

GUIDELINES FOR THE MANAGEMENT OF DIABETIC MACULAR EDEMA BY THE EUROPEAN SOCIETY OF RETINA SPECIALISTS (EURETINA)

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INTRODUCTION

The prevalence of diabetic macular edema (DME) is continuously rising worldwide and has become one of the major causes of vision loss in the working-age population. Clinical parameters and new diagnostic parameters from imaging with optical coherence tomography (OCT) as well as the overall advances of OCT technology have been identified to stage the disease. However, a large variety of therapeutic strategies are available to the ophthalmologist: laser photocoagulation, anti-vascular endothelial growth factor (VEGF), steroid and surgical therapy are applied with different procedures and their own complications. A novel era of DME therapy has started with these diverse approaches. These guidelines shall give an overview on the current available diagnostic and therapeutic procedures and recommend their application.

CLINICAL FEATURES OF DIABETIC RETINOPATHY

Diabetic retinopathy (DR) is the term applied to describe the microvascular abnormalities that are seen in the fundus of persons with diabetes on

clinical examination or on color fundus photography. The earliest and the least severe manifestation is the dot-like microaneurysms (MA) which are localized saccular outpouchings of the capillary wall and appear as tiny red dots with sharp margins. MA occur frequently in relation to areas of capillary nonperfusion, but the latter is an angiographic diagnosis. Retinal hemorrhages are another important manifestation of DR and are found throughout the fundus (Fig. 1). They may be flame-shaped, if located in the nerve fiber layer, or dot or blot-like, if located in the middle layers of the retina. Intraretinal microvascular abnormalities (IRMA) are tortuous and dilated intraretinal microvascular segments. Venous dilation and beading are typical DR-related changes, and the latter in particular represent focal increases in venous caliber, resembling a string of beads. Hard exudates are another manifestation of DR, arising as a consequence of chronic localized leakage from the retinal vessels (Fig. 1). Hard exudates are mainly composed of lipid and appear as yellowish white lesions usually with distinct margins and occur close to clusters of MAs. Soft exudates, otherwise termed cotton wool spots, arise when there is a block in the flow of axoplasm in

the retinal nerve fiber layer which occurs due to focal ischemia. They represent infarcted inner retina and appear as greyish-white round or oval areas with ill-defined feathery edges.

DIABETIC MACULAR EDEMA

DME represents an accumulation of fluid within the central portion of the retina, which arises as a consequence of failure of the blood-retinal barrier (BRB). Diffuse edema is caused by extensive capillary leakage, whereas localized edema is caused by focal leakage from grouped MAs. DME can occur in isolation without other signs of microangiopathy in the fundus; therefore, it merits being classified as a separate entity. It is often associated with hard exudates and causes blurring and distortion of central vision, which is reflected in a reduction in best-corrected visual acuity (BCVA). The Wisconsin Epidemiologic Study of Diabetic Retinopathy found that 20% of patients with type 1 diabetes and 25% of those with type 2 diabetes will develop DME after 10 years of follow-up [1].

PROLIFERATIVE DR

This entity is described in the context of the management of DME as diagnostic and therapeutic studies have recently shown that the pathways of DME and DR are tightly interconnected and that pharmacological therapy affects both manifestations in an interchangeable manner.

Proliferative DR (PDR) refers to the development of vascular and fibrous tufts that arise from the retinal blood vessels and ramify into a network that spreads either within the retina or at the interface between the retina and the vitreous. Retinal hypoxia is the main driver for neovascularization, and as these vessels carry little or no pericytes, they are friable and bleed easily. The neovascularization seen on the fundus has been described as new vessels elsewhere (NVE) when located away from the optic disc, and as new vessels on the disc (NVD) when either on the optic disc or within 1 disc diameter of its margin. Hemorrhage from these vessels can lie within the retina, at the vitreoretinal interface or in severe cases within the vitreous. When preretinal, the hemorrhage may be crescentic shaped, oval, or

linear. Hemorrhage further forward into the vitreous cavity is considered vitreous hemorrhage. The presence of blood particularly in the macular retina and within the vitreous leads to severe loss of vision. Blood is also inimical to the integrity of the retina. Subsequent development of fibrous bands resulting from organized hemorrhage can consecutively result in traction of the retina.

