Management of Diabetic Macular Oedema – Challenges and Solutions Along the Patient Journey

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Expert review by: Albert J Augustin, Sue Lightman, Anat Loewenstein and José Cunha-Vaz

Abstract

A symposium hosted by the European Society of Ophthalmology discussed challenges in the management of diabetic macular oedema (DMO). Clinical evidence suggests that the longer the duration of DMO, the worse the response to anti-vascular endothelial growth factor (anti-VEGF) agents and better the response to corticosteroids. This is explained by the fact that inflammation is involved in the perpetuation of retinal changes in diabetes. At early disease stages, VEGF is primarily responsible for retinal changes; however, chronic microglia activation resulting from retinal damage leads to cytokine production by retinal cells and subsequent inflammatory cascades. Steroids are most effective at this stage. Clinical trial data have demonstrated the efficacy of the Iluvien® fluocinolone acetonide (FA) intravitreal implant, which retains its efficacy in disease of long duration. However, it is important to remember two things: that diabetes is a multifactorial disease with potential complications and to monitor for safety effects. In terms of the latter, anti-VEGF agents are associated with potential systemic effects, whereas steroids raise intraocular pressure and are associated with increased incidence of cataract.

Keywords

Anti-VEGF, diabetic macular oedema, steroids

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Dr Anat Loewenstein opened the symposium by outlining the aims of the symposium: to review current definitions for diabetic macular oedema (DMO) and discuss their relevance and interpretation for aiding DMO diagnosis and management; to evaluate current concepts in the pathogenesis of DMO, including the importance of inflammation, and how this may impact treatment; and to identify challenges in optimising outcomes in resistant DMO, and factors influencing treatment choice and to discuss the long-term management of DMO.

Current Definitions for Diabetic Macular Oedema – Do They Meet the Clinical Need?

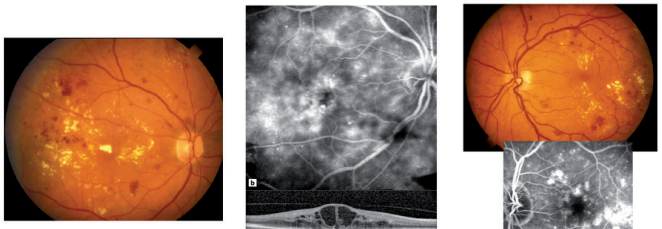
Albert J Augustin, Professor and Chairman of the Department of Ophthalmology, Klinikum Karlsruhe, Germany

Dr Albert Augustin began by outlining the seriousness of DMO – it is the most common cause of vision loss in patients with diabetes[1] and its incidence is likely to rise as a result of the increasing prevalence of diabetes, which is projected to increase by 22 % between 2011 and 2030.[2]

Although DMO can occur at any stage of diabetic retinopathy,[3] the cumulative risk increases with diabetes duration: among individuals with early onset diabetes, the incidence of DMO is 9.2–23.8 % in those of disease duration ≤10 years, but in those with longer disease duration (10–20 years), the incidence rises to 20.7–34.4 %.[4] The condition is progressive and may cause permanent central vision impairment.[5]

Understanding the origins and better definitions of DMO are necessary for improved patient management. Parameters required for an accurate

Figure 1: Anatomic Appearance of Diabetic Macular Oedema



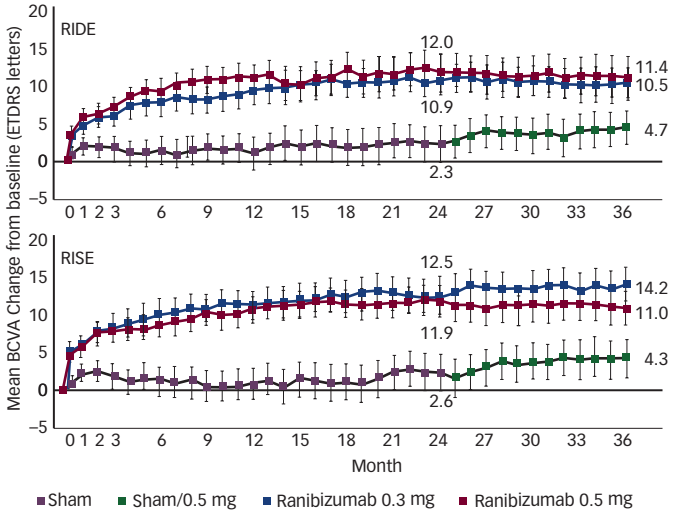
Colour fundus photograph of extensive yellow circinate exudates in the macula; intraretinal haemorrhages are also visible

