Subthreshold Nano-Second Laser Treatment

Subjects: Ophthalmology

Submitted by: Amy Cohn

Definition

The presence of drusen is an important hallmark of age-related macular degeneration (AMD). Laser-induced regression of drusen, first observed over four decades ago, has led to much interest in the potential role of lasers in slowing the progression of the disease. In this article, we summarise the key insights from pre-clinical studies into the possible mechanisms of action of various laser interventions that result in beneficial changes in the retinal pigment epithelium/Bruch's membrane/choriocapillaris interface. Key learnings from clinical trials of laser treatment in AMD are also summarised, concentrating on the evolution of laser technology towards short pulse, non-thermal delivery such as the nanosecond laser. The evolution in our understanding of AMD, through advances in multimodal imaging and functional testing, as well as ongoing investigation of key pathological mechanisms, have all helped to set the scene for further well-conducted randomised trials to further explore potential utility of the nanosecond and other subthreshold short pulse lasers in AMD.

1. Introduction

Tremendous advances have been made in the treatment of neovascular age-related macular degeneration (AMD) with the introduction of anti-vascular endothelial growth factor (anti-VEGF) intravitreal injections [1][2][3]. However, there has been very little advance in our ability to intervene in the early or intermediate stages of the disease, in order to prevent or slow disease progression. There remains an urgent unmet need for proven, efficacious intervention strategies at earlier stages of AMD to prevent progression to vision-threatening, late stages of this common and devastating disease [4].

Drusen are extracellular, lipid-rich deposits that accumulate over time in between the retinal pigment epithelium (RPE) and Bruch's membrane (BM) and are one of the earliest clinical hallmarks of AMD, representing an important biomarker for risk of disease progression to vision threatening late complications of AMD [5]. Drusen composition using histological markers has been well documented. Although drusen are known to contain carbohydrates [6], zinc [7], proteins [8][9][10] and constituents of the complement system [11], the largest component is lipids [12][13][14][15]. Another well-known hallmark of AMD—albeit one not readily imaged in the clinic, but seen histopathologically—is thickening of the BM, where an accumulation of lipid-rich debris reduces essential transport across the membrane [16][17][18][19]. With advances in multi-modal imaging, in particular optical coherence tomography (OCT), other biomarkers have been identified that confer an increased risk of AMD disease progression, including reticular pseudodrusen (RPD) [20][21][22][23][24], hyper-reflective foci [25], drusen with heterogeneous internal reflectivity [26] and nascent geographic atrophy [27]. These features have enhanced our understanding of the disease stage, the risk of progression, and the appreciation of various clinical phenotypes within AMD. This is especially evident with the increasing appreciation of RPD—both in its prevalence and potential underlying pathophysiology [23][24]. This new, more granular ability to phenotype the disease, will likely need to be considered as we work towards targeted intervention strategies to prevent progression to late atrophic or neovascular AMD complications.

The time of progression from the development of drusen to vision-threatening late stage complications is often many decades, providing a large window of time in which to intervene to slow progression. Laser, in particular its non-thermal application through subthreshold, very short pulses, offers a potential therapeutic option to explore. In this review, we discuss the evolution of laser use in AMD from the early observations using continuous wave (CW) thermal lasers through to the newer short pulse, subthreshold laser treatment trials and histological findings. We also present a body of preclinical work that explores the potential mechanism of action of a nanosecond laser that provides a rational for its possible efficacy in slowing AMD disease progression.