FEATURES IN OPTICAL COHERENCE TOMOGRAPHY

Rationale

Since its first introduction, OCT has become the most frequently used diagnostic tool in ophthalmology and has revolutionized clinical imaging for diagnosis and disease management in most retinal diseases including DME. OCT is a fast, noninvasive technology that produces *in vivo* images of the retina. The most recent third-generation OCT technology uses a swept-source (SS) light source that allows very fast imaging and provides three-dimensional raster images of high microstructural resolution, also referred to as optical histology [20]. The most commonly used second-generation OCT nowadays is SD-OCT allowing three-dimensional raster scans of up to a few hundred B-scans, also creating high-resolution images, but working slower than SS-OCT. It supersedes time-domain (TD)-OCT that allowed imaging of 6 radial cuts only.

All OCT generations are able to generate central retinal thickness (CRT) values, but TD-OCT is less accurate due to its more likely decentration from the fovea and less available B scans. Nevertheless, CRT has been used as a quantitative feature to evaluate disease activity, progression, and treatment response ever since OCT was available in ophthalmology. Although there is a correlation between best-corrected visual acuity (BCVA) letter score and CRT in DME under therapy with anti-VEGF agents, this correlation is weak during the first year of therapy ($r = 0.34\text{--}0.41$) and largely lost in the long term [21]. The new OCT generations of SD- and SS-OCT are able to visualize qualitative features in more detail than TD-OCT, among others subretinal fluid (SRF), intraretinal cystoid fluid (IRC), disruption or thickness changes of retinal layers (e.g., disorganization of the retinal inner layers [DRIL]), and the status of

the vitreo-macular interface (Fig. 1). These devices can also visualize the destructive response of the retina when applying laser [22]. However, TD-OCT had been used in most large clinical phase III trials evaluating the use of anti-VEGF agents in DME (RIDE/RISE [23], RESTORE [24-26], DRCR.net protocol I [27]); only few recent large trials have used SD-OCT (VIVID DME/VISTA DME [28], DRCR.net protocol T [29], RETAIN [30]). Advances in OCT like Doppler-OCT and OCT-A allow the visualization of vascular structures and can differentiate between perfusion and nonperfusion. Nevertheless, these advances are still lacking the ability of visualizing vascular leakage.



Fig. 1. A single scan with macular fluid and diffuse retinal edema. Arrows point to the following features: (a) vitreomacular traction (VMT); (b) intraretinal cystoid fluid (IRC); (c) subretinal fluid (SRF); (d) hyperreflective foci (HRF). Reproduced with permission from Heng et al. [167]

Evidence

The gold standard in diagnosing DME still remains FA. It can detect different hallmarks of DR like MAs, PDR, ischemic areas and especially DME due to vascular leakage. OCT can be used for screening, classification, monitoring, and treatment evaluation of DME. It has the ability to provide information on CRT as well as distinct morphological features of the edema (Fig. 2). Additionally, it can show persistent morphological changes after DME treatment. Morphological signs of de novo, persisting, or resolved DME are: SRF (nonreflective space between the neurosensory retina and the retinal pigment epithelium; Fig. 3), IRC (minimally reflective round or oval spaces within the neurosensory retina; disorganization of inner retinal layers (DRIL) [31], other in-

tegrity changes of inner and outer photoreceptor segments line, and external limiting membrane (ELM; Fig. 2) [32], MA, hard exudates/hyperreflective foci (Fig. 2) [33], epiretinal membranes, or changes in choroidal thickness [34]. Many of these features can be seen best (or exclusively) on OCT images and were therefore missed by the early DME guideline studies for laser therapy. The ETDRS was the gold standard for classification and laser therapy planning in DR including, e.g., focal laser for DME for many years [35]. But for anti-VEGF therapy management, evaluation and monitoring of individual treatment responses, OCT is the most used modality today, particularly as OCT captures fluid-pooling as a result of active leaking in DME disease. Therefore, new classification systems for DME were proposed in the past years. One of these is the SAVE protocol that proposes to characterize DME into categories of SRF, area of affected retina by IRC, vitreoretinal interface abnormalities (interface abnormalities).

In large clinical trials to date, CRT was the only OCT criterion used for evaluation. In the RIDE/RISE [23] studies, treatment was performed monthly with intravitreal anti-VEGF, but additional laser treatment was performed on an as needed (PRN) basis based on CRT in OCT. In the RESTORE [24] study, where intravitreal anti-VEGF monotherapy and laser were compared with a combination therapy of both for DME, retreatment was based on BCVA letter score and the investigator's decision which could include OCT changes and clinical examination. In the DRCR.net protocol I [27] intravitreal anti-VEGF injections were compared with laser treatment and with intravitreal corticosteroid injections. In this study, retreatment was also based on the investigator's discretion without predefined OCT retreatment criteria. In the VIVID DME/VISTA DME [28] studies with SD-OCT, a fixed treatment regimen was used for intravitreal anti-VEGF therapy, and laser retreatment was allowed as indicated by ETDRS guidelines. CRT was used as the secondary efficacy endpoint. In the DRCR.net protocol T [29], CRT from OCT was one parameter for retreatment decisions. In conclusion, all these trials show that BCVA played the most important role with regard to retreatment; therefore, CRT as an OCT parameter has played little role in the study design and analyses of most large clinical phase III trials on DME. However, ophthalmologists to date