Fluorescein angiography and OCT showing a diffuse DMO, which is difficult to visualise on the colour photograph

Colour fundus photography and fluorescein angiography

DMO = diabetic macular oedema; OCT = optical coherence tomography.

Figure 2: Ranibizumab in Diabetic Macular Oedema – The RISE and RIDE Studies



BCVA = best corrected visual acuity; ETDRS - Early Treatment Diabetic Retinopathy Study. Vertical bars are 95 % confidence intervals; missing data are imputed by last observation carried forwards. Visual acuity gain in previously sham-treated patients is less pronounced, indicating that chronic Diabetic Macular Oedema does not respond as well to ranibizumab than 'acute'.

definition of DMO involve the collation of information from multiple sources including those associated with diabetes, e.g. duration of diabetes and other systemic factors. Treatment history is important: the number and type of medications, treatment response and compliance. A DMO definition should also include clinical features and baseline characteristics, e.g. visual acuity (VA), macular thickness and leakage. It is also important to consider the patient's lifestyle and treatment expectations, as therapeutic goals may differ in terms of what is achievable and desired.

The clinical definition of DMO is retinal thickening and oedema resulting in capillary leakage involving the macula, occurring at any stage of diabetic retinopathy. Anatomical features of DMO include hard exudates (yellow deposits of lipid and protein and represent a residuum of more copious leakage that has been principally reabsorbed) leaving behind the least soluble lipid components. They may form a circinate pattern that appears on fundus photography. These exudates have an arc-like appearance due to the demarcation of areas of damaged retinal vessels from adjacent more normal areas that are capable of reabsorbing the oedema. Diffuse DMO is better visualised on fluorescein angiography, while fundus photography and fluorescein angiography may be used for focal DMO (see *Figure 1*).

In advanced DMO, widespread or diffuse leakage is present; the macula becomes thickened and even cystic without the presence of visible yellow exudates, since no normal vessels remain to resorb the leaked fluid. Patients with diffuse or cystoid oedema typically have the most profound visual decrease.[6] Clinically significant macular oedema (CSMO) is defined as retinal thickening within 500 mm of the fovea or hard exudates within 500 mm of the fovea if associated with adjacent retinal thickening or one or more areas of retinal thickening at least 1,500 mm in diameter that is within one disc diameter (1,500 mm) of the fovea.[7]

Dr Augustin next considered the definitions of chronicity and therapeutic resistance. Chronic disease results from long-lasting degenerative changes of physical or mental conditions or a disorder that results in permanent physical or mental damage or disability. If a disease is not curable (elimination of disease cause is not possible or the disease is not healing), chronicity occurs. About 20 % of the people in the developed world are chronically ill, and it is a problem of modern medicine. In the 19th century, about 80 % of the people died from infectious diseases whereas in 1980, only 1 % died from infectious diseases.

Therapeutic resistance is defined as no or inadequate therapeutic effect despite multiple medical treatments, which regularly lead to a significant improvement in the course of a disease if used alone or in combination. Before therapeutic resistance is diagnosed, several parameters must be confirmed: a correct definition of the therapeutic targets, a correct diagnosis and exclusion of damage. When the therapeutic target is not achieved, the diagnosis should be revised and occult disease should be pursued. Therapeutic compliance must also be assured. Adequate drug levels should also be confirmed.

There are different types of therapeutic resistance. The effect of a therapy may be temporary and medical re-treatment may be needed. This is typically seen in long-term treatment of a chronic disease. The effect may also decrease over time. The dose and frequency of application should be raised to achieve an adequate therapeutic effect, remembering that this will increase the incidence of adverse events (AEs). A decrease of effect over time is unfavourable, while an increase in effect is a prognostically positive sign. A therapy may have little or no impact on the symptoms and course of the disease. Therapeutic resistance is determined by multiple factors, related to the patient, disease, time of therapeutic intervention or patient comorbidities and other medication use.

