



# Management of diabetic macular edema in Japan: a review and expert opinion

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Received: 5 June 2017 / Accepted: 29 August 2017 / Published online: 5 December 2017  
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## Abstract

Diabetic retinopathy is a frequent cause of visual impairment in working-age adults ( $\geq 30$  years) and in Japan is most commonly observed in those aged 50–69 years. Diabetic macular edema (DME) is one of the main causes of vision disturbance in diabetic retinopathy, which is a clinically significant microvascular complication of diabetes. Anti-vascular endothelial growth factor (VEGF) therapy is becoming the mainstay of treatment for DME. However, to achieve sustained long-term improvement in visual acuity, conventional laser photocoagulation, vitrectomy and steroid therapy are also expected to play a role in the treatment of DME. This review summarizes the epidemiology and pathology of diabetic retinopathy and DME, evaluates the findings regarding the diagnosis and treatment of DME, and underscores the importance of systemic management of the disease in the context of the current health care situation in Japan. Finally, the unmet needs of patients with DME and prospects for research are discussed. The weight of evidence suggests that it is important to establish a multipronged treatment strategy centered on anti-VEGF therapy.

**Keywords** Diabetic retinopathy · Diabetic macular edema · Vascular endothelial growth factor · Multidisciplinary treatment · Expert opinion

## Introduction

The numbers of patients with diabetes is rapidly increasing worldwide. The International Diabetes Federation estimated that 415 million adults had diabetes in 2015 and that 642 million adults will have the disease by 2040 [1]. Diabetic macular edema (DME) is a clinically significant microvascular complication of diabetes associated with diabetic retinopathy. DME can occur at any stage of diabetic retinopathy, and is a major cause of impaired vision in patients with diabetes [2]. Therefore, appropriate management of this disorder is important [2–4].

In recent years, the treatment of DME has changed greatly with the advent of anti-vascular endothelial growth factor (VEGF) agents [5]. Large clinical studies demonstrate that the effects of anti-VEGF therapy (alone or in combination with laser photocoagulation) on DME are functionally and anatomically superior to those of conventional laser photocoagulation (alone or in combination with steroids) [6–10]. Use of anti-VEGF agents as a treatment for DME is currently increasing throughout the world [11], and is recommended as

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first-line therapy for center-involving DME, which is a leading cause of vision impairment [12, 13]. A recent survey in Italy found a clear consensus among DME experts on the appropriateness of medical intervention regardless of the status of visual acuity and center involvement, except when DME is predominantly tractional [14].

In 2015, retinal experts in Japan were surveyed to assess current real-world clinical practice in the diagnosis and treatment of DME, including use of anti-VEGF therapy [15]. According to this survey, there were discrepancies between some of the evidence-based literature and actual clinical practice patterns [15]. In this paper, we summarize the important findings within the literature on DME and discuss the future prospects and unmet needs concerning clinical management of DME in Japan.

## Epidemiology and pathogenesis of DME

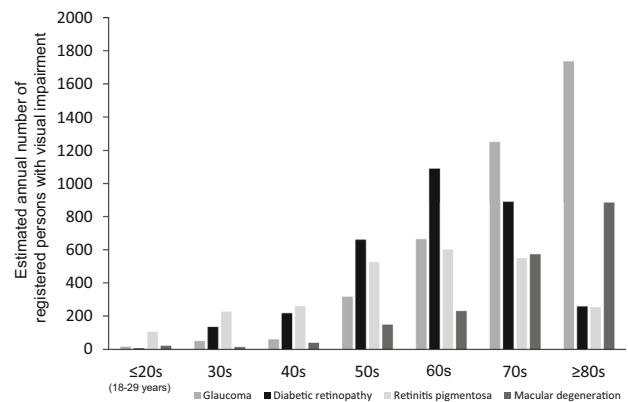
### Epidemiology in the world and Japan

Although the incidence of diabetic retinopathy and visual impairment has been decreasing with advances in diabetes care [4], the number of patients with diabetes continues to grow worldwide [1]. As a result, visual impairment associated with diabetes remains a major challenge. A meta-analysis of studies of the global prevalence of and major risk factors for diabetic retinopathy in 2012 estimated that approximately 35.4% of individuals with diabetes had one type of diabetic retinopathy, 7.2% had proliferative diabetic retinopathy, 7.5% had DME, and 11.7% had vision-threatening diabetic retinopathy (proliferative diabetic retinopathy and/or DME) [16]. Further, the quality of life in patients with diabetic retinopathy is markedly diminished in the vision-threatening stages [17].

The reported prevalence of diabetic retinopathy in patients with diabetes in Japan ranges from 15 to 23% [18, 19]. A Japanese survey conducted in 2007–2010 identified glaucoma as the most common cause of visual impairment, followed by diabetic retinopathy [20]; this is consistent with a previous report for 2001–2004. The proportion of patients with visual impairment attributable to diabetic retinopathy increases from the age of 30 years onward and becomes predominant in those aged 50–69 years (Fig. 1) [20]. Therefore, diabetic retinopathy is a condition with a major impact in working-age adults.

