Macular Edema in Vascular Retinal Diseases

Subjects: Ophthalmology

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Macular edema (ME) is a disease characterized by the swelling of the macula due to the abnormal accumulation of fluid. It is associated with increased macular thickness and significantly reduced visual acuity, and it may develop in various ocular conditions.

Keywords: macular edema ; diabetic macular edema ; Retinal vein occlusion

1. Introduction

Macular edema (ME) is a disease characterized by the swelling of the macula due to the abnormal accumulation of fluid [1]. It is associated with increased macular thickness and significantly reduced visual acuity, and it may develop in various ocular conditions.

Postoperative cystoid macular edema (PCME) typically occurs after cataract surgery; however, it can occur after any ocular surgery [2]. The increased phacoemulsification energy and phacoemulsification time or postoperative pseudophakodonesis can significantly contribute to PCME development [3]. It is thought that topical prostaglandin analogs used for glaucoma treatment may also promote PCME [3][4].

Corticosteroid eyedrops are prescribed postoperatively by most cataract surgeons to prevent the formation of PCME [5]. Topical steroids, non-steroidal anti-inflammatory eye drops, and ocular steroid injections (sub-tenon or intravitreal) are the main treatment options for PCME [2].

ME is the most common cause of vision loss in patients with uveitis [6][7]. Although both regional and systemic steroids are considered effective treatments, other treatment options are available, including immunomodulatory agents and anti-vascular endothelial growth factor (VEGF) intravitreal injections [7][8].

Cystoid macular edema (CME) is observed in patients with various retinal pathologies. It is considered a complication in patients with retinitis pigmentosa (RP), whereas tractional CME is associated with the persistent attachment of the vitreous at the macular region [9][10].

However, in most eyes undergoing treatment of ME related to retinal vascular disease, it is diabetic macular edema (DME) and retinal vein occlusion (RVO) that are the driving forces.

ME affects approximately 7 million patients with diabetic retinopathy (DR) and 3 million patients with retinal vein occlusion (RVO) [11].

The role of inherited genetic polymorphisms in DME development and treatment response is still poorly understood; nevertheless, possible DME risk genes have been identified. Graham and colleagues did not find any significant genome-wide associations with DME risk; however, they identified the top-ranked single nucleotide polymorphism (SNP) for DME in rs1990145 on chromosome 2 [12]. A trend toward an association between DME and DR was detected in two SNPs: rs12267418, near *MALRD1* (p = 0.008), and rs16999051 in the diabetes gene *PCSK2* (p = 0.007) [12][13]. It is clear that there is a need for larger studies.

CME involves fluid accumulation in the outer plexiform layer of the retina due to abnormal perifoveal retinal capillary permeability, whereas DME is associated with the leakage of macular capillaries and is observed in patients suffering from diabetes [14]. ME is also associated with an increase in VEGF and interleukin 6, which induce vascular permeability and vasodilation [15].

Chronic ME leads to permanent visual impairment by altering the outer limiting membrane, affecting photoreceptor segments (outer nuclear layer thinning and outer segment atrophy), and disorganization of inner retinal layers [11].

2. Diabetic Macular Edema

The main DME treatment options are intravitreal injections of anti-VEGF agents and intravitreal corticosteroid injections. Formerly, macular LP was the gold standard for DME treatment; however, it is now utilized as an additional treatment. The two most common techniques of LP in patients with DME are focal photocoagulation targeting focal lesions (e.g., leaking microaneurysms or ischemic areas on fluorescein angiography (FA) for focal DME cases) and the grid laser technique, in which the laser is applied to diffuse leakages or nonperfusion areas; the latter is recommended for diffuse or more severe forms of DME [16][17]. According to the European Society of Retina Specialists (EURETINA) guidelines published in 2017, the focal and grid laser techniques should be utilized for non-center involving DME [18]. The laser can reportedly be applied in the vasogenic subform of DME, which is clinically characterized by the presence of focally grouped microaneurysms (MA) and leaking capillaries [19]. The primary reason grid laser is not recommended further is because of retinal scarring; however, when targeting capillary microaneurysms, a focal laser is beneficial as a second-line treatment [19][20]. In addition, it can be considered as a combined treatment option to reduce the number of anti-VEGF injections. Paques and colleagues performed a pilot study and reported significantly reduced macular thickness and improved visual acuity after elective photocoagulation of capillary microaneurysms in patients with chronic macular edema and severe hard exudates due to diabetic retinopathy or RVO [21].

