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Exploring the role of retinal fluid as a biomarker for the management of diabetic macular oedema

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Anti-VEGF therapies are associated with significant gains in visual acuity and fluid resolution in the treatment of diabetic macular oedema (DMO) and have become the standard of care. However, despite their efficacy, outcomes can be unpredictable, vary widely between individual eyes, and a large proportion of patients have persistent fluid following initial treatment, with a negative impact on visual outcomes. Anatomical parameters measured by optical coherence tomography (OCT), in addition to visual acuity, are key to monitoring treatment effectiveness and guiding retreatment decisions; however, existing guidelines on the management of DMO lack clear recommendations for interpretation of OCT parameters, or proposed thresholds of various markers to guide retreatment decisions. Although central subfield thickness (CSFT) has been widely used as a marker for retreatment decisions in clinical trials in DMO, and a reduction in CSFT has generally been shown to accompany improvements in best-corrected visual acuity with treatment, analyses of the relationship between these parameters show that the correlation is small to moderate. A more direct relationship can be seen between an increased magnitude of CSFT fluctuations over time and poorer visual acuity, suggesting that control of CSFT could be important in maximising visual outcomes. The relationship between visual outcomes and qualitatively assessed intraretinal fluid and subretinal fluid is also unclear, although quantitative assessments of fluid parameters suggest that untreated intraretinal fluid and subretinal fluid negatively impact visual outcomes. These findings highlight a need for clearer guidelines on the management of retinal fluid to improve visual outcomes for patients with DMO.

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INTRODUCTION

The prevalence of diabetic macular oedema (DMO) was estimated to be 4% among people with diabetes in 2020, accounting for 18.83 million adults worldwide, with a projected increase to 28.61 million adults by 2045 [1]. DMO is a leading cause of visual impairment in patients with diabetes, particularly type 2 diabetes. Although DMO can occur at any age, a relatively high proportion of those affected come from a young, working-age population who are diagnosed on average at 50 years of age [2–5].

Patients with diabetes are at increased risk of several comorbidities, which can be complex to manage, and DMO is associated with a substantial treatment burden for patients, caregivers, and healthcare systems. The overall visit burden, time investment and complexity of therapy may limit capacity for anti-vascular endothelial growth factor (VEGF) treatment and reduce adherence [2, 6–9]. As a result, in real-world settings, the frequency of treatment received by patients can be lower than in clinical trials, which may lead to sub-optimal visual outcomes [10–13].

Another potential contributor to undertreatment in DMO is a lack of clear recommendations on retreatment in current treatment guidelines, particularly on the interpretation of retinal thickness or fluid on optical coherence tomography (OCT) images, resulting in variation in disease management between countries, regions, and private or public healthcare settings. This review aims to summarise existing knowledge on the role of retinal fluid in the pathophysiology of DMO and the short- and long-term impact on functional outcomes of unresolved fluid following treatment.

PATHOPHYSIOLOGY OF DMO

DMO can occur at any stage of diabetic retinopathy and is characterised by thickening of the macula leading to impairment of central visual function [14, 15]. Leakage of fluid and lipid-rich exudate into the retina, due to breakdown of the blood-retinal barrier, or focal leakage of microaneurysms distorts the retinal architecture, leading to thickening and reduced visual acuity if the centre of the macula is affected [14–17]. In addition to an increase in central subfield thickness (CSFT), morphologic hallmarks of DMO visualised by OCT are the accumulation of intraretinal fluid (IRF) and subretinal fluid (SRF), decreased reflectivity in the outer retinal layers, hyperreflective foci, and vitreomacular traction (Fig. 1) [14, 15, 18, 19].

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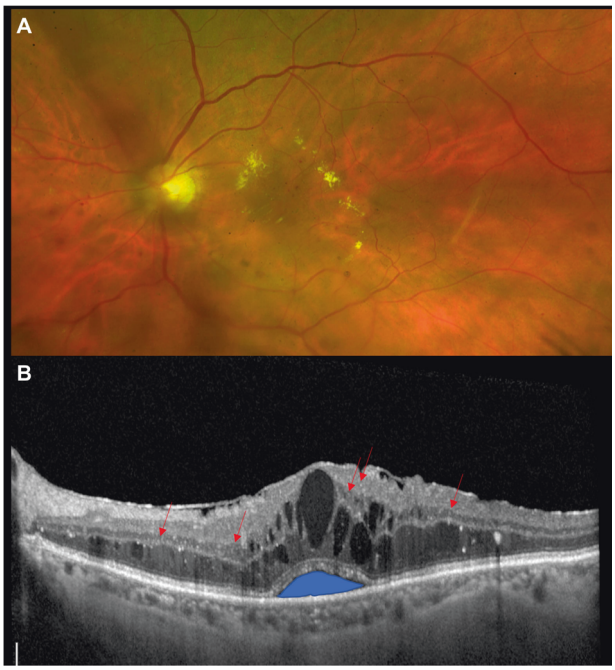