2. Development of Newer Retinal Laser Technology to Allow Shorter Duration Pulses and a More Targeted Effect

In order to treat diseases of the macula, researchers have sought a means whereby they could harness the potential positive effects of thermal CW lasers in a way that avoided the bystander thermal damage to the neurosensory retina and choroid. The ability to restrict laser-induced effects to just the RPE was introduced by Anderson and Parrish in 1983 in a method termed “selective photothermolysis” [28] They proposed the application of extremely brief laser pulses to the RPE to limit heat dissipation into the surrounding tissues. This led to the development of lasers with pulse durations in the microsecond range, such as the retinal laser described by Pankratov [29] that delivered laser energy in short pulses (“micro-pulse”) rather than as a continuous wave. The technology allowed for greater control over laser treatments due to the innate concept of alternating an active “on” cycle with an “off” cycle, where the duty cycle refers to the “pulsing” and is defined as the length of time the power is “on” divided by the total time the laser is used. Using this definition, a CW laser has a duty cycle of 100%, whereas a 5% duty cycle laser refers to a laser that is pulsed “on” for 100 milliseconds (ms), with a 1900 ms “off” time. The advantage of pulsed lasers is that the temperature rise within the tissue during the “on” time is dissipated during the “off” cycle [30]. Modelling has shown that the ideal duty cycle is less than 5% to maximise efficacy and safety [30][31].

The diode micro-pulse (SDM) lasers, developed in the 1990s, employed the rapid application of a burst of laser pulses with a pulse duration of 100–300 microseconds over a 100–500 ms time window. More recently, selective retinal therapy (SRT) is an approach that utilises the application of a burst of very short laser pulses of 1.4 ms in duration, and a duration between pulses of about 10 ms. Although the laser pulses in both SDM and SRT systems induce a temperature rise within the RPE (i.e., cause thermal effects), the time between each pulse is sufficient for the temperature to theoretically return to baseline, thereby reducing the potential for diffusion of heat into surrounding tissues, such as the neural retina. The thermal relaxation time, a measure of ability of thermal energy to diffuse through the cell, is calculated to be approximately 10 ms for the RPE. This suggests that intervals between pulses that are >10 ms would result in very little, if any, thermal energy diffusion into photoreceptors [32]. Thus, the length of the interval between laser pulses, together with the pulse duration, determines whether thermal damage extends beyond the RPE [33].

The mechanism(s) of cell destruction induced by short-pulsed lasers are distinct to those induced by thermal CW lasers [34]. Laser energy is absorbed by melanosomes within the RPE, and when laser pulse durations are >4 ms, there is liberation of heat within the cell that can extend into the surrounding neural retina [60]. When RPE cells are irradiated with pulse durations that are less than 4 ms, mechanical disruption of the cell is thought to occur, because heating of melanosomes is below the temperature to cause thermal effects within the cell, such as the coagulation of proteins. Rather, small bubbles of steam develop around the melanosomes within the RPE which lead to the transient expansion of the cell and ultimately mechanical disruption [34]. Based on this information, it is likely that even some short pulse lasers could induce thermal damage to surrounding tissue, whereas nanosecond and microsecond lasers could potentially deliver more selective loss of the RPE. Indeed, evidence to suggest thermal changes can be seen when using micro-pulse lasers comes from an evaluation of the heat shock proteins in the RPE, especially HSP70, an indicator of thermal changes, in response to the SDM laser [35]. More research is needed to determine the extent of any more widespread thermal effects when using pulses in the microsecond range, and what the effect of repetitive laser bursts could be if there is a gradual increase in cell temperature over time. These would be an important consideration in the application of these lasers for the treatment of macula diseases.

A laser in the range of nanoseconds has been developed (2RT®, Ellex Pty Ltd. Adelaide, Australia), which uses a Q-switched frequency doubled laser to deliver 3 nanosecond (ns) pulses to the posterior eye [36]. The energy absorbed by the RPE in response to these short pulses is 1/500th of that delivered by thermal CW lasers, and it employs a speckled beam, resulting in sporadic and selective loss of RPE cells [36][37]. In view of the extremely short pulse duration, the nanosecond laser provides a mechanism for inducing selective changes in the RPE in the absence of thermal cellular changes with a wide safety margin.