Most studies found anti-VEGFs to be superior to laser treatment in DME patients. The REFINE study was conducted in Chinese patients with DME who received intravitreal ranibizumab injections or LP [22]. The results revealed a significantly greater improvement in mean best-corrected visual acuity (BCVA) at month 12 with ranibizumab than with LP [22]. Singh and colleagues reported that BCVA improvement was significantly greater with aflibercept than with laser techniques and was not influenced by any baseline factors [23][24]. A subthreshold micropulse laser (SML) is a relatively new tissue-sparing laser technique; it avoids protein coagulation and prevents retinal scars, allowing the preservation of retinal anatomy and function [25].

SML helps improve or stabilize visual function and decrease macular thickness in DME [26]. Vujosevic and colleagues performed a study that evaluated the effectiveness of SML treatment in patients with DME [26]. They reported that 31 patients (83.8%) required retreatment (mean number of SML treatments over 12 months: 2.19 ± 0.7); however, no eyes needed any additional treatments (anti-VEGF, steroids, and/or conventional laser) [26]. Al-Barki et al. compared the outcomes between short-pulse continuous wavelength and infrared micropulse lasers in DME treatment [27]. The authors concluded that the infrared micropulse system improved functional outcomes in patients with DME, whereas the short-pulse system resulted in a greater temporary reduction in edema [27]. Gawęcki and colleagues performed a systematized review and proposed that combining the SML treatment with anti-VEGFs may require fewer intravitreal injections than anti-VEGF monotherapy with equally favorable functional and morphological results in the ME treatment. However, SML alone was not superior to intravitreal treatment alone or combined treatment [28]. The authors noted that the studies under review varied in treatment protocols and inclusion criteria [28]. Altinel and colleagues compared the efficacy and safety of SML and intravitreal bevacizumab (IVB) injection combined therapy with IVB monotherapy in DME treatment [29]. They concluded that fewer IVB injections were needed when laser treatment was added; however, a significant increase in BCVA was not achieved [29]. Similarly, Furashova et al. reported that patients treated with ranibizumab combined with additional laser treatment experienced greater visual improvement and required fewer ranibizumab injections compared with patients treated only with ranibizumab [30].

Valera-Cornejo et al. evaluated the effect of SML treatment in center-involved DME in previously untreated (naïve) patients and patients who did not respond to prior treatment [31]. No significant changes in BCVA were observed between the groups after 3 months [31]. The change in central macular thickness (CMT) at 3 months was statistically but not clinically significant in the treatment-naïve group only, and no adverse events were reported [31]. Passos et al. reported that SML treatment used alone was not as effective as it could be when combined with other treatments [32]. DME cases associated with subretinal fluid had the best anatomical response, whereas intraretinal edema responded poorly to laser monotherapy [32]. The authors concluded that SML might be used in a combination treatment for ME [32]. Other authors also suggest considering laser therapy as an additional treatment in combination with intravitreal injections [16].

Anti-VEGFs utilize different molecules to achieve their effect: aptamers (pegaptanib); antibodies to VEGF (bevacizumab); antibody fragments to VEGF (ranibizumab); and fusion proteins, which combine a receptor for VEGF with the constant region of a human immunoglobulin (aflibercept and conbercept) [23]. Bevacizumab, ranibizumab, and aflibercept are the most common anti-VEGFs, and many studies have not observed significant differences in outcomes between them [23][33]. However, it has been suggested that the choice of anti-VEGF can be guided by the untreated BCVA. When it is lower, aflibercept has been suggested as the drug of choice [23][24]. The remaining anti-VEGFs, including bevacizumab, ranibizumab, and aflibercept, provide similar functional outcomes when the baseline BCVA is higher [23]. Bressler and

colleagues, however, reported that after six consecutive injections, more patients presented with persistent ME following bevacizumab treatment compared with ranibizumab and aflibercept [34]. On this basis, Haritoglou et al. suggested switching from bevacizumab to either aflibercept or ranibizumab if DME persists while using bevacizumab [35].

3. Macular Edema Secondary to Retinal Vein Occlusion

Retinal vein occlusion (RVO) includes branch RVO (BRVO), central RVO (CRVO), and hemi-RVO, which are categorized according to the anatomic location of the occlusion [36]. In all hemorrhages and ME occur, leading to significant visual impairment [37].

