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RETINAL DISORDERS

Selective retina therapy (SRT) in patients with geographic atrophy due to age-related macular degeneration

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Abstract
Background For geographic atrophy (GA) due to age-related macular degeneration (AMD) there is so far no approved treatment option. Usually, increased autofluorescence (AF) levels of different patterns adjacent to the atrophic area indicate lipofuscin-laden retinal pigment epithelium (RPE) cells at a high risk for apoptosis. Herein, SRT was used to selectively treat these cells to stimulate RPE proliferation, in order to reduce or ideally stop further growth of the atrophic area.
Material and methods Six eyes of six patients with bilateral equally pronounced GA were treated by SRT, while the fellow eye served as control. Irradiation was performed using a prototype SRT laser (Medical Laser Center Lübeck, Nd:YLF laser; 527 nm; 200 ns/1.7 µs pulse duration; 30 repetitive pulses at 100 Hz). Test lesions with increasing energies were applied at the lower vessel arcade to determine the individual angiographic and ophthalmoscopic threshold radiant exposures. Treatment was then performed in the area of increased AF adjacent to the GA using energies between both thresholds. The GA progression rates of treated and fellow eyes were evaluated.
Results After a 1-year follow-up, a progression of the atrophic area was observed in the treated eyes (0.7–8.0 mm^2/yr, mean 3.0 mm^2/yr; 46%/yr) whereas the progression rates of the fellow eyes were insignificantly lower (0.46–4.04 mm^2/yr, mean 1.9 mm^2/yr; 30%/yr; p= 0.134). The progression rate in the treated eyes of two patients increased significantly, while in the other four patients, the progression rates were nearly the same between both eyes. Moreover, one of these two eyes showed an unexpected RPE reaction after treatment, since all laser lesions led to RPE atrophy and thus an accelerated enlargement of the GA occurred.
Conclusion SRT in the hyperautofluorescent areas of GA was not able to stop or slow down the progression of GA. However, modified treatment strategies might be more promising, e.g. placing the spots outside the hyperautofluorescent areas where RPE apoptosis is postulated. Moreover, SRT studies on GA might be more successfully performed on specific subgroups of GA, based on autofluorescence and other findings.

Keywords Geographic atrophy · AMD · RPE · Laser photocoagulation · SRT · Selective retina treatment

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Introduction

Age-related macular degeneration (AMD) remains the major cause of severe vision loss of the elderly in western civilizations. In late stage-AMD, central vision is impaired by choroidal neovascularization, geographic atrophy (GA) or retinal pigment epithelium (RPE) detachment [1–4]. GA is thought to be responsible for 20% of cases of legal blindness attributable to late-stage AMD. Unlike recent therapeutic advances in exsudative AMD, there is still no

approved treatment option in atrophic AMD. Due to the aging population, the prevalence is expected to double in the next decades [3].

In postmitotic RPE cell degradation, products of photoreceptor outer segments accumulate over lifetime in forms of lipofuscin and other related compounds [5]. Delori et al. have shown that in in vivo fundus autofluorescence measurements RPE lipofuscin is the dominant fluorophore [6]. Holz et al. did observe areas of increased autofluorescence preceding atrophy enlargement in the junctional zone of patients with GA [7]. This finding indicates the presence of lipofuscin-laden RPE cells in the junctional zone adjacent to the atrophic areas that are at increased risk of apoptosis. Moreover, recently it was shown that distinct patterns of increased autofluorescence are of prognostic value for GA progression [8].

Selective retina therapy (SRT) using short laser pulses within the microsecond regime has been shown to selectively treat RPE cells without affecting the overlying photoreceptor layer [9, 10]. The laser-induced RPE defect in SRT is covered in the same way as in conventional laser photocoagulation within 7 days, by migration and proliferation of neighboring RPE cells recreating an intact RPE layer [11–13]; however, in contrast to conventional laser photocoagulation, no laser scotoma due to preserved photoreceptors [14, 15] and also no consecutive late-onset RPE atrophy appear [16]. It has been possible to prove the concept of SRT in some clinical trials, showing an improvement in macular diseases as drusen maculopathy [15, 17], diabetic maculopathy [15, 17, 18], and central serous chorioretinopathy [15, 17, 19].