agree that treatment regimens must be individualized because OCT biomarkers are key to identify the best PRN treatment scheme for each individual patient. A PRN regimen is the most frequently used treatment regimen for DME in anti-VEGF therapy in real life today, but the PRN criteria are not standardized. The individual patient's morphology has a close relationship with the treatment response and needs to serve as the basis for these criteria. Focal edema classified with the earlier described system, for example, may benefit most from anti-VEGF therapy with regard to BCVA letter score gain [36]. Some individual OCT biomarkers have already been identified from post hoc analyses of the multicenter studies and some smaller monocentric studies.

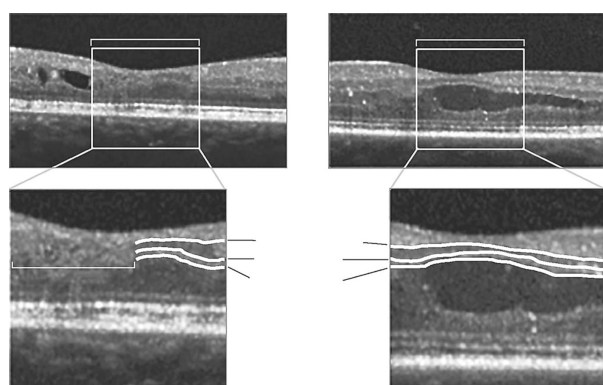


Fig. 2. Representative images of the presence or absence of disorganization of the retinal inner layers (DRIL). a) DRIL is present, and retinal layer boundaries can only be partially identified at the right-hand edge of the 1-mm box. b) DRIL is absent, and all retinal layer boundaries can be identified throughout the 1-mm box. The presence or absence of DRIL is independent of other pathology, such as intraretinal cystic changes. Insets are magnifications of the central 1-mm-wide area to show segmentation of the inner retinal layers, with white lines demarcating interfaces between ganglion cell/inner plexiform complex (GCL-IPL), inner nuclear layer (INL), outer plexiform layer (OPL), and outer nuclear layer (ONL). Reproduced from Sun et al. [31] with permission from American Medical Association

In the RESTORE study, patients have been treated after an initial loading phase of 3 consecutive monthly injections on a PRN basis. Here, it could be shown in a post hoc analysis that patients with SRF at baseline had higher BCVA gains at the end of the first study year than patients without SRF at baseline, although no difference in their baseline BCVA letter score was detected [21]. This protective role of SRF was reconfirmed by an OCT post hoc study analysis of the RIDE/RISE trials [37]. When looking at IRC, in RESTORE about 80% of patients had IRC at baseline. Pa-

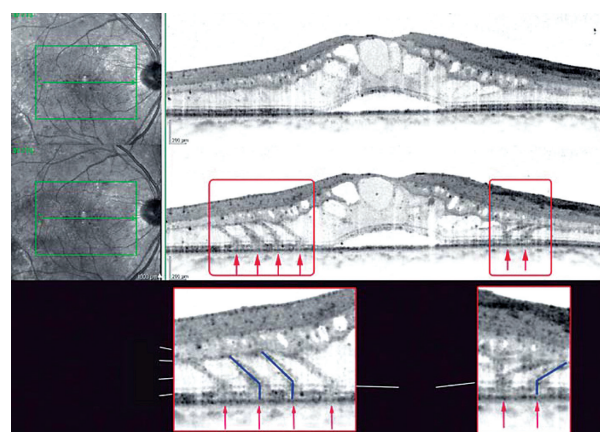


Fig. 3. Immediate morphologic changes after grid photocoagulation. Morphologic findings before (first line) and 1 day after (middle line) laser treatment are shown in infrared imaging (left) and OCT (right). The green line in the infrared image indicates the position of the scan performed exactly at the same position in both examinations. The red boxes indicate the areas (a, b) magnified in the lower line. Laser lesion site (red arrows) at the level of the pigment epithelium. The blue lines in the magnifications indicate the characteristic angulated alteration pattern in each single laser lesion. ELM, external limiting membrane; INL, inner nuclear layer; ONL, outer nuclear layer; OPL, outer plexiform layer; PRL, photoreceptor layer. Reprinted from Bolz et al. [22] with permission from Elsevier

tients with less IRC at baseline had a better baseline BCVA letter score and remained at a better score throughout the entire study duration [21]. This finding is supported by an analysis of another study of preserved tissue in 129 DME patients. Here, baseline vision correlated with the volume of preserved neurosensory tissue is less IRC between inner and outer retina [38]. Another finding from RESTORE indicated that throughout the entire study duration, patients with vitreomacular adhesion showed higher BCVA scores at baseline and maintained these better scores under any therapy, whereas patients with a posterior vitreous detachment started with lower BCVA letter scores and improved less than patients with vitreomacular adhesion [21].