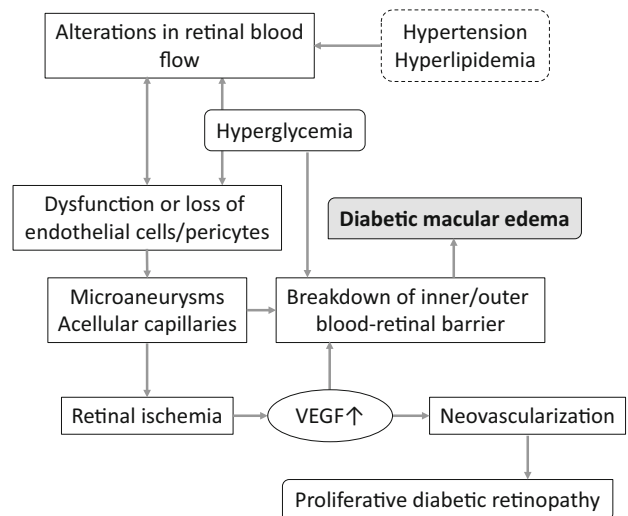
### Pathogenesis

Hyperglycemia in diabetes triggers a cascade of events affecting the eye, including impairment of retinal blood flow, loss of endothelial cells and pericytes, formation of microaneurysms, and breakdown of the blood-retinal



**Fig. 1** Estimated number of newly registered persons with visual impairment caused by the top four diseases between April 2007 and March 2010 in Japan. Diabetic retinopathy was frequently observed in working-age adults ( $\geq 30$  years) and most commonly observed as a cause of visual impairment in adults aged 50–69 years. Reproduced from Wako et al. [20]

barrier. These events cause retinal ischemia and increased vascular permeability, leading in turn to increased production of VEGF, neovascularization, and/or macular edema (Fig. 2) [3, 4, 21]. The intraocular concentration of VEGF is higher in patients with diabetic retinopathy than in those without the condition [22–24]. Further, concentrations of VEGF, placental growth factor, and various inflammatory cytokines, including interleukin (IL)-6, IL-8, and monocyte chemoattractant protein-1, are shown to be higher in the vitreous fluid and aqueous humor in patients with DME [25–28]; a correlation has been demonstrated



**Fig. 2** Summary of the pathology of diabetic retinopathy resulting from retinal blood flow/vascular impairment due to hyperglycemia. Cytokines such as VEGF as well as the change in capillary structure due to loss of vascular endothelial cells or pericytes are associated with a breakdown of the blood-retinal barrier, leading to diabetic retinopathy. VEGF expression is increased by retinal ischemia [3, 4, 21]. Abbreviation: VEGF vascular endothelial growth factor

between aqueous levels of VEGF and IL-6 and the severity of DME [25].

VEGF is a cytokine with a key role in the breakdown of the blood-retinal barrier and development of macular edema [29–31]. A study in non-human primates demonstrates that intravitreal injections of VEGF at 3-day intervals for 15 days was associated with retinal changes similar to those seen in diabetic retinopathy, i.e., dilation or tortuosity of vessels, tortuosity, areas of capillary non-perfusion, and microaneurysmal-like structures [32]. Intraocular injection of ranibizumab, a humanized anti-VEGF monoclonal antibody Fab fragment that binds to VEGF-A, significantly decreases central retinal thickness and improves visual acuity in patients with DME [33]. VEGF is known to induce migration of macrophage lineage cells via VEGF receptor-1 expressed on these cells, leading to production of inflammatory cytokines such as IL-6 [34]. Thus, VEGF plays multiple important and complex roles in the pathogenesis of diabetic retinopathy and DME in humans [2, 4].

Previous research suggests that the consensus among retinal experts in Japan is that levels of inflammatory cytokines in the eye start to increase early in the development of diabetic retinopathy and that the primary pathological mechanism involved in the development of DME is an increase in vascular permeability in response to elevated VEGF-A levels early in the course of diabetes [15].

## Perspectives

**Epidemiology:** The worldwide prevalence of diabetes is increasing. Accordingly, the number of patients with diabetic retinopathy and DME is also assumed to be increasing. The prevalence of diabetes is particularly high in the elderly Japanese population. To prevent vision loss or visual field disorders in patients with diabetes, we need to identify the characteristics of patients with diabetic retinopathy/DME and use the findings to promote early diagnosis and treatment.

**Pathology:** VEGF is the most important factor in the pathology of diabetic retinopathy and DME. With progression in research on diabetic retinopathy and DME, additional culprit molecules will be identified and pathways in the pathogenesis of these disorders revealed. We have identified some molecules other than VEGF as therapeutic targets [2, 35]. We believe that development of therapies targeting these molecules will have benefits for patients.

## Importance of systemic management in DME

### Glycemic control

The association between diabetic retinopathy and glycemic control was assessed in four pivotal studies. The Diabetes Control and Complications Trial [36] in patients with type 1 diabetes and the UK Prospective Diabetes Study (UKPDS) [37], Action to Control Cardiovascular Risk in Diabetes (ACCORD) [38], and Action to Control Cardiovascular Risk in Diabetes Follow-On (ACCORDION) studies [39] in patients with type 2 diabetes demonstrate that better control of glycated hemoglobin (HbA<sub>1c</sub>) levels might contribute to a lower risk of diabetic retinopathy. In all of these studies, intensive glycemic control was more effective in preventing the development and progression of diabetic retinopathy than conventional treatment. Further, the Diabetes Control and Complications Trial demonstrates that higher HbA<sub>1c</sub> values are associated with a greater risk of progression to diabetic retinopathy over time in patients receiving conventional antihyperglycemic therapy [40].