Due to the potential of SRT to selectively stimulate the RPE cell layer, in this study the technique was evaluated for the first time in treating proposed apoptotic RPE cells at the rim of GA to ideally stop or slow down further growth of the atrophic area. With the applied selective laser treatment the pathologic RPE cells of increased autofluorescence were anticipated to be damaged without causing scotoma—ideally leading to the biologic reaction of RPE migration and proliferation resulting in new cell populations in these areas.

Therefore, a SRT prototype laser with refined SRT laser parameters using less energy [20, 21] was prospectively used in one eye of patients with equally pronounced bilateral GA due to AMD, while the other eye served as a control.

Material and methods

Six patients were included in the study. All patients were informed concerning the experimental nature of the study and gave their informed consent. The study was approved by the local ethics committee.

A complete ophthalmologic examination including ETDRS visual acuity, slit-lamp evaluation, indirect stereoscopic ophthalmoscopy after pupil dilatation, fluorescein angiography, autofluorescence imaging and optical coherence tomography were performed before treatment and during follow-up at 3, 6 and 12 months after laser irradiation.

Laser

For this study a prototype SRT laser system (SRT vario; Medical Laser Center Lübeck, Germany) was used. The laser was manufactured in accordance with the European medical product law. The system consists of a diode laser excited Q-switched Nd:YLF laser with intracavity frequency conversion to a wavelength of 527 nm. The duration of the Q-switched pulse can be adjusted from 200 ns up to 3 µs by increasing the efficiency of the second harmonic generation up into the overcoupling regime [22]. The laser was operated at a repetition rate of 100 Hz, and a train of 30 pulses was always applied on each retinal spot. The duration of laser pulses was reduced from the initial 1.7 µs used for standard SRT [10] to 200 ns during this study, since less laser energy is required and thus less overall heat is created when treating within the therapeutic window [20, 21]. Maximal pulse energy of this laser system was 1 mJ.

Settings

The laser energy was transmitted by a 105 µm core diameter fiber (Ceram Optec GmbH, Optran UV-A 105/125/250, NA=0.1). The length of the fiber was 50 m in order to minimize spatial intensity modulation (speckle formation) due to fiber mode beating. This fiber was directly coupled to the slit-lamp fiber (Zeiss, ∅100 µm, NA 0.1). The laser beam was delivered to a clinical ophthalmic laser slit lamp (SL/L 30, Zeiss, Oberkochen, Germany). The pulse energy emerging from the slit lamp was restricted to 400 µJ (1.7 µs) and 200 µJ (200 ns). A green helium–neon laser beam (543 nm) served as aiming light. The distal fibre tip was imaged onto the retinal surface with an irradiated diameter of 200 µm using an ophthalmoscopic contact lens (Mainster, OMRA-S) with an integrated ultrasonic transducer (Medical Laser Center Lübeck, Germany [23]) in order to detect microbubble formation as the origin of selective RPE cell damage. With this optoacoustic device, the desired RPE cell damage for the ophthalmoscopically invisible SRT laser lesions was detected online during treatment [21, 23].

Treatment and dosimetry

In all patients, the eye with the inferior visual acuity was treated by SRT, while fellow eyes were observed and acted

as controls. Due to the invisibility of the SRT lesions, the energy necessary for cell damage is individually unknown. Thus, each patient received five to 16 test exposures at the lower vessel arcade, which were simultaneously recorded by optoacoustic measurements. Test lesions were applied with increasing energies, up to the level where lesions became ophthalmoscopically visible or maximal laser energy was reached. Fluorescein angiography was performed 1 hour after test exposures to determine the individual threshold energy for angiographic visibility. Correlations to optoacoustic values within this study have been previously published [21].

