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Low-Energy Selective Laser Trabeculoplasty Repeated Annually: Rationale for the COAST Trial

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At the 2018 annual meeting of the Association for Research in Vision and Ophthalmology (ARVO), Stephano Gandolfi presented a retrospective study of his patients at the University of Parma, Italy, in which a regimen of low-energy selective laser trabeculoplasty (SLT) repeated annually irrespective of intraocular pressure (IOP) produced significantly longer medication-free survival than standard SLT repeated as needed, in patients with primary open-angle glaucoma (POAG) or high-risk ocular hypertension (OHTN).[1] Specifically, newly-diagnosed POAG eyes were treated primarily either with ALT 360° performed once, standard SLT 360° repeated as needed at standard energy, and low-energy 360° SLT (0.4 mJ/spot x 50-60 spots) repeated annually at low energy regardless of IOP. After 10 years of follow-up, medication-free rates were 22.6% in the ALT group, 25.0% in the standard SLT group, and 58.3% in the low-energy SLT group ($p<0.001$). The median times to medication were 2.8 years, 3.2 years, and 6.2 years, respectively. In light of the recent Laser in Glaucoma and Ocular Hypertension Trial (LiGHT) publication, in which primary SLT was shown to be at least as effective as medical therapy in newly-diagnosed and treatment naïve patients with mild-moderate POAG or high-risk OHTN and the likelihood of a paradigm shift toward a laser-first regimen, Gandolfi's data suggested that the long-term utility of SLT in glaucoma management may be improvable by altering the energy level and frequency at which SLT is performed. These intriguing observations led us to conduct a comprehensive review of the SLT literature in search of a basis for the biological plausibility of such an approach. The results of that literature review, summarized herein, prompted application to the National Eye Institute (NEI) at the National Institutes of Health for funding to conduct a pair of multicenter randomized trials to evaluate outcomes of SLT performed annually at low energy. These trials—collectively named the Clarifying the Optimal Application of SLT Therapy (COAST) trial—were funded in late 2020 by NEI to compare standard versus low-energy primary SLT and annual versus pro re nata (PRN) repeat SLT and are currently in the pre-enrollment phase. In this report, we share the background and rationale that informed the design of the COAST trial.

The Glaucoma Treatment Paradigm Is Overdue For Reconsideration

Past. The therapeutic approach to POAG is the reduction of intraocular pressure (IOP). The traditional approach to IOP reduction utilizes topical medications first, followed if needed by laser therapy and then incisional surgery. This historical strategy, based on the Hippocratic principle of doing no harm, reflects an era of surgical options with significant sight-threatening adverse events and a laser procedure (argon laser trabeculoplasty [ALT]) that wore off over time, was generally less effective with repeat treatment, and was not generally considered safe to repeat,[2] thus limiting its role in long-term disease management.

Present. The therapeutic landscape for glaucoma has changed significantly since the establishment of the medication-first paradigm, and the glaucoma treatment paradigm is overdue for an update that reflects the modern body of knowledge regarding contemporary IOP-lowering options. The advent of minimally invasive glaucoma surgeries (MIGS) has significantly improved the safety profile of incisional glaucoma surgery and expanded its applicability to a broader spectrum of glaucoma patients.[3-7] The development of SLT and the establishment of its safe and effective repeatability when its effect wanes[8-16] offer an alternative to medical therapy for first-line application and long-term disease management. And while modern glaucoma medications offer superior efficacy and safety to older drugs, a wealth of research over the past 2 decades has demonstrated that the efficacy of medical therapy established in clinical trials does not translate to real-world effectiveness due to widespread non-adherence. In fact, therapeutic non-adherence may be the single biggest limitation of topical medical therapy. Poor adherence has been well documented to be common among glaucoma patients and is a complex, multifactorial behavior that is not easily identified or overcome.[17-23]

In addition to poor adherence, medical therapy for glaucoma has other limitations. Many patients require more than 1 medication to achieve IOP control. In the Ocular Hypertension Treatment Study (OHTS), nearly half of patients required 2 or more medications to achieve a modest 20% IOP reduction.[24] In the SLT-MED study, 27% of eyes randomized to the medication-first group required 2+ medications within 1 year when treated to target IOP.[25] Multi-drug glaucoma regimens are also linked to reductions in quality of life,[26-29] the preservation of which is the ultimate goal of glaucoma therapy.[30,31] Contributing to the

negative impact on quality of life are the side effects of topical medical therapy, which range from cosmetic nuisances to severe adverse events. Topical medications—potentially related to their preservative ingredients—also contribute to high rates of ocular surface disease among glaucoma patients,[32,33] and subclinical ocular surface inflammation can reduce the success of subsequent filtration surgery.[34] The cost of medical therapy is often borne at least in part by patients and can be substantial for the un- or under-insured. Side effects and cost likely contribute in part to nonadherence.

