographic leakage in the treated area at 9 and 12 months. The frequency of eyes with angiographic leakage at 12 months post-treatment was significantly ($p<0.0001$; Fisher exact test) less than that at baseline.

The effect of PDT on the interconnecting neovascular network was partial and inconsistent. At baseline, 25 of the 31 study eyes (80.6%) had a well defined plaque on late-phase ICGA. At 12 months follow-up, this plaque was still clearly visible in 14 out of 30 eyes (46.6%) with an increase of size in 2 eyes. Signs of RPE atrophy were detected in 16 out of 30 eyes (53.3%).

OCT scans showed that the frequency of eyes with complete occlusion of the polypoidal dilations generally increased from none at baseline to 73.3% (n=22 out of 30 eyes) at 12 months (Tab. II). The frequency of eyes with complete occlusion of the polypoidal dilations at 12 months post-treatment was significantly ($p<0.0001$; chi-square test) higher than that at baseline.

OCT revealed that mean retinal thickness, in the foveal area, at baseline was 292 (SD 124) µm and decreased to a mean 226 (SD 82) µm at 6 weeks following (Tab. I). At 12 months post-PDT, the mean thickness of 224 (SD 104) µm was significantly ($p<0.03$) reduced compared with baseline.

The frequency of serous detachment of the macula progressively decreased during the follow-up period (Tab. II). Only five eyes (16.7%) continued to have macular detachment at 12 months. The frequency of serous detachment of the macula at 12 months post-treatment was significantly ($p<0.0001$; chi-square test) less than that at baseline.

At 12 months post-treatment, 28 eyes were followed for a mean period of 11.7 months. After 12 months, 13 eyes were retreated with V-PDT; ICGA showed dilation of the vessels of the interconnecting network in 11 of these 13 eyes (84.6%) and leakage of these vessels in 9 of these 13 eyes (69.2%). In the 15 eyes not requiring treatment, dilation of the vessels of the interconnecting network was found in 6 eyes (40%) and leakage of these vessels in 2 eyes (13.3%). In spite of these results, there was no statistically significant correlation between the presence of dilation and leakage of the vessels of the interconnecting vascular network on ICGA and the risk of recurrences.

TABLE I - MEAN (SD) OF THE VARIOUS EVALUATED PARAMETERS DURING THE STUDY

	Examination visits					
Study parameters	**Baseline**	**6 wk**	**3 mo**	**6 mo**	**9 mo**	**12 mo**
Visual acuity	0.38 (0.24)	0.44 (0.24)	0.47 (0.32)	0.45 (0.31)	0.48 (0.33)	0.50 (0.34)
Contrast sensitivity	1.23 (0.36)	1.29 (0.30)	1.29 (0.35)	1.28 (0.38)	1.27 (0.37)	1.28 (0.33)
Foveal thickness	292 (124)	226 (82)	255 (97)	265 (122)	219 (88)	224 (104)

TABLE II - NUMBER (PERCENT) OF EYES WITH THE VARIOUS EVALUATED FEATURES DURING THE STUDY

	Examination visits					
Evaluated features	**Baseline (n=31)**	**6 wk (n=31)**	**3 mo (n=31)**	**6 mo (n=31)**	**9 mo (n=30)**	**12 mo (n=30)**
Retinal hemorrhages	21 (68)	20(60)	22 (71)	14 (45)	8 (27)	6 (20)
Fluorescein leakage	31(100)	16 (52)	16 (52)	10 (32)	11 (37)	11 (37)
Occlusion of polypoidal dilations	0(0)	18 (58)	13 (42)	13 (42)	20 (67)	22 (73)
Serous macular detachment	31 (100)	21(68)	18 (58)	14 (45)	10 (33)	5 (17)

