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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

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. The recent line of DME pathogeneses is as follows: A) macular microaneurysms (MAs), which arise secondary to hypoxic state in the neurosensory retina and are considered the hallmark of "focal" DME [5]. In the past, focal laser photocoagulation of individual leaky MA was the standard of care, but outcomes were limited [5]. Studies are ongoing on MA-related therapy using advanced laser instruments, anti-vascular endothelial growth factor (-VEGF) medication, surgery, or a combination of these, to achieve durable macular drying [6-8]. Recently, two studies reported on intravitreal 6 mg faricimab (Vabysmo; Roche/Genentech; Basel, Switzerland) treatment to be efficacious in attaining macular drying by affecting the MA-related DME [9,10]. B) There are four types of pathogeneses for diffuse DME (DDME): a) vitreofoveal (often termed vitreomacular) traction (VFT) and, b) macular epiretinal membrane (ERM), both of which often durably respond to pars plana vitrectomy (PPV), with or without ILM peeling. The two more recent DDME pathogeneses are, c) extrafoveal traction (Ext-FT) [11-13], a tractional type that might emerge in any site of the area centralis, i.e., extrafoveal vitreoretinal traction, or as vitreopapillary traction [14]; and, d) "vasogenic" DDME, without detected traction. Extrafoveal vitreoretinal traction could be detected by using three-dimensional (3D)-OCT images and video clips (such as SD-OCT 1000, Topcon, Tokyo, Japan). This is because the plane of the area centralis 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)**.** Ext-FT has been found to be the most common DDME pathogenesis. Diagnosis of vasogenic DDME was made when presence of Ext-FT was definitely excluded by using the 3D-OCT [11]. Histological studies have shown that vasogenic DDME presents early vitreoretinal traction, before it is detectable by OCT [17,18]. Other options in diagnosing extrafoveal vitreous traction were previously summarized [15]. Both 'focal', MA-related DME and DDME eyes were included in the large randomized controlled trials (RCTs), unless specified otherwise [19-22].

Because the two novel DDME pathogeneses were unknown, major RCTs, real world and hundreds of other therapeutic studies, using anti-VEGFs, their biosimilars, various injectable steroids, as well as modified grid laser photocoagulation (GLP), were carried

out for more than a decade through a trial and error (T and Er) approach [19-24]. However, the overlooked Ext-FT, the most common pathogenesis of DDME, could avoid reaching the aim of therapy (i.e. durable dry maculae), as was explained [25]. Yet, these medications can affect the junctional complexes or the inflammatory processes in these eyes, thus reducing the capillary leakage and edema temporarily, and most often partially. For example, in protocol-T RCT of the DRCR.net, the three major anti-VEGF monotherapy treatments for DME [ranibizumab (Lucentis, Genentech, San Francisco, CA), bevacizumab (Avastin, Genentech) and aflibercept (Eylea, Regeneron, Tarrytown, NY] required rescue therapies by using laser photocoagulation in approximately 45% (mean) of eyes [21]; and bevacizumab monotherapy switches were necessary in 70% of eyes during a 2-year study [23]. These are examples that most DME eyes have attained a "suboptimal response", "statistically significant improvement" or "reduction" of edema following anti-VEGF monotherapy or in combination with GLP, and none achieved a durable drying. However, these studies regularly report on allegedly therapeutic success, but the residual and recurrent edema are actually indicative for further treatments, i.e., express therapeutic failure in reaching the DME aim.

In protocol-T DME 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 laser rescue therapy [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 5-year 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 [19-24].

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. The authors noted that, "for each day PPV is delayed, gaining >5 letters at 24-months decreases by 1.8%". 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 in the RCTs [11-13], we may accept that early PPV in naïve-treated eyes was also highly efficacious in the vasogenic DDME type in these four 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 not detected by OCT preoperatively nor intraoperatively [17]. However, trans-differentiation of hyalocytes to myofibroblasts was detected at the vitreoretinal interface of those eyes. These contractile cells could result in 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. Similarly, in a review study on hyalocytes in vitreoretinal diseases, Jones et al. summarized that hyalocytes are important in early pathophysiology, stimulating cell migration and proliferation, as well as subsequent membrane contraction and vitreoretinal traction, yet undetected by OCT, except for the edema. Vitreoschisis into anterior and posterior lamellae ensues [18], as detected clinically [33,34]. They concluded that eliminating the role of vitreous and hyalocytes may entirely prevent proliferative vitreoretinal diseases [18]. The histological findings in vasogenic DDME may also be one possible explanation of the emergence of Ext-FT membranes seemingly early, already within 5 to 9 months following GLP in 17% (3/18) of those eyes [31]. The notion on an early vitreoretinal traction in the vasogenic DDME before is detectable by 3D-OCT, supported by the surgical outcomes [27-30], suggests that unless MAs dominate in a DME eye, all others DDME eyes are tractional in essence.