Clinical trials to date have used several parameters to define DMO in study populations, including duration of diabetes, baseline VA and macular thickness, and prior therapy. By examining the baseline characteristics of clinical trial data,[8–10] it is difficult to draw useful conclusions. Prior therapy is also too heterogeneous, and disease duration is too inconsistently reported to be of any use.

There is therefore a need for another parameter to more accurately define DMO. Clinical trial data support the use of duration of diabetes or DMO, and control of diabetes. Glycaemic exposure (measured in terms of glycated haemoglobin [HbA_{1c}]) has been found to predict retinopathy progression.[11] In addition, strict glycaemic control reduces the risk of retinopathy.[12] Poorer VA outcomes are seen with longer DMO duration, which become significant after 2.5 to 3 years.[13]

Chronicity is a useful parameter: the RISE and RIDE clinical trials data show that chronic disease does not respond well to anti-vascular endothelial growth factor (anti-VEGF) treatment, presumably a result of factors, e.g. inflammation (see *Figure 2*).[9] The VA improvement of patients given sham injections for 2 years, when switched to ranibizumab, failed to catch up with patients treated with ranibizumab from baseline onwards.

He finished by stating that chronicity is clearly defined in medicine but not in DMO. Chronicity, however, has a significant impact on the treatment of DMO: the longer the duration of DMO, the worse the response to anti-VEGF agents. Evidence suggests that the longer the DMO duration, the better patients respond to corticosteroids. It therefore seems likely that the longer the DMO duration, the more inflammation is likely to be present. ■

Evaluating Disease Pathogenesis and Pathology Along the Patient Journey – How May It Guide Our Clinical Decisions?

Sue Lightman, Professor of Clinical Ophthalmology, UCL/Institute of Ophthalmology and Moorfields Eye Hospital, London

Dr Sue Lightman introduced the discussion of disease pathogenesis by stating that the changes in diabetic retinopathy occur at an early disease stage. The characteristic early features of DMO are basement membrane thickening, pericyte dropout and capillary dropout.[14] A change in colour vision is also an early sign.[15] In the eye, the high pericyte to capillary endothelial cell ratio is integral to keeping the blood–retinal barrier (BRB) intact. As pericytes degenerate and drop out, the BRB becomes weakened, causing focal leakage, which may be observed in patients before symptoms of visual loss occur.[16] However, diffuse and cystic DMO is more common at presentation in patients with non-insulin dependent diabetes, who often have good VA and a differential may be seen between oedema appearance on optical coherence tomography (OCT) and the VA, which may still be good.[17,18] This presents the problem of when to initiate treatment: should we treat the DMO based on OCT findings or on VA?

The changes in the retina associated with DMO involve more factors than those relating to hyperglycaemia. If glycaemia is normalised, a degree of retinopathy persists.[19] Inside the retina, fluid and proteins damage the capillary endothelium, causing capillary closure and leukostasis, which causes further wall damage. This causes chronic subclinical inflammation and ischaemia, the resulting hypoxia leading to increased expression of VEGF.[20] Aqueous and vitreous samples taken from DMO patients show increased levels of cytokines and VEGF that significantly correlate with the severity of diabetic retinopathy.[21] VEGF is produced by a variety of cells in the retina and targets the vascular endothelial cell, inducing a cascade of inflammatory cytokines that have secondary effects and result in local inflammation. Anti-VEGF therapy is effective over 2 years in many patients.[1] However, its lack of consistent long-term effectiveness leads to the question: is the DMO that results from increased VEGF potentially reversible at an early stage, but not when there is chronic disease?