Irradiations below the RPE damage threshold do not result in fluorescein leakage, and indicate insufficient therapeutic laser energy. Lesions leading to RPE damage result in a breakdown of the outer blood–retinal barrier and leakage through the laser-induced RPE break indicating the desired treatment effect (Fig. 1). By further increasing the energy, retinal whitening as known from conventional laser photocoagulation could be observed (ophthalmoscopic threshold), most likely indicating unwanted adverse neuroretinal tissue effects.

The treatment energy was chosen slightly above the detected angiographic threshold to provide an adequate safety margin (therapeutic window up to ophthalmoscopic threshold) to avoid central neuroretinal damage. Since human fundus pigmentation may intra-individually vary across the fundus by the factor of 2 [24], this factor between angiographic and ophthalmoscopic threshold was ensured during treatment.

After threshold determination, the rim of the central atrophic area was treated using the determined treatment energy. Treatment exposures were placed non-confluent in one to two rows circumferentially around the central geographic atrophy (Fig. 1). In patients with stable fixation, a 200 µm safety area around the point of fixation was left untreated. One hour after placement of treatment lesions, a second fluorescein angiography was performed to ensure that necessary energies for RPE damage were reached.

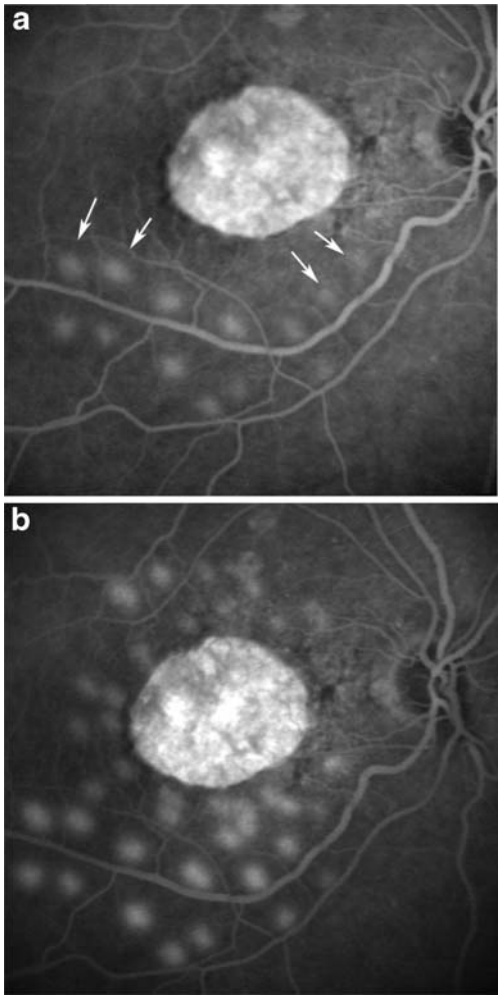

Fig. 1 Fluorescein angiography of patient #4 (Table 1) 1 hour after application of SRT test lesions at the lower arcade with increasing laser energies (**a**). Corresponding to supra-threshold SRT energy levels, a different amount of fluorescein leakage was observed in distinct lesions (*arrows*). After threshold determination, treatment lesions with energies within the therapeutic window were applied surrounding the geographic atrophy zone. Fluorescein angiography 1 hour after treatment revealed desired RPE damage by progressive central leakage of ophthalmoscopically invisible SRT lesions (**b**)

Image acquisition and processing

Fluorescein angiographic and fundus autofluorescence images were recorded using a confocal scanning laser ophthalmoscope (Heidelberg Retina Angiograph 2, Heidelberg Engineering, Germany). The blue laser wavelength (488 nm) was used for excitation and emitted light above 500 nm was recorded after passing a barrier filter. For fundus autofluorescence, eight to 16 consecutive images of 512×512 pixels were recorded. A mean image was computed after manual inspection for motion artifacts to improve the signal to noise ratio, using the Heidelberg Eye Explorer software package (Heidelberg Engineering, Germany). Images were exported to Adobe Photoshop (Adobe Systems, San Jose, CA, USA), and atrophic areas were measured semi-automatically using the Photoshop magic wand tool, based on the contrast of healthy RPE and GA in fundus autofluorescence images. In one patient, fluorescein angiographic images have been used to determine exact atrophic area size due to insufficient fundus autofluorescence image quality. Atrophic areas were calculated using the scale conversion factor of 17.21 µm/Pixel provided by the manufacturer. Progression rates in square millimeters per year were calculated as differences from baseline exam divided by follow-up time in years and are also given in percentage growth.