In an academic study with 120 patients, the importance of DRIL was shown. DRIL that constituted more than 50% of the central millimeter on OCT was associated with a worse BCVA score in current and resolved edema; DRIL was able to predict a worse change in BCVA score until the end of the first year of treatment if it occurred in the first 4 months of treatment [39] (Fig. 2).

When monitoring anti-VEGF therapy responses, the thickness of the ganglion cell layer (GCL), retinal nerve fiber layer (RNFL), and choroidal layer may

decrease; a correlation with vision loss could only be shown for the GCL, whereas a decrease in choroidal thickness during therapy does not correlate with less vision gain [40–42]. On the other hand, a thick subfoveal choroid at baseline may predict good vision outcomes [43]. The peripapillary RNFL is thickened in all patients with DME before and after anti-VEGF therapy compared to non-DME patients with signs of DR, although it decreases after anti-VEGF [42]. The appearance of hyperreflective foci (Fig. 3) in OCT may precede formation of hard exudates that can be seen in fundus biomicroscopy. During anti-VEGF therapy, hard exudates increase in number and size [44, 45].

When looking at OCT changes after laser photocoagulation therapy, one day after laser application an oblique disruption of the outer retinal layers (retinal pigment epithelium, photoreceptor layer, and outer nuclear layer) can be observed [22] (Fig. 3). This disruption is repaired in about 50% of the cases within 3 months after photocoagulation therapy, but clearly highlights the destructive nature of photocoagulation [46].

These morphological analyses show that excellent results can be achieved for a PRN regimen in DME, with a decreasing number of injections during the disease course. In the RESTORE Extension Study, vision improvement could be maintained in year 2 (3) with less than 4 (3) mean injections compared to 7–8 injections in the first year of the study even with the use of CRT changes as the only diagnostic criterion. Other than in age-related macular degeneration, where a continuous injection therapy is necessary, the disease activity seems to plateau in DME, which is explained by a diseasemodifying mechanism of VEGF inhibition. This is also confirmed by the DRCR.net protocol I, where BCVA score improvement could be maintained for 5 years with fewer than 5 anti-VEGF injections in years 3–5 (about one-quarter of patients having no more injections in year 2, one-third in year 3, and half no more injections in years 4 and 5 of the study) [47, 48]. Patients had only been treated with anti-VEGF for 6 months and discontinued if no more change could be seen (improvement or worsening) – even if retinal fluid persisted [27]. The examples of multimodal imaging in patients with different therapy responses are presented in Figures 9 and

10. Compared to age-related macular degeneration where a “no tolerance” retreatment is usually used (CATT, HARBOR) and recommended [49], this means that a restrained treatment frequency based on BCVA and OCT monitoring can be chosen in DME. Further analyses must prove if a certain morphology pattern can be identified for patients who lose vision after discontinuing treatment in persisting DME after 6 months. Here, especially high resolution SD- and SS-OCT with its tight B-scan spacing will be of great value. The ability of imaging the vascular network with Doppler-OCT and OCT-A (Fig. 4) will further increase the insight in DME as a vascular disease and may deliver new hypotheses on imaging biomarkers. Individualized retreatment criteria based on OCT biomarkers may be established in the future.

Recommendation

In order to diagnose DME, OCT should be accompanied by baseline FA and continued fundus biomicroscopy. When diagnosed and treated, a recurrence of edema can usually be monitored solely by OCT in combination with visual acuity measurements. Robust OCT biomarkers need to be reassured in large-scale clinical studies, but evidence indicates that good baseline predictors for a good treatment response with regard to high vision gains and/or good final visual acuity are SRF and/or small IRC and/or vitreomacular adhesion at baseline [21, 50]. The disorganization or disruption of the inner retinal layers [31], disruption of the inner and outer photoreceptor segments and/or ELM [32], and a thin subfoveal choroid at baseline [43] may predict bad visual acuity after therapy.

