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Retinal photocoagulation for proliferative sickle cell retinopathy: A prospective clinical trial with new sea fan classification

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PURPOSE. *To compare the clinical outcome of stage III proliferative sickle cell retinopathy (PSR) treated by peripheral retinal scatter photocoagulation to natural course disease.*
METHODS. *Long-term follow-up of 101 patients enrolled in a prospective trial of photocoagulation for PSR has been completed. Among 202 eyes of 101 patients enrolled at the University Eye Clinic of Créteil, 73 eyes showed a stage III PSR, which the authors further divided into five new grades (A, B, C, D, E) considering size, hemorrhage, fibrosis, and visible vessels. Grading was based on a three-mirror fundus examination, 360° color photographs, and fluorescein angiography. Mean follow-up was 4 years.*
RESULTS. *Thirty-eight treated eyes and 35 untreated eyes were included in this study. The evolution was not statistically significant between treated and untreated groups concerning flat sea fan <1 MPS disc area (grade A) or elevated sea fan with partial fibrosis (grade C). Progression and regression were compared between the two groups for grade B, resulting statistically significant ($p<0.05$). Nine complications (13%) were observed, which only occurred in untreated patients with elevated sea fan and hemorrhage (grade B) or complete fibrosed sea fan with well defined vessels (grade E) ($p<0.05$).*
CONCLUSIONS. *These data suggest that patients with grade A or C new sea fan classification should not be initially treated but observed. (Eur J Ophthalmol 2008; 18: 248-54)*

KEY WORDS. *Classification, Clinical trial, Photocoagulation, Retinopathy, Sea fan, Sickle cell*

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INTRODUCTION

Sickle cell hemoglobinopathies result from an abnormality in the beta chain of the hemoglobin molecule. The principal manifestations are chronic hemolytic anemia and vaso-occlusive crises that produce severe pain as well as long-term and widespread organ damage. There are several clinically important hemoglobin variants that constitute sickle syndromes. Patients with sickle-cell disease are susceptible to develop peripheral retinal neovascularization (proliferative sickle cell retinopathy [PSR]), also called sea fan, and vitreous hemorrhage, and occasionally rhegmatogenous, tractional, or exudative retinal detachments, which carry the threat of permanent visual loss. Visual loss in patients with sickle cell disease (homozygous sickle cell disease, sickle cell-hemoglobin C disease, and sickle cell-B+ thalassemia disease) has been reported to occur in 10% to 12% of eyes. Spontaneous autoinfarction and regression of neovascularization is well documented in PSR according to many mechanisms (1-7). Treatment

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modalities advocated to prevent the blinding complications have included diathermy, cryotherapy, and feeder vessel photocoagulation, without demonstrating convincing results (8-18). However, a randomized clinical trial showed the benefit on visual loss of scatter laser peripheral photocoagulation on proliferative sickle retinopathy behavior in sickle cell hemoglobin (SC) (19). Since vitrectomy and scleral buckling surgery in these patients may include side effects and adverse events, emphasis has been placed on sea fan lesion of PSR early treatment by photocoagulation with argon laser.

We report our experience on a long-term follow-up of patients enrolled in a prospective clinical trial to compare scatter laser photocoagulation to natural course of PSR by analyzing different sea fan characteristics.

METHODS

Consecutive series of patients presenting sickle cell disease were included in a prospective comparative clinical trial for argon laser photocoagulation. Patients were enrolled at the Sickle cell Disease Center and the University Eye Clinic of Créteil from January 1991 to January 2004. Eyes with cataract, vitreous hemorrhage, retinal detachment, previous photocoagulation, and ocular surgery were excluded as well as patients with systemic diseases (diabetes mellitus, high blood pressure). Patients presenting at the initial examination with sea fan >1 Macular Photocoagulation Study (MPS) disc area (20), hemorrhage, vitreoretinal traction as bride, tears or retinal hole at the new vessel site, or history of complication in the fellow eye were treated and excluded from the study as well. All eyes underwent a complete ophthalmologic examination. Direct and indirect ophthalmoscopy were performed through dilated pupils by using tropicamide 1% and phenylephrine hydrochloride 10%. Fundus color photographs (360°) and fluorescein angiography were performed at each visit. Routine follow-up was performed every 6 months, or more as needed. The retinal drawings were updated and the color photographs and angiograms were repeated as often as needed to document changes of the sickle cell retinopathy. Stage III Goldberg classification of proliferative sickle retinopathy (neovascular and fibrous proliferations) (4) was defined by leakage, associated or not with fibrosis, of intravenously administered fluorescein. At the first examination, the stage III lesions (sea fan) were further classified as described in Table I. Each patient was randomized to treatment or no treatment (treated or untreated group). Disease progression, regression, no change, and complications were evaluated and recorded, based on the difference between the first and last control for the five new grade sea fan characteristics. After the first 6-month follow-up, all patients underwent fundus examination, retinal color, and fluorescein angiography: if the sea fan size exceeded 1 MPS disc area, patients were treated and excluded from the study.