The precise mechanism by which lasers induce protective effects on the posterior eye remain to be definitively elucidated, but one possibility is via the release of various protective factors from the RPE. In this section, we provide an overview of the cellular effects of nanosecond laser application (2RT®, Ellex Pty Ltd. Adelaide, Australia) to the posterior eye. The positive effects of this laser provide the foundation for understanding how nanosecond lasers might be efficacious when used to treat macular diseases, including AMD.

3. Nanosecond Laser Treatment Abrogates Changes in the Posterior Eye Important in the Development of AMD

Having established that the nanosecond laser selectively ablates the RPE in the absence of damage to neighbouring structures, it is important to address its effect on the posterior eye that has the potential to reduce the progression of AMD. The formation of drusen and a thickening in the BM are critical in the development of early AMD. Investigation of BM thickness in an animal model with features of early AMD demonstrated a thinning of the BM in response to nanosecond laser application [37]. ApoEnull mice, which have a thickened BM, were treated with the 2RT® laser. Ten spots were delivered in each eye at nine months of age, and eyes were then evaluated three months later. In contrast to ApoEnull mice eyes that were sham-treated and showed a substantially thickened BM (~900 nm thick), animals that had received nanosecond laser treatment to one eye showed a significant reduction in thickness (~700 nm thick) in the treated eye (Figure 2) [37].

In order to investigate the mechanism of this apparent nanosecond laser effect, it is important to realise that the BM is a dynamic structure consisting of extracellular matrix, including alternating layers of collagen and elastin. Its turnover is controlled by signalling pathways within the RPE, including the expression of matrix metalloproteinases (MMP) and tissue inhibitors of matrix metalloproteinases (TIMPs), which are important for the formation and degradation of constituents of the BM. In vitro studies on cultured human RPE cells have revealed that treatment with the nanosecond laser showed induced expression of MMP2 and MMP9, with these enzymes being released within two days of subthreshold nanosecond laser (SNL) treatment [38]. Expressional analysis of genes associated with the formation and degradation of the extracellular matrix has also been carefully examined in a mouse model with features of AMD. Changes in gene expression of 84 genes associated with extracellular matrix turnover have been examined in 12-month-old C57Bl6 (control) and ApoEnull (AMD-like model) mice three months after nanosecond laser treatment. A total of nine genes were significantly dysregulated by more than two-fold, including Mmp2 and Mmp3, a finding that was also confirmed by quantitative RT-PCR [37]. These data suggest that treatment of the RPE of aged ApoEnull mice with a nanosecond laser alters the turnover of extracellular matrix components of Bruch's membrane by altering the expression of MMPs within the RPE [37].

One of the more intriguing findings in animals treated with the nanosecond laser was the observation that changes in gene expression in the RPE occurred in both the laser treated and the untreated fellow eye. Indeed, both Mmp2 and Mmp3 were upregulated by similar amounts in both eyes, alongside seven other genes associated with extracellular matrix turnover [37]. Although the BM was not significantly thinned in untreated contralateral eyes, these results suggest that the nanosecond laser could have distant effects, the mechanisms and significance of which require further study.

Overall, these findings suggest that nanosecond laser application selectively ablates RPE cells without inducing overt visible damage in adjacent structures. Moreover, absorption of nanosecond laser energy by the RPE induces gene expressional changes that are associated with thinning of the BM, particularly involving the MMPs. These findings support the evaluation of this laser in macular conditions, including AMD.

4. Future Applications and Directions of Subthreshold Laser Treatments for Treating Macula Disease

Extensive research into short duration lasers have heralded the development of selective retinal therapy (SRT) and subthreshold diode micro-pulse (SDM) and nanosecond lasers. Although the use of many short duration lasers has been explored for use in retinal disease, to the best of our knowledge, the 2RT® laser developed by Ellex (now Nova Eye Medical, Pty Ltd. Fremont, CA, USA) represents the only laser functioning in the nanosecond range for ophthalmic use. As such, the results of the LEAD study are only applicable for use with such a laser and cannot be extrapolated for other short pulse lasers. In addition, the LEAD study is, to the best of our knowledge, the only large randomised-controlled trial to examine the potential efficacy of a subthreshold, nanosecond laser in slowing progression of intermediate AMD to advanced disease. Nova Eye Pty Ltd. (Fremont, CA, USA) plans to continue its research using the 2RT® laser in management of iAMD.