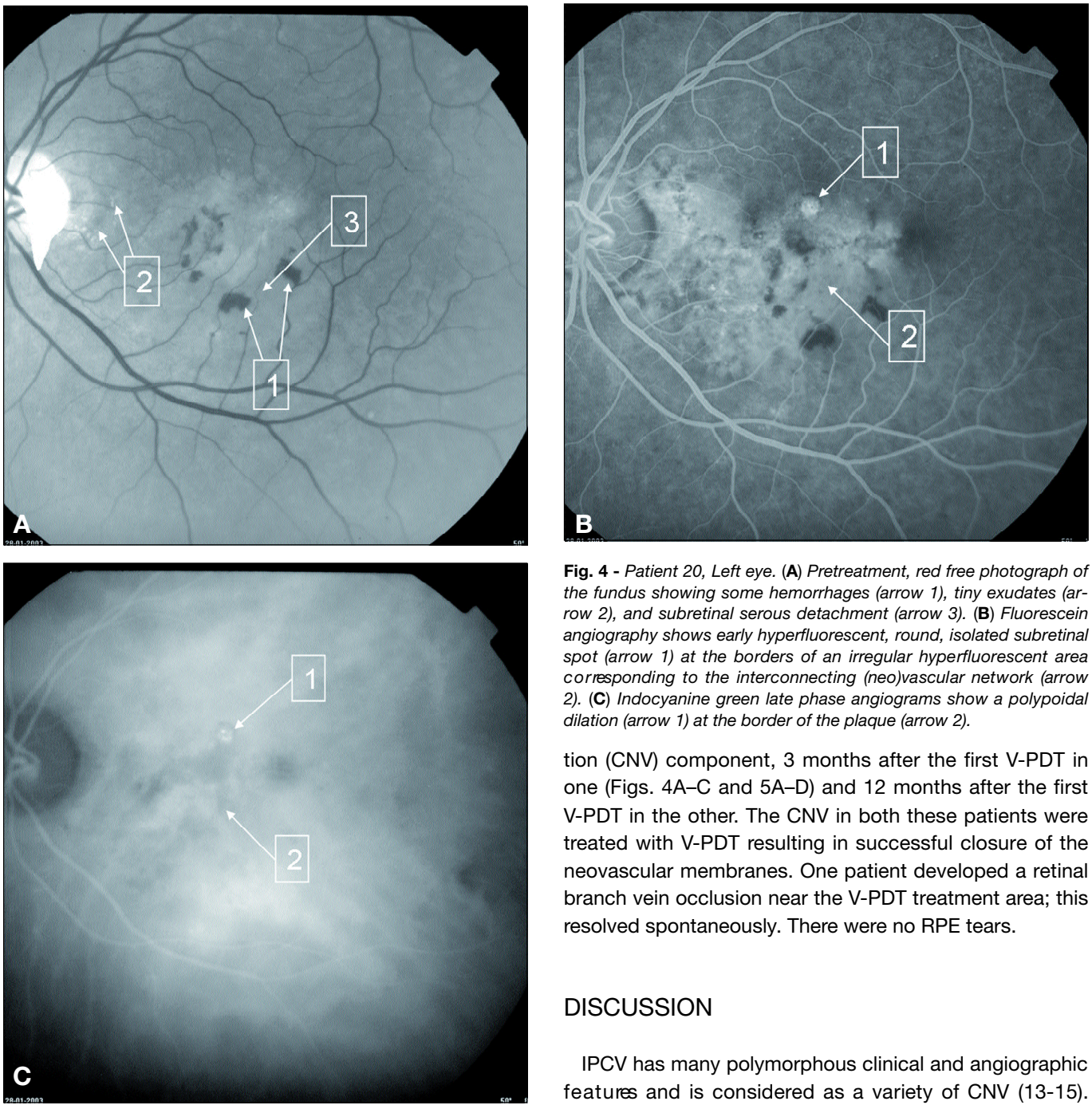

Fig. 4 - *Patient 20, Left eye.* (**A**) *Pretreatment, red free photograph of the fundus showing some hemorrhages (arrow 1), tiny exudates (arrow 2), and subretinal serous detachment (arrow 3).* (**B**) *Fluorescein angiography shows early hyperfluorescent, round, isolated subretinal spot (arrow 1) at the borders of an irregular hyperfluorescent area corresponding to the interconnecting (neo)vascular network (arrow 2).* (**C**) *Indocyanine green late phase angiograms show a polypoidal dilation (arrow 1) at the border of the plaque (arrow 2).*

Adverse events

One eye developed, immediately after PDT, a severe but transient visual loss due to a macular hemorrhage. One patient had persistent exudative polypoidal dilations after three PDT sessions; this required laser photocoagulation. Two eyes developed a classic choroidal neovascularization (CNV) component, 3 months after the first V-PDT in one (Figs. 4A–C and 5A–D) and 12 months after the first V-PDT in the other. The CNV in both these patients were treated with V-PDT resulting in successful closure of the neovascular membranes. One patient developed a retinal branch vein occlusion near the V-PDT treatment area; this resolved spontaneously. There were no RPE tears.