New evidence indicates that retinal inflammation is important in the pathogenesis of diabetic retinopathy. Inflammatory cytokines are upregulated in both the serum and vitreous and aqueous samples of subjects with diabetic retinopathy, and these can have multiple interactions that affect the pathogenesis of the disease. The major inflammatory events involved in BRB alteration appear to be: increased expression of endothelial adhesion molecules such as intercellular adhesion molecule (ICAM-1), vascular cell adhesion molecule (VCAM-1), platelet endothelial cell adhesion molecule (PECAM-1) and P-selectin; adhesion of leukocytes to the endothelium; release of inflammatory chemokines, cytokines and vascular permeability factors; alteration of adherent and tight junctional proteins between the endothelial cells; and infiltration of leukocytes into the neuroretina.[22] Vitreous levels of VEGF but also ICAM-1, interleukin 6 (IL-6), monocyte chemotactic protein (MCP-1) and pigment epithelium-derived factor are strongly correlated to retinal thickness.[23]

Table 1: Diabetic Macular Oedema – Contributing Anatomical/Physiological Changes and Biochemical Features

Anatomical and Physiological Changes	Biochemical Features
Thickened basement membrane	NOS
Tight junctions	Occludin
Antioxidant capacity of RPE	Cytokines
Taurine transport of RPE	ICAM-1
Leukostasis	VEGF
Chronic inflammation	Stromal-derived factor-1
Capillary non-perfusion	Endothelin 1
Pericyte loss	PEDF
Hypoxia	PKC
	HIF-1a
	AGE and RAGE
	DAG
	Aldose reductase
Affected by corticosteroids.	
Affected by anti-VEGF agents.	

AGE = advanced glycation end products; DAG = diacylglycerol; HIF = hypoxia-inducible factor; ICAM = intercellular adhesion molecule; NOS = nitric oxide synthase; PEDF = pigment epithelium-derived factor; PKC = protein kinase C; RAGE = receptor for AGE; RPE = retinal pigment epithelium; VEGF = vascular endothelial growth factor.

Given the evidence of markers of inflammation in diabetic retinopathy, it is surprising that inflammation does not resolve in DMO. The abnormal environment of diabetes may be creating non-resolving inflammation. Diabetes induces inflammatory proteins that persist at elevated levels despite normoglycaemia. It is unlikely that systemic inflammation causes the retinal inflammation in diabetes; it is most likely driven by retinal glial cells. Microglia sense abnormal stimuli to neural tissue and release pro-inflammatory and neurotoxic substances when activated. Retinal glial cells are likely to be involved in local inflammatory mechanisms and involved in production of cytokines such as tumour necrosis factor alpha (TNF-α).[24] Once the inflammatory cascade is activated, an enormous number of anatomical and biochemical changes occur in the retina.[18,23,25–32] It is therefore unsurprising that anti-VEGF therapies are ineffective at this stage. They are extremely useful at early stages when simple mechanisms are inducing oedema, but at advanced stages corticosteroids affect a greater number of pathways (see *Table 1*). Clinical evidence also supports the use of steroids. Intraocular steroids, such as triamcinolone, are often

used where laser and anti-VEGF therapy fails. Retisert® (fluocinolone acetonide [FA]) was the first intravitreal implant and contains 0.59 mg FA. It is not approved for DMO use in Europe. A clinical trial (n=196 eyes) in patients with persistent or recurrent DMO found that Retisert is effective in controlling DMO up to 3 years in one-third of patients. The most common AEs included cataract progression and elevated IOP.[33]

More recently, the Iluvien® injectable intravitreal implant, containing 190 µg FA, has become available. It has a more posterior implantation[34] and a lower FA release rate compared with Retisert. The Fluocinolone Acetonide in Diabetic Macular Edema (FAME) clinical studies in subjects with persistent DMO despite ≥1 macular laser treatment showed an improvement in visual efficacy that was sustained to 3 years.[35]

