Subthreshold Laser Treatment Versus Threshold Laser Treatment for Symptomatic Retinal Arterial Macroaneurysm

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Purpose. This study was designed to compare the effects of subthreshold laser treatment (STLT) with threshold laser treatment (TLT) in patients affected by symptomatic retinal arterial macroaneurism (RAM).

Methods. Patients affected by symptomatic RAM, characterized by exudative manifestations involving the fovea and best-corrected visual acuity (BCVA) worse than 20/80 Snellen equivalent, were recruited. Patients were randomly assigned to STLT or TLT and regularly followed up for 12 months. Primary outcome measures were changes in central point thickness (CPT) at the end of the follow-up. Secondary outcome measures were changes in mean BCVA at the end of the follow-up and identification of postlaser alterations.

Results. In this single center, randomized, clinical trial, 12 patients were randomized to STLT and 13 to TLT. CPT in STLT was 332 μm at baseline and changed to 249 μm at the 12-month examination. CPT in TLT was 341 μm and reduced to 226 μm at the end of the follow-up. BCVA in STLT changed from 0.72 logMAR to 0.28 logMAR. BCVA in TLT changed from 0.76 logMAR to 0.26 logMAR. The statistical analyses revealed a significant difference comparing the baseline values for both CPT and BCVA in each subgroup from the third month ($P < 0.001$). No difference was found comparing the two subgroups at any point in time. Three eyes (23%) treated with TLT developed an epiretinal membrane with subjective metamorphopsia.

Conclusions. This pilot randomized clinical trial shows that both STLT and TLT can achieve similar improvements in BCVA and CPT. The lower laser energy delivered by STLT can reduce the complication rate. (Clinicaltrials.gov number, NCT01301326.) (*Invest Ophthalmol Vis Sci.* 2012;53:1783–1786) DOI:10.1167/iovs.11-8772

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Retinal arterial macroaneurysms (RAM) are acquired dilations of the large retinal arterioles and can bring about several complications, including subretinal, preretinal or vitreous hemorrhages, macular edema, serous macular detachment, macular deposition of hard exudates, macular holes, and branch retinal artery occlusion.[1–15] Even though there is no consensus about the management of RAM, treatment is advised in cases of exudative manifestations involving the fovea with visual acuity deterioration.[9] In such cases, the most commonly employed approach is conventional threshold laser treatment (TLT).[5] Subthreshold laser treatment (STLT) was recently reported to be effective in achieving the cessation of leakage, associated with functional improvement.[16]

The aim of the present study was to compare the effects of TLT and STLT for symptomatic RAM.

Methods

All the consecutive patients affected by symptomatic RAM and referred to our center were considered for the study. This research was approved by the institutional review board, adhered to the tenets of the Helsinki Declaration, and was registered at the Clinicaltrial.gov registry under the number NCT01301326. Each patient provided signed informed consent to the study.

Inclusion criteria comprised diagnosis of symptomatic RAM, which was defined as RAM associated with exudative manifestations involving the fovea (including subretinal/intraretinal fluid, hard exudates, hemorrhages, or all three), best-corrected visual acuity (BCVA) worse than 0.6 logMAR (approximately corresponding to 20/80 Snellen equivalent).

Exclusion criteria included any other previous treatment for RAM and identification of any other ocular disease able to affect BCVA. The patients' randomization to either STLT or TLT was performed by means of sequentially numbered envelopes, which were stored by an investigator unaware of the purpose of the study.

Each patient underwent a complete ophthalmological examination, including BCVA, on standard ETDRS charts, fluorescein angiography, and optical coherence tomography (OCT). The patients were regularly scheduled for follow-up at 3-month intervals for up to 12 months after laser treatment.

BCVA measurement and OCT scans were performed by masked staff members who were unaware of the purpose of the study and the condition of the patients. Uncertain cases were evaluated by a third author.