Future. Primary SLT overcomes many of the imitations of the medication-first paradigm. Foremost, SLT eliminates the issue of nonadherence by obviating the need for daily self-dosing by patients. SLT can also reduce the medication burden, thus reducing multi-drug regimens and their detrimental effects on the ocular surface and quality of life. In SLT-MED, 0% of eyes treated with primary SLT required any medications at 12 months compared to 100% requiring 1+ medications and 27% requiring 2+ medications.[25] In the Laser in Glaucoma and Ocular Hypertension (LiGHT) study, 78% of SLT-first eyes versus only 3% of medication-first eyes were medication-free at 3 years.[16] Further, SLT is more cost-effective than medical therapy for glaucoma.[16,35,36] These benefits come with no efficacy costs. SLT provides IOP-lowering efficacy comparable to a prostaglandin analogue, the preferred first-line medication for glaucoma.[16,25,37,38] SLT provides mean IOP reductions on the order of 6-8 mmHg (25-30%),[16,25,37,38] consistent with the guidelines for initial IOP reduction for most eyes with early or moderate POAG.[30,31] SLT's efficacy has also been established in people of African descent,[39-43] where POAG has the highest prevalence and glaucoma-related blindness is most common.[44,45] While SLT's effect on IOP dissipates over time, most eyes will remain controlled after a single SLT treatment for 3-5 years,[16,46] and repeat SLT consistently and safely restores IOP control to levels achieved by initial SLT.[8-16] Further, the safety profile of SLT is at least as favorable as prostaglandin therapy, and unlike with medical therapy, side effects of SLT are generally transient and self-limited, resolving within 3-5 days post-treatment.[47,48]

The Paradigm Shift

Several studies have evaluated the role of primary trabeculoplasty for POAG. The landmark Glaucoma Laser Trial (GLT) demonstrated better IOP control (albeit potentially related to crossover effect from timolol therapy to the contralateral eye) and less visual field and optic nerve progression in eyes treated with ALT first compared to medications first through up to 9 years of follow-up.[2] This seminal study did not drive a paradigm shift to laser first, likely due to the fact that most laser-first eyes required medications over time as ALT was not felt to be safely repeatable (see below).

ALT has largely been supplanted by SLT, which has a similar efficacy profile but is performed with far less energy.[49-55] The SLT-MED study compared SLT-first and medication (prostaglandin)-first treatment strategies in newly-diagnosed and treatment naïve POAG eyes. The study was terminated early due to enrollment issues, and while the final data set was underpowered to compare the two treatments, the mean IOP reduction in the two groups was arithmetically similar (6.3 mmHg for SLT and 7.0 mmHg for medications).[25] Unsurprisingly, this underpowered study also failed to drive the paradigm from medications to laser.

More recently, in the landmark LiGHT study,[16,56] 718 newly-diagnosed and treatment-naïve POAG patients were assigned to therapy with SLT or medications. Eyes in the SLT arm received SLT, repeat SLT, and then medications to achieve target IOP, while eyes in the medication arm received sequentially added medications to achieve target IOP. At the 3-year time point, mean IOP was similar between groups, but glaucoma progression was more common in the medication group (10.0% versus 6.4%) and all 11 trabeculectomy procedures in the study occurred in the medication arm. Medication-free disease control in the SLT arm (allowing for 1 repeat SLT as needed) was achieved by 85.2%, 79.2%, and 74.6% of eyes at 1, 2 and 3 years, respectively. Also, a slightly larger proportion of eyes treated with medication demonstrated rapid visual field progression compared to SLT-treated eyes (26.2% versus 16.9%, $p<0.001$), which is likely explained by the adherence issue affecting medical but not laser therapy.[57]

The COAST research team believes strongly that the LiGHT study's results, and the effect of its publication on raising the level of discourse regarding the role of SLT in glaucoma management, will lead

to a paradigm shift in which SLT becomes the preferred first-line therapy for glaucoma. We designed the COAST trial to optimize SLT technique so as to optimize clinical outcomes.