Findings in OCT include qualitative and quantitative measures. CRT is an established quantitative measurement. As a CRT increase consists of SRF and/or IRC and/or diffuse thickening, distinguishing between the different qualities may be useful. PRN treatment based solely on CRT changes is a practical approach for the management of DME; other promising more robust individual OCT features have to be confirmed before they can feed into retreatment decisions. The next development will likely allow the quantification of these qualitative biomarkers. Segmentation of retinal layers, IRC and SRF and volumetric com-

putation for these features may have an impact on individualized PRN regimens [51, 52].

Once criteria are validated, most recent OCT technology with high resolution and dense scanning will help three-dimensional image analysis to be automated and to detect disease activity as smallest morphological changes early on. Therefore, the optimal recommendation is to monitor disease activity on a monthly basis with OCT even if no treatment is needed or intended in order to identify morphological changes as early as possible. These recommendations are based on evidence levels I and II.

THERAPEUTIC STRATEGIES

Anti-VEGF Agents

Aflibercept

Rationale. Aflibercept (Eylea) is a recombinant decoy receptor type of inhibitor of VEGF and placental growth factor that has shown efficacy and safety in adequate clinical trials in DMA [28, 29].

Evidence. The evidence for the value of DME treatment by intravitreal injections of aflibercept is dominated by the twin pair of randomized con-

trolled clinical studies VIVID DME (Europe) and VISTA DME (US) [28, 79], with a total of 872 study participants, which compared aflibercept with laser therapy, and the DRCR.net Protocol T study [29], with a total of 660 participants, which compared intravitreal aflibercept with ranibizumab and bevacizumab.

The VIVID-VISTA DME studies had their primary endpoint at 1 year and were planned to follow patients up to 3 years. Laser or aflibercept were administered in eyes with DME involving the foveal center with rescue therapy, consisting of laser treatment, permitted after 24 weeks. Aflibercept 2 mg was given every 4 weeks or every 8 weeks after 5 initial monthly loading doses. The studies enrolled patients with a BCVA letter score of 24–73 ETDRS letters and an OCT central subfield thickness ≥ 300 μm .

The mean BCVA gain at 1 year for the combined studies was 11.6 BCVA letters for 4-weekly injections, and it remained stable at 10.7 letters after 100 weeks. For 8-weekly injections, BCVA had similarly increased by 10.7 letters after 52 weeks and was also stable after 100 weeks with a gain of 10.3 letters. These clinically and statis-

