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Editorial

Diabetic Macular Edema: Approaching a Curative Situation

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Abbreviations

DME: Diabetic Macular Edema; VA: Visual Acuity; Mas: Microaneurysms; DDME: Diffuse DME; RCT: Randomized Controlled Trial; GLP: Modified Grid Laser Photocoagulation; OCT: Optical Coherence Tomography; 3D-OCT: Three-Dimensional OCT; T and Er: Trial and Error; PPV: Pars Plana Vitrectomy; VFT: Vitreofoveal Traction; VMT: Vitreomacular Traction; ERM: Epiretinal Membrane; A-VEGF: Anti-Vascular Endothelial Growth Factor; DRCR.net: Diabetic Retinopathy Clinical Research Network; ETDRS: Early Treatment Diabetic Retinopathy Study; PVD: Posterior Vitreous Detachment

Introduction

Diabetic macular edema (DME) is the major cause of vision deterioration in working-age population world-wide. The primary aim of DME therapy is to achieve early, long-lasting dry macula in order to improve or sustain visual acuity. Treating the pathogenesis of a disease is the state-of-the-art practice in medicine. In diffuse DME (DDME), except for vitreofoveal traction and ERM, the complete pathogenesis line was until recently unknown. Therefore, extended therapeutic studies for DDME by anti-VEGFs and other medications, and by laser photocoagulation and other techniques, were undertaken through a trial & error approach, thus the aim of therapy was not achieved. Using 3D-OCT and histopathological studies, two more tractional pathogeneses of DDME were disclosed, and completed the pathogenesis line of DME. Consequently, early pars plana vitrectomy in naïve-treated DDME eyes achieved long-lasting dry maculae in 92-100% of eyes, thus approaching a curative situation for DME.

Pathogeneses and therapies of DME

In diabetic macular edema (DME), the longer the edema the greater macular layers injury and visual acuity (VA) loss [1-4]. Therefore the primary aim of DME therapy is to achieve early, long-lasting dry macula in order to improve or sustain VA. The basic pre-condition for achieving an efficacious therapy is to treat the pathogenesis.

Microaneurysm-related ("focal") DME

Leaking microaneurysms (MAs) are considered the hallmark of "focal" DME [5]. Direct focal laser photocoagulation to the MAs was the standard of care for decades. However, repeated treatments were required [5]. Studies are ongoing on using advanced laser instruments, anti-VEGF medications, surgery, and likely faricimab (Vabysmo; Roche/Genentech; Basel, Switzerland), to improve the rate of durable outcomes [6-10].

Diffuse DME

There are four types of pathogeneses for diffuse DME (DDME): a) vitreofoveal (often termed vitreomacular) traction (VFT) and, b) ERM, both of which often durably respond to PPV, with or without ILM peeling. The two more novel DDME pathogeneses are, c) extrafoveal traction (Ext-FT) [11-13], which might emerge in any site of the area centralis, i.e., extrafoveal vitreoretinal traction, or as vitreopapillary traction [14]; and, d) "vasogenic" DDME, without clinically detected traction. Ext-FT was detected by using 3D-OCT images and video clips (e.g. SD-OCT 1000, Topcon, Japan) [11]. 3D-OCT was needed because the plane of the area centralis regularly differs from that of the vitreoretinal traction site. The traction membrane

beyond the traction site is detached anteriorly, and thus appearing as a short free posterior hyaloid (PH; posterior vitreous cortex) membrane in different B-scan meridians. The 3D-OCT enables the observation of the whole examined field, including the traction membrane, and its association with the central macula edema, as explained [15,16]. (Figure 1**).** Diagnosis of vasogenic DDME was made when presence of Ext-FT was definitely excluded by using the 3D-OCT [11]. Other options in diagnosing extrafoveal vitreous traction, in difference from adhesion, were previously summarized [15]. Histological studies have shown that vasogenic DDME presents an early vitreoretinal traction, before it is detectable by OCT [17,18]. Both 'focal', MA-related DME and DDME eyes were included in all the large randomized controlled trials (RCTs), unless specified otherwise [19-22].