Photocoagulation was performed with an argon green laser through a three-mirror lens. Focal scatter photocoagulation burns were placed around all sea fans, without treating the sea fan or its feeder vessels directly. Burns were spaced approximately one burn diameter apart and usually placed from 2 disc diameters anterior to the sea fan and 2 clock hours to each of its sides. Spot diameter

TABLE I - NEW GRADING OF STAGE III PROLIFERATIVE SICKLE RETINOPATHY

Grade	Description
A	Sea fan flat with leakage <1 MPS disc area
B	Elevated sea fan with hemorrhage
C	Elevated sea fan with partial fibrosis
D	Complete sea fan fibrosis without well demarcated vessels
E	Complete sea fan fibrosis with well demarcated vessels

TABLE II - DEMOGRAPHIC CHARACTERISTICS OF PATIENTS ON ADMISSION TO STUDY

Characteristics	Treated, n=38	Untreated, n=35
Age, yr (median)	29	31
Male (n=39)	17	22
Female (n=62)	30	32
Follow-up, yr	4,1	4
PSR Stage III Hb genotypes (n=73)		
SC	16	19
SS	22	16
Sß+	0	0

Initial classification of 202 eyes (101 patients): stage I (n=79), stage II (n=50), stage III (n=73), stage IV (n=0), stage V (n=0). No differences were significant.

PSR = Proliferative sickle retinopathy; Hb = Hemoglobin; SC = Sickle cell hemoglobin C disease; SS = Homozygous sickle cell disease; S + = Sickle cell B+ thalassemia

was 300 to 500 m, during 0.1 second, with a mild whitening of the retina. A first follow-up visit was scheduled 6 weeks later to perform fluorescein angiography and determine if retreatment by administering additional laser burns was necessary .The endpoint of complete closure was reached when, at least at one follow-up visit, the absence of flow was observed by clinical examination and confirmed by fluorescein angiography. Patients missing one visit were excluded from the study. Statistical analyses were performed by using Fisher exact test and the chi square test. $p<0.05$ was considered statistically significant.

RESULTS

A total of 101 patients (202 eyes) were analyzed, 62 women and 39 men, aged from 18 to 63 years (mean age was 29 years). Among this cohort, there were 33 patients with sickle cell hemoglobin C disease (SC), 63 with homozygous sickle cell disease (SS), and 5 with sickle cell B+ thalassemia (S +). Mean follow-up was 4 years (range, 1–13 years).

Stage III proliferative sickle cell retinopathy was present at initial examination in 57 (28%) of 202 eyes and developed later, during the study course, in 16 further eyes (8%) diagnosed initially as stage II. All demographic data of patients are listed in Table II. Age distribution analysis of patients with SC disease developing PSR for the first time indicated that the highest risk age, accounting for 73% of cases, was 20–31 years. Sex ratio was similar in each group. Sea fan development was more common in sickle cell-hemoglobin C disease (61.7%) than in homozygous patients (28.3%). No case was described in sickle cell B+ thalassemia (S +). Bilateral stage III PSR was initially observed in 3 of 101 patients. There were 67 unilateral cases. An average of two photocoagulation procedures per eye (range, 1–3) was performed in the treated group. There were 38 argon laser-treated eyes and 35 untreated eyes (controls). Evolutions criteria were compared in each group between the first and last examination.