Similarly, the Kumamoto study in Japanese patients with type 2 diabetes reports that intensive glycemic control could delay the onset and progression of diabetic retinopathy, indicating glycemic thresholds to be HbA<sub>1c</sub> < 6.9%, fasting blood glucose concentration < 110 mg/dL, and 2-h post-prandial blood glucose concentration < 180 mg/dL [41]. In the Japan Diabetes Complications Study (JDACS), a higher HbA<sub>1c</sub> or a longer duration of diabetes is associated with a higher incidence and progression rate of diabetic retinopathy [42]. In addition, a study of patients with younger-onset type 1 diabetes in Japan shows that the set of mean HbA<sub>1c</sub> values covering the entire duration of diabetes has a substantial capacity to predict retinopathy at 20 years after onset of the disease [43]. The 2013 Kumamoto Declaration defined a target HbA<sub>1c</sub> of < 7.0% for prevention of the complications of diabetes in the Japanese population.

A meta-analysis of 35 studies of DME from around the world reveals that the age-standardized prevalence of DME in both type 1 and type 2 diabetes was higher in patients with HbA<sub>1c</sub> ≥ 7.1% than in those with levels ≤ 7.0% and in patients with a diabetes duration ≥ 10 years relative to those with a duration < 10 years [16]. In addition, a US study shows that higher HbA<sub>1c</sub> (per 1% point) or having had diabetes for ≥ 10 years was significantly associated with a higher risk of DME [44]. Therefore, hyperglycemia and a prolonged duration of diabetes are risk factors not only for diabetic retinopathy but also for the development of DME.

## Blood pressure and lipid control

The effect of blood pressure control on diabetic retinopathy was evaluated in UKPDS 38, which shows that patients with type 2 diabetes assigned to tight blood pressure control had a 37% reduction in risk of microvascular disease, including retinopathy [45]. In a meta-analysis of studies investigating the effects of blood pressure control on cardiovascular events published in 2016, intensive blood pressure control tended to decrease the risk of progression of retinopathy in patients with diabetes [46]. However, a recent Cochrane review reveals no significant effects of blood pressure control on progression to proliferative diabetic retinopathy or on clinically significant macular edema during 4–5 years of follow-up [47].

In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, administration of the lipid-lowering agent Fenofibrate significantly reduced the cumulative risks of retinopathy, proliferative diabetic retinopathy and DME requiring laser therapy in patients with type 2 diabetes, although there were no clinically relevant differences in serum lipid parameters between the Fenofibrate group and the placebo group at the end of the study [48]. However, the Wisconsin Epidemiologic Study of Diabetic Retinopathy, which evaluated the effects of lipid control in patients with type 1 diabetes over a period of 30 years, reveals no significant association between the incidence of proliferative diabetic retinopathy and/or DME and total cholesterol and high-density lipoprotein cholesterol levels, but does show an association with HbA<sub>1c</sub> [49]. In addition, a recent systematic review of the association between dyslipidemia and DME shows that lipid-lowering therapy did not reduce the risk of progression of hard exudates in DME or the severity of DME [50]. Despite evidence from cohort studies and a meta-analysis of case–control studies suggesting a strong relationship between lipid levels and DME, this was not confirmed by the meta-analysis, which included only prospective randomized controlled trials. Yet, when patients with hard macular exudates were compared with those with regressed macular exudates, serum cholesterol, especially low-density lipoprotein cholesterol, was associated with the hard macular exudates [51]. Therefore, lipid-lowering therapy may need to be considered in the management of DME.

Hypertension and hyperlipidemia are possible risk factors in the development and progression of diabetic retinopathy. However, their association with DME is unclear, and further investigation is required. Nevertheless, given the known cardiovascular complications of diabetes, control of blood pressure and lipids are clearly important, and optimal management is required.

## Renal function

Renal disease is associated with an increased likelihood of worsening diabetic retinopathy [52]. In a retrospective study from the US that involved more than 4000 patients with non-proliferative diabetic retinopathy, the presence of nephropathy increased the risk of progression to proliferative diabetic retinopathy by 29% (hazard ratio 1.29 [95% confidence interval 0.99–1.67]) [53]. Although one study reports finding no significant differences in systemic factors between ranibizumab-treated patients and sham-treated patients [54], multivariate analysis of the sham-treated patients in the Phase III (RISE/RIDE) studies of ranibizumab indicates that a history of renal disease was a significant predictor of poor visual outcome (best-corrected visual acuity [BCVA] of 20/100 or worse) [55]. In addition, the proportion of patients with severe renal dysfunction (estimated glomerular filtration rate < 30 mL/min/1.73 m<sup>2</sup>) was higher in patients who underwent bilateral vitrectomy than in those who underwent unilateral vitrectomy [56]. In some patients with nephrotic syndrome, treatment of diabetes and nephropathy markedly improved weight, visual acuity, and central retinal thickness [57]. Therefore, management of nephropathy is essential in the treatment of DME.

## Perspectives

Close collaboration between physicians and ophthalmologists is imperative in the management of patients with diabetic retinopathy and DME. To ensure early diagnosis and treatment all diabetic patients should be screened for diabetic retinopathy. Control of blood pressure, serum lipids, and renal function are all important treatments aimed at prevention of visual impairment associated with diabetic retinopathy and DME. However, the most important intervention is the management of blood glucose levels. Intensive follow-up is also required in these patients to prevent premature discontinuation of treatment.

Two diabetes management and communication tools targeting patients are available in Japan. One is the “Diabetes Coordination Notebook” issued by the Japan Association for Diabetes Education and Care for use by patients with diabetes and their health care providers, including ophthalmologists and dentists. The other is the “Diabetic Eye Notebook”, an educational tool outlining the ocular complications of diabetes issued by the Japanese Society of Ophthalmic Diabetology to facilitate sharing of patients’ ophthalmic information. Both patients and health care providers are urged to use these notebooks to support cooperation among physicians and ophthalmologists.

