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Macular laser photocoagulation in the management of diabetic macular edema: Still relevant in 2020?

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Abstract:

Macular laser photocoagulation (MLP) is inferior to intravitreal vascular endothelial growth factor (VEGF) inhibitors in the treatment of center-involved diabetic macular edema (DME). Ultra-widefield fluorescein angiography-guided laser photocoagulation to presumed ischemic areas of the peripheral retina or MLP do not reduce the treatment burden nor improve the visual outcomes of eyes treated with anti-VEGF drugs. Destruction of retinal tissue is not necessary to induce a therapeutic response in DME. Modern lasers are capable of producing invisible laser "burns" that do not destroy the targeted tissue using micropulse subthreshold (ST) mode where the laser's duty cycle is modified or alternatively selective retinal therapy (SRT) where ultrashort pulses of continuous wave laser selectively target the RPE. The best results with micropulse ST laser are obtained in eyes with a central macular thickness ≤400 μm. Eyes need to be treated in a continuous manner with no spaces between burns in the edematous area. Micropulse ST-MLP downregulates inflammatory biomarkers produced by activated microglial cells and Müller cells. Micropulse ST-MLP may reduce the anti-VEGF injection burden in DME. In SRT, the diseased RPE is targeted and heated with the laser with the hope that the adjacent RPE migrates and proliferates into these areas to heal the diseased RPE. There is much less experience with SRT, but the results are promising and deserve further study.

Keywords:

Diabetic macular edema, diabetic retinopathy, macular laser photocoagulation, micropulse laser, subthreshold laser, subliminal laser, selective retinal therapy, Müller cell, vascular endothelial growth factor

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Introduction

Although diabetes mellitus may cause vision loss by several means, including optic neuropathy, cataract formation, macular ischemia, and proliferative retinopathy, diabetic macular edema (DME) is the most common cause of moderate visual loss in diabetes.[1]

The development of laser photocoagulation and fluorescein angiography (FA) in the 1960s and 1970s ushered in an era that culminated in the Early Treatment of Diabetic Retinopathy Study (ETDRS). Macular laser photocoagulation (MLP) was the first proven treatment for DME.[2-4] For a quarter of a century, MLP was the treatment of choice of DME. Over the past decade, several randomized clinical trials have shown that vascular endothelial growth factor (VEGF) inhibitors have superior functional and anatomic outcomes than MLP.[5-8] The question arises as to what role does MLP play in the current management of DME. Is MLP currently obsolete?

Laser Physics

Laser energy effects on ocular tissues depend on the wavelength, pulse duration of the laser light, laser power, and the

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absorption characteristics of the tissue in question, which is largely determined by the pigments contained within it. During conventional MLP, a continuous wave of energy is delivered to the target tissue throughout the entire duration of the laser pulse. Light energy is converted into heat energy if the wavelength coincides with the absorption spectrum of the tissue pigment on which it falls. Pigmented tissues that absorb laser energy in the macular area include the RPE, choroid, hemoglobin within red blood cells, and the xanthophyll pigment. These pigments absorb the laser energy and convert it to heat which leads to an increase in tissue temperature. Depending on the duration and magnitude of the laser pulse, the heat wave will expand laterally and vertically and often results in collateral damage to adjacent tissues. In the past, visible burns were believed to be necessary for a successful treatment. Thus, the traditional endpoint was the achievement of a visible (threshold) grayish burn.[4,9] The ETDRS guidelines called for burns that were gray-white in intensity in a grid-like fashion in the area of diffuse edema. Those grayish-white burns translate histopathologically to tissue necrosis of not only the targeted tissue but also adjacent tissue.[10]

The best light absorber is melanin, but its light absorption decreases with longer wavelengths. Lasers with different wavelengths are available. Longer laser wavelengths such as the infrared or krypton red produce deeper, less visible, and more painful burns than green lasers.[10] There are certain theoretical advantages of a yellow laser over a green laser. Yellow's longer wavelength requires less power to achieve the same degree of retinal burn, produces less scatter by nuclear sclerotic lenses, and induces less iatrogenic macular damage from heat absorption by the xanthophyll pigment.[11] Despite these purported advantages, there is no study that has been able to demonstrate better outcomes of one wavelength over another in DME using suprathreshold or subthreshold (ST) macular photocoagulation protocols.[10,12,13]

The biggest downside to MLP is the iatrogenic tissue damage caused by the treatment.[14,15] Subretinal fibrosis, choroidal neovascularization, and laser scar enlargement have all been reported.[14,15] Even though there was an initial success in resolving DME, with time, eyes tended to develop insidious visual loss secondary to atrophic RPE and laser scar enlargement through the fovea. Despite these limitations, MLP became the treatment of choice for DME for close to 25 years.