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 [19]. 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 extension in frequency of injections for DME over anti-VEGFs in a designated group of eyes is 6 mg faricimab administered intravitreally (n = 1,891 patients) [38]. It is a bispecific antibody targeting VEGF-A and angiopoietin-2. The authors attitude underscores the importance of achieving a dry macula, and the longer period the better. After 1- and 2-year follow-up of the faricimab innovative RCT using a T and 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 enabled extension of injections to every 8 weeks due to absence of intraretinal fluid. This means that ~60% of maculae remained edematous during most of the entire 2-year trial. Similarly, in a real world study using the standard DME criterion, Rush reports on faricimab treatment (n = 51 patients) that has followed failures using 2 mg aflibercept [40]. About 39% of patients reached a treatment interval of ≥8 weeks and had a fluid-free macula on OCT at 12 months. Choosing this T and Er approach means that a reduction in the number of faricimab injections to approximately half (compared with anti-VEGFs) in only 40% of eyes would continuously put the other 60% of eyes at risks associated with persistent edema throughout the whole trial period. However, since the DDME eyes were found tractional, including an early tractional process in the vasogenic DDME type, we could expect that none of the current medications, including faricimab, would dry DDME for many weeks. A dilemma.

Takamura., *et al.* provided the answer: They found that 3 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 the temporary impacts of faricimab 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), by detecting marked disappearance of MAs and diminished edema [10]. Since the 2-year T and Er faricimab RCT included both MA-related and diffuse DME [38,39], it seems most probable that the 8 weeks extension between injections in ~40% of the eyes relates to its drying effects on the leaking MAs [9]. It is noteworthy that 40% of the studied eyes were diagnoses with macular ischemia [38], which is typically associated with MA production (individual correlation between these two pathologies was not stated). 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].

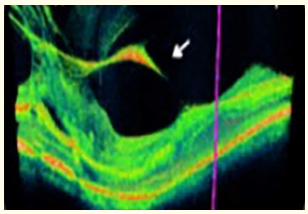

Figure 1: Diffuse diabetic macular edema due to extrafoveal vitreous traction (arrow). The central macula (marked by the vertical line) is free from traction. If only macular OCT B-scans were undertaken, the eye could be destined to repeated intravitreal injections of various medications and GLPs for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

Conclusions and Concerns

Failures in reaching the primary aim of durable complete macular drying by the short-lived T and Er intraocular anti-VEGFs or steroids, with or without GLP, resulted in repeat treatments for years. Despite these, T and Er anti-VEGF treatment is still the mainstay of DME therapy in many centers world-wide. Their biosimilars and new medications continuously appear in the market, and novel techniques for administration of these same medications are presented in the pipeline [41]. The summary of the 5-year extension protocol-T study by DRCR.net [22] underscores that there is no justification in initiating T and Er studies for DME, or continuing DME

treatment tightly by medications for years (as in RCTs) through T and Er approach in order to temporally improve or sustain VA. This is because the residual, persistent edema, though less in thickness, naturally results in progressive foveal tissue injury. This 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, for example, in the protocol-T extension 5-year study [21,22].

In contrast, treating the pathogenesis of a disease is the state-of-the-art practice in medicine. Treatment of DDME, i.e., the non-MA-related DME, using early PPVs in naïve-treated eyes achieved very high rate of long-lasting dry maculae. Except for Ext-FT, the notion on an emergence of vitreoretinal traction in the vasogenic DDME before it is detectable by OCT, supported by the surgical outcomes [26-29], suggests that all DDME eyes are tractional in essence. Based on further confirmatory studies, the cumulative data on DDME pathogeneses and the highly efficacious PPV seem to signify an imminent cure for DDME.

Regarding MA-related DME, pathogenetically-guided studies by using various therapeutics or their combinations for achieving durable dry macula, often present positive efficacies [6-8]. However, further studies are required to reach the aim of DME therapy in this DME type. Durable increase of tissue oxygenation (by PPV?) and blocking Ang-2/Tie-2 signaling might be other potential therapeutic targets, directed to prevent pericyte loss [9].

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