## Diagnosis of DME and interventional decision-making

### Diagnosis and classifications

Fundus examination, optical coherence tomography (OCT), and fluorescein angiography (FA) are routinely used to diagnose DME in clinical practice. OCT in particular has become an essential tool in the era of anti-VEGF therapy [58–60].

Fundus examination is used mainly to detect the presence or absence of retinal thickening and/or hard exudates, and if present, to identify the locations affected [61]. OCT provides a quantitative assessment of macular thickness and a qualitative assessment of the location of edema and is useful for determining whether the macular edema involves the fovea [58, 59, 62]. FA is useful for identifying the sites of blood vessel leakage associated with edema and for monitoring specific patterns of leakage [58].

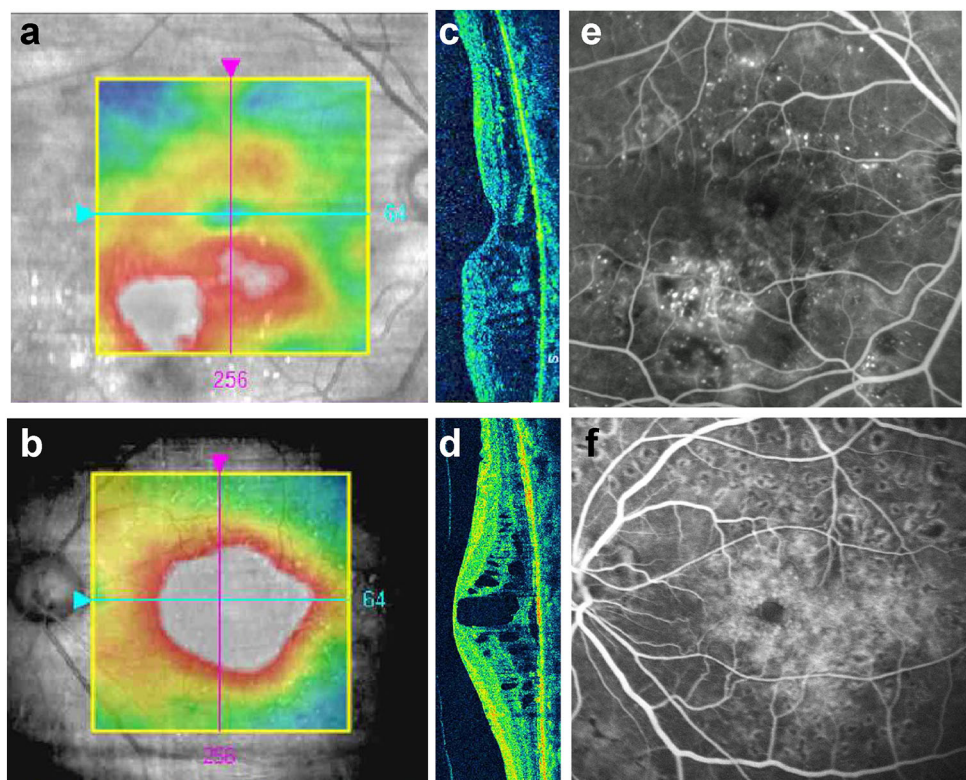
DME can be classified as focal or diffuse (Fig. 3). The characteristics of focal macular edema are: (1) location outside the foveal center with or without center involvement (Fig. 3a); (2) asymmetric increases in retinal thickness on B-scan OCT (Fig. 3c); and (3) accumulation of pin-point leakage in the early phase (Fig. 3e). The characteristics of diffuse macular edema are: (1) increased retinal thickness with center involvement on the macular

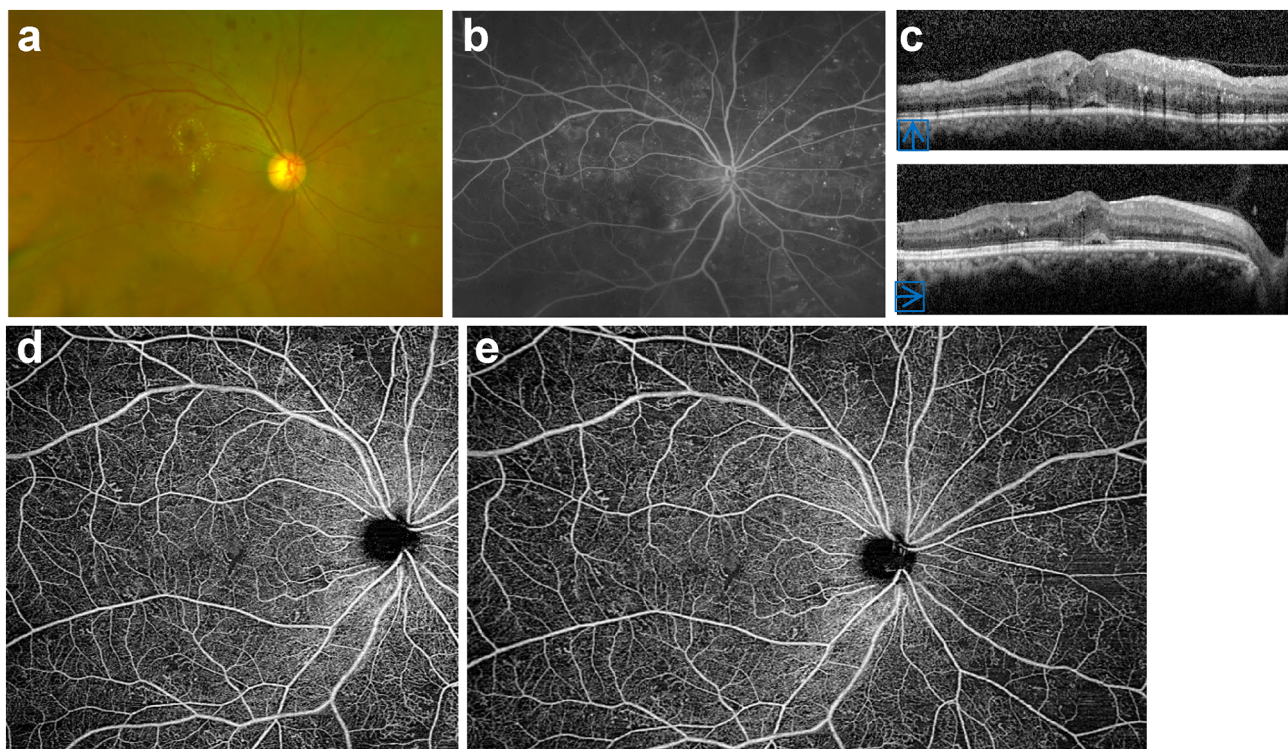
thickness map (Fig. 3b); (2) symmetrically increased retinal thickness on B-scan OCT (Fig. 3d); and (3) fluorescein leakage starting from early phase and continuously increasing to late phase (Fig. 3f).