Although MLP has been in clinical use for more than three decades, its mechanism of action is not completely understood. It was hypothesized that the death of photoreceptors, induced by the thermal insult of the laser burn, led to a decreased oxygen consumption alleviating the oxygen demand and resulting hypoxia. In addition, MLP destruction of the outer retina and RPE allowed oxygen diffusion from the choroid to reach the inner retina.[16] It has subsequently been shown that there is no need to cause a full thickness retinal burn in order to achieve the clinical benefits of MLP. The effects of photocoagulation are most likely due to an altered gene expression of the surviving RPE surrounding the burn.[17] It is thought that elevating retinal tissue temperature below the threshold of tissue necrosis leads to an upregulation of heat-shock proteins (HSPs).[18] Whenever cells encounter stressful situations, such as hyperthermia, cold exposure, and ischemia, HSPs are expressed. HSPs play an important role in maintaining proper protein structure. They assist in refolding proteins that were damaged during the stress event. HSPs also stabilize new proteins so that they are properly folded.[18] It became apparent that destruction of retinal tissue was not necessary to induce a therapeutic response. Since this realization, several investigators have shown that ultrashort pulses of energy, in the order of microseconds to nanoseconds, selectively target the intracellular melanosomes of the RPE. The melanosomes are vaporized creating microbubbles that rupture the RPE without causing thermal damage to the underlying choriocapillaris, overlying photoreceptors, and internal retina. The goal is to confine the laser energy to the targeted RPE and stimulate the adjacent RPE to migrate and proliferate into these areas to heal the diseased RPE.[19,20] This mode of laser treatment has been named selective retinal therapy (SRT). SRT leads to RPE damage, which can be visualized by FA.

The initial lasers relied on gas-tube systems that used mechanical shutters to deliver laser energy. These mechanical shutters open and close to produce the laser pulse that lasts in the order of hundreds of milliseconds. In contrast, current solid state lasers use electronic shutters that can deliver repetitive multiple short pulses of a few microseconds in duration separated by an off period which allows the tissue to cool down between the short pulses; thus, the inability to observe a color change in the target tissue.[21] These invisible laser burns have been described as ST micropulse (subliminal) burns. Since ST laser does not induce ophthalmoscopically visible laser burns, it can therefore be used to treat subfoveal or juxtafoveal focal and diffuse leaks. In essence, it diminishes the risk of iatrogenic thermal damage.[22] Depending on the duration of the cooling period, collateral damage may be prevented. The duty cycle refers to the ratio of time that the laser is actually firing to the total duration of the laser pulse. The lower the duty cycle, the longer the tissue has to cool down widening the therapeutic window of micropulse ST-MLP.[10] Currently, commercially available lasers can lower the duty cycle to 5%. Several imaging

modalities including FA, fundus autofluorescence, OCT, microperimetry, and fundus photography confirm the absence of any detectable retinal damage following micropulse ST-MLP.[13,23,24]