The Case For Low Energy SLT

Standard SLT Causes TM Damage. The energy level at which trabeculoplasty has been performed has evolved over time and may not yet be optimized. ALT used a high-energy argon laser platform and consisted of ~80-100 treatment spots spaced ~4 spot widths apart through the full 360° of trabecular meshwork (TM) or 40-50 spots over 180°.[58] ALT caused focal coagulative and contractile destruction of TM and presumably lowered IOP by indirect effects on untreated intervening TM tissue through mechanical, biochemical, and/or cellular mechanisms.[59,60] Cumulative TM damage ultimately compromised IOP control with repeat ALT as a critical mass of TM was destroyed and too little intervening TM remained to permit aqueous outflow. In fact, repeat ALT sometimes produced paradoxical IOP elevations (presumably due to cumulative coagulative damage to the trabecular outflow pathway[61]) that often required surgical intervention.[62-67] On this basis, repeat ALT was not incorporated into the GLT study design: when additional IOP reduction was required in laser-first eyes, medical therapy was initiated.[68]

SLT uses the Q-switched, frequency-doubled Nd:YAG laser platform and consists of ~100 contiguous nonoverlapping treatment spots over the full 360° of TM. Now 2 decades after its commercialization, SLT is almost exclusively performed as first described by Latina and colleagues in 1998: beginning at 0.8 mJ, energy is titrated during the first few treatment spots to the lowest setting that still produces champagne-sized cavitation bubbles, then reduced by a further 0.1 mJ for the remaining treatment.[69] This now-standard approach is based not on the optimal balance of efficacy and safety as might be derived from traditional clinical dose-response studies, but rather was described based on observations of optimal laser energy absorption by cultured TM cells *in vitro*.[70] The energy fluence delivered with SLT is several thousand times less than with ALT, which reduces but does not eliminate coagulative damage to the meshwork tissue.[61,71-73] Kramer and Noecker reported that while SLT caused far less damage to the TM than ALT, there was nevertheless ultrastructural evidence of laser-tissue interaction that included cracking of intracytoplasmic pigment granules and disruption of trabecular endothelial cells in eye bank eyes.[61] Wood and colleagues demonstrated in cultured bovine TM cells that SLT in the standard energy range (0.75-1.0 mJ) caused rapid necrotic cell death within 1-8 hours and delayed apoptotic cell death within 2-3 days after laser irradiation.[71] In three human eyes scheduled for unrelated enucleation, histologic damage to the TM was also documented following SLT at standard energy (mean 0.7 mJ/spot) that was identical in nature to, but less severe than, the damage produced by ALT: TM cell disorganization and fragmentation, trabecular beam disruption, and tissue debris in the intertrabecular spaces.[72] In human cadaver eyes treated with SLT at a range of energy, transmission electron microscopy revealed disrupted TM cells with cracked and extracellular pigment granules; at higher SLT energy, scanning electron microscopy revealed TM destruction with scrolling of trabecular beams.[73] These findings have led researchers to question whether the "champagne bubble" tissue endpoint represents optimal care and postulated a role for low energy SLT.[74]

Safety Issues With Standard SLT. While SLT is generally considered a safe procedure, postoperative complications can occur. Transient anterior chamber inflammation is common (incidence 30-83%) but typically resolves quickly without sequelae.[38,49,69,75,76] Post-laser IOP spikes occur in up to 27% of eyes.[38,49,69,77] However, this appears to be far less common when SLT is performed as primary therapy; in the LiGHT study, only a single case—out of 776 SLT treatments—experienced and IOP spike necessitating medical therapy.[16] Vision-threatening complications of SLT are exceedingly rare. Recently, several case reports and small case series have identified a variety of potentially vision-threatening corneal complications of SLT. These include short-term reductions in endothelial cell density,[78] corneal edema (in up to 0.8% of treated eyes[79]) complicated in some cases by irregular astigmatism, decompensation, and permanent reduction in visual acuity,[80-85] keratitis,[86,87] and corneal thinning with permanent hyperopia shifts of up to 6D.[82,84]