Statistical analysis

After calculation of the progression rates of the treated and fellow eyes, a 2-tailed paired student's *t*-test was performed to test for a difference of mean progression rates. The distribution of the progression rate was assumed to be normal. A probability value of 0.05 was considered to be statistically significant.

Results

Six patients with bilateral and equally pronounced geographic atrophy were treated by SRT. Patient age at the time of treatment was 72±6 years (mean ± SD). Mean atrophic area size at baseline was 6.3 mm^2 (range 1.5–14.9 mm^2) and 6.4 mm^2 (0.9–15.4 mm^2) in treated and fellow eyes respectively.

Five to 16 test lesions with various energies ranging from 60–200 µJ, step 20 µJ (200 ns) respectively 100–350 µJ, step 50 µJ (1.7 µs) were applied in all patients. After threshold determination, eight to 21 ophthalmoscopically non-visible treatment exposures were applied. Treatment lesions were angiographically visible in all patients as determined 1 hour after SRT; thus, treatment within the therapeutic window was ensured in all patients (Fig. 1). The treatment energies applied were 140–160 µJ (200 ns) and 200–300 µJ (1.7 µs). No adverse events during or immediately after treatment were noticed.

After follow-up of 1 year, mean geographic area size was 9.2 mm^2 (range 3.1–16.4 mm^2) in the treated eye and 8.3 mm^2 (range 1.4–16.8 mm^2) in the fellow eye respectively. Thus, the mean measured progression rate was 3.0± 2.8 mm^2/year (mean ± SD) in the treated eyes and 1.9± 1.6 mm^2/year (mean ± SD) in the fellow eyes respectively (Figs. 2, 3). In two out of the six patients, a faster progression of the treated eye compared to the fellow eye was noted; however, statistical significance was not reached (p=0.134). In four patients progression rates were nearly the same between both eyes, with slightly enhanced progression of the treated eye (Fig. 3; Table 1). From these, only one treated eye revealed a slightly slower progression of GA compared to the non-treated fellow eye (0.71 mm^2 vs 0.84 mm^2). Individual results of all six patients are presented in Table 1; descriptive statistics are shown in Fig. 4.

As usually seen in SRT, laser lesions lead to RPE proliferation as suggested by increased autofluorescence levels at the sites of laser impact (Fig. 2), but they do not lead to late-onset atrophy. This was herein also routinely observed in five of the six patients; however, in one patient all test and treatment lesions led to RPE atrophy and a consecutively enhanced progression of the atrophic zone (Patient #1 from Table 1, Fig. 5). Treatment energy was ensured to be within the therapeutic window, slightly above the angiographic threshold. An unusual fast progression however, was also noted in the fellow eye of this patient (see Table 1). Nevertheless, the new atrophic areas were exactly correlated to the laser impact, giving hints of different biologic RPE reactions to SRT in patients with GA. When excluding this exceptional patient from calcu-