Based on OCT findings, DME can be classified as sponge-like retinal swelling, cystoid macular edema, or serous retinal detachment [63]. The Early Treatment Diabetic Retinopathy Study (ETDRS) has also defined clinically significant macular edema (CSME) as DME amenable to photocoagulation based on fundus examination [61]. In Japan, classification of DME as focal or diffuse is most commonly used to determine therapeutic strategies. Center-involved DME, as defined by the Diabetic Retinopathy Clinical Research Network (DRCR.net), is also widely recognized by examination using OCT [64, 65]. Central subfield retinal thickness is another indicator that can be evaluated by OCT. It should be noted that the definition of “central retinal thickness” may vary depending on the model of the OCT machine and the settings used (e.g., central retinal subfield thickness, thickness within 1 mm of the fovea, or foveal thickness). DRCR.net has some possible definitions [65], but a general consensus regarding these terms is yet to be reached.

Recently, hyperreflective foci seen in DME have been identified on OCT [66], and seem to be a precursor of hard exudates. The presence of hyperreflective foci in the outer retina is reported to be closely associated with disruption of

**Fig. 3** Focal and diffuse DME observed with an OCT macular thickness map, an OCT B-scan, and fluorescein angiography. The OCT macular thickness map is delineated with white (> 500  $\mu\text{m}$ ) or red (400–500  $\mu\text{m}$ ) color. Focal edema is restricted in one or two quadrants (a) whereas diffuse edema lies in four quadrants (b). The OCT B-scan image confirms thickening of the retina corresponding to white or red colored areas that indicates thickening of the retina in the OCT macular thickness map in c focal DME and d diffuse DME. Fluorescein angiography shows a cluster of leakage points corresponding to the areas colored in white or red. Foveal leakage is usually minimal in focal DME (2'35") (e) but prominent in diffuse DME (1'51") (f). DME diabetic macular edema, OCT optical coherence tomography





**Fig. 4** Multimodal imaging of diabetic retinopathy with macular edema. **a** Trimmed fundus photograph from ultra-widefield fundus photograph, **b** fluorescein angiography, **c** structural optical coherence tomography, **d** a single shot (12 mm × 12 mm), and **e** composite

swept-source optical coherence tomographic angiography at the initial visit in the right eye of a 50 year-old man with diabetic macular edema

the external limiting membrane and the junction between the inner and outer segment (IS/OS) line on spectral-domain (SD)-OCT images and with decreased visual acuity in DME [67].

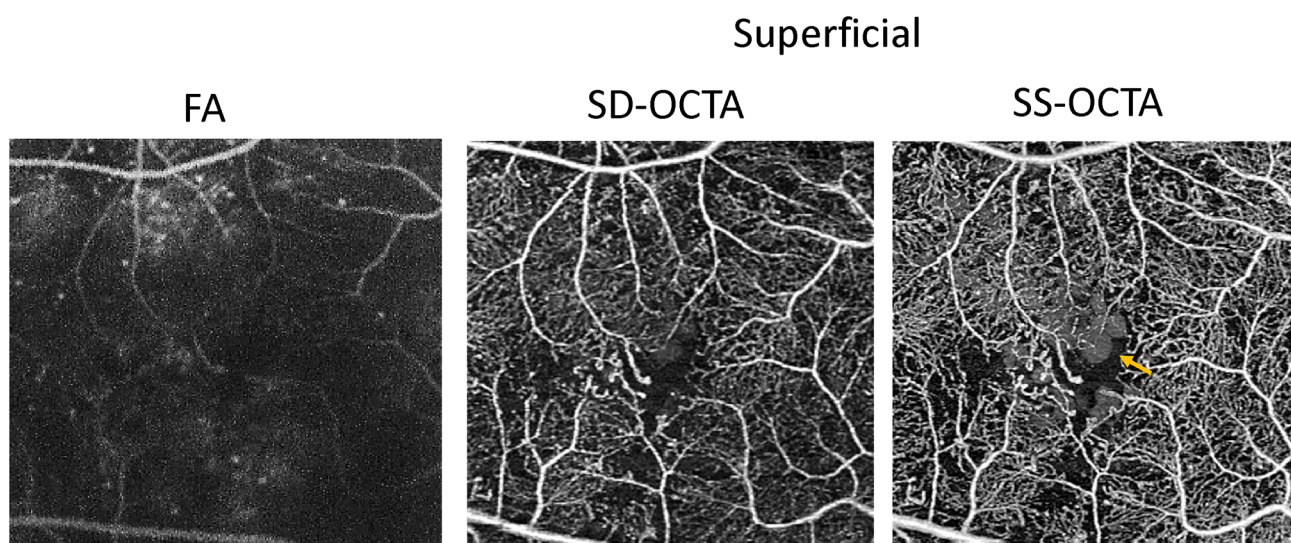
The number of hyperreflective foci seen in the outer retinal layer on SD-OCT is reported as related to the final visual acuity in eyes with DME after bevacizumab injection [68]. A relationship between a disrupted outer layer on SD-OCT images and the visual prognosis after microincision vitrectomy for proliferative diabetic retinopathy is also reported [69].