DISCUSSION

IPCV has many polymorphous clinical and angiographic features and is considered as a variety of CNV (13-15). IPCV is characterized by a neovascular complex of dilated and leaking choroidal vessels perfused by a feeder-vessel emerging from an “ingrowth site” in the choroid (16). Polypoidal choroidal dilations may present with some similarities to hemangiomas (17), e.g., have a vascular tubular component and identical reddish-orange color of the saccular dilations seen best during ICGA. Occasionally, IPCV can be seen associated with diffuse dis-

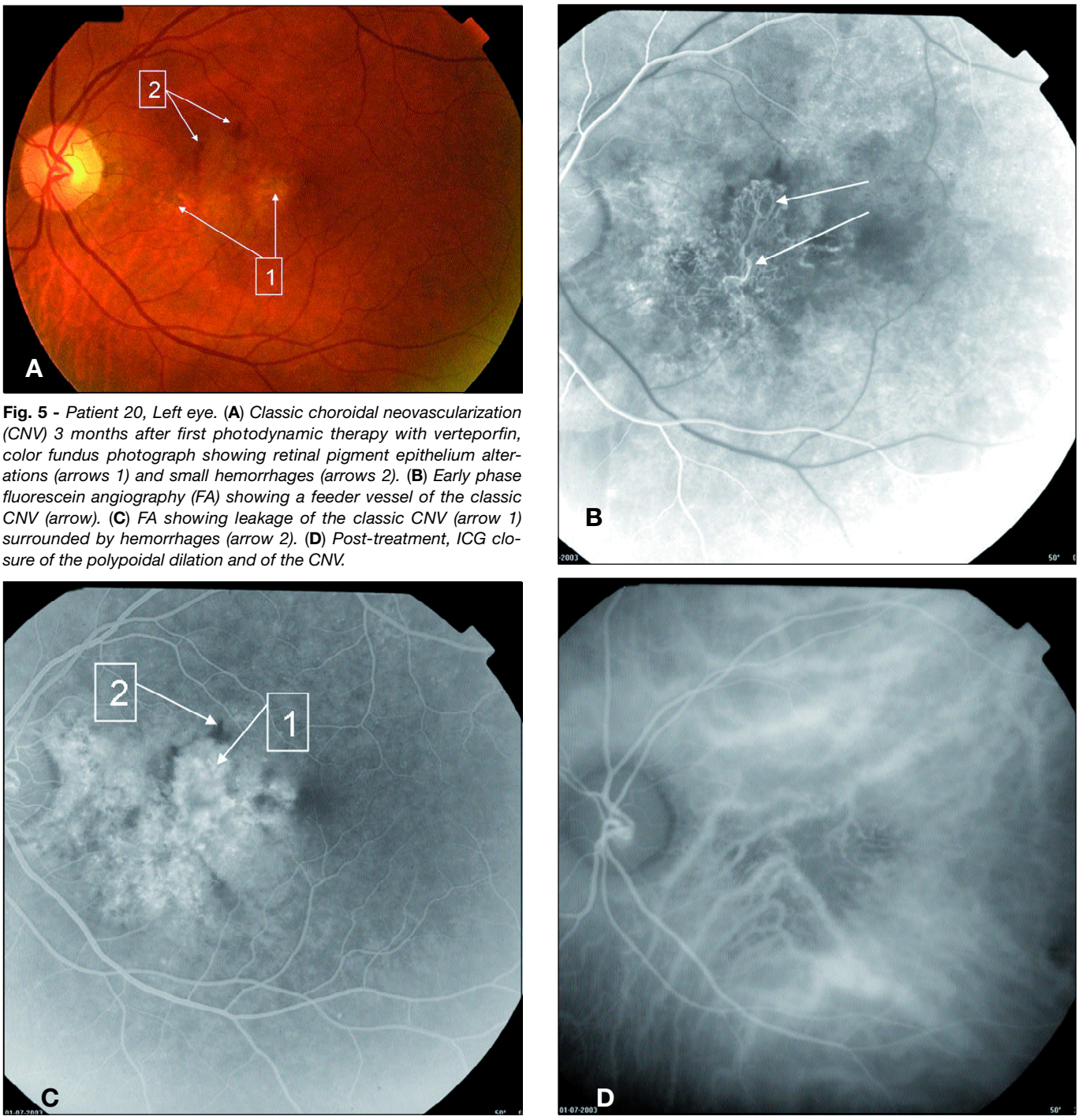

Fig. 5 - *Patient 20, Left eye.* (**A**) *Classic choroidal neovascularization (CNV) 3 months after first photodynamic therapy with verteporfin, color fundus photograph showing retinal pigment epithelium alterations (arrows 1) and small hemorrhages (arrows 2).* (**B**) *Early phase fluorescein angiography (FA) showing a feeder vessel of the classic CNV (arrow).* (**C**) *FA showing leakage of the classic CNV (arrow 1) surrounded by hemorrhages (arrow 2).* (**D**) *Post-treatment, ICG closure of the polypoidal dilation and of the CNV.*

turbances of the RPE evoking the diagnosis of atypical CSC or DRE (18). Other similarities between IPCV and atypical CSC or DRE include ICG angiographic areas of choroidal dilations with diffusion and occurrence of RPE detachments.