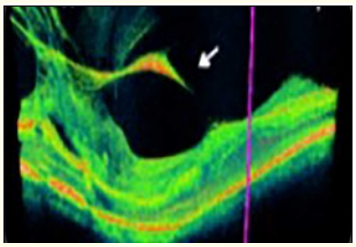

Figure 1: Diffuse diabetic macular edema due to extrafoveal vitreous traction (arrow). The central macula (marked by the vertical line) is free from traction. If only macular OCT B-scans were undertaken, the eye could be destined to repeated intravitreal injections of various medications and GLPs for months or years.

Because the DDME pathogeneses in the treated eyes were unknown, all therapeutic studies were carried out for more than a decade through a trial and error (T&Er) approach [19-24]. However, the overlooked Ext-FT, the most common pathogenesis of DDME, would avoid reaching the aim of therapy (durable dry maculae), as was explained [25]. Yet, these medications can affect the capillary junctional complexes or the inflammatory processes, thus reducing leakage and edema temporarily, and most often partially. In DME protocol-T trial (n=660 patients), mean VA and edema improved in each of the three major anti-VEGF medication-groups during the first 2-year trial, with or without of laser rescue therapy in 45% (mean) of eyes [21]. However, VA loss was recorded during the subsequent 3-year real-world study (n=317). It was attributed to recurrent or persistent edema during the whole 5-year study [22]. DRCR.net authors concluded the trial, claiming that a change in therapeutic strategy from anti-VEGFs to a long-lasting efficacious treatment is required [22]. This study reasserted the importance of the ultimate goal of DME therapy - attaining an early and long-lasting macular drying rather than temporarily improvements of VA [19-23]. However, T&Er studies by medications continued, and outcomes were regularly expressed as "suboptimal response" or "statistically significant improvement" even though residual or recurrent edema persisted, which are indicative for further treatments. But these therapeutic failures in achieving the aim were often recommended for therapy, e.g. by a large study reporting on a switch of an anti-VEGF medication in 70% of eyes [23].

In contrast, four studies have shown that early PPV with ILM pealing in naive-treated DDME eyes, following exclusion of VFT and ERM, have achieved complete, long-lasting macular drying in 92–100**%** of eyes associated with improved VA [26-29]. The largest of these, a multi-national study (n=120 eyes) reported on achieving completely dry maculae, from mean of 593μm to 260μm (±33), in 100% of eyes already one month following surgery [28]. After two years, all maculae remained dry, associated with improved VA. In contrast, when PPV was performed as a last resort, even if it was efficacious in achieving anatomic improvement it was often too late for reviving VA due to irreversible foveal injury [30]. For vasogenic DDME, following exclusion of Ext-FT, GLP was found durably efficacious in 13 (72%) eyes (n=18) after 4 - 24 months (mean, 15.9) of follow-up [31]. Complications, resulting in recurrent DDME, were mostly (4 eyes) related to the emergence of Ext-FT membranes (3 eyes) between months 5 to 9, and ERM (one eye) at month 12, which were operable.

Vasogenic DDME

Based on the expected high prevalence of vasogenic DDME type (following exclusion of VFT and ERM) in treated eyes [11-13], we may accept that early PPV in naïve-treated eyes was also highly efficacious in the vasogenic DDME type in the four PPV studies [26-29]. This outcome may be explained by the removal of VEGF and pro-inflammatory cytokines from the posterior vitreous cortex, as well as by the increase in macular oxygenation postoperatively [32]. Moreover, in Hagenau et al.'s histological studies in vasogenic DDME eyes following PPV, vitreoretinal traction membranes were neither detected by OCT preoperatively nor intraoperatively [17]. However, trans-differentiation of hyalocytes to myofibroblasts was detected at the vitreoretinal interface of those eyes. These contrac-

tile cells could cause vitreoretinal traction, retinal leakage and DME. The authors concluded that their findings argue for an early PPV in DDME irrespective of the presence of traction formation on OCT imaging. In a review study on hyalocytes in vitreoretinal diseases, Jones et al. similarly summarized the early pathophysiology, yet undetected by OCT except for the edema, followed by vitreoschisis into anterior and posterior lamellae [18], as detected clinically [33,34]. They concluded that eliminating the role of vitreous and hyalocytes may entirely prevent proliferative vitreoretinal diseases [18]. This notion suggests that unless MAs dominate in a DME eye, all other DME eyes are tractional in essence ('DDME').