Fig. 1 Pathophysiology of diabetic macular oedema. A Colour fundus photograph showing exudative diabetic macular oedema and moderate non-proliferative diabetic retinopathy. **B** Optical coherence tomography image showing diabetic macular oedema with sub-foveal neuroretina detachment (subretinal fluid), intraretinal cysts (intraretinal fluid) and hyperreflective spots showing activated microglial cells (indicated with arrows).

Although both IRF and SRF are markers of DMO, IRF tends to be present in almost all patients at treatment initiation, while SRF is present in less than half [20–23]. SRF is generally considered to be associated with worse visual acuity than IRF at baseline and indicative of more severe disease, although it usually responds quickly to treatment [22–26]. Untreated fluid, irrespective of compartment, results in a gradual loss of vision over time and a delay in therapy initiation can lead to poorer treatment outcomes [27, 28].

CURRENT DMO MANAGEMENT AND IMPACT OF PERSISTENT OEDEMA

Historically, the mainstay of DMO treatment was focal or grid laser photocoagulation; however, this has largely been supplanted with the availability of anti-VEGF therapies as a first-line treatment as, although laser can be effective in preventing DMO progression, the rate of vision improvements is low [29]. Certain indications remain for laser, however, including the vasogenic subform of DMO, eyes with DMO and central retinal thickness (CRT) less than 300 µm, or eyes with persisting vitreomacular adhesion. Subthreshold grid laser treatment can be useful in eyes with higher visual acuity affected by early diffuse DMO [30]. Anti-VEGF therapies are associated with significant gains in visual acuity and fluid resolution and have become the standard of care for DMO treatment [31–33]. Intravitreal corticosteroids are another, less common treatment option for patients who are non- or incompletely responsive to anti-VEGFs [34–36].

Despite the efficacy of available treatments for DMO, outcomes can be unpredictable and vary widely between individual eyes. In addition to visual acuity, anatomical parameters measured on OCT are key to monitoring treatment effectiveness and guiding treatment decisions; current guidelines on DMO management recommend that retreatment decisions should be based on a combination of visual acuity and OCT findings [30, 37, 38]. However, the association between anatomic parameters and visual outcomes is not fully defined and there is a lack of clear guidance on the interpretation of OCT parameters in relation to treatment decisions or on a threshold for OCT markers to denote treatment response. In a clinical setting, retreatment decisions are often qualitative rather than quantitative and consider factors such as the pattern of DMO, involvement of the centre of the fovea, integrity of the inner and outer retinal layers, presence and quantity of hyperreflective foci, and extension/reflectivity of retinal cysts. Other considerations are visual acuity of the contralateral eye, the general systemic condition of the patient, and the ability of the patient to attend frequent appointments. Examples of response to anti-VEGF treatment are shown in Fig. 2.

Although CSFT has been widely used as a marker for retreatment decisions in clinical trials in DMO, often in combination with visual acuity criteria, there is a large degree of variation in re-treatment thresholds applied. In trials of adaptive treatment regimens, such as pro re nata or treat-and-extend, retinal thickness thresholds for retreatment ranged from 225 to 325 µm, with or without additional criteria such as a change of >10% from the previous visit, the absence of stable measurements over consecutive visits or associated SRF and/or IRF [28, 39–44].

A lack of response to treatment is associated with poor visual outcomes for patients with DMO. In a post hoc analysis of Protocol I, eyes receiving ranibizumab plus prompt or deferred laser with higher average levels of oedema (calculated as excess CRT [≥250 µm] averaged over 52 weeks) gained 9.3 fewer Early Treatment Diabetic Retinopathy Study (ETDRS) letters than those with lower levels at the end of Year 3. Patients with the longest duration of persistent oedema (calculated as the number of study visits with CRT ≥ 250 µm during the first 52 weeks of treatment) gained 4.4 fewer letters than those with the least persistent oedema [45]. The negative correlation between duration and extent of oedema and visual outcomes was suggested to be due to photoreceptor degeneration [45, 46].