OCT examination (Stratus OCT, Carl Zeiss, Meditec Inc., Germany) was performed using the fast macular thickness map protocol. STLT was performed using an infrared diode laser (810 nm) (Iris Medical Oculight, SLx Photocoagulator, Iridex Corp., Mountain View, CA). The laser parameters were based on those of our previous study.[16] In particular, the STLT power was arbitrarily set at 1400 mW. Complete laser settings are shown in Table 1. The STLT spots were delivered in a

Table 1. Laser Settings

	STLT	TLT
Spot diameter	125 μm	100 μm
Exposure	0.3 seconds (duty cycle 15%)	0.2 seconds
Power	1400 mW	100–300 mW (mean, 233 ± 55 mW)
Spot number	9–14 (mean, 11 ± 1.7)	5–10 (mean, 7.4 ± 1.6)

Table 2. Demographics and Clinic Characteristics at Baseline

	STLT (12 Eyes)	TLT (13 Eyes)
Age	68.2 years	66.5 years
Sex	6 females/6 males	7 females/6 males
Hypertension	10	12
Diabetes mellitus	1	1
Neurosensory detachment	7	8
Subretinal hemorrhage	3	3
Intraretinal edema	5	5

contiguous mode with no free space between each spot application, and covered both the entire RAM lesion and the surrounding area in order to prompt a response in the neighboring RPE as well.

Conventional TLT was carried out by means of krypton laser (647 nm; Coherent Novus Omni Photocoagulator, Coherent Inc., Santa Clara, CA) using the following parameters in order to produce a gentle retinal whitening surrounding the RAM, but not over it: 100-μm laser spot diameter, 0.2-second exposure, power 100 to 300 mW. The laser treatments were performed by the same surgeon (MBP).

Primary outcome measures were the changes in central point thickness (CPT) at the end of the follow-up. Secondary outcome measures included changes in mean BCVA at the end of the follow-up, and identification of postlaser alterations.

The sample size for this trial was estimated using the hypothesis that both interventions are equivalent regarding the anatomic outcome. The aim was to show that in the STLT arm, the anatomic result is comparable to that of the TLT group. With reference to our previous investigation, we know that STLT leads to a progressive reduction in the CPT with a final CPT value of about 200 μm with an SD of about 15 μm. We assumed that both treatment effects could be considered comparable, estimating a final difference of 50 μm with an SD of 25; two groups of six patients were included, yielding a 90% power with an alpha level of 0.05. At least eight patients per arm were recruited, in anticipation of a 30% loss in the follow-up. Statistical analyses were performed using Student's *t*-test. A *P* value under 0.05 was considered to be statistically significant.

Results

Overall, 25 patients fulfilled inclusion and exclusion criteria.

The mean age of the patients was 67.5 ± 6.5, including 13 females. All demographic and clinical features at baseline are summarized in Table 2. All RAMs were located within the major vascular arcades of the posterior pole and showed fluorescein leakage and exudative manifestations involving the macular region. Twelve patients were randomized to STLT and 13 to TLT. Complete results are listed in Figures 1 and 2. In both subgroups, the laser treatment was required only once and was not associated with complications.

CPT in STLT was 332 ± 25 μm (±SD) at baseline and changed to 249 ± 34 μm at the 12-month examination. CPT in TLT was 341 ± 31 μm and reduced to 226 ± 14 μm at the end of the follow-up.

BCVA in STLT changed from 0.72 ± 0.13 (±SD) logMAR (corresponding approximately to a Snellen equivalent of 20/100) to 0.28 ± 0.01 logMAR (corresponding approximately to a Snellen equivalent of 20/40). BCVA in TLT was 0.76 ± 0.01 logMAR (corresponding approximately to a Snellen equivalent of 20/100) and changed to 0.26 ± 0.01 logMAR (corresponding approximately to a Snellen equivalent of 20/40).

The statistical analyses revealed a significant difference comparing the baseline values for both CPT and BCVA in each subgroup from the third month ($P < 0.001$). No difference was found comparing the two subgroups at any point in time.

An atrophic scar surrounding the treated RAM was detectable in all the cases that had undergone TLT and in no case experiencing STLT (Fig. 3). Moreover, three cases (23%) treated with TLT developed an epiretinal membrane with metamorphopsia. All the cases showed absence of leakage on fluorescein angiography and resolution of the exudative manifestations at the end of the follow-up.