Disease progression, defined by an increased size of existing lesions associated to leakage, occurred in 13 of 73 stage III eyes (8 SC; 5 SS) during the observation period. Five of the 38 eyes in the treated group at initial visit were retreated because of new sea fans or extensive new ves-

TABLE III - OUTCOMES OF NEW GRADE STAGE III PROLIFERATIVE SICKLE RETINOPATHY

Grade	Evolution	Treated (n=38)	Untreated (n=35)	p
A (n=20)	Progression	1 (SC)	2 (1 SC, 1 SS)	NS
	Regression	10 (4 SC, 6 SS)	6 (3 SC, 3 SS)	NS
	No change	1 (SS)	0	NS
	Complications	0	0	NS
B (n=20)	Progression	1 (SC)	6 (4 SC, 2 SS)	<0.05
	Regression	9 (3 SC, 6 SS)	2 (1 SC, 1 SS)	0.02
	No change	1 (SS)	1 (SS)	NS
	Complications	0	5 (4 SC, 1 SS)	0.04
C (n=11)	Progression	2 (1 SC, 1 SS)	1 (SS)	NS
	Regression	2 (SS)	2 (1 SC, 1 SS)	NS
	No change	2 (SC)	2 (1 SC, 1 SS)	NS
	Complications	0	0	NS
D (n=8)	Progression	0	0	
	Regression	0	0	
	No change	5 (2 SC, 3 SS)	3 (1 SC, 2 SS)	NC
	Complications	0	0	
E (n=8)	Progression	0	0	
	Regression	0	0	
	No change	4 (2 SC, 2 SS)	1 (SS)	NS
	Complications	0	4 (3 SC, 1 SS)	<0.05

SC = Sickle cell hemoglobin C disease; SS = Homozygous sickle cell disease; NS = Not significant; NC = Not calcolated

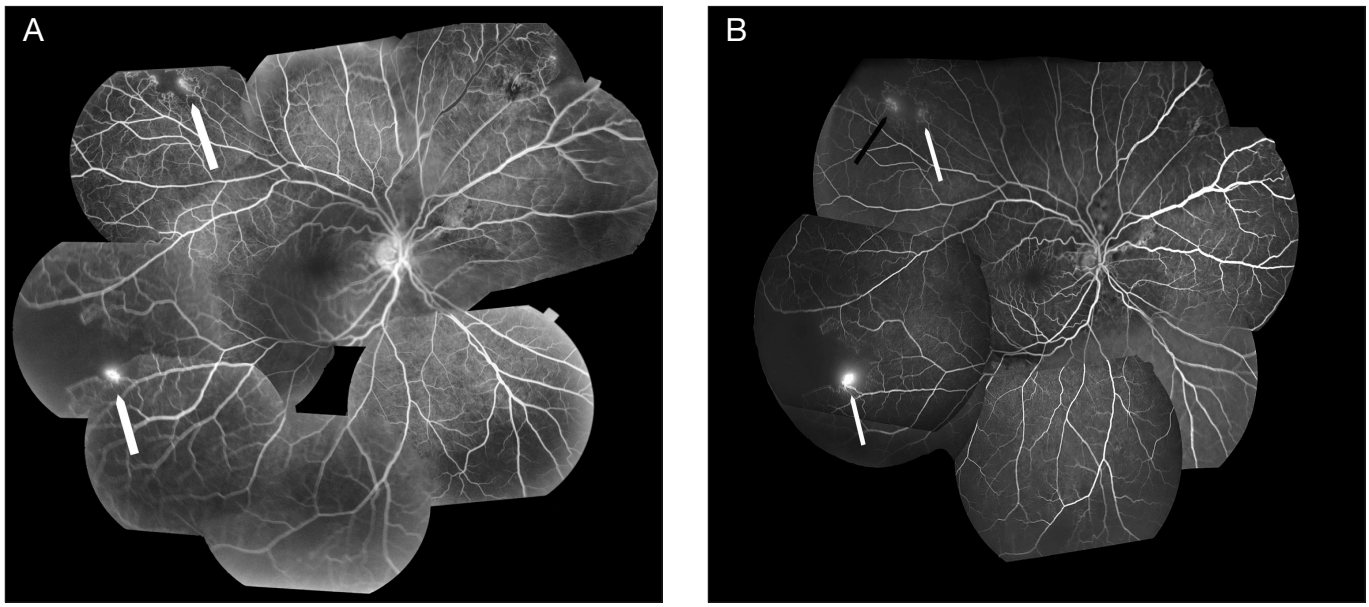

Fig. 1 - (A) *A 24-year-old man with sickle cell disease. Fluorescein angiography demonstrates in a composite of peripheric multifield two neovascular proliferations <1 MPS disc area (grade A) (white arrows) on the superior field and the inferotemporal periphery. No treatment was decided.* **(B)** *Five years later, fluorescein angiography peripheric composite indicates the regression of superior sea fan (white arrow) with the appearance of a new lesion (black arrow).The temporal-inferior sea fan (white arrow) has changed to fibrotic lesion. The ischemic area is similar to initial presentation.*