Another development in short duration laser use for ophthalmic conditions is the release of the R:GEN laser by Lutronic Vision (South Korea). The R:GEN is an SRT laser with a 527 nm wavelength and 1.7 µs pulse duration designed to selectively target the RPE, with its effect delivered through microbubble formation in the RPE. As discussed previously,

lasers delivered at subthreshold levels have no visual feedback at the time of application, which can make the titration of laser power for adequate tissue effect extremely difficult. The R:GEN laser utilises Dual Dosimetry technology to measure reflectometry (back-scattered light) and opto-acoustic signalling (thermo-elastic pressure waves) to offer real-time titration of laser energy delivery to the RPE. Opto-acoustic (OA) imaging technology (also known as photo-acoustic imaging) is a non-invasive way to determine the temperature rise in the RPE cell at the time of laser treatment, utilising both light and sound wave principles. When short duration laser light is absorbed by chromophores within a tissue (such as melanosomes within the RPE), the cell undergoes thermoelastic expansion and acoustic waves are generated. These optoacoustic signals can be measured by an ultrasonic transducer. During irradiation of the RPE, the baseline temperature of the cell increases, resulting in a change to the pressure signal and acoustic waves emitted and microbubble formation can be detected within the RPE cells using OA techniques [39][40]. These methods can then indicate when sufficient energy has been generated by the laser within the RPE cell, and at this point the laser automatically switches off. It is possible that this will result in a more accurate, individualised titration of laser energy delivery. The R:GEN laser has already been studied in macular disease central serous chorioretinopathy with promising results [41], and further studies are planned in other diseases.

Another difficulty in conducting interventional trials for the early stages of AMD is the natural history of the disease itself. The disease progresses slowly over years, which renders reaching clinically meaningful results within a reasonable time frame difficult. Significant advances have been made to address this, through describing potential early disease endpoints. Nascent geographic atrophy (nGA) is one such early biomarker, signifying early atrophic changes as seen on OCT imaging. These changes were incorporated into a combined atrophic endpoint in the LEAD study (the first trial to do so), and in so doing, enabled a more time- and cost-efficient study to be conducted [25]. Similarly, the Classification of Atrophy Meeting (CAM) international consensus group have proposed a classification of atrophy defined on OCT features of both incomplete and complete retinal pigment epithelium and outer retinal atrophy (iRORA and oRORA, respectively) in AMD [42][43]. Having consensus on nomenclature around early atrophic changes in AMD will help facilitate early intervention studies, making it more feasible to assess the efficacy of novel early interventions.