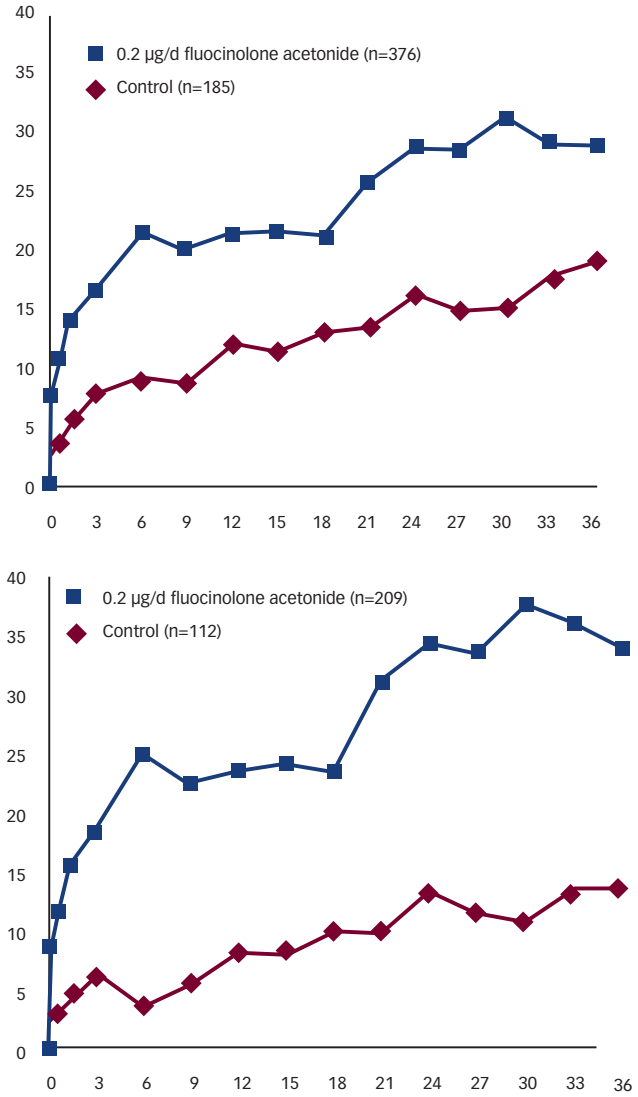
Summary

Inflammation is involved in the perpetuation of retinal changes in diabetes. At early disease stages, VEGF is important and with increasing ischaemia is a major driver of retinal changes. However, chronic microglia activation resulting from retinal damage leads to cytokine production by retinal cells. Steroids may be the most effective therapeutic approach to breaking down the inflammatory cascades that perpetuate persistent DMO. ■

Optimising Treatment Choices in Resistant Diabetic Macular Oedema – Applying the Evidence to Practice

Anat Loewenstein, Professor and Director, Tel Aviv Medical Center; Incumbent, The Sidney A Fox Chair in Ophthalmology and Vice Dean, Sackler Faculty of Medicine, Tel Aviv University, Israel

Figure 3: FAME Studies – Patients with ≥15-letter Improvement in Best Corrected Visual Acuity from Baseline; Patients with Diabetic Macular Oedema ≥3 years



Dr Anat Loewenstein opened her presentation by stating that the pathogenesis of DMO, involving the release of VEGF, cytokines and numerous other chemicals, suggests that pharmacological treatment will be the most effective treatment for DMO. This is supported by clinical trial data: in a study to evaluate intravitreal ranibizumab or triamcinolone combined with focal/grid laser compared with focal/grid laser alone, intravitreal ranibizumab with prompt or deferred laser proved more effective for at least 1 year compared with prompt laser alone. In pseudophakic eyes, intravitreal triamcinolone plus prompt laser treatment had equivalent efficacy to ranibizumab but frequently increased the risk of intraocular pressure (IOP) elevation.[8]

An expert panel has recommended that ranibizumab monotherapy is used for DMO with centre involvement and vision loss due to DMO.[36] Data from the RISE (n=377) and RIDE (n=382) clinical trials in which patients were randomised to intravitreal ranibizumab (0.3 mg or 0.5 mg) or sham injections showed excellent VA results. There was a gain of ≥15 letters in best-corrected VA (BCVA) in 12.3 % of sham patients versus 33.6 % of 0.3 mg patients and 45.7 % of 0.5 mg ranibizumab patients, although patients received, on average, 24 injections of ranibizumab. Compared with control, there was a decreased need for rescue laser, retinal thickness improved and retinopathy was less likely to progress. However, sham-treated patients had little response, even when switched to ranibizumab 0.5 mg at 24 months (see *Figure 2*). This appears to support earlier use of anti-VEGF therapy. If ranibizumab is used earlier, then the effect is maintained to 3 years, although the latest RISE/RIDE data suggest that the number of non-responders top ranibizumab doubles between 1 and 3 years.[9]