Evidence For An SLT Dose-Response Relationship. Can SLT be performed at a lower energy level and still deliver the efficacy achieved at standard energy? Several studies seeking to identify factors associated with success/failure of SLT have included measures of laser dose (total energy, number of spots, energy per spot, etc.) and have generally found no evidence for a dose-response effect on IOP reduction.[88-91] These studies are limited, however, in that each study delivered standard SLT in all eyes, and standard SLT is performed in such a way as to eliminate a dose-response relationship. A dose-response relationship exists when a heterogeneous array of doses produces a heterogeneous array of responses that are related non-randomly. In standard SLT, a heterogeneous dose of energy is *administered* to the TM but is titrated to produce a standardized tissue response (champagne-like cavitation bubbles) which in turn likely represents a homogenous dose of energy *absorbed* by the tissue. Thus, standard SLT produces a homogenous dose at the tissue level. This is akin to adjusting systemic gentamycin dosing by body weight to achieve consistent therapeutic serum drug concentrations—a heterogeneous dose is administered but a homogenous tissue-level dose is achieved. This approach, in fact, is designed to *negate* a dose-response relationship.

Comparative studies varying the extent of angle treated with SLT have produced mixed results. Two randomized clinical trials (RCTs) demonstrated that 90°[92] and 180°[93] of standard SLT produced similar efficacy to 360° standard SLT, while a third RCT showed a dose-response effect with greater IOP reductions but commensurately more pain, inflammation, and IOP spikes when more angle was treated.[38] Retrospective studies have also shown limited efficacy with 180° treatment compared to 360° treatment.[94-97] Placing 100 treatment spots over 180° had twice the failure rate of standard 50 spots/180° in a retrospective study, demonstrating that more is not necessarily better.[98]

Few studies have specifically compared multiple energy levels directly in head-to-head fashion. Wong and colleagues retrospectively evaluated outcomes of SLT performed before and after a practice pattern change in which eyes received 120 spots (before) or 160 spots (after) of standard energy 360° SLT; mean IOP and survival at target IOP were statistically similar between groups, indicating no perceptible benefit to higher total energy delivered.[99] It has been suggested that a lower-energy laser would likely reduce the adverse event profile of SLT with minimal impact on efficacy.[100] Two prospective trials compared standard SLT to lower energy SLT. Zhang and colleagues compared standard SLT to SLT performed at 2/3 of standard energy (but failed to define how this low energy level was established for each eye).[101] No differences in mean IOP were seen at 12 months in this single-site study with no *a priori* power/sample size analysis. Tang and colleagues prospectively compared standard and ½ standard energy SLT (again not describing what constituted ½ of standard energy for each eye) and found similar mean IOP reduction between groups but fewer adverse events in the low-energy group.[102] The reduction in adverse events with lower energy is consistent with the findings of a study of variable SLT energy (0.05 – 1.0 mJ) applied to cultured trabecular meshwork cells that found no histological evidence of cell damage at energies below 0.75 mJ,[71] and also to a similar study that found no morphological changes or alterations in expression of apoptosis or necrosis genes at <0.5 mJ.[103]

These studies have a number of significant limitations. Most are retrospective, uncontrolled, conducted at single centers by single surgeons, have small sample sizes with no *a priori* hypotheses or power and sample size calculations, and most combine primary and adjunctive SLT cases. However, while not definitive due to their limitations, the results of these studies cumulatively suggest that energy above standard SLT energy does not improve efficacy but does increase the risk of adverse events, while energy below standard SLT energy provides comparable IOP reduction while also reducing the rate of adverse events.

The Case For Annual Low Energy Repeat SLT

Cumulative Damage With Repeat SLT. The efficacy and safety of repeat SLT—at least to the extent that a single repeat SLT is performed—have now been definitively established.[8-16] In the context of an SLT-based approach to long-term management of POAG, consisting of primary SLT repeated as needed, there may be an upper limit to the number of times SLT can be repeated[8] before cumulative TM damage from

both the underlying glaucoma process and multiple SLT treatments reduces TM responsivity to further SLT treatment.