References

1. Brown, D.M.; Kaiser, P.K.; Michels, M.; Soubrane, G.; Heier, J.S.; Kim, R.Y.; Sy, J.S.; Schneider, S. ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N. Engl. J. Med. 2006, 355, 1432–1444.
2. Rosenfeld, P.J.; Brown, D.M.; Heier, J.S.; Boyer, D.S.; Kaiser, P.K.; Chung, C.Y.; Kim, R.Y.; MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. N. Engl. J. Med. 2006, 355, 1419–1431.
3. Brown, D.; Michels, M.; Kaiser, P.K.; Heier, J.S.; Sy, J.P.; Ianchulev, T. ANCHOR Study Group. Ranibizumab versus Verteporfin Photodynamic Therapy for Neovascular Age-Related Macular Degeneration: Two-Year Results of the ANCHOR Study. Ophthalmology 2008, 116, 57–65.
4. The Age-Related Eye Disease Study Research Group. The Age-Related Eye Disease Study (AREDS): Design Implications AREDS Report No. 1. Control Clin. Trials 1999, 20, 573–600.
5. Ferris, F., III; Wilkinson, C.P.; Bird, A.; Chakravarthy, U.; Chew, E.; Csaky, K.; Sadda, S.R. Beckman Initiative for Macular Research Classification Committee. Clinical Classification of Age-related Macular Degeneration. Ophthalmology 2013, 129, 844–851.
6. Mullins, R.F.; Hageman, G.S. Human ocular drusen possess novel core domains with a distinct carbohydrate composition. J. Histochem. Cytochem. 1999, 47, 1533–1539.
7. Lengyel, I.; Flinn, J.M.; Peto, T.; Linkud, D.H.; Bird, A.C.; Lanzirotti, A.; Frederickson, C.J.; van Kuijk, F.J. High concentration of zinc in sub-retinal pigment epithelial deposits. Exp. Eye Res. 2007, 84, 772–780.
8. Pikuleva, I.; Curcio, C.A. Cholesterol in the retina: The best is yet to come. Prog. Retin. Eye Res. 2014, 41, 64–89.
9. Mullins, R.F.; Russell, S.R.; Anderson, D.H.; Hageman, G.S. Drusen associated with aging and age-related macular degeneration contain proteins common to extracellular deposits associated with atherosclerosis, elastosis, amyloidosis, and dense deposit disease. FASEB J. 2000, 14, 835–846.
10. Malek, G.; Li, C.M.; Guidry, C.; Medeiros, N.E.; Curcio, C.A. Apolipoprotein B in cholesterol-containing drusen and basal deposits in eyes with age-related maculopathy. Am. J. Pathol. 2003, 162, 413–425.
11. Johnson, L.; Ozak, S.; Staples, M.K.; Erikson, P.A.; Anderson, D.H. A potential role for immune complex pathogenesis in drusen formation. Exp. Eye Res. 2000, 70, 441–449.
12. Anderson, D.H.; Ozaki, S.; Nealon, M.; Neitz, J.; Mullins, R.F.; Hageman, G.S.; Johnson, L.V. Local cellular sources of apolipoprotein E in the human retina and retinal pigmented epithelium: Implications for the process of drusen formation. Am. J. Ophthalmol. 2001, 131, 767–781.
13. Pauleikhoff, D.; Zuels, S.; Sheraidah, G.S.; Marshall, J.; Wessing, A.; Bird, A.C. Correlation between biochemical composition and