There is a need to predict success or failure to ranibizumab. A review of baseline factors and anatomic responses during the Diabetic Retinopathy Clinical Research Network (DRCRnet) trial found that baseline characteristics associated with visual improvements during the first year of ranibizumab treatment included younger age, less-severe diabetic retinopathy, absence of surface wrinkling retinopathy and the presence of hard exudates. Central subfield thickness is the strongest predictor of anatomical outcome, and reduction in central subfield thickness during the first treatment year is associated with better VA outcomes.[37] However, it was not possible to determine which

patients would respond poorly. Aflibercept is another anti-VEGF agent that is currently been studied for DMO. The phase II DME And VEGF Trap-Eye (DA VINCI): Investigation of Clinical Impact (DA VINCI) trial (n=220) enrolled patients with clinically significant DMO with central involvement. All four groups treated with aflibercept demonstrated a significant improvement in BCVA.[38]

The 36-month FAME studies are the only clinical trials to address the patient subgroup with long-term DMO (≥3 years). These comprised two phase III studies (n=953) of the efficacy and safety of the Iluvien intravitreal insert (FA) in patients with DMO despite one or more macular laser treatments. Subjects were randomised 1:2:2 to sham injection (n=185), low-dose insert (n=375) or high-dose insert (n=393).[35,39] The primary outcome as a function of the median duration of DMO at baseline was a pre-planned subgroup analysis: patients with long and short median disease duration. Baseline characteristics showed no significant difference in VA between patients of long and short disease duration. At month 36, the percentage of patients who achieved an increase of ≥15 letters response in BCVA from baseline in the full population was 28.7 % in the low-dose group (0.2 µg/g) versus 18.9 % in the control group (p=0.03), a difference of 9.8 %, and was paralleled by a decrease in central retinal thickness (see *Figure 3*). However, the subpopulation of patients with long-term DMO showed twice the treatment improvement in BCVA versus control groups compared with the whole study population. At study completion, 34.0 % of this subgroup had achieved an increase of ≥15 letters in BCVA versus 13.4 % in the control group (p<0.001). In the subgroup with long-term DMO, there was a marked reduction in the need for rescue laser treatments (40.7 % versus 60.7 %) and off-protocol treatments (11.5 % versus 29.5 %) compared with that of control groups.

When data from the control group is isolated, it can be seen that patients of shorter DMO duration had a greater potential for BCVA improvement compared with those of long duration. However, in the Iluvien-treated groups, it is apparent that the patients with longer disease duration had the greatest potential for improvement. In the subgroup of shorter DMO duration, no additional benefit could be attributed to the drug compared with other treatments, whereas in the longer duration subgroup, a clear benefit was attributable to the drug. Given that the risks associated with the chronic subgroup are similar to the risks in the full population, this identifiable patient subgroup shows even greater benefit to risk than the full patient population through month 36 of the study

Dr Loewenstein concluded by stating that anti-VEGF agents are beneficial in early disease, but there is a strong rationale for the use of steroids, particularly in disease of long duration. The results of the dexamethasone implant in DMO are awaited (dexamethasone is not licensed for use in DMO). A suggested treatment regimen is to initiate treatment with anti-VEGF therapy (three consecutive injections). Injections should be continued if an improvement is seen (even small) with monthly monitoring and OCT. Additional focal laser should be considered following several injections if there are treatable lesions. For persistent DMO, switching between anti-VEGF drugs should be considered. Intravitreal steroids are an option in long-standing DMO. Vitrectomy may be considered in cases involving vitreomacular traction. ■

Considerations in the Longer-term Care of Patients with Diabetic Macular Oedema

José Cunha-Vaz, Emeritus Professor Ophthalmology and
President of the Association for Innovation and Biomedical Research on Light (AIBILI), University of Coimbra, Portugal

Dr José Cunha-Vaz began by outlining the vascular complications of diabetes. Medical consequences of hyperglycaemia include retinopathy, neuropathy, nephropathy, infections, cataracts and connective tissue disorders cardiovascular disorders. Patients with diabetes without previous myocardial infarction (MI) have as high a risk of MI as patients without diabetes with previous MI.[40]