Rates of persistent DMO in clinical studies (based on CSFT ≥ 250 µm) can be in the range of 20–60% after 2 years of treatment [47–49]. A secondary analysis of Protocol T showed rates of persistent DMO at Week 24 (defined as CSFT ≥ 250 µm at each completed study visit through Week 24) of 31.6% for aflibercept, 41.5% for ranibizumab and 65.6% for bevacizumab. Among these patients, rates of chronic persistent DMO (defined as failure to achieve CSFT < 250 µm and a reduction in CSFT of at least 10% relative to the Week 24 visit on at least two consecutive visits) at 2 years were 44.2% with aflibercept, 54.5% with ranibizumab and 68.2% with bevacizumab [50].

In clinical practice, where anti-VEGF administration tends to be less frequent than in clinical trials, response to treatment can be even lower. A retrospective chart review of patients receiving anti-VEGF therapy at 10 sites in the US assessed the proportion of patients with best-corrected visual acuity (BCVA) of 20/40 or better combined with CRT ≤ 250 µm on time domain (TD)-OCT or ≤300 µm on spectral domain (SD)-OCT over 12 anti-VEGF injections. For injections 1–9, BCVA of 20/40 or better was achieved by 52–62% of patients and the defined CRT threshold was achieved by 26–34% of patients. The proportion of patients achieving both BCVA and CRT endpoints ranged from only ~20–40% over all 12 injections [51].

A post hoc analysis of eyes with persistent DMO from Protocol I (approximately 40% of patients in that study) showed that eyes receiving ranibizumab with prompt or deferred laser with chronic persistent DMO (failure to achieve CSFT <250 µm and a ≥10% reduction from the 24-week visit on ≥2 consecutive study visits) at 3 years had worse visual acuity than those without, highlighting the importance of optimising anatomical outcomes for these patients [47].

Factors associated with an increased likelihood of persistent DMO, including high baseline CSFT and limited early visual and