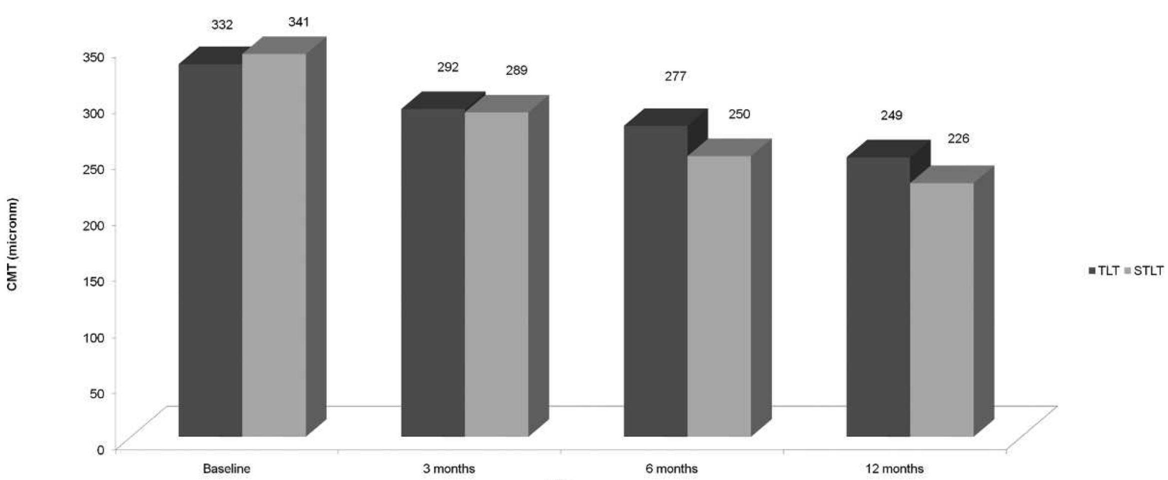

Figure 1. Mean CPT changes over 12-month follow-up. A statistically significant improvement in the CPT in comparison with the baseline values was demonstrated in both groups from the 3-month examination on. No difference was noted between the two groups at any point in time. TLT, threshold laser treatment; STLT, subthreshold laser treatment.

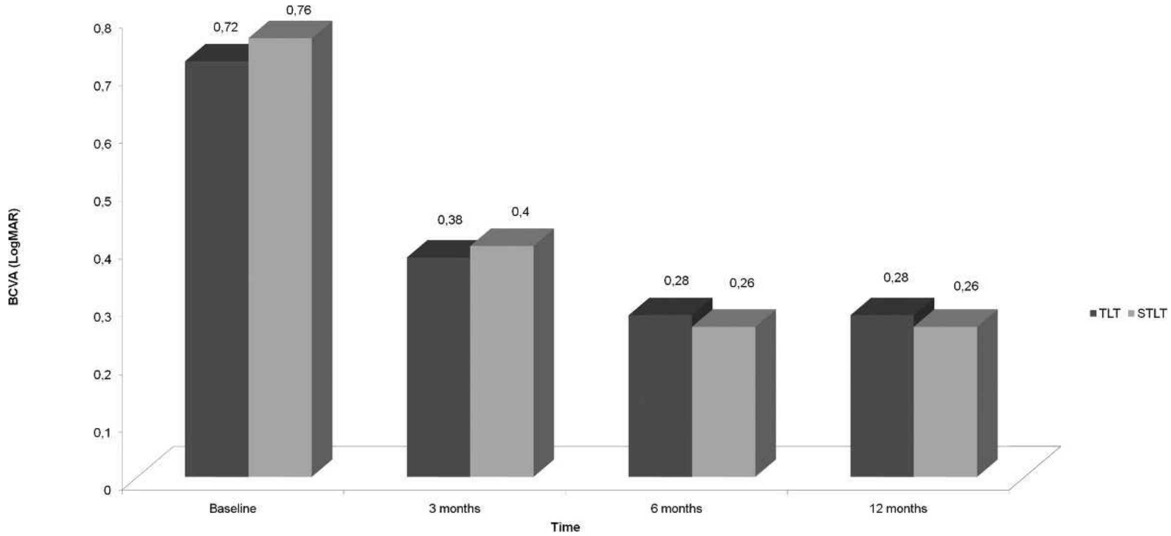

Figure 2. Mean BCVA changes over 12-month follow-up. In comparison with the baseline values, BCVA improved significantly at 3 months in both groups. Subsequently, the improvement persisted until the 12-month visit. No difference was noted between the two groups at any point in time. TLT, threshold laser treatment; STLT, subthreshold laser treatment.