fluorescein binding of deposits in Bruch's membrane. Ophthalmology 1992, 99, 1548–1553.
14. Curcio, C.; Presley, J.B.; Malek, G.; Medeiros, N.E.; Avery, D.V.; Kruth, H.S. Esterified and unesterified cholesterol in drusen and basal deposits of eyes with age-related maculopathy. Exp. Eye Res. 2005, 81, 731–741.
15. Wang, L.; Clark, M.E.; Crossman, D.K.; Kojima, K.; Messinger, J.D.; Mobley, J.A.; Curcio, C.A. Abundant lipid and protein components of drusen. PLoS ONE 2010, 5, e10329.
16. Booji, J.; Baas, D.C.; Beisekeeva, J.; Gorgels, T.G.M.F.; Bergen, A.A.B. The dynamic nature of Bruch's membrane. Prog. Retin. Eye Res. 2010, 29, 1–18.
17. Karampelas, M.; Sim, D.A.; Keane, P.A.; Papastefanou, V.P.; Sadda, S.R.; Tufail, A.; Dowler, J. Evaluation of retinal pigment epithelium-Bruch's membrane complex thickness in dry age-related macular degeneration using optical coherence tomography. Br. J. Ophthalmol. 2013, 97, 1256–1261.
18. Starita, C.; Hussain, A.A.; Pagliarini, S.; Marshall, J. Hydrodynamics of ageing Bruch's membrane: Implications for macular disease. Exp. Eye Res. 1996, 62, 565–572.
19. Hussain, A.; Starita, C.; Hodgetts, A.; Marshall, J. Macromolecular diffusion characteristics of ageing human Bruch's membrane: Implications for age-related macular degeneration (AMD). Exp. Eye Res. 2010, 90, 703–710.
20. Finger, R.P.; Wu, Z.; Luu, C.D.; Kearney, F.; Ayton, L.N.; Lucci, L.M.; Hubbard, W.C.; Hageman, J.L.; Hageman, G.S.; Guymer, R.H. Reticular pseudodrusen: A risk factor for geographic atrophy in fellow eyes of individuals with unilateral choroidal neovascularization. Ophthalmology 2014, 121, 1252–1256.
21. Zhou, Q.; Daniel, E.; Maguire, M.G.; Grunwald, J.E.; Martin, E.R.; Martin, D.F.; Ying, G.S. Pseudodrusen and incidence of late age-related macular degeneration in fellow eyes in the Comparison of Age-related Macular Degeneration Treatment Trials. Ophthalmology 2016, 123, 1530–1540.
22. Domalpally, A.; Agron, E.; Pak, J.W.; Keena, T.D.; Ferrris, F.L., III; Clemon, T.E.; Chew, E.Y. Prevalence, Risk, and Genetic Association of Reticular Pseudodrusen in Age-related Macular Degeneration. Age-Related Eye Disease Study 2 Report 21. Ophthalmology 2019, 126, 1659–1666.
23. Curcio, C.; Messinger, J.D.; Sloan, K.R.; McGwin, G.; Medeiros, N.E.; Spaide, R.F. Subretinal Drusenoid Deposits in Non-Neovascular Age-related Macular Degeneration: Morphology, Prevalence, Topography and Biogenesis. Retina 2013, 33, 265–276.
24. Spaide, R.F.; Ooto, S.; Curcio, C.A. Subretinal drusenoid deposits AKA pseudodrusen. Surv. Ophthalmol. 2018, 63, 782–815.
25. Christenbury, J.G.; Folgar, F.A.; O'Connell, R.V.; Chiu, S.J.; Farsiu, S.; Toth, C.A. Progression of intermediate age-related macular degeneration with proliferation and inner reitnal migration of hyperreflective foci. Ophthalmology 2013, 120, 1038–1045.
26. Tan, A.C.S.; Pilgrim, M.G.; Fearn, S.; Bertazzo, S.; Tsolaki, E.; Morell, A.P.; Li, M.; Messinger, J.D.; Dolz-Marco, R.; Lei, J.; et al. Calcified nodules in retinal drusen are associated with disease progression in age-related macular degeneration. Sci. Transl. Med. 2018, 10, eaat4544.
27. Wu, Z.; Luu, C.D.; Ayton, L.N.; Goh, J.K.; Lucci, L.M.; Hubbard, W.C.; Hageman, J.L.; Hageman, G.S.; Guymer, R.H. Optical Coherence tomography defined changes preceding the development of drusen-associated atrophy in age-related macular degeneration. Ophthalmology 2014, 121, 2415–2422.
28. Anderson, R.R.; Parrish, J.A. Selective photothermolysis: Precise microsurgery by selective absorption of pulsed radiation. Science 1983, 220, 524–527.
29. Pankratov, M.M. Pulse delivery of laser energy in experimental thermal retinal photocoagulation. Proc. Soc. Photo Opt. Instrum. Eng. 1990, 1202, 205–213.
30. Framme, C.; Schuele, G.; Roider, J.; Birnbruger, R.; Brinkman, R. Influence of pulse duration and pule number in selective RPE laser treatment. Lasers Surg. Med. 2004, 34, 206–215.
31. Dorin, G. Subthreshold and mircopulse diode laser photocoagulation. Semin. Ophthalmol. 2003, 18, 147–153.
32. Brinkmann, R.; Roider, J.; Birngruber, R. Selective retina therapy (SRT): A review on methods, techniques, preclinical and first clinical results. Bull. Soc. Belge Ophtalmol. 2006, 302, 51–69.
33. Tode, J.; Richert, E.; Koinzer, S.; Klettner, A.; vonder Burchard, C.; Brinkman, R.; Lucius, R.; Roider, J. Selective Retina Therapy Reduces Bruch's Membrane Thickness and Retinal Pigment Epithelium Pathology in Age-Related Macular Degeneration Mouse Models. Transl. Vis. Sci. Technol. 2019, 8, 11.
34. Brinkmann, R.; Huttmann, G.; Rogener, J.; Roider, J.; Birngruger, R.; Lin, C.P. Origin of retinal pigment epithelium cell damage by pulsed laser irradiance in the nanosecond to microsecond time regimen. Lasers Surg. Med. 2000, 27, 451–464.
35. Wang, J.; Quan, Y.; Dalal, R.; Palanker, D. Comparison of Continuous-Wave and Micropulse Modulation in Retinal Laser Therapy. Investig. Ophthalmol. Vis. Sci. 2017, 58, 4722–4732.
36. Wood, J.P.; Plunkett, M.; Previn, V.; Chidlow, G.; Casson, R.J. Nanosecond pulse lasers for retinal applications. Lasers Surg. Med. 2011, 43, 499–510.
37. Jobling, A.I.; Guymer, R.H.; Vessey, K.A.; Greferath, U.; Mills, S.A.; Brassington, K.H.; Luu, C.D.; Aung, K.Z.; Trogrlic, L.; Plunkett, M.; et al. Nanosecond laser therapy reverses pathologic and molecular changes in age-related macular degeneration without retinal damage. FASEB J. 2015, 29, 696–710.
38. Zhang, J.J.; Sun, Y.; Hussain, A.A.; Marshall, J. Laser-mediated activation of human retinal pigment epithelial cells and concomitant release of matrix metalloproteinases. Investig. Ophthalmol. Vis. Sci. 2012, 53, 2928–2937.
39. Wang, L.; Yao, J. A practical guide to photoacoustic tomography in the life sciences. Nat. Methods 2016, 13, 11.
40. Schüle, G.; Huettman, G.; Roider, J.; Wirbelauer, C.; Birngruger, R.; Brinkman, R. Optoacoustic measurements during µs-irradiation of