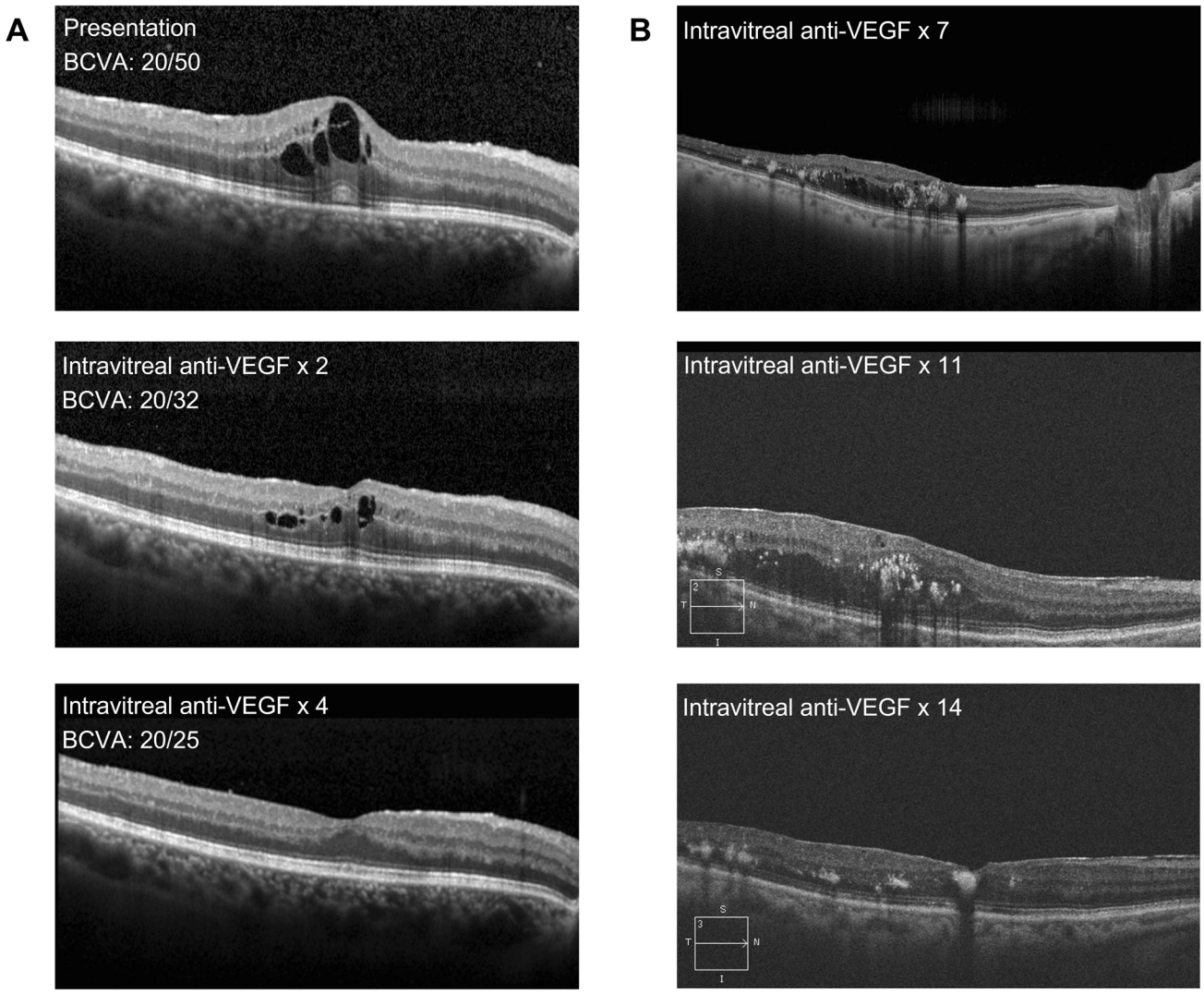

Fig. 2 Optical coherence tomography images showing response to anti-vascular endothelial growth factor treatment in patients with diabetic macular oedema. A An example of 'good' response with resolution of retinal fluid after 4 monthly anti-vascular endothelial growth factor injections. **B** Delayed response to monthly anti-vascular endothelial growth factor treatment.

morphologic responses, have been shown to be predictive of long-term outcomes; therefore, the identification of a simple biomarker of treatment response would further support the management of patients with DMO [52–55].

RELATIONSHIP BETWEEN OCT MARKERS OF RETINAL FLUID AND VISUAL OUTCOMES

Generally, in clinical studies in DMO, including treatment with anti-VEGF, laser, or corticosteroids, BCVA improvement in response to treatment is accompanied by a reduction in retinal thickness [32, 39, 49, 56–58]. However, the nature of the relationship between visual outcomes and retinal thickness and whether a direct association exists is unclear. CSFT is the most used OCT biomarker in DMO management based on the association between central involvement of DMO and visual acuity, and greater reproducibility compared with other measures of retinal thickness such as foveal centre point thickness [18, 59].

Post hoc analyses of multiple clinical trials (Protocol T, TREX-DME, and DAVE trials using anti-VEGF therapies; TYBEE and HULK trials of corticosteroids; and the Protocol I trial of focal/grid laser) showed a correlation between CSFT and BCVA at baseline and following treatment, or in change in CSFT and BCVA over time. Furthermore, the correlation increased in groups with higher CSFT when stratified by baseline levels. However, the correlations were small to moderate at best, with changes in CSFT accounting for a small proportion of the total changes in visual acuity, leading the authors to conclude that the findings did not support CSFT as a surrogate for BCVA [60–63]. A further post hoc analysis of patients receiving ranibizumab and/or laser photocoagulation in the RESTORE/RESTORE-extension studies showed a low correlation between CSFT and BCVA at baseline, which was lost over time [64]. Low to moderate correlations were also seen in a number of smaller retrospective cohort analyses or consecutive case series, although further small studies showed a lack of significant correlation [23, 65–71].