Bipolar and Müller cell nuclei comprise the bulk of the inner nuclear layer (INL). One of the earliest changes in diabetic patients is an increased thickness of the INL and the outer plexiform layer, which has been attributed to Müller cell dysfunction.[25] Regulation of the blood–retinal barrier is one of the myriad functions of Müller cells. Understandably, it follows that Müller cell dysfunction is accompanied by dysregulation of the blood–retinal barrier and edema formation.[26] Vascular changes in DME are more pronounced in the deep capillary plexus (DCP) as compared to the superficial capillary plexus (SCP).[27] The exact mechanism of action of ST-MLP remains unclear. Recently, Midena *et al*.[28,29] performed aqueous humor proteomic analysis to determine which cytokines were affected by ST-MLP. In one small trial, 18 patients with treatment naive, nonischemic, center-involved DME with a central retinal thickness ≤400 μm underwent yellow ST-MLP at baseline, 3 months, 6 months, and 9 months.[29] Before initiating treatment, an aqueous sample was obtained to measure the levels of several inflammatory and vasoactive cytokines. These were compared to a control group of nondiabetic patients undergoing cataract surgery. Patients with DME have elevated levels of Fas Ligand, macrophage inflammatory proteins 1 alpha, regulated on activation normal T cell expressed and secreted (RANTES), glial fibrillary acidic protein, inwardly rectifying potassium channel (Kir 4.1), and VEGF compared to nondiabetic patients. Following ST-MLP, the levels of these cytokines decreased.[28,29] Since these inflammatory biomarkers are produced by activated microglial cells and Müller cells, it appears that ST-MLP acts through the downregulation of these cells. OCTA has shown that 3 months after ST-MLP, there is a significant reduction in the number of microaneurysms in the DCP. By 6 months, there is also a reduction of microaneurysms in the SCP.[30] Following ST-MLP, the inner nuclear and outer retinal layers undergo a significant decrease in thickness.[31]

Continuous Wave Macular Laser Photocoagulation Monotherapy and Diabetic Macular Edema

Spalter[32] pioneered the use of photocoagulation to treat DME. He demonstrated the resolution of lipid exudates upon treatment with xenon photocoagulation. Several small controlled studies confirmed Spalter's observations.[33-35] These small trials showed that the likelihood of visual improvement was greater in eyes that had undergone MLP compared to those eyes that did not undergo MLP. Furthermore, photocoagulated eyes also demonstrated less visual loss than the nonphotocoagulated eyes.[33-35] Because of these early reports, the ETDRS was launched. One of the key objectives of the ETDRS was to answer whether or not MLP was effective in the treatment of DME.[4] According to the ETDRS protocol, in eyes with visible microaneurysms, surgeons target the microaneurysms with enough intensity to cause blanching. In eyes with diffuse DME, a grid of the edematous area is targeted with the laser.

The ETDRS introduced the term clinically significant macular edema (CSME).[36] The ETDRS found that MLP was effective in reducing visual loss from CSME. Moderate visual loss was reduced in half and 30% of eyes had an improvement in BCVA. Despite treatment, 15% of eyes still experienced visual loss.[4] In the ETDRS, in the subgroup of eyes with mild-to-moderate nonproliferative diabetic retinopathy with DME, visual acuity improved in 16%, remained unchanged in 77%, and worsened in 7% of treated eyes, whereas visual acuity improved in 11%, remained unchanged in 73%, and worsened in 16% of untreated eyes after 2 years of follow-up. After 3 years of follow-up, vision worsened in 12% of treated eyes compared to 24% of untreated eyes.

More recent clinical trials show that on average, eyes with center-involved DME treated with MLP experienced anywhere from a 2-letter loss to a 6-letter gain at 24 months of follow-up.[4,5,7,9,12,37] A recent Cochrane review concluded that at 1–3 years of follow-up, MLP improved the chances of DME resolution and decreased the chances of visual loss compared to the natural history.[38] Patients with persistent DME are usually retreated with MLP at 4-month intervals. On average, patients received 3–4 MLP treatments.[39] The DRCR network explored the course of response to MLP.[40] In this study, 122 eyes with center-involved DME received MLP. At the 16-week visit, the eyes were assessed for retreatment with MLP. If the visual acuity had improved at least 5 letters or the central macular thickness decreased >10%, the MLP could be deferred. They reported that 23% of eyes had partial resolution of the DME by 16 weeks. Traditionally, these eyes would have been eligible for repeat MLP. Instead, they were observed. Of this subset of eyes with partial resolution of DME, 42% continued to improved over the next 16 weeks. Visual acuity improvement as a criterion to defer MLP was poorly predictive of MLP need. These results suggest that in eyes with partial resolution of DME following MLP, there is no need to rush to a repeat MLP.[40]

Aiello *et al*.[41] performed a multivariate analysis of eyes that were subjected to MLP to try to elucidate factors

that were associated with improvement and worsening of visual acuity following MLP. Surprisingly, no demographic factors, OCT characteristics, funduscopic findings, or factors related to diabetes were associated with the visual outcomes. The only factors associated with visual outcomes were baseline visual acuity and baseline OCT macular volume. Eyes with worse baseline visual acuity were more likely to gain vision whereas eyes with better baseline visual acuity were more likely to lose vision. These are most likely ceiling and floor effects in these eyes. Eyes with greater baseline OCT macular volume, after correcting for baseline visual acuity, were more likely to lose vision.[41]