Preserve Versus Rescue. The pathogenesis of glaucoma includes impairment of TM function with reduction in cellularity, reducing trabecular outflow facility and raising IOP. The overall mechanism by which SLT lowers IOP is by increasing outflow facility and thus increasing aqueous egress from the eye via the trabecular outflow pathway.[104] The tissue-level mechanism of action of SLT is incompletely characterized and includes contributions from cytokine secretion, matrix metalloproteinase induction, increased cell division, repopulation of burn sites, and macrophage recruitment.[105] Alterations in both TM and Schlemm's canal endothelial cells (TMEs and SCEs) may mediate trabecular outflow enhancement after SLT. Laser irradiation of TMEs and SCEs induced upregulation of various cytokine genes; direct SCE irradiation is not necessary, however, as exposure of SCEs to media conditioned by irradiated TMEs (as would occur post-SLT *in vivo* as TME effluent washes downstream into Schlemm's canal) also upregulates cytokine genes in SCEs.[106] In response to this increased cytokine exposure, SCEs become more permeable, which may enhance aqueous egress through the trabecular outflow pathway and contribute to IOP reduction.[107,108] Further, monocytes are recruited to the TM following SLT in quantities 4- to 5-fold higher than usual, and infusion of autologous monocytes into the anterior chamber of rabbits increases outflow facility 2-fold in a rapid and sustained manner.[109]

In the setting of TM impairment from glaucoma with elevated IOP, SLT can be considered to rescue impaired TM cell function and restore aqueous outflow through the trabecular pathway, lowering IOP. As SLT does not affect the underlying glaucoma disease process, glaucoma-related TM impairment recurs over time, manifested clinically as IOP elevation over time. Repeat SLT may again rescue impaired TM cells, once again improving trabecular outflow and lowering IOP. There is likely a finite number of such cycles the TM can go through before cumulative TM tissue damage both from the underlying glaucoma disease process and from coagulative SLT effects limits subsequent TM responsiveness to subsequent SLT. In seeking a strategy to optimize and extend patients' responsivity to SLT over time, with the goal of extending medication-free survival, Gandolfi's preliminary clinical work supports the hypothesis that low energy SLT may increase the possible number of such cycles by minimizing the cumulative TM damage caused by SLT. But a vital question remains unanswered: would it be advantageous to deliver low energy repeat SLT annually, regardless of IOP, to *preserve* TM cells and *maintain* TM health rather than await glaucomatous TM re-impairment before *rescuing* impaired TM cells? This approach is analogous to the management of neovascular age-related macular degeneration with anti-VEGF therapy, which has evolved from PRN retreatment (in which retreatment is administered as rescue therapy only when the prior dose wears off and the macula thickens and/or the visual acuity drops) to treat-and-extend retreatment (in which retreatment is administered before clinical decline to preserve macular health) with the treat-and-extend approach producing better outcomes than the PRN approach because it prevents the recurrent disruption of macular structure and function between each retreatment that incrementally leads to irreversible damage.

Summary and Clinical Relevance

To summarize, we hypothesize in the COAST trial—based on Gandolfi's proof-of-concept study and evidence-based biological plausibility—that low energy SLT, repeated annually irrespective of IOP, may reduce both SLT-related and glaucoma-related cumulative TM damage, thus preserving TM responsivity to SLT and extending the duration of which SLT can maintain glaucoma control and prevent or delay the need for medications or surgery. If our hypothesis is proved correct, the findings would have great significance in the management of our patients with glaucoma. The therapeutic landscape for glaucoma is undergoing an evolutionary renaissance of new drugs, new delivery systems, new lasers, and new surgeries, including MIGS. The glaucoma treatment paradigm will inevitably evolve to embrace these new therapeutic options. It has been estimated that patients live an average of ~15 years after the diagnosis of POAG.[110] If we validate an SLT treatment strategy that extends the duration of medication-free disease control, we move one step closer to the possibility of a drop-free lifetime for our patients. Delaying the need for medications by 3, or 5, or 7 years not only confers all the benefits of medication-

freedom during this period (which will be all that many patients would need in their lifetimes)—it also allows time for development of safer and more effective drugs dosed infrequently via sustained-release delivery systems, as well as better surgical options, for patients whose lifespans exceed SLT responsiveness. Thus, a new treatment paradigm consisting of SLT, then sustained-release medications, followed by minimally invasive glaucoma surgery and then—for the few who will progress this far—filtering procedures could offer the majority of glaucoma patients the very real possibility of a drop-free lifetime of therapy. As instruments to measure glaucoma *treatment-related* qualify of life are developed and validated, the benefits of freedom from the responsibility and detractions of daily medication self-dosing on our patients' well-being are likely to become apparent as well.

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