While a strong correlation may not exist between CSFT and BCVA at discrete timepoints or based on a specific difference between two timepoints, a more recent post hoc analysis of data from the Protocol T and Protocol V studies and a retrospective cohort study at the Cleveland Clinic (Cleveland, OH, USA) have shown a significant correlation between increased fluctuations in CSFT over the course of anti-VEGF treatment and worse visual outcomes [72, 73]. Based on data from the Protocol T and V trials (in eyes receiving anti-VEGF therapy or focal/grid laser), there was a difference of 1.61 and 3.04 ETDRS letters, respectively, between

patients in quartiles with the highest and lowest CSFT fluctuations (measured as the standard deviation [SD] of a patient's CSFT over treatment) after 12 months [72]. In the Cleveland Clinic study of eyes receiving anti-VEGF therapy, with the same measure of fluctuation, there was a mean difference of 6.87 ETDRS letters over 12 months per 100 µm CSFT SD and the difference between the quartiles with the highest and lowest fluctuations was 9.7 ETDRS letters after 12 months [73]. These findings suggest that CSFT fluctuations over time may be prognostic of visual outcomes in patients with DMO treated with anti-VEGFs.

CSFT is reflective of a number of parameters and pathophysiological processes, which is assumed to be based to a large degree on the contribution of retinal fluid. However, a study using a deep-learning approach to assess the correlation between CSFT and IRF or SRF volume showed that CSFT is only partly driven by IRF, and not SRF, volume at baseline and during anti-VEGF treatment and is therefore not a direct measure of exudative activity. Using SD-OCT images from 656 patients from Protocol T, a moderate correlation was seen between CSFT at baseline and IRF alone (0.688) or IRF and SRF combined (0.753), whereas the correlation between CSFT and SRF was low (0.408). Under anti-VEGF therapy, the correlation between CSFT and IRF alone (0.797) and IRF and SRF combined (0.805) increased to high, whereas the correlation between CSFT and SRF alone decreased (0.082) [24]. This and other recent studies using artificial intelligence approaches suggest that retinal fluid volume may be a more reliable biomarker for the monitoring of DMO than CSFT [22, 24, 26].

In terms of the impact of individual fluid types on visual outcomes, a post hoc analysis of the RESTORE study showed that patients treated with ranibizumab, laser photocoagulation, or both, with baseline intraretinal cystoid fluid (IRC) height ≤380 µm had better BCVA than those with IRC > 380 µm at both baseline and Month 12; IRC height at baseline was also a better predictor of outcomes than CSFT. However, in patients followed up through the RESTORE-extension study, there was no significant difference between IRC groups at Month 36 [64]. A moderate negative correlation between IRC height and BCVA was also seen in a retrospective case series of 66 patients that had not received treatment with anti-VEGFs in the prior 3 months or steroids in the prior 6 months [69]. Conversely, a retrospective cohort study of 119 patients receiving ranibizumab showed no significant correlation between IRC and BCVA [68], while a study of 159 patients receiving bevacizumab showed that baseline 'severe IRF' (≥50% of the linear scan of the horizontal raster scan of the fovea) was significantly more likely in eyes gaining 3 or more lines of BCVA compared with eyes that lost 3 or more lines. Similar findings were also seen in patients with more moderate vision changes (gain or loss of ≥1 line of vision). The authors suggested that eyes with less IRF have more baseline macular ischaemia and thus less room for improvement, or that greater IRF at baseline may simply allow for a more significant reduction with anti-VEGF therapy, resulting in improved BCVA [23].

In a sub-analysis of the RISE and RIDE trials, SRF at baseline was predictive of better visual outcomes following treatment with ranibizumab [25]. A retrospective cohort study of eyes treated with an intravitreal dexamethasone implant also showed that SRF at baseline was predictive of better visual outcomes following treatment with dexamethasone implants, with treatment-naïve eyes showing a better response than refractory eyes [71]. The VIVID-DME and VISTA-DME studies, however, showed similar BCVA gains at Weeks 52 and 100 for patients treated with aflibercept irrespective of baseline SRF but BCVA loss of approximately 2 letters for those with baseline SRF treated with laser compared with a gain of greater than 2 letters for those without baseline SRF [21]. A post hoc analysis of the RESTORE/RESTORE-extension studies also showed worse BCVA outcomes in patients with baseline SRF at 12 months following laser treatment, while patients treated with ranibizumab with baseline SRF had better BCVA outcomes than those without and patients receiving combination treatment of ranibizumab plus laser had similar outcomes regardless of SRF presence or absence [64].