In eyes with DME that did not involve the center, the ETDRS reported that the MLP treatment was less effective and recommended close observation, especially in those cases where the leakage arose close to the center of the fovea.[42] The DRCR network reported 22 eyes with non-center-involved DME that were treated with a modified ETDRS focal grid MLP. In these eyes, the visual acuity and the retinal thickness remained stable at 12 months. The fluorescein leakage area decreased after MLP.[43]

In the hopes of reducing iatrogenic complications, a mild macular grid was proposed. In this technique, the microaneurysms were not treated directly and small mild burns were placed throughout the macular area regardless of the presence or absence of edema. A randomized clinical trial compared mild macular grid to the modified ETDRS focal/grid photocoagulation in eyes with DME.[9] At 12 months, the functional outcomes were similar between the two techniques, but the conventional modified ETDRS focal/grid photocoagulation was more effective in resolving DME than the mild macular grid.

Micropulse Subthreshold Macular Laser Photocoagulation and Diabetic Macular Edema

Since the first report by Friberg and Karatza in 1997,[44] several studies have concluded that micropulse ST-MLP is effective in improving visual acuity and reducing DME.[45-47] A recent meta-analysis of six randomized clinical trials compared the outcomes of eyes treated with micropulse ST-MLP to those treated with conventional MLP.[48] At 12 months, the visual outcomes were superior with micropulse ST-MLP even though there were no changes in the resolution of DME between the two groups.[48] The better visual outcomes with ST-MLP were not related to a greater resolution of DME but rather to decreased iatrogenic macular damage as evidenced by microperimetry.[13,23] A double-masked randomized multicenter clinical trial comparing ST-MLP to MLP in eyes with DME with a CMT <400 μm is currently underway in the United Kingdom. The primary endpoint will be the average change in best-corrected visual acuity from baseline to month 24.[49]

Lavinsky *et al*.[50] demonstrated the importance of the spacing between burns when using ST-MLP. In their clinical trial, they compared a modified ETDRS-MLP compared to ST-MLP with the burns placed two burn widths apart compared to ST-MLP with no spacing between burns. They found that at 12 months of follow-up, the group with the greatest improvement in visual acuity and the greatest reduction in central macular thickness was the ST-MLP with no spacing between burns group. Since ST-MLP burns are invisible, this implies that lasers need to have an automatic pattern scan technology in order to provide the best results.[50]

Baseline macular thickness is another variable to take into account. Mansouri *et al*.[51] compared the outcomes following ST-MLP in eyes with a baseline central macular thickness >400 μm to eyes with a baseline central macular thickness <400 μm. The eyes with a baseline central macular thickness <400 μm had reduction in CMT, visual gain, and none of the eyes required rescue treatment with intravitreal bevacizumab. In contrast, none of eyes with a baseline CMT ≥400 μm had an improvement in visual acuity or significant reduction in CMT. Furthermore, all the eyes required rescue treatment with intravitreal bevacizumab.[51]

Selective Retinal Therapy and Diabetic Macular Edema

Currently, there are two commercially available SRT laser systems (R: Gen; Lutronic, Goyang-si, South Korea and the 2RT, Ellex R and D Pty Ltd; Adelaide, Australia). The R: Gen laser consists of a Q-switched Nd: YLF laser that fires laser spots of 200 μm with a single pulse duration of 1.7 μs and a pulse repetition rate of 100 Hz with a maximum of 15 micropulses in a single burst. Pretreatment FA is required to titrate the laser power. Alternatively, optoacoustic and reflectometric methods have been developed *in lieu* of a pretreatment FA.[52] In contrast, the 2RT laser delivers laser pulses of a 400 μm spot size, lasting 3 ns using a 532 nm Q switched YAG laser. Power selection with the 2RT laser is performed by firing test spots outside the macular area. The power intensity of the test spots is slowly increased until a barely visible reaction is seen and a slightly lower power is selected for treatment.[19]

The 2RT laser is applied in a grid pattern to the edematous retina with each burn separated by another burn width. The fovea is avoided and treatment is applied at least

500 μm from the foveal center. A very small, randomized, short-lasting, noninferiority trial compared SRT using the 2RT laser (20 eyes) and conventional MLP (18 eyes) in eyes with DME. At 6 months, the change in central macular thickness and visual acuity was similar in both groups.[19] Pelosini *et al*.[53] treated 38 eyes of treatment-naïve DME with the same laser parameters. At 6 months, there were no complications recorded by microperimetry and patients experienced a statistically significant improvement in visual acuity from 20/44 at baseline to 20/27 at 6 months.