V-PDT is known to induce photochemical thrombosis in subretinal new vessels (19). Moreover, in pilot studies, V-PDT resulted in complete anatomic regression of hemangiomas by occluding the angiomatous net without recanalization (20). V-PDT also has the potential to narrow dilated choroidal vessels and reduce choroidal permeability in CSC (21). All these factors may explain the relatively

good immediate responses of IPCV to V-PDT that are observed in this study as well as in all the previous published studies (5-10). The establishment of appropriate management modalities for IPCV is difficult, however, because of the variability in the evolution of this disease with occasionally acceptable long-term preservation of good vision.

The aim of IPCV treatment is to occlude the polypoidal structures when they are a source of serous exudation and hemorrhagic complications that threatens central vision. In the event of extrafoveal location, focal laser photocoagulation of the leaking polypoidal dilations is usually performed without treating the entire vascular complex (22, 23). The results of this treatment approach are inconsistent with occasional persistence or worsening of the exudation (3). Some authors would, therefore, recommend treating the whole lesion (4).

In the case of juxtafoveal or subfoveal choroidal polypoidal dilations, studies have shown the favorable results of laser photocoagulation either after inferior limited macular translocation (24) or after ICGA-assisted identification of the feeder vessels supplying the idiopathic polypoidal choroidal vasculopathy (25). However, the numbers of patients included in these studies are too small to allow statistically significant results (16).

In our study, 58.1% of the polypoidal dilations were occluded 6 weeks after V-PDT and 73.3% were occluded 12 months after a mean of 2.5 V-PDT treatments. These observations are consistent with the results of previous reports. Both visual acuity and fluorescein leakage improved while OCT scans showed resolution of the serous retinal detachment.

We found that the visual acuity at 12 months was significantly better in younger patients and in males. In our study, the male patients were 9 years younger than the females and this may explain the observed difference between the sexes in their response to V-PDT.

There was a trend for increased treatment in patients who had more advanced ARMD signs in the fellow eye; the latter may suggest the presence of more significant RPE disease. It is possible that the state of the RPE could influence the response to the V-PDT treatment and justify the need for more treatment.

FA, ICGA, and OCT allow identification and treatment of the polypoidal structures and are useful in the follow-up after treatment. OCT scans, in particular, provide images of the different phases of maturation of the polypoid elements, their exudative components, and the changes induced by treatment (26-30).

The good results observed in IPCV following V-PDT may be due to a combination of V-PDT induced factors: thrombosis in the neovascular structure, occlusion of the angioma-like elements, and narrowing of the dilated choroidal vessels (seen on ICG angiograms) along with a reduction in the blood flow inside the abnormal choroidal network and remodeling of the choroidal vascularization. These ICG angiographic findings, including the absence of leakage and reduction of the dilation of the vessels of their interconnecting network, were usually seen in our patients who experienced good functional results and no recurrences. Poor results were observed mostly in IPCV where the vessels of the branching network were not readily modifiable by V-PDT. This was clearly visible on ICG angiograms, which showed steady dilation and leakage of these vessels.

Two of our patients developed classic CNV. One patient, 64 years old, had clinical signs of early ARMD and some fibrosis; CNV occurred 3 months after the initial V-PDT treatment. The other patient had a long-standing IPCV with an extensive plaque and large areas of RPE atrophy. The patient was 77 years old, had clinical signs of ARMD, and the CNV occurred 12 months after her initial V-PDT treatment. This patient also experienced a dense macular hemorrhage immediately after her initial V-PDT treatment; this hemorrhage spontaneously resolved in 3 months. The CNVs in both these patients were treated with V-PDT, resulting in successful closure of the neovascular membranes.

Our study shows that V-PDT usually closes the polypoidal dilations observed at the border of the neovascular network in IPCV. However, the plaques may continue to be visible on post-treatment angiograms. This explains the recurrences of the disease at the same site or in another place along the border of the plaque unless the plaque becomes atrophic.

CONCLUSIONS

Most of our patients showed a reduction in exudative signs and improvement in vision following V-PDT. V-PDT was safe and well-tolerated although there were some complications, particularly classic CNV, which occurred mainly in the presence of clinical signs of ARMD and fibrosis.

Our results suggest that V-PDT is a good choice for treating IPCV exudative lesions that are juxtafoveal or subfoveal. We recommend further investigation of V-PDT in large, controlled studies with long-term follow-up in order to confirm the useful role of V-PDT in the management of IPCV.

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