sels. Progression events were described for grade A and C without finding any significant difference between treated and untreated groups ($p>0.05$). Most of the progression events were described for grade B with statistically significant difference between treated and untreated groups ($p<0.05$). No case of progression was reported for grade D and E. Balance of outcomes in the current end study are summarized in Table III.

Disease regression was diagnosed by reduction of sea fan size, no perfusion or no leakage on the fluorescein angiography, or autoinfarction described as the complete disappearance of the preretinal new vessels on the color retinograph and fundus examination. In many cases sea fan appeared either as completely fibrous without hemorrhage, either as well-demarcated atrophic vessels. This was observed during the study in 21 of 38 treated eyes (55 %) (7 SC; 14 SS) and 10 of 35 eyes (28.6%) (5 SC; 5 SS) in the untreated group. Regression was observed in 10 eyes treated with a small sea fan <1 MPS (grade A) and in 6 eyes in the untreated group. Regression was observed in 2 grade C treated eyes and in 2 grade C untreated eyes. There was no statistical difference for regression in grade A and C patients ($p>0.05$). Conversely, there was a statistical difference for regression in grade B patients: regression was observed in 9 treated patients and 2 eyes in the untreated group ($p=0.02$). No case of sea fan infarction was described for grade D or E. Average age of patients presenting autoinfarction was 30 years (SS group) and 29 years (SC group). Example of pattern regression in untreated patients is illustrated in Fig. 1, A and B.

Sea fan evolution was considered as stable or unchanged if size and leakage were identical during the follow-up. PSR showed no change in 20 of 73 eyes (27%). It was predominant for complete sea fan fibrosis without well demarcated vessels (grade D) at the first examination. Thirteen eyes were observed in the treated group (13/20) and seven cases in the untreated group (7/20). The difference was not statistically significant ($p>0.05$) for grade D and E. Stability tended to be a feature of older patients, mean ages being 40 in SC and 42 in SS.

Complications of this series were observed in 9 eyes (13%) and appeared only in grade B and E of untreated patients ($p<0.05$). Three eyes had rhegmatogenous retinal detachment and four vitreous hemorrhages were diagnosed. All these patients underwent surgery (vitrectomy and/or scleral buckling). Vitreous hemorrhage was followed by autoinfarction of neovascularization lesions in

two eyes, and visual acuity was unchanged from the initial examination. There were no significant differences between treated and control groups in age, sex, hemoglobin genotype distribution, or size and characteristics of sea fan lesions. Of the 73 eyes evaluated, 72 had the same visual acuity from entry to final visit. Three eyes with visual acuity of 20/200 due to vitreous hemorrhage underwent vitrectomy, endolaser of sea fan, and recovered 20/20 at the last visit. One eye with complete retinal detachment and visual acuity of 20/400 recovered 20/50 after surgery.

DISCUSSION

The classification of sickle retinopathy described by Goldberg in 1971 includes 5 stages (4). In stage I, peripheral arteriolar occlusion is present. Stage II corresponds to peripheral arteriovenous anastomoses. Stage IV is defined by intravitreal hemorrhage and V by retinal detachment. Stage III corresponds to the neovascular and fibrous proliferations. Based on our experience, we decided to subdivide stage III into different subgroups of sea fan, by introducing clinical and angiographic characteristics of new vessels, to evaluate their respective prognosis and therapeutics. We classified as grade A the presence of sea fan flat with leakage <1 MPS disc area; grade B the presence of elevated sea fan with hemorrhage; grade C the presence of elevated sea fan with partial fibrosis; grade D complete sea fan fibrosis without well demarcated vessels; and grade E complete sea fan fibrosis with well demarcated vessels.