Mixed capillary leakage secondary to both vitreoretinal traction and MAs may also be detected in DME. The 'RESTORE' study group has proposed the diagnosis of focal DME over DDME if >67% of leakage originated from leaking MAs in the whole edema area [20]. In this RCT (n= 345 patients), 53.5% (mean) had focal DME; but it is often less prevalent in others [20]. Extrafoveal vitreoretinal traction, in contrast to adhesions, has been associated with other pathological entities, such as branch retinal vein occlusion, high myopia and age-related macular degeneration [35-37].

Faricimab and MA-related DME

The only non-steroidal medication that has reached extensions between injections for DME is 6 mg faricimab administered intravitreally (n= 1,891 patients) [38]. Faricimab is a bispecific antibody targeting VEGF-A and angiopoietin-2. The authors' attitude express and underscore the importance of achieving a dry macula. After 1- and 2-year follow-up of the faricimab innovative RCT using a T&Er approach, the authors reported an extended macular drying for up to 12 weeks in 70% and ~80% of eyes, and 16 weeks in 50% and >60% of eyes, respectively [38,39]. These results were based, however, on a proposed new DME criterion: central retinal thickness of 325µm or more. However, when the standard OCT criterion of a dry macula was applied, approximately 40% (mean) of eyes have attained absence of intraretinal fluid that enabled extension of injections to every 8 weeks. Similarly, in a real world study using the standard DME criterion, Rush reports that 39% of patients reached a faricimab treatment interval of ≥8 weeks and had a fluid-free macula on OCT at 12 months (n= 51 patients) [40]. However, choosing this T&Er approach means that a reduction in the number of faricimab injections to approximately half (compared with anti-VEGFs) in only 40% of eyes within the trial period, would continuously put the other 60% of eyes at risks associated with persistent edema throughout this whole period.

However, a dilemma has arose: Is an extended drying in DDME by a medication that does not affect traction possible? Takamura et al. have found that three monthly treatment of DME by faricimab (n = 27) achieved a remarkably high macular drying rate by its effects on the MAs [9]. Durations of dryness were not provided. This outcome was documented to be related to its temporary impacts on the turnover of MAs, both in causing their shrinkage and disappearance, and reduced production. Another recent faricimab study for DME supports this outcome (n = 2; 4 monthly injections) [10]. Therefore, if proven by further studies, pathogenetically-guided faricimab therapy to leaking MAs ('focal' DME) is expected to become another management strategy in the ongoing studies in order to achieve the aim of DME treatment [6-8].

Conclusions and concerns

Despite the claim by DRCR.net following the pivotal 5-year study [22], underscoring the importance of avoiding T&Er anti-VEGF tight treatments in order to temporally improve VA, more T&Er therapeutic DME studies and novel techniques for administering anti-VEGFs continuously appear [41,42]. The long-term persistent edema will become clinically apparent when the tight treatment schedule is halted for one reason or another, which would necessitate changing into a real-world practice. Then the accompanying sequelae of VA loss would prevail, as reported [21,22].

In contrast, treating the pathogenesis of a disease is the state-of-the-art in order to achieve the best outcome. Thus, treatment of DDME, i.e., the non-MA-related DME, using early PPVs in naïve-treated eyes achieved very high rates of long-lasting dry maculae. Based on further confirmatory studies, these repeated outcomes, and typically by one intervention, seem to signify an imminent cure for DDME.

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