Discussion

The best approach to the management of RAM is still a matter of controversy. It is well known that RAM can evolve into spontaneous obliteration with functional recovery. Nevertheless, the long-term persistence of exudative manifestations, especially involving blood, leads to a progressive photoreceptor deterioration with consequent functional impairment.[9] Thus, in cases of symptomatic RAM, defined as RAM associated with exudative manifestations involving the fovea with visual acuity deterioration, early treatment may be desirable in attempting to avoid irreversible anatomic and visual damage.

Conventional laser application is currently the most commonly employed treatment for symptomatic RAM.[5] The technique involves delivering visible laser burns to the retina, with light absorption, especially at the RPE and pigmented choroid. Heat conduction extends the temperature increase to the overlying nonpigmented and adjacent cells, until threshold laser lesions become visible owing to a change in the scattering properties of the overlying retina. Conventional TLT may be burdened by many complications, including enlargement of the laser scar, choroidal neovascularization, and subretinal fibrosis.[17–25] In addition to these complications, branch retinal artery occlusion, increased retinal exudation and scarring, with possible retinal traction, have also been reported as possible consequences of the laser photocoagulation of RAM.[2–10] Our recent pilot study showed that RAM obliteration with functional improvement can also be achieved using STLT, with no visible laser scars or complications.[16]

Figure 3. *Left*: Fluorescein angiography showing a retinal arterial macroaneurysm with wide macular hemorrhage before treatment. *Right*: same case after STLT with no visible scar.

The underlying STLT mechanism is thought to be related to the effects of the retinal hyperthermia below the cell death threshold, although the details of this interaction remain uncertain. STLT works by reducing the duration of laser exposure and using a subvisible clinical endpoint. The selective damage to the RPE cells may lead to an improved balance in angiogenic factors and cytokine release, perhaps including an upregulation of basic fibroblast growth factor, and heat shock proteins.[26,27]

In order to evaluate the effects of STLT in symptomatic RAM more precisely, we designed a pilot randomized clinical trial to compare STLT and TLT. In order to minimize the possible side effects of TLT, laser energy was applied indirectly to produce a gentle retinal whitening surrounding the RAM, but not over it. STLT was employed with a different approach, applying a combined indirect and direct technique. Overall, the results at the 1-year follow-up revealed comparable results in both laser systems regarding functional and anatomic outcomes, with complete resolution of exudative manifestations secondary to RAM lesion. Nevertheless, all the eyes treated with TLT showed the development of a laser scar, associated in 23% of cases with an epiretinal membrane causing metamorphopsia. On the other hand, no scar was detectable in the eyes that had undergone STLT, and there was no evidence of vitreo-retinal anomalies.

Even though the mean values of BCVA and CPT turned out to be comparable in both treatment subgroups, the three cases developing epiretinal membranes were symptomatic, and displayed reduced visual recovery and higher macular thickness. Epiretinal membrane formation may be ascribable to the high levels of energy absorption related to TLT.

In conclusion, STLT and TLT can achieve similar effects in the treatment of symptomatic RAM. STLT prevents the development of laser scars and vitreo-retinal interface alterations. Further studies with larger case series are required to confirm our results and to define the best treatment in the management of RAM.