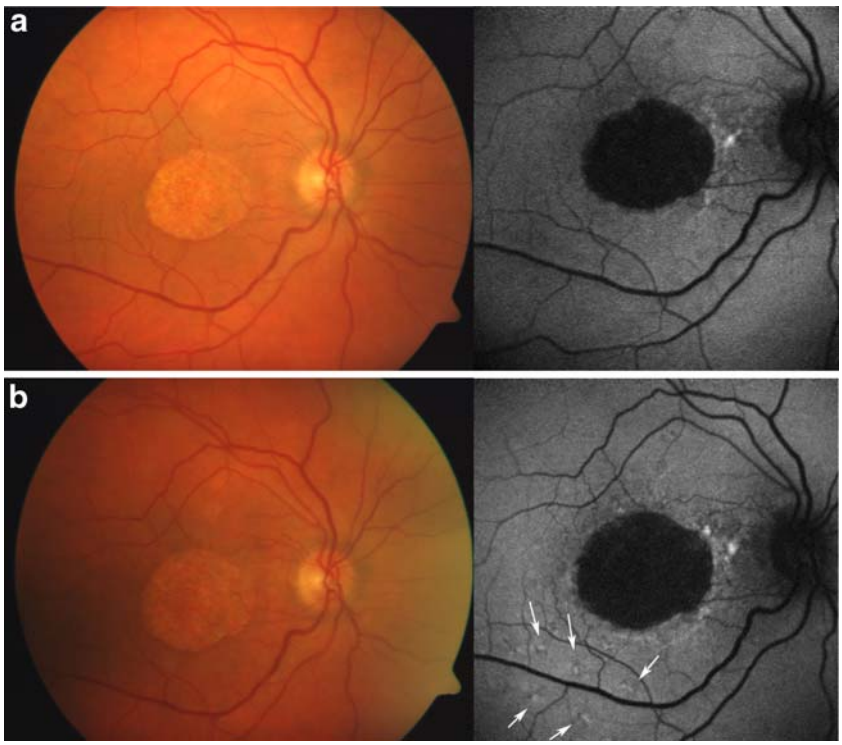

Fig. 2 Color fundus photo and fundus autofluorescence images of patient #4 at baseline (**a**) and 1 year after treatment (**b**). Note the slightly irregular fundus autofluorescence pattern of SRT lesions (*arrows*) indicating RPE reproliferation after treatment. No hints of laser induced RPE atrophy were observed in this eye (**b**)