In a survey of retinal experts in Japan, all respondents reported using OCT and approximately 70% reported using three modalities (fundus examination, OCT, and FA) to diagnose DME. Most experts consider OCT to be the most important modality for therapeutic decision-making and use central retinal thickness and the OCT retinal map as the determining parameters [15]. FA, especially ultra-widefield FA of the whole retina in addition to the macular area, is useful for distinguishing focal from diffuse macular edema and for evaluating the severity of diabetic retinopathy and ischemia [58, 70]. Areas of peripheral non-perfusion are detected well by ultra-widefield FA, but their relationship with DME is variable [71–73].

Structural OCT can distinguish between the type and degree of DME but cannot assess capillary leakage or non-perfusion areas dotting the entire macular retina (Fig. 3). A new imaging technique known as OCT angiography can visualize the retinal vasculature without dye injection (Fig. 4). Vascular images on Swept Source (SS)-OCT are more detailed than on Spectral Domain (SD)-OCT with the image of pooling hyper viscous material (Fig. 5). It also provides a separate layer of the vascular plexus. For example, microaneurysms located in the deep capillary plexus can be visualized and assessed for their relationship with DME [74]. Combination of en-face and B-scan flow images clarifies the depth of the microaneurysms (Fig. 6). Although this technique has some limitations that are yet to be overcome, including the limited range of the visual field covered, segmentation errors, inability to detect leakage points and motion and projection artifacts [75], it holds promise for the evaluation of microvascular abnormalities in the retina that are potentially associated with DME [76, 77].

### Determining therapeutic interventions

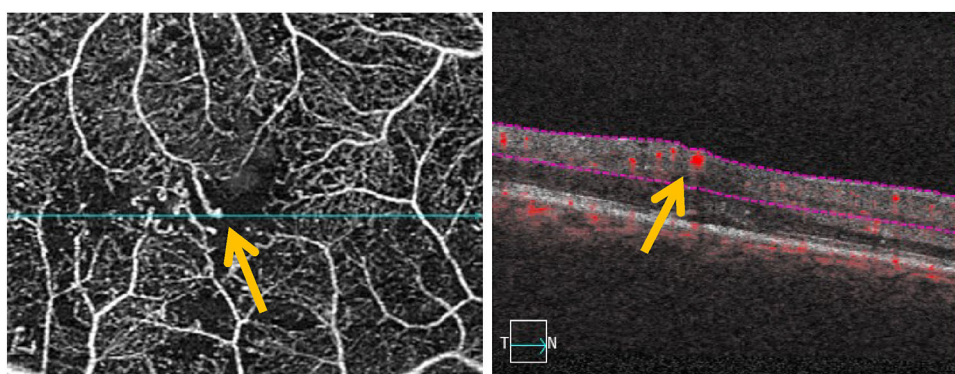
Most of the landmark clinical studies of anti-VEGF agents [6–10, 78] were performed in patients with visual acuity of



**Fig. 5** Fluorescein angiography and vascular imaging of the superficial vascular plexus by spectral-domain OCT and swept-source OCT (3 mm × 3 mm). On fluorescein angiography, microaneurysms are visible as hyper-fluorescein dots. On both types of OCT angiography, club stick-like dilated capillaries in the capillary network are well

documented. On swept-source OCT angiography, more precise vascular images with round and relatively dark hyperfluorescein plaques (arrow) are detected, which might reflect pooling of hyperviscous material in the retina. *OCT* optical coherence tomography

**Fig. 6** En face image and B-scan of swept-source optical coherence tomographic angiography in an eye with diabetic macular edema. Arrows indicate a large microaneurysm. A B-scan (right) at the blue line of the en face image (left) shows a large area of blood flow in a dilated superficial capillary (microaneurysm)



20/32 to 20/320. When deciding on an appropriate therapeutic intervention in everyday clinical practice, experts are likely to consider visual acuity to be more important than retinal thickness [15].

Most of the patients in the aforementioned clinical studies [6–10, 78] had a central retinal thickness  $\geq 300$   $\mu\text{m}$  (SD-OCT equivalent). However, there is no consensus on the threshold of retinal thickness warranting therapeutic intervention for center-involved macular edema. In a recently reported meta-analysis of 10 studies that assessed the diagnostic accuracy of OCT, including time-domain OCT, the median central retinal thickness cut-off was 250 (range 230–300)  $\mu\text{m}$  [79]. Retinal thickness in patients with CSME is reported to range between 300 and 600  $\mu\text{m}$ , or more [79]. It should be noted that the retinal thickness at baseline can vary according to the OCT model used and

patient background factors, such as sex and the presence of myopia and glaucoma.