To date, owing to side effects and spontaneous regression in some eyes, need for treatment is not always clear. Treatment by feeder vessel occlusion (13, 14), although effective on the sea fan closure, presented many complications such as choroidal neovascularization, intravitreal hemorrhage, and hemorrhagic or tractional retinal detachment. This treatment is currently discontinued. The effect of 360° peripheral circumferential scatter photocoagulation on PSR is effective and well-described. In a series of 70 eyes with 220 sea fans, 78% regressed completely or partially after treatment (8). On the other hand, the series was not controlled and patients with more than one genotype were studied. Considering the absence of a controlled trial, this treatment remains to be definitively validated, but it still may be preferred for selected patients with extensive neovascularization and unreliable follow-up. Scatter sectoral photocoagulation is actually the most effective treatment on new vessels occlusion (9, 10, 16-19), although its mechanism is not precisely known and theories suggest a reduction of endothelial proliferation factors by destruction of ischemic retina. This treatment is often incomplete with persistence of a neovascular perfusion justifying several argon laser sessions. In a study of 174 eyes with proliferative retinopathy treated using sectoral scatter laser photocoagulation, regression of 81.2% treated patients and of 45.7% untreated patients was reported (19). However, the series included only patients with PSR when sea fan was described on angiograms without describing varieties.

Possible evolution of PSR to autoinfarction is well-described as natural history. A series documented cases of untreated sea fan with spontaneously favorable evolution (1): 27% presented complete autoinfarction and 33% partial autoinfarction (60% of total regression). Downes et al found that spontaneous regression occurred in 32% of PSR-affected eyes (21).

Mechanisms contributing to autoinfarction are not completely known and include occlusion of feeder vessels arterioles or vitreous traction causing hemodynamic alterations in the sea fan and its feeder vessels, resulting in sluggish blood flow and eventual occlusion (6), although it occurs initially at preretinal capillary level rather than at feeding arterioles with preferential sea fan site at arteriovenous crossings (7).

In this study we compared standard scatter photocoagulation to control and showed a different evolution during follow-up. In our series, the characteristics of both groups are homogeneous regarding frequency of examinations, sex, genotype, and age, since young patients between 20 and 31 years were involved and followed for an average of 4 years.

Spontaneous regression occurred in10 out of 35 patients (32%) in the untreated group. However, the analysis of subtype of sea fan shows that the flat sea fan (grade A) and elevated sea fan with partial fibrosis (grade C) regress in the same proportion in both groups ($p>0.05$), whereas in grade B there is a significant difference for regression ($p=0.02$). Regarding complications, grades B and E have higher risks (9 events in the untreated group versus 0) ($p<0.05$).

Presence of hemorrhage in grade B appears to be of pejorative prognosis. Analysis of untreated eyes in a prior study showed that presence of pre-existing intravitreal blood at the initial evaluation represents risk factors for vitreous hemorrhage (14). In addition, no complication

was reported for grades A, C, and D, suggesting therapeutic abstention specially for small sea fans (grade A).
A potential variable that might affect outcome is the genotype. Patients with SC genotype have highest risk of sea fan development and spontaneous regression is more common in untreated SS patients aged 40 years and over (22).
Our series is not easily comparable because no previous study described the different characteristics of sea fan group as done in our study. Regression rate in treated and control groups is the same as in previous results.
The primary limitation of this prospective study is the small number of patients. We were not able to include more patients with grade C, D, and E with all similar clinical characteristics.
The strength of the present study is that a new classification of stage III proliferative sickle retinopathy is proposed according to the data and our results. Our major finding is that each subdivided sea fan type has a different prognosis, suggesting the use of this new classification.
In conclusion, the treatment of stage III peripheral retinal neovascularization (sea fan) seen in sickling hemoglobinopathies is currently a topic of much debate. Because most of these lesions are peripheral, the majority of patients retain excellent visual acuity in absence of a vitreous hemorrhage or retinal detachments. According to prior study, retinal peripheral scatter photocoagulation is currently the most effective way to control eyes with neovascular proliferation. According to our results, this treatment should be a matter of discussion. These findings and our experience suggest that no treatment should be considered in selected patients with flat sea fan <1 MPS disc area (grade A) or elevated sea fan with partial fibrosis (grade C). This new classification and the results of the follow-up suggest that a small group of patients requires specific follow-up and decision for laser treatment. The patients at risk are thus better identified, which also allows decrease of the clinical load.

The authors have no proprietary commercial interests.

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