References

1. Nadel AJ, Gupta KK. Macroaneurysms of the retinal arteries. *Arch Ophthalmol*. 1976;94:1092–1096.

2. Lewis RA, Norton EW, Gass JD. Acquired arterial macroaneurysms of the retina. *Br J Ophthalmol*. 1976;60:21–30.
3. Abdel-Khalek MN, Richardson J. Retinal macroaneurysm: natural history and guidelines for treatment. *Br J Ophthalmol*. 1986;70:2–11.
4. Lavin MJ, Marsh RJ, Peart S, Rehman A. Retinal arterial macroaneurysms: a retrospective study of 40 patients. *Br J Ophthalmol*. 1987;71:817–825.
5. Rabb MF, Gagliano DA, Teske MP. Retinal arterial macroaneurysms. *Surv Ophthalmol*. 1988;33:73–96.
6. Panton RW, Goldberg MF, Farber MD. Retinal arterial macroaneurysms: risk factors and natural history. *Br J Ophthalmol*. 1990;74:595–600.
7. Brown DM, Sobol WM, Folk JC, Weingeist TA. Retinal arterial macroaneurysm: long term visual outcome. *Br J Ophthalmol*. 1994;78:534–538.
8. Moosavi RA, Fong KC, Chopdar A. Retinal artery macroaneurysms: clinical and fluorescein angiographic features in 34 patients. *Eye*. 2006;209:1011–1020.
9. Tsujikawa A, Sakamoto A, Ota M, et al. Retinal structural changes associated with retinal arterial macroaneurysm examined with optical coherence tomography. *Retina*. 2009; 29:782–792.
10. Russell SR, Folk JC. Branch retinal artery occlusion after dye yellow photocoagulation of an arterial macroaneurysm. *Am J Ophthalmol*. 1987;104:186–187.
11. Ciardella AP, Barile G, Schiff W, et al. Ruptured retinal arterial macroaneurysm associated with a stage IV macular hole. *Am J Ophthalmol*. 2003;135:907–909.
12. Colucciello M, Nachbar JG. Macular hole following ruptured retinal arterial macroaneurysm. *Retina*. 2000;20:94–96.
13. Sagara N, Kawaji T, Koshiyama Y, et al. Macular hole formation after macular hemorrhage associated with rupture of retinal arterial macroaneurysm. *Br J Ophthalmol*. 2009;93:1337–1340.
14. Parodi MB, Bondel E, Saviano S, Ravalico G. Branch retinal vein occlusion after spontaneous obliteration of retinal arterial macroaneurysm. *Retina*. 1998;18:378–379.
15. Takahashi K, Kishi S. Serous macular detachment associated with retinal arterial macroaneurysm. *Jpn J Ophthalmol*. 2006; 50:460–464.
16. Parodi MB, Iacono P, Ravalico G, Bandello F. Subthreshold laser treatment for retinal arterial macroaneurysm. *Br J Ophthalmol*. 2011;95:534–538.
17. Schatz H, Madeira D, McDonald HR, et al. Progressive enlargement of laser scars following grid laser photocoagulation for diffuse diabetic macular edema. *Arch Ophthalmol*. 1991;109:1549–1551.
18. Morgan CM, Schatz H. Atrophic creep of the retinal pigment epithelium after focal macular photocoagulation. *Ophthalmology*. 1989;96:96–103.
19. Early Treatment Diabetic Retinopathy Study Research Group. Focal photocoagulation treatment of diabetic macular edema. Relationship of treatment effect to fluorescein angiographic and other retinal characteristics at baseline: ETDRS report no. 19. *Arch Ophthalmol*. 1995;113:1144–1155.
20. Lewen RM. Subretinal neovascularization complicating laser photocoagulation of diabetic maculopathy. *Ophthalmic Surg*. 1988;19:734–737.
21. Lewis H, Schachat AP, Haimann MH, et al. Choroidal neovascularization after laser photocoagulation for diabetic macular edema. *Ophthalmology*. 1990;97:503–510.
22. Guyer DR, D'Amico DJ, Smith CW. Subretinal fibrosis after laser photocoagulation for diabetic macular edema. *Am J Ophthalmol*. 1992;113:652–656.
23. Rutledge BK, Wallow IH, Poulsen GL. Sub-pigment epithelial membranes after photocoagulation for diabetic macular edema. *Arch Ophthalmol*. 1993;111:608–613.
24. Fong DS, Segal PP, Myers F, et al. Subretinal fibrosis in diabetic macular edema. ETDRS report 23. Early Treatment Diabetic Retinopathy Study Research Group. *Arch Ophthalmol*. 1997; 115:873–877.
25. Han DP, Mieler WF, Burton TC. Submacular fibrosis after photocoagulation for diabetic macular edema. *Am J Ophthalmol*. 1992;113:513–521.
26. Xiao M, Sastry SM, Li Z-Y, et al. Effects of retinal laser photocoagulation on photoreceptor basic fibroblast growth factor and survival. *Invest Ophthalmol Vis Sci*. 1998;39:618–630.
27. Sramek C, Mackanos M, Spitler R, et al. Non-damaging retinal phototherapy: dynamic range of heat shock protein expression. *Invest Ophthalmol Vis Sci*. 2011;52:1780–1787.