Sub-threshold nanosecond laser (SNL) treatment in intermediate AMD (IAMD)

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Summary

The Laser intervention in early stages of age-related macular degeneration (LEAD) study (1) is a 36-month, multicenter, randomized, sham-controlled trial conducted from 2012–2015 of 292 participants with bilateral soft drusen, aka intermediate AMD (iAMD), who underwent q 6-month treatment with sub-threshold nanosecond laser (SNL) or sham treatment to the study eye.

The primary efficacy outcome was the time to develop late AMD [geographic atrophy (GA) or choroidal neovascularization (CNV)] defined by multimodal imaging (MMI), which comprised spectral domain optical coherence tomography (SD-OCT), autofluorescence imaging (AF) and near-infrared reflectance imaging (NIR-R). Although progression to late AMD was not significantly slowed with SNL compared to sham for the entire group, post-hoc analysis showed a significant benefit to those subjects without reticular pseudodrusen (RPD), and a worse outcome for those subjects with RPD, aka subretinal drusenoid deposits (SDD). SNL treatment may thus have a role in slowing progression for subjects without coexistent RPD/SDD and may be inappropriate in those with RPD/SDD. Further study is clearly warranted.

The important questions

A historically important question is examined in this paper. Is there a role for laser intervention in iAMD? There is a checkered history of laser for drusen from prior literature. Despite the fact that macular thermal laser caused drusen resorption (2), some studies showed that even light thermal burns could lead to worse visual outcomes than observation (3). A Cochrane review of such studies later concluded that although drusen regression did occur, there was no reduction or increase in progression to late AMD (4). Subthreshold treatment herein reasonably explores the lower end of the dose-response curve to seek safety while still maintaining a therapeutic response.

It is also important to recognize that the 2RT laser is quite novel in the realm of retinal therapy. It is a non-thermal device that delivers single pulse Q-switched neodymium yttrium aluminum garnet (Nd-YAG) laser at a wavelength of 532 nm with pulse duration of 3 ns (5). The laser spot size is fixed at 400 µm diameter, with a fine speckle energy distribution beam profile. The treatment spots are placed just inside the arcades and the treatment energy is approximately 1,000 times less than is used in thermal laser treatment to the macula for diabetic macular edema and uses pulses approximately 33,000,000 times shorter in duration (5). Animal and tissue models demonstrate that such treatment has a measurable effect on RPE melanin, with cytokine up-regulation and on melanin granules themselves (6). So compared with previous thermal laser in the macula, we are in completely new biophysical territory.

What about other lasers? In fact, subthreshold micropulse laser, though not 2RT, and not nano-second laser, has been widely used in diabetic retinopathy with diabetic macular edema (DME) and other retinal diseases (7), and its effects have been studied with OCTA (8). It is also claimed that these lasers spare the neurosensory retina and are selectively absorbed by the RPE. One

meta-analysis of 6 randomized controlled trials for DME demonstrated superior visual outcome over conventional laser, although the differences were thought likely to be too small to be of clinical relevance (9). As for AMD, one retrospective study of subthreshold micropulse laser in dry AMD eyes found a low incidence CNV over 2 years (10), but the entrance criteria and treatment parameters were not well-specified, and there was no control group.

Finally, in the present study, the post hoc analysis also delivered an unexpected and important message about the two main phenotypes of iAMD, soft drusen and RPD aka subretinal drusenoid deposits (SDD). It showed a marked division between outcomes for eyes with and without RPD. Progression was slowed for the 222 (76.0%) participants without coexistent RPD/SDD at baseline, while an *increased* progression rate was observed for the 70 (24.0%) participants with RPD/SDD. These observations together suggest that there may be a therapeutic effect of nano-pulse laser in iAMD as long as the eye is not burdened with RPD/SDD, despite the fact that the study was not designed to test this hypothesis. Indeed, the high-risk phenotype of RPD/SDD may in fact be a contra-indication for such treatment.