When selecting a therapeutic intervention, some ophthalmologists are now more likely to take into account the type of macular edema seen on OCT than absolute retinal thickness. This is because of the recent findings of a greater reduction in macular retinal thickness and improvement in visual acuity after intravitreal steroid injection in eyes with cystoid macular edema as compared with eyes afflicted with other types of DME as well as the observation that intravitreal injection of bevacizumab is the most effective treatment for sponge-like retinal swelling [80, 81]. It was also found in the post hoc analysis of the RISE/RIDE studies that patients with subretinal fluid had good visual outcomes following ranibizumab injections [55]. The impact of intraretinal cysts on BCVA was not significant in

patients treated with ranibizumab but was significant in those who received sham injections [55]. However, in clinical practice in Japan, most ophthalmologists would not switch therapeutic agents on the basis of the morphological characteristics of center-involved diffuse DME [15].

## Perspectives

OCT is essential both for the diagnosis of DME and decision-making regarding therapeutic interventions. Recently, there have been remarkable advances in the diagnostic equipment available, and newer technologies such as OCT angiography are expected to be used extensively in the future. However, conventional FA continues to be important for staging of retinopathy. Ultra-wide field FA in particular can demonstrate the extreme peripheral vascular changes associated with intractable DME and the target of scatter photocoagulation. Further research concerning selection of therapeutic agents according to type of DME and anatomical findings is needed. More studies are also needed to determine how other information, such as the structure of the retinal layer and the location of hyperreflective foci on OCT, and the presence or absence of hard exudates on fundus photographs, influences treatment decisions and outcome. Standardized parameters based on comprehensive assessment of visual acuity and

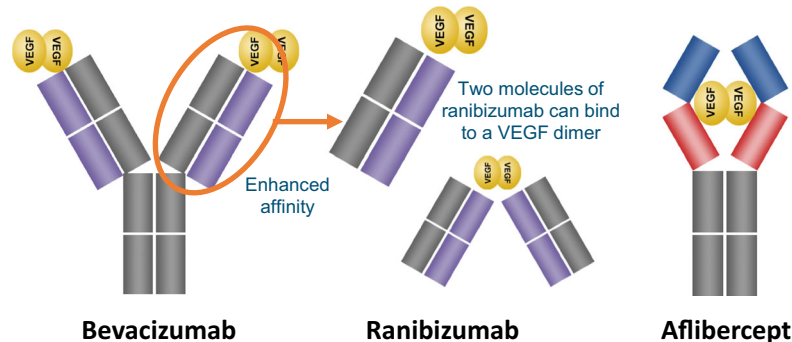
retinal thickness, and other parameters such as retinal sensitivity on microperimetry, are required for evaluation of DME and decision-making regarding therapeutic interventions.

## Anti-VEGF agents for DME

The advent of anti-VEGF agents has greatly changed the treatment of DME [5]. Laser photocoagulation became an established treatment for DME in the 1980s [61], vitrectomy was introduced during the 1990s [82, 83], and medical therapy (consisting mainly of the steroid triamcinolone acetate) has been used since 2000 [84]. The anti-VEGF agents were added to the arsenal for DME in around 2006, starting with the off-label use of bevacizumab [65]. Since then, ranibizumab has been approved worldwide (in Europe in 2011 [85], the US in 2012 [86], and Japan in 2014 [87]), as has aflibercept (in Europe, the US, and Japan in 2014 [88–90]). Anti-VEGF therapy is now widely considered to be the gold standard treatment for DME.

## Anti-VEGF agents

Bevacizumab, ranibizumab, and aflibercept have unique structures and characteristics (Fig. 7) [91–95]. Bevacizumab



	<b>Bevacizumab</b>	<b>Ranibizumab</b>	<b>Aflibercept</b>
Structure	Humanized IgG monoclonal antibody	Fab fragment of humanized IgG monoclonal antibody	2nd Ig domain of VEGFR1 and 3rd Ig domain of VEGFR2 fused to the Fc portion of human IgG1
Size (kDa)	149	48	115
Target	VEGF-A	VEGF-A	VEGF-A, VEGF-B, PlGF, Galectin-1
$K_D$ for VEGF-A <sub>165</sub> (pM)	58	46	0.490
Intravitreal half-life (days)	6.7–10	7.1	9 (estimate)
Reference	[91, 94, 95]	[92, 94, 95]	[35, 93–95]

**Fig. 7** Structure and characteristics of anti-VEGF agents, including bevacizumab [91, 94, 95], ranibizumab [92, 94, 95], and aflibercept [35, 93–95]. VEGF vascular endothelial growth factor, VEGFR vascular endothelial growth factor receptor, PlGF placental growth factor



is a humanized anti-VEGF monoclonal antibody [91], ranibizumab is a humanized anti-VEGF monoclonal antibody Fab fragment with no Fc portion [92], and aflibercept is a fusion glycoprotein consisting of extracellular domains of VEGF receptors 1 and 2 and the Fc domain of human immunoglobulin [93]. Bevacizumab and ranibizumab can bind to VEGF-A and aflibercept can bind to VEGF-A, VEGF-B, placental growth factor, and Galectin-1 [35, 94]. The systemic half-life of these agents varies depending on the presence or absence of Fc fragments in their molecules; however, the intravitreal half-life is reported to be 6.7–10 days for bevacizumab, 7.1 days for ranibizumab, and approximately 9 days for aflibercept [95].