Park *et al*.[20] used the R Gen laser to treat 23 eyes with DME. They reported gains in visual acuity and macular sensitivity following SRT at 6 months of follow-up. Almost 30% of eyes gained at least two lines of BCVA. Interestingly, the central macular thickness did not change significantly.

Macular Laser Photocoagulation Plus Antivascular Endothelial Growth Factor and Diabetic Macular Edema

Head-to-head clinical trials have shown that anti-VEGF monotherapy is superior to MLP monotherapy in the treatment of DME.[5-8] However, despite continuous treatment, 40% to 60% of eyes, depending on the anti-VEGF used, will have persistent DME after 6 consecutive monthly injections.[54] The question arises what role does MLP play in the management of these eyes.

In Protocol I of the DRCR network, ranibizumab plus immediate MLP was compared to ranibizumab plus deferred MLP, which was defined as MLP after 6 months. At 5 years, there was a small trend toward better visual outcomes in the deferred MLP group, particularly in those eyes with worse visual acuity at baseline. In addition, 56% of eyes in the deferred MLP group never received MLP. The immediate MLP group received 13 intravitreal injections of ranibizumab compared to 17 in the deferred MLP group.[55,56] The READ-2 trial reported less injections with similar visual outcomes when combined with ranibizumab. Nevertheless, the READ-2 used an injection protocol that is quite different than the current DRCR recommendations (loading dose of 6 monthly anti-VEGF injections). Furthermore, the follow-up and reinjection criteria were quite different. After month 6, patients randomized to intravitreal ranibizumab were evaluated every 2 months and were eligible to receive ranibizumab if the central macular thickness was >250 μm. Patients randomized to combination therapy of focal grid laser and ranibizumab were evaluated every 3 months, and if center subfield thickness was >250 μm, they could receive ranibizumab followed by MLP within 7 days or ranibizumab alone. No other study, including the RESTORE, RETAIN, and REVEAL studies, showed that there was an advantage of adding MLP to ranibizumab over ranibizumab monotherapy.[7,57,58]

A few studies suggest that micropulse ST-MLP may diminish the anti-VEGF treatment burden.[59,60] A retrospective study of 19 eyes with DME treated with micropulse ST-MLP plus ranibizumab was compared to a group of 19 eyes with DME treated solely with ranibizumab. The visual outcomes of both groups were similar at 12 months of follow-up, but the number of injections was much less in the combination arm.[61] In two recent prospective single-center randomized clinical trials, treatment-naïve eyes with center-involved DME received a loading dose of three intravitreal injections of aflibercept. Thereafter, half of the cohort was randomly assigned to treatment with micropulse ST-MLP and PRN intravitreal injections. The other half of the cohort was treated solely with PRN injections. In one study, micropulse ST-MLP significantly reduced the mean number of injections over 12 months from 8.4 to 7.5.[59] In another study, the mean number of injections over 1 year decreased from 5.4 to 3.2 in the eyes treated with the micropulse ST-MLP.[60] The differences in the overall number of injections in both studies are probably due to the different retreatment criteria. As new and longer acting VEGF inhibitors enter the market, the role of micropulse ST-MLP will need to be reassessed.

Targeted Laser Photocoagulation of Ischemic Peripheral Retina and Diabetic Macular Edema

Chronic hyperglycemia activates multiple molecular pathways that result in diabetic retinopathy. Prior to the development of any clinical sign of diabetic retinopathy, retinal glial cells become activated. These activated glial cells release cytokines and other growth factors. Hypoxia, through the secretion of VEGF, is a major driver of diabetic retinopathy and DME.