The role of RPD/SDD

To understand why RPD/SDD could make such a difference, it is necessary to understand the significantly adverse impact in general on AMD and vision they convey compared to large soft drusen. RPD/SDD are common, and are also the highest risk phenotype of intermediate AMD, doubling the rate of conversion to advanced AMD over soft drusen alone (11). SDD are associated with choroidal thinning (12,13), suggesting vascular insufficiency at the outer retina as the second component of a combined phenotype with lesions in two compartments, subretinal and choroidal. For this reason, the term reticular macular disease (RMD) (14) was advanced to convey a more complex disease process than SDD alone, and to help explain the increased morbidity of this phenotype. For example, RMD is linked to GA progression and is a strong spatial determinant of the subsequent expansion of GA locally (15,16). Indeed, there is a nearly universal association of RMD with the multilobular, and fastest growing, phenotype of GA, which led us to hypothesize that they are a continuum of a single disease process, perhaps related to an underlying lobular choroidal insufficiency (15,17).

The RPD/SDD phenotype also has a genetic correlate. The stronger association of the ARMS2 risk allele than the CFH risk allele with the SDD/RMD phenotype was first pointed out in a sub-study of the Columbia Macular Genetics Study (18,19) and has been subsequently confirmed in other studies, including a recent meta-analysis (20), and in genetic and imaging analysis of 755 subjects from the CATT trial (21).

Next, RPD/SDD are associated with marked losses of rod-mediated dark adaptation (RMDA), emphasizing damage to rod function. The pathophysiology of RMDA impairment in AMD, initially attributed mostly to age-changes in RPE-Bruch's membrane complex, is now understood to include the presence of SDD between photoreceptors and RPE with particularly devastating effect (22-24). Like drusen, SDD also involve increased diffusion distance from the choriocapillaris and reduced transfer from the RPE, plus direct cytotoxicity to photoreceptors, which the deposits contact. Strikingly, the presence of SDD and ellipsoid zone disruption were a consistent predictor of RMDA impairment, whether located within the DA testing spot or *anywhere* in the macula ($P<0.001$ for both). The presence of classic drusen were only significantly associated with impaired RMDA if they fell within the testing spot ($P\leq0.018$) (23).

Finally, the genetics of SDD and their adverse effect on RMDA are themselves connected, because the ARMS2 A69S risk polymorphism is *independently* associated with delayed RMDA, even in eyes that have not yet developed AMD! (25). This is an important link between the mysterious ARMS2 risk allele and the development and progression of AMD, with all signs so far pointing to preferential rod damage, and implicating SDD. Further, here we have a direct connection of ARMS2 with a functional deficit in dark adaptation that seems to appear before SDD, or even before any clinically evident AMD. This in turn could be consistent with radical new disease models in which the damage is done in early development.

Future steps

If we then posit that sub-threshold nanosecond laser intervention may be helpful for intermediate AMD, excluding the highest risk phenotype of RPD/SDD, the next steps forward seem clear. The findings in this study provide compelling evidence for further trials of the 2RT laser. Specifically, further trials of the 2RT laser in the large soft drusen and pigment abnormality class of iAMD are clearly warranted. Also, a careful re-examination of all available time-sequence imaging, demographic and clinical data in the original RPD/SDD subgroup should be carried

out to find further clues to the apparent adverse outcome of laser treatment in this group. This might improve our understanding of the pathogenesis and adverse natural history of this high-risk phenotype.

Conclusions

A startlingly good outcome has now been shown in one study for treatment with sub-threshold nanosecond laser for the non-RPD/SDD phenotype of iAMD, and is contrasted with an apparently poor outcome for the RPD/SDD phenotype. It is important that we learn more about both types of iAMD from carefully phenotyped, genotyped and controlled treatment trials. Appropriate caution is of course always in order, but a sorely needed new management for early AMD may be at hand.

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Footnote

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