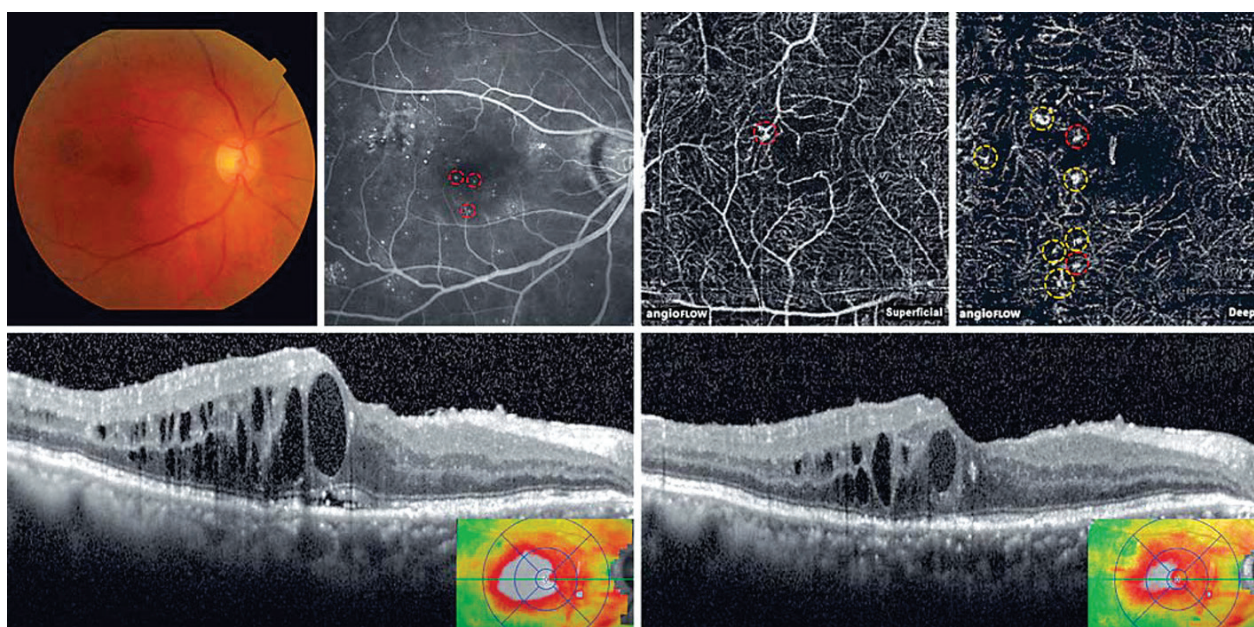


Fig. 4. A diabetic macular edema (DME) eye showing a good response to anti-vascular endothelial growth factor treatment. Baseline fundus photography (a) and fluorescein angiography (FA) (b) of the eye. Optical coherence tomography angiography showing multiple microaneurysms in the deep capillary plexus (d), but none in the superficial capillary plexus (c). Yellow circles indicate microaneurysms that were not depicted on FA. Red circles indicate a microaneurysm that is also seen on the FA images. Compared with the baseline spectral-domain optical coherence tomography (SD OCT) (e), the follow-up SD OCT (f) showed improved macular edema after 3 bevacizumab injections. Reprinted from Lee et al. [170]

tically insignificant differences suggest that the 8-weekly interval regimen should be preferred, if a fixed regimen is chosen.

The outcome in eyes that had previously received anti-VEGF therapy was comparable to the outcome in treatment-naïve eyes. After 100 weeks, 31.2 and 24.1% of eyes initially treated with laser in VIVID and VISTA, respectively, received aflibercept therapy and BCVA gradually increased, but a mean deficit of 5–6 letters persisted after 100 weeks highlighting the benefit of timely treatment initiation.

A conspicuous finding in VIVID-VISTA DME was that the switch to bimonthly injections after 24 weeks was followed by an oscillating pattern of CRT variation with an amplitude of 25–50 μ m and period of 8 weeks. There was no evidence that this fluctuation was associated with a poorer BCVA outcome overall compared to eyes receiving injections every 4 weeks throughout the first 100 weeks of the study. Based on the results of the VIVID-VISTA DME studies, aflibercept was approved in Europe (2014) by the EMA and in the US (in 2015) by the FDA for treatment of DME. The approved dose is 2 mg per injection. The medication was approved for 5 monthly injections followed by bimonthly injections in the US, and the European label adds the possibility of extending the treatment interval after the first year of treatment.

The DRCR.net Protocol T study [29] (refer to the section “Bevacizumab” for full study results) compared aflibercept, ranibizumab, and bevacizumab. The loading phase and subsequent flexible retreatment phase regimen was the same for all 3 study drugs. The study enrolled eyes with BCVA letter scores of 24–78 (approx. Snellen 20/320 to 20/32) and DME involving the foveal center with CRT greater than roughly 325 μ m on modern SD-OCT (>250 μ m on Zeiss Stratus with gender-specific cutoffs) [80]. The interim results after 1 year showed a mean gain that was +2.1 letters higher for aflibercept 2 mg than for ranibizumab 0.3 mg (the approved dose in the US, 0.5 mg is the approved dose in Europe) ($p = 0.03$). Patients were monitored as often as every 4 weeks. A subgroup analysis showed that the superior effect of aflibercept was driven by the study participants with poorer baseline BCVA (< 69 letters). Of a maximum possible number of injections of

13 in the first year, the aflibercept arm received a median of 9 injections; the bevacizumab and ranibizumab arms received a median of 10 injections. Intravitreal bevacizumab was inferior to both aflibercept and ranibizumab in most comparisons. Serious adverse event rates were comparable between study arms.

The 2-year results [65] of the Protocol T study slightly changed this scenario. The difference in BCVA gain between aflibercept and ranibizumab for eyes with poorer baseline BCVA that was noted at 1 year decreased at 2 years. Nevertheless, the first-year behavior and the slightly better mean BCVA gain confirmed the superiority of aflibercept over ranibizumab in patients with poorer baseline BCVA (Fig. 14) when considering the area under the curve. It remains unclear if the 0.5 mg dose that is approved in Europe would have led to different results in the first year of Protocol T in favor of ranibizumab 0.5 mg. Longer follow-up is needed to determine the rate at which aflibercept treatment of DME can be tapered after 1 year and whether long-term aflibercept treatment is associated with a diminishing need for reinjection, as in the case of ranibizumab in the 5-year follow-up of the DRCR.

At least the 2-year results of Protocol T suggest that the need for anti-VEGF injection generally decreases in DME from year to year. In Protocol T, for all anti-VEGF agents about half of the injections needed in the first year were needed in the second year of the study.