Almost four decades ago, Shimizu *et al*.[62] used a novel ultra-widefield FA (UWF-FA) montage technique to demonstrate midperipheral capillary nonperfusion in many diabetic eyes. They noted that panretinal photocoagulation (PRP) benefited the macula despite the absence of direct laser treatment of the macular area. Ten years later, Gardner *et al*.[63] described the reduction of severe DME following PRP. The advent of modern UWF-FA devices permit relatively easy imaging of the midperipheral and peripheral retina allowing detection of peripheral capillary nonperfusion. Wessel *et al*.[64] reported that there was a direct correlation between DME and peripheral retinal ischemia as seen on UWF-FA. They

hypothesized that these areas of capillary nonperfusion are responsible for VEGF secretion and consequently DME. Targeted laser photocoagulation guided by UWF-FA has been suggested to decrease the treatment burden and improve visual outcomes. Takamura *et al*.[65] treated 52 eyes with focal grid MLP and then randomized them to either intravitreal bevacizumab or intravitreal bevacizumab plus targeted laser photocoagulation using a manual fluorescein angiographic montage from the seven standard ETDRS fields. They reported that at 6 months, the eyes that were treated with the targeted laser photocoagulation had a better visual outcome and less fluctuations in central retinal thickness.[65] Suñer *et al*.[66] conducted a randomized, controlled, prospective phase I/II study where 30 eyes were randomized to intravitreal ranibizumab plus UWF-FA targeted laser photocoagulation or MLP plus intravitreal triamcinolone. At 6 months, the eyes treated with ranibizumab plus targeted MLP had fewer recurrences. In contrast, in another prospective Phase I/II trial, 40 eyes were injected with four consecutive monthly ranibizumab injections and were then randomized to ranibizumab monotherapy or ranibizumab plus UWF-FA targeted laser photocoagulation. Patients were then followed monthly for 36 months and reinjected on a *pro re nata* basis if DME persisted. In the combination arm, eyes were eligible for laser photocoagulation retreatment at specified time points if additional areas of retinal nonperfusion were identified in UWF-FA. At the end of 3 years, targeted laser photocoagulation did not reduce the treatment burden or improve visual outcomes.[67] These somewhat surprising results may be attributed to the inability of UWF-FA to distinguish between ischemic retina and necrotic retina.[68] Whereas ischemic retina will secrete VEGF, necrotic retina is dead and no longer able to secrete VEGF. Photocoagulating dead necrotic retina will not modify intraocular levels of VEGF. In addition, there is a differential topographic density of photoreceptors across the retina.[69] There are many more photoreceptors in the posterior pole than the peripheral retina. To decrease metabolic demand to reduce VEGF levels, one would have to target and destroy those photoreceptors in the posterior pole as well.

Conclusion

For a quarter of a century, MLP was the treatment of choice of DME. Over the past decade, several randomized clinical trials have shown that anti-VEGF drugs have superior functional and anatomic outcomes than MLP. However, in order to obtain the best results, multiple monthly injections, on the order of 8–9 just in the 1st year, are required. Patients that for one reason or another cannot keep up with this regimen may be better suited to be treated with MLP.

Many diabetic eyes exhibit equatorial or peripheral capillary nonperfusion. Some have hypothesized that these areas of capillary nonperfusion are responsible for VEGF secretion and consequently DME. However, adding MLP to an anti-VEGF or targeting areas of peripheral retinal nonperfusion with laser photocoagulation does not decrease the treatment burden nor improve visual outcomes. The biggest downside to MLP is the iatrogenic tissue damage caused by the treatment. Since micropulse ST-MLP leads to retinal hyperthermia without causing tissue necrosis, it diminishes the risk of iatrogenic thermal damage. Micropulse ST-MLP obtained better visual results than continuous wave MLP despite similar rates of DME resolution. Micropulse ST-MLP appears to target activated retinal microglial cells and Müller cells. Micropulse ST-MLP may decrease the anti-VEGF injection burden and deserves further study. Similarly, SRT offers advantages over MLP and should be studied further.

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Conflicts of interest
Dr Lihteh Wu has served as consultant and received speaking fees from Quantel Medical and Bayer. Quantel Medical manufactures retinal lasers used in the treatment of diabetic macular edema. Bayer commercializes the use of intravitreal aflibercept (eylea) used in the treatment of diabetic macular edema.

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