the retinal pigment epithelium. Proc. SPIE 2000.
41. Park, Y.; Kang, S.; Kim, M.; Yoo, N.; Roh, Y.J. Selective retina therapy with automatic real-time feedback-controlled dosimetry for chronic central serous chorioretinopathy in Korean patients. Graefes Arch. Clin. Exp. Ophthalmol. 2017, 255, 1375–1383.
42. Guymer, R.; Rosenfeld, P.J.; Curcio, C.A.; Holz, F.G.; Staurenghi, G.; Freund, K.B.; Schmitz-Valckenberg, S.; Sparrow, J.; Spaide, R.F.; Tufail, A.; et al. Incomplete Retinal Pigment Epithelial and Outer Retinal Atrophy in Age-Related Macular Degeneration: Classification of Atrophy Meeting Report 4. Ophthalmology 2019, 127, 3394–3409.
43. Sadda, S.; Guymer, R.H.; Holz, F.G.; Schmitz-Valckenberg, S.; Curcio, C.A.; Bird, A.C.; Blodi, B.A.; Bottoni, F.; Chakravarthy, U.; Chew, E.Y.; et al. Consensus Definition for Atrophy Associated with Age-Related Macular Degeneration on OCT: Classification of Atrophy Report 3. Ophthalmology 2017, 125, 537–548.

Keywords

drusen;age-related macular degeneration;laser