Recommendation. Aflibercept has shown clear superiority to laser therapy in visual and anatomical outcomes. It can be used equivalent for improving vision in eyes with a baseline BCVA letter score of 69 or more. Aflibercept is the drug of choice in DME eyes with baseline BCVA below 69 letters, as it shows superiority to bevacizumab over 2 years and over ranibizumab in the first year of treatment.

The evidence base for the use of aflibercept in DME leaves it an open choice as to whether a course of loading injections at 4-weekly intervals should be followed by a regimen of fixed bimonthly injections or a PRN regimen with monthly monitoring only. The gain of 13.3 letters at 1 year in Protocol T with 2.0 mg aflibercept PRN and the gain of 10.7 letters with 2 mg aflibercept bimonthly after a loading phase of 5

monthly injections in VIVID-VISTA DME were obtained in different trials and a direct comparison of the 2 regimens has not been made. Intravitreal aflibercept offers most patients with visual loss secondary to DME that involves the foveal center a chance that their visual acuity will significantly improve after treatment and fewer injections might be needed from the second year onwards.

Steroids

Rationale

Recent evidence highlights to the role of inflammation in the development of DME. The pathological processes include leukostasis, which is the accumulation of leukocytes on the surface of retinal capillaries and is thought to be a major player and early event in the dysfunction of the BRB [81]. Such leukostasis leads to the upregulation of intracellular adhesion molecule (ICAM)-1, which mediates attraction of monocytes and neutrophils to the vascular endothelium. ICAM-1 has been found to further enhance retinal leukostasis, vascular permeability, and breakdown of the BRB in diabetes [82].

After binding to the vascular endothelium, leukocytes produce reactive oxygen species and inflammatory cytokines, which leads to increased vascular permeability [83]. Animal experiments showed that elevated glucose levels in the blood serum may lead to the expression of interleukin-6 (IL-6), tumor necrosis factor, lymphotoxin, and cyclooxygenase-2 [84]. IL-6 and pigment epithelium-derived factor expression have been found to be significantly increased in the vitreous of diabetic eyes [85].

Corticosteroids produce an anti-inflammatory effect through various mechanisms, including the decrease in the synthesis of inflammatory mediators, as well as the decrease in VEGF synthesis [86]. Intravitreal treatment with glucocorticoids has been found to significantly decrease the inflammatory processes with improved BRB function through inhibition of ICAM-1 expression in rat retinas [87]. A study that evaluated the changes in aqueous levels of inflammatory (IL-6, IL-8, interferon-induced protein-10, monocyte-chemoattractant protein-1, platelet-derived growth factor [PDGF]-AA) and angiogenic (VEGF) cytokines after intravitreal injection of corticosteroid triamcino-

lone in comparison to the anti-VEGF agent bevacizumab in patients with DME, found that IL-6, inducible-protein 10, monocyte-chemoattractant protein-1, PDGF-AA and VEGF were significantly decreased in triamcinolone-treated eyes, but only VEGF levels were decreased in the eyes treated with bevacizumab [88]. Therefore, their use in the treatment of DME may be more comprehensive than anti-VEGF treatment, which targets only a part of the inflammatory cascade [89].

Evidence

Commercially available corticosteroid compounds for intravitreal use include triamcinolone acetonide, dexamethasone posterior segment delivery system (Ozurdex), and fluocinolone (Iluvien).

Triamcinolone Acetonide. The DRCR.net protocol B was an important milestone in evaluating triamcinolone's role in DME management. It was a multicenter, randomized clinical trial with a total of 840 study eyes of 693 subjects with DME involving the fovea and BCVA of 20/40 to 20/320. Patients were randomized to focal/grid laser therapy, 1 mg intravitreal triamcinolone, or 4 g intravitreal triamcinolone. Retreatment was given at 4-month intervals. While at 4 months, the mean BCVA was better in the 4 mg group than in the laser or 1 mg groups, by the end of the first year there were no significant differences among the groups with regard to mean BCVA. At the 16-month visit and extending through 2 years, mean BCVA was better in the laser group than in the 2 triamcinolone groups. The majority of patients in the triamcinolone groups had developed cataract by this time, but the differences could not be attributed solely to cataract formation. More eyes in the 4 mg group (40%) than in the 1 mg group (20%) or laser group (10%) suffered from an ocular hypertension-related adverse event, including either an elevation of intraocular pressure (IOP) of ≥ 10 mm Hg from baseline, an IOP of ≥ 30 mm Hg, an initiation of IOP-lowering medications or the diagnosis of glaucoma. Glaucoma surgery was performed in 4 eyes in the 4 mg group. Among phakic eyes at baseline, cataract surgery was performed by the end of the second year in 23% of eyes in the 4/1 mg groups vs. 13% only in the laser group [90].