Many analyses on the association between fluid and visual outcomes rely on qualitative rather than quantitative assessment of fluid parameters, which may not provide a complete reflection of this relationship e.g. measures of IRC height may only take the highest cyst into account and only a moderate correlation exists between SRF fluid volume and fluid height at baseline and during treatment [24]. A volumetric analysis of SD-OCT images from eyes receiving anti-VEGF treatment in the Protocol T trial using a deep-learning algorithm showed significantly higher IRF and SRF in eyes with worse BCVA at baseline, and for IRF after a year of treatment. SRF had a stronger association with BCVA than IRF, with every 10 nL reduction in fluid in the central fovea translating to an improvement in ETDRS letter score of 0.34 and 0.15, respectively, during Year 1. Although the presence of SRF was associated with worse BCVA and higher IRF volume at baseline, and with greater improvements in BCVA at each assessment through 12 months of treatment, there was no difference in BCVA or IRF between eyes with or without SRF after 12 months [22]. A retrospective cohort study using a similar approach to quantify IRF, SRF, and total retinal fluid showed that presence of IRF or SRF after 12 months of anti-VEGF treatment was associated with significantly lower BCVA. In a comparison of fluid volume quartiles (quartile 1 having the lowest volume), IRF alone was associated with a significant difference in BCVA for the second, third, and fourth fluid quartiles of −2.23, −4.41, and −8.63 letters, respectively, at 1 year; SRF was associated with a significant difference in the fourth quartile only (of −5.38 letters); a combination of the two was associated with significant differences in the third and fourth quartile, of −4.79 and −8.85 letters, respectively [26].

In addition to CSFT and retinal fluid, ellipsoid zone integrity and, in particular, the relative ellipsoid zone reflectivity ratio has been identified as a potential biomarker for therapy surveillance and prediction of visual acuity outcomes. A longitudinal study showed a correlation between elipsoid zone integrity and visual acuity from baseline to Year 5, demonstrating the relationship beyond 1 year of therapy [74]. Another study assessed semi-automated quantification of retinal and choroidal biomarkers on OCT in patients with diabetic retinopathy complicated by macular oedema. All three OCT biomarkers evaluated—number of hyperreflective foci, ellipsoid zone reflectivity ratio, and choroidal vascularity index—have been suggested to correlate with visual acuity change or treatment outcomes. The study demonstrated excellent reproducibility of these biomarkers on SD-OCT with and without enhanced depth imaging mode, regardless of the presence of macular oedema [75]. A further retrospective review of visual outcomes in DMO patients receiving anti-VEGF therapy showed the extent of ellipsoid zone and external limiting membrane disruption at 12 months is negatively correlated with the area and number of intraretinal cysts at baseline [76].

CONCLUSIONS

In current practice, anti-VEGFs are the first-line treatment option for DMO patients. However, there is a large proportion of patients with persistent fluid in the real world despite initial anti-VEGF treatment. This persistent oedema is associated with negative visual outcomes, highlighting an unmet need for a significant cohort of patients and a gap in existing treatment guidelines in terms of clear recommendations relating to retinal fluid in disease management. CSFT has been widely adopted as a marker of treatment response, although various analyses suggest the association between CSFT and visual outcomes is moderate at best. While CSFT itself may not be strongly associated with visual outcomes, CSFT fluctuations seem to be a good correlate, suggesting that control of CSFT is important in maximising visual

outcomes and CSFT fluctuations may be considered by clinicians when making retreatment decisions. Additionally, fluid parameters play a role in assessing the effectiveness of treatment, retreatment decisions, and therefore ability to extend treatment intervals. Studies using quantitative assessments of fluid parameters suggest that untreated IRF and SRF are associated with a negative impact on visual outcomes, which may correlate with fluid volume in the case of IRCs. A more stringent approach to the treatment of retinal fluid and clearer recommendations on the integration of fluid parameters into retreatment decisions may improve visual outcomes for patients with DMO.

METHODOLOGY

Search terms:

'Diabetic macular o/edema' OR 'clinically significant macular o/edema'

AND

'treatment guideline / recommendation'; 'retinal fluid'; 'intraretinal fluid'; 'intraretinal cysts'; 'intraretinal cystoid o/edema'; 'cystoid o/edema'; 'cystoid macular o/edema'; 'subretinal fluid'; 'subretinal pigment epithelial fluid'; 'serous retinal detachment'; 'central retinal thickness'; 'central subfield thickness'; 'fluid management'; 'optical coherence tomography'; 'spectral domain-optical coherence tomography'; 'optical coherence tomography-angiography'.

Search criteria: English language

Databases searched: Embase and Medline

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ADDITIONAL INFORMATION

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