Safety considerations in the use of intravitreal anti-VEGF therapy include endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, ocular haemorrhage and systemic safety.[41] VEGF-A has an important functional role in the eye, but might have unexpected detrimental AEs. It is important to screen for long-term effects of VEGF inhibition on VA, as well as potential systemic effects.[42] Intraocular pharmacokinetics should also be considered.[43] Bevacizumab has a serum half-life of 20 days and may decrease blood VEGF levels to levels similar to intravenous (IV) therapy. Furthermore, it has been detected in contralateral eyes in rabbit models. Ranibizumab, by contrast, has a serum half-life of 6 hours and has not been detected in contralateral eyes; its systemic level is relatively low.

In a recent retrospective cohort study, it was found that the incidence of MI or stroke were higher in patients with DMO than in diabetes controls.[44] Data from the RISE and RIDE trials showed that serious AEs potentially related to systemic anti-VEGF were seen in 5.6–11.9 % of the ranibizumab group compared with 10.6% and 9.4% in control groups. However, vascular deaths, deaths of unknown cause and non-fatal MI/stroke ranged from 2.4 to 8.8 % compared with 4.9 % and 5.5 % in control groups.[9] Therefore systemic effects should always be considered when administering anti-VEGF agents.

As previously discussed, the FAME studies demonstrated the efficacy of the Iluvien FA intravitreal implant, particularly in terms of 15-letter BVCA improvement in patients with chronic (≥3 years) DMO (34 % of patients), which was independent of being phakic or pseudophakic. Compared with the full population this represented a doubling of benefit relative to sham injections (see *Figure 3*). However, steroids are also associated with AEs, i.e. cataracts and elevations in IOP. In a prospective cohort study (n=4,425) the presence of diabetes was associated with an increased risk of cataract surgery, cortical cataract and posterior subcapsular cataract. Further, increased diabetes duration may increase the risk of cataract.[45]

In a randomised trial evaluating 1 mg and 4 mg doses of preservative-free intravitreal triamcinolone compared with focal/grid photocoagulation for treatment of DMO, the cumulative probability of cataract surgery by 3 years was 31 %, 46 % and 83 % in the laser and 1 mg and 4 mg triamcinolone groups, respectively.[46]

In the Fluocinolone Acetonide in Human Aqueous (FAMOUS) study, the aqueous levels of FA were monitored following the administration of FA implants. Low- and high-dose FA inserts both provided stable long-term release of FA with similar levels in the aqueous.[47] In the FAME studies, cataracts developed in treatment and control groups, but FA accelerated the development of cataract.[35,39] Cataract events occurred primarily in the first 2 years of study and coincided with diminished vision improvements during months 6 to 18. However, cataract surgery did not diminish post-surgery or long-term BCVA gains.

The FAME studies also monitored IOP-related events over 36 months. Of the 0.2 µg/d FA-treated patients, 38 % received IOP-lowering therapy at some point during the trial, and this tended to be a low dosage. Incisional surgery for elevated IOP was required in only 4.8 % of low-dose patients.[35] However, a recent case study has suggested that IOP change may be reversible following removal of the implant.

A quarterly visit schedule is recommended to detect IOP changes. In addition, patient monitoring within the first 2 to 7 days following the injection may permit early identification and treatment of ocular infection, IOP increase or other complications. Elevation of IOP did not diminish VA outcomes.[39]

Dr Cunha-Vaz concluded by emphasising that diabetes may bring a number of complications, and that intravitreal therapy for DMO is generally effective. We should continue to monitor all our patients for treatment efficacy and safety. There are safety considerations with both intraocular anti-VEGF and steroids; we need to learn how best to manage them.

Concluding Remarks

DMO is an important cause of vision loss and challenges exist in defining this progressive disease. An understanding of the evolving pathogenesis of the condition is essential for its management. The disease appears to change and fluctuate over time, and inflammation plays a major role. Understanding how to best adopt treatments in both the initial and long-term settings should optimise outcomes. Finally, it is important to remember that each case is unique and an individualised approach to treatment should be taken. ■

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