Another important milestone for triamcinolone acetonide was the DRCR.net protocol I study. As mentioned earlier, this was a 5-year, independent, multicenter, randomized, controlled clinical trial. A total of 854 eyes of 691 participants with BCVA of 20/32 to 20/320 and DME involving the fovea were randomized to sham injection + prompt laser, 0.5 mg ranibizumab + prompt laser, 0.5 mg ranibizumab + deferred (≥ 24 weeks) laser, or 4 mg triamcinolone acetonide + prompt laser. At 1 year, treatment with triamcinolone and laser resulted in a gain of 4 letters from baseline compared with a 3-letter gain in the laser group, and a 9-letter gain in both the ranibizumab and laser groups. In a subgroup of pseudophakic patients treated with triamcinolone and laser, BCVA gain was comparable to that of pseudophakic eyes treated with ranibizumab and superior to that of pseudophakic eyes treated with laser only. More eyes in the triamcinolone group (50%) than in the ranibizumab groups (9%) or the laser group (11%) had an IOP elevation ≥ 10 mm Hg, IOP > 30 mm Hg or initiation of IOP-lowering medications during 2 years of follow-up. Glaucoma surgery was performed in 4 eyes (one eye in the laser group, one eye in the ranibizumab + prompt laser group, and two eyes in the triamcinolone group). More eyes in the triamcinolone group (59%) underwent cataract surgery over two years of follow-up than in the laser group (14%) or the ranibizumab groups (14%) [27].

Iluvien has been approved by the FDA in September 2014 for the treatment of DME in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant elevation of IOP. It was approved by the EMA in April 2014 for the treatment of vision impairment associated with chronic DME considered insufficiently responsive to other available therapies. The approved dose for the fluocinolone acetonide is 1.19 mg. Pharmacokinetic studies showed that it provides sustained delivery in the eye for at least one year [98]. Therefore, repeated treatment may be given after a year according to evidence of central fluid and visual acuity parameters. The official product label in Europe recommends additional treatments after one year and does not recommend administration to both eyes concurrently.

RECOMMENDATION

Based on the data that exist thus far, corticosteroids are important in our armamentarium of drugs for treating DME patients, but largely on a second choice level. In nonresponders who have already been treated with anti-VEGF (after 3–6 injections, depending on the specific response of each patient), it is reasonable to switch to a steroid.

As first-line therapy, the use of steroids may be considered in patients who have a history of a major cardiovascular event as these patients were excluded from all major anti-VEGF trials. A meta-analysis assessing the risk in anti-VEGF-treated DME patients has shown that high-risk patients who received monthly anti-VEGF treatment over the course of two years possibly have an increased risk for death and potentially for cerebrovascular accidents [99]. The authors conclude that the cumulative exposure to anti-VEGF might be an independent risk factor. Especially in aforementioned patients, steroids might be the better option. Another group of patients in whom corticosteroids may be considered as first-line therapy are patients who are not willing to come for monthly injections (and/or monitoring) in the first 6 months of therapy. However, these patients' IOP still needs to be monitored. Dexamethasone shall be used first; fluocinolone may be appropriate for nonsteroid responders with chronic macular edema that is not responsive to other treatments. Since triamcinolone is not approved and causes more increase in IOP and cataract, it should be used only in patients who cannot get the approved agents for this indication.

Pseudophakic patients are preferred for the use of steroids, otherwise patients have to be informed about the high risk for cataract surgery. The IOP has to be monitored frequently in all cases. Retreatment can be considered after around 6 months (dexamethasone)/year (fluocinolone acetonide) if there is still evidence of residual edema and impaired vision.

RECOMMENDATION

Clearly, diabetes as a severe and chronic systemic disease must be managed systemically by expert physicians, which is an endocrinologist or an

internal medicine specialist. Ophthalmologists who may be the first ones to identify type 2 diabetes by ophthalmoscopy have an important responsibility to instruct the patient about the need to have the diabetic control consolidated. Asking for the HbA1c levels gives an orientation about the systemic condition and may lead to rereferral to the diabetologist. Another systemic feature worsening DME as well as DRP is systemic hypertension, which also requires a systemic approach. Interestingly, HbA1c levels do not correspond tightly to anti-VEGF treatment effects in the eye, and neither the absolute benefit

nor the prognosis is associated with HbA1c levels. Timing of ocular therapy on the other hand is very important, suggesting early ocular intervention and systemic workup should not substantially delay retinal therapy. The tightness of glycemic management and ups and downs in this regimen appear to influence the progression of DRP; therefore, a solid communication between the diabetologist and the retinologist is crucial.

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