The efficacy and safety of these three anti-VEGF agents in patients with DME have been evaluated in clinical studies [6–10, 78, 96], and all are incorporated into the recommendations and guidelines for the treatment of DME [12–14, 58].

### Efficacy

Bevacizumab, ranibizumab, and aflibercept significantly improve visual acuity and reduce retinal thickness in patients with DME (Table 1) [6–10, 78]. The post hoc analyses of the RISE/RIDE studies report that ranibizumab improved the visual outcome in patients with poor visual prognostic factors, such as subretinal fluid, intraretinal cysts, severe retinal thickening, or a history of renal disease [55].

Previous large-scale clinical studies of anti-VEGF agents for DME have mainly included patients with a visual acuity of 20/32 or worse [6–10]. The Protocol T study conducted by DRCR.net demonstrated the effectiveness of anti-VEGF agents in patients with visual acuity of 20/32–20/40 [78], but did not evaluate their effectiveness in patients with good visual acuity (20/25 or better). Since publication of the results of the recent survey of retinal experts in Japan [15], which suggests that patients with DME and good visual acuity might benefit from anti-VEGF therapy, DRCR.net has embarked on a study of anti-VEGF therapy in patients with center-involved DME and visual acuity of 20/25 or better [97]. This study has three treatment arms: a prompt intravitreal anti-VEGF (aflibercept) group, a prompt focal (direct)/grid photocoagulation (+ deferred anti-VEGF) group, and an observation (+ deferred anti-VEGF) group. The primary efficacy endpoint is the percentage of eyes that have lost at least 5 letters of visual acuity in 2 years [97].

There has been a suggestion that anti-VEGF agents could play a role in the treatment of diabetic retinopathy. The exploratory analysis of the RISE/RIDE studies showed that treatment with ranibizumab for 12–36 months

decreased the severity of diabetic retinopathy and prevented progression to proliferative diabetic retinopathy [98]. In the VIVID/VISTA studies, a significantly greater proportion of patients in the aflibercept group showed an improvement of at least 2 steps on the ETDRS Diabetic Retinopathy Severity Scale when compared with the photocoagulation group at weeks 52 and 100, suggesting that aflibercept may help to prevent progression of diabetic retinopathy [9, 99].

The recently reported longer-term studies of anti-VEGF therapy show that visual acuity gained by year 1 was maintained at year 3 or 5 [100, 101]. This durable effect would be valuable in the treatment of a chronic disease like DME. These studies also report a decrease in the frequency of injections during the 5-year study period. At the end of the 2-year RESTORE extension study, patients who were switched to anti-VEGF therapy had the same degree of improvement in visual acuity as those who had received anti-VEGF therapy during the core study and continued treatment [100]. However, Bressler et al. report that the patients in their long-term study who crossed over to anti-VEGF therapy did not show the same degree of improvement in visual acuity as those who started on anti-VEGF therapy [102].

Post hoc analyses have been performed to identify patients who would benefit from anti-VEGF agents [54, 103]. It appears that anti-VEGF therapy might have benefits in patients with early DME, and interestingly this effect seems to be independent of control of blood pressure and blood sugar levels.

### Safety

The safety profiles of the anti-VEGF agents in patients with DME are generally favorable [5]. The incidence of endophthalmitis in the Phase III studies of ranibizumab was approximately 1% [6–8]. There were no reports of endophthalmitis in the Phase III studies of aflibercept (VIVID/VISTA) [9]. In the RISE/RIDE studies of ranibizumab, death and stroke were more common in the 0.5 mg group than in the 0.3 mg group [7]. Meanwhile, in the DRCR.net Protocol I study, the cardiovascular and cerebrovascular event rates in the ranibizumab (0.5 mg + prompt or deferred laser) group were lower than in the sham (+ prompt laser) group [10]. A further indirect analysis comparing aflibercept (five 2-mg injections every 4 weeks followed by 2-mg injections every 8 weeks) with ranibizumab (0.5 mg PRN) in eyes with center-involved DME reported no significant difference in safety outcomes between the two agents, including for ocular/non-ocular adverse events and all-cause mortality [104]. In the meta-analysis of the RISE/RIDE and VIVID/VISTA studies, a higher risk of

**Table 1** Summary of pivotal clinical trials

	RESTORE [6]	RISE/RIDE [7]	REVEAL [8]	VIVID/VISTA [9]
Participants	345 patients aged $\geq 18$ years, with type 1 or 2 diabetes mellitus and visual impairment due to DME	377/382 patients aged $\geq 18$ years, with type 1 or 2 diabetes mellitus and vision loss from DME, and macular edema	396 patients aged $\geq 18$ years, with type 1 or 2 diabetes mellitus, BCVA of 78–39 ETDRS letters, and visual impairment due to DME	406/466 adult patients with type 1 or 2 diabetes mellitus and DME with central involvement
Treatment arms	Ranibizumab (n = 116) Ranibizumab + laser (n = 118) Laser (n = 111) 3 consecutive monthly injections of ranibizumab 0.5 mg, followed by 1 injection per month, to be continued if stable visual acuity was not achieved	Ranibizumab 0.3 mg (n = 125/125) Ranibizumab 0.5 mg (n = 125/127) Sham (n = 127/130) Monthly injections of ranibizumab 