Although LP has long been considered a primary treatment option, similar to DME, it has been replaced by other treatment methods. It was reported that although macular grid laser treatment reduced vision loss and the risk of vitreous hemorrhage in eyes with ME due to BRVO, it was ineffective against ME due to CRVO [15][36]. Zhang and colleagues additionally reported that LP cannot be performed in cases of retinal swelling with hemorrhage because the laser energy is absorbed and reduced; however, laser therapy may be used as rescue therapy for ME secondary to RVO [36].

Hayreh et al. has reported that in patients with ME due to RVO who respond poorly to anti-VEGF therapy or are incapable or reluctant to attend clinics for frequent anti-VEGF injections, grid laser treatment can be used combined with anti-VEGF therapy [38].

Intravitreal anti-VEGF injections are now considered the first-line treatment for ME associated with RVO, and their efficacy and superiority over other treatment methods have been demonstrated in many studies. Qian et al.'s meta-analysis reported that anti-VEGFs were the most effective therapy for ME secondary to both CRVO and BRVO [39]. The survey study, which was performed among retina specialists in Japan, revealed that anti-VEGF therapy was chosen as the first-line treatment for ME secondary to BRVO, and most specialists (82.4%) selected initial injection followed by a pro re nata (PRN) regimen; however, the opinions about the initiation and switching therapy varied between specialists [40]. As additional treatment in refractory cases, laser therapy was reported as the most common choice (35.9%), with 25.6% selecting vitrectomy, and 15.4% chosing to add steroid injections [40].

Anti-VEGFs used to treat ME due to RVO are similar to those used to treat DME; ranibizumab and aflibercept are used on label, whereas bevacizumab and conbercept have been used off label. Hykin and colleagues performed a prospective study to evaluate the effectiveness of ranibizumab, aflibercept, and bevacizumab for the management of ME due to CRVO [41]. They reported that mean changes in vision after 100 weeks of follow-up and treatment were not inferior with aflibercept than with ranibizumab; however, the mean number of injections given in the aflibercept group was lower than that in the ranibizumab group [41]. The mean changes in vision using bevacizumab compared with those using ranibizumab were similar, suggesting that the effectiveness of bevacizumab was neither equal nor superior to ranibizumab [41]. Conbercept is one of the newest anti-VEGFs and provided good treatment results in Chinese patients with RVO in a randomized clinical trial [42]. Xia and colleagues reported that conbercept significantly reduced retinal structural remodeling, inflammation, and oxidative stress in mice as well as in patients with ME due to RVO [37]. However, some patients with severe ME due to RVO did not experience significant benefit from conbercept [37]. The authors hypothesized that this may have been because conbercept only inhibits downstream VEGF inflammatory mediators and does not affect the upstream inflammatory mediators of VEGFs, such as PGE1, PGE2, and PGF2a [37]. Costa et al. reported that intravitreal anti-VEGF injections are prioritized over other treatment methods, including macular grid photocoagulation [43]. Compared with steroid injections, anti-VEGFs are superior because they have fewer side effects; as with their use in DME, steroids are associated with a higher incidence of increased IOP and cataract formation [43]. A systematic review and meta-analysis were performed by Liu and colleagues to evaluate the efficacy of conbercept and ranibizumab with or without LP in patients with ME secondary to RVO [44]. Both intravitreal conbercept and ranibizumab therapy with or without LP were effective in improving vision function in patients with ME secondary to RVO. The two anti-VEGFs did not differ significantly in BCVA improvement or adverse effects, and they resulted in similar visual gains [44]. However, conbercept reduced CMT more than ranibizumab with fewer injections [44]. Another systematic review performed by Spooner and colleagues evaluated 17 studies involving 1070 eyes [15]. It demonstrated that the management and outcomes of patients with CRVO varied greatly; however, anti-VEGF therapy significantly improved the anatomical and functional outcomes [15]. Although most eyes obtained a significant visual acuity gain, those treated with aflibercept and bevacizumab had significantly better outcomes than ranibizumab-treated eyes [15]. The incidence rates of ocular complications were low, including neovascular glaucoma (3.6%), vitreous hemorrhage (<1%), glaucoma (1.2%), and neovascular glaucoma (<1%) [15].

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