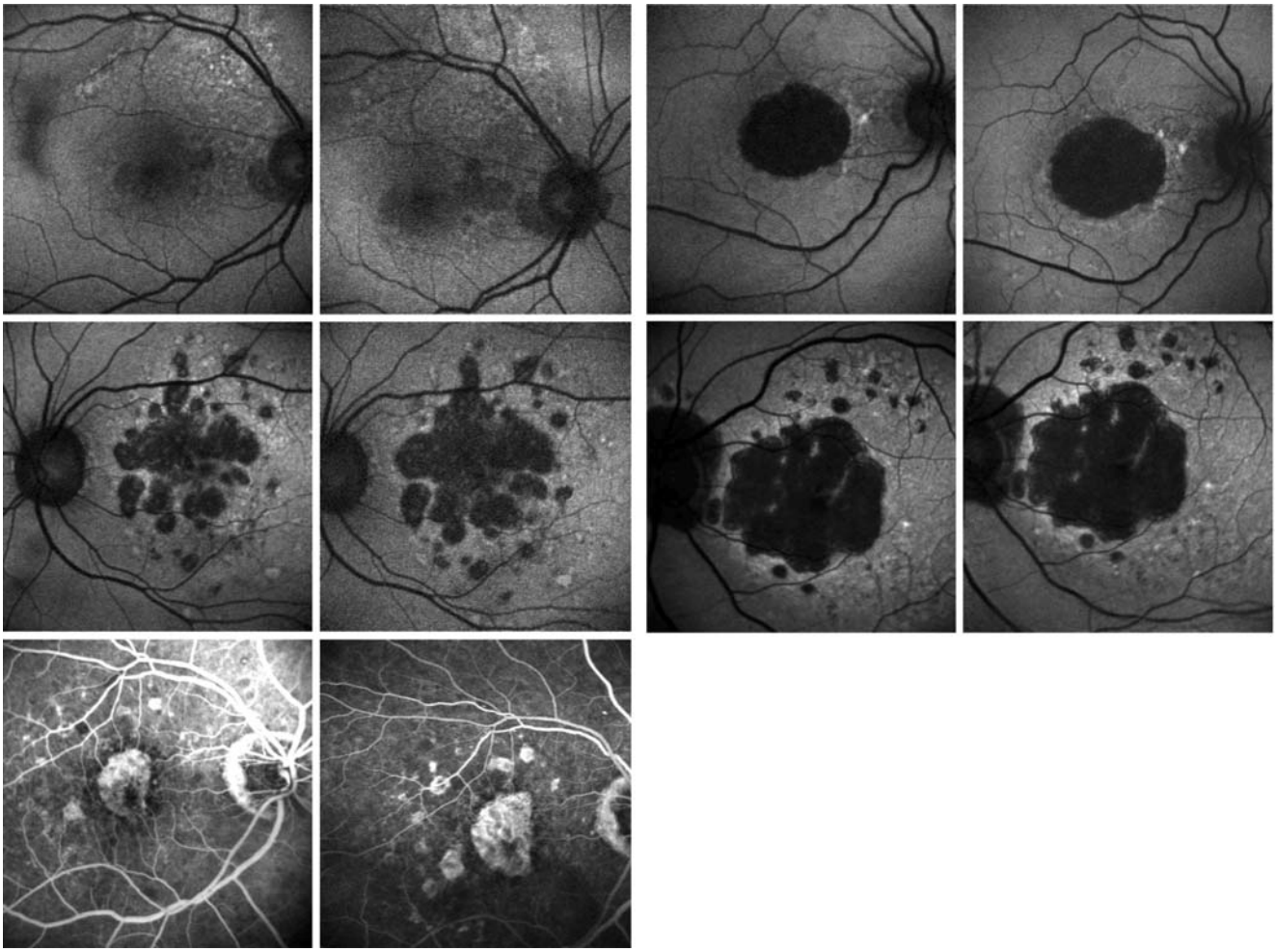

Fig. 3 Fundus autofluorescence images at baseline (*left*) and 1 year after treatment (*right*) of five patients without atrophic laser lesions. In one patient, fluorescein angiographic images are shown because of insufficient quality of autofluorescence images. In general, SRT was not able to stop GA progression

Table 1 Characteristics of the six patients (patient number, patient age, number of treatment lesions, SRT pulse duration, minimum angiographic and ophthalmoscopic threshold radiant exposures, atrophic area of treated eyes at baseline and 1 year after treatment, and calculated absolute and relative progression rates for treated and untreated eyes)

Pat. #	Age	Number of Lesions	Pulse duration	Threshold radiant exposures		Atrophic area baseline (top) 1year (bottom) [mm^2]		Progression rates relative (top) abs. (bottom) [mm^2/year]	
				angiogr. [μJ]	ophth. [μJ]	treated eye	fellow eye	treated eye	fellow eye
1	69	13	1.7 μs	200	250	3.39	4.59	235%	88%
						11.37	8.63	7.98	4.04
2	69	14	1.7 μs	300	>350	9.32	9.6	47%	39%
						13.7	13.32	4.38	3.72
3	76	8	260 ns	100	180	2.11	0.91	45%	51%
						3.06	1.37	0.95	0.46
4	65	21	260 ns	100	>200	6.43	6.63	11%	13%
						7.14	7.47	0.71	0.84
5	82	8	260 ns	140	200	1.52	1.51	147%	49%
						3.76	2.25	2.24	0.74
6	70	16	260 ns	120	>180	14.87	15.43	10%	9%
						16.38	16.82	1.51	1.39

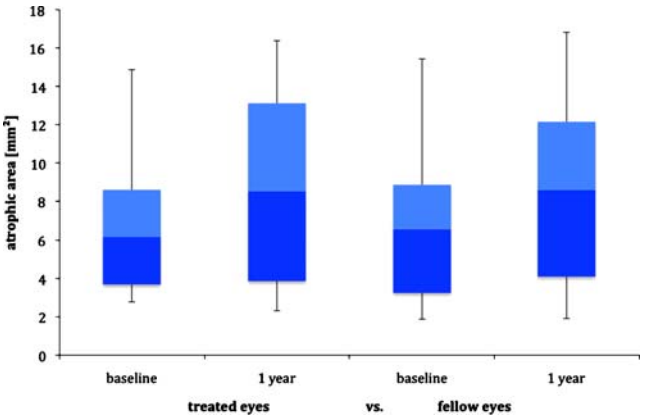

Fig. 4 Descriptive statistics of atrophic area sizes of treated and fellow eyes at baseline and 1 year after treatment

lations, the mean progression rate in the treated eyes of the remaining five patients [2.0±1.5 mm^2/year (mean ± SD)] was still elevated compared to the mean progression of fellow eyes [1.4±1.3 mm^2/year (mean ± SD)]; (p=0.132).

Discussion

In this pilot study, patients presenting with bilateral and equally pronounced geographic atrophy due to AMD were treated unilaterally by SRT. The rationale was based on autofluorescence findings in GA, often revealing high autofluorescence levels in the junctional zone of atrophy suggesting RPE cells with a high content of lipofuscin designated for apoptosis [7]. SRT has been shown to be effective in terms of generating angiographic RPE leakage without ophthalmoscopically visible laser lesions, indicating the sparing of photoreceptors followed by consecutive recreation of the RPE blood barrier [9, 10]. Therefore, SRT might be a potential laser technique to stimulate the pathologically altered RPE by irradiating the junctional zone of the GA without the risk of enlarging the atrophic area due to laser scotoma, and to ideally stop or reduce further growth of the GA by RPE cell stimulation. In this small number of patients (n=6) a 1-year follow-up after SRT was obtained. Herein, the desired goal of stopping GA enlargement was not reached; thus, further SRT with the strategy to target the hyperautofluorescent areas was closed after six patients.

Out of the six treated eyes, only in one patient the enlargement of the atrophic zone was a little smaller in the treated than in the fellow eye. However, the enlargement rates of both eyes of this patient (Pat.#4; Table 1; Figs. 2, 3) were only small compared to the other treated eyes, which showed insignificantly faster enlargement rates in the treated eyes (Table 1). Thus, it must be considered that SRT—used in the technique of treating the direct rim of the atrophic zone—could potentially have a negative impact on GA progression. However, derived from the relative

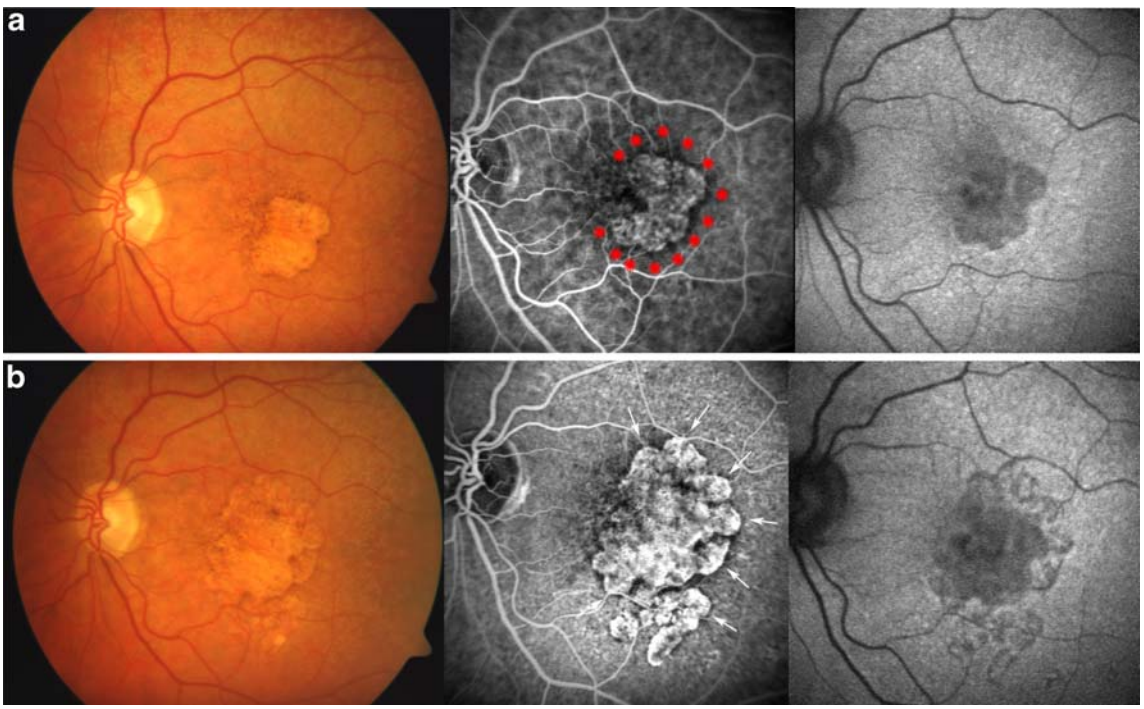

Fig. 5 Color fundus photo, fluorescein angiography and fundus autofluorescence images of patient #1 at baseline (**a**) and 1 year after treatment of marked areas (*red stars*) (**b**). Note that all initially ophthalmoscopically invisible SRT lesions led unexpectedly to RPE atrophy and enlargement of the initial GA (*arrows*)

progression rates in four patients, the treated and the fellow eye progressed nearly equally fast. Thus, a negative impact of SRT in GA cannot generally be concluded. In general, the progression rates of GA observed in this study are comparable to other studies [8, 25–27]. It is known that progression of GA shows great inter-individual variations as also observed in our patients, and it is obvious that quantitative statistical deductions cannot be made by a sample size of the magnitude presented herein.

The enlargement of the atrophic area in our patients seemed not to be mainly attributed to the distinct laser impact, which—as described above—does usually not lead to atrophy. This is in general contrast to older laser lesions after conventional laser photocoagulation, that always lead to RPE atrophy [28]. However, in one patient also all SRT lesions directly led to consecutive RPE atrophy, despite treatment within the therapeutic window. The reason for this unknown biologic reaction is unclear, and might be attributed to individual but unknown RPE features in GA. This must evidently be described as an adverse event leading consequently to a stop of further treatment, especially in the context of an at least possible enhanced progression rate after SRT.

The different observed biologic RPE reactions herein have also been reported for SRT in drusen maculopathy due to AMD [29]; however, complete atrophy has never been observed. In that report, drusen disappeared in one patient after SRT correlating to laser induced hyperpigmentation, whereas no drusen disappearance occurred in another patient with ophthalmoscopically invisible changes after SRT [29]. Thus, it might be speculated that the ability of the RPE to recreate an intact monolayer after SRT is reduced in patients with AMD and especially in those presenting with rapid enlargement of GA. Although the pathophysiology of GA is not completely understood, the concept of a "pathologic state" with reduced ability of RPE cells to re-proliferate might be a reasonable assumption. This idea is underlined by recent autofluorescence findings by Holz et al. showing distinct patterns of autofluorescence in rapidly progressing GA [8]. According to this classification, our patient with the unexpected biologic SRT reaction could be classified as "diffuse trickling" showing highest progression rates—even in the non-treated fellow eye. However, especially patients with autofluorescence patterns designated for faster progression would undoubtedly profit most from a sufficient treatment. Thus, if SRT would be considered for future GA treatment (despite our first non-encouraging results) it should be focused on the "fast progression"-autofluorescence patterns [8], carefully evaluating the post treatment RPE reactions. It might also be reasonable to apply SRT lesions not directly to the atrophic rim but more distanced from the atrophy within presumably still healthy RPE of normal autofluorescence in the more temporal macular area. Thus, a broader stimulation of RPE around the atrophic zone might positively affect GA progression.

Conclusion

In this small series, SRT performed in the hyperautofluorescent areas of GA was not able to stop GA progression. Moreover, unexpected different RPE reactions after SRT have been observed. The effects ranged from complete atrophy of all laser lesions in one patient to minimal irregularities on autofluorescence images after SRT irradiation. A positive therapeutic effect could not be detected with this spot application strategy in the limited amount of treated eyes. However, specific fundus autofluorescence patterns around the GA might not only predict the rate of GA progression over time, but also a certain non-ability of the RPE to regenerate after damaging processes including SRT. Further studies with different application strategies should be performed, e.g. placing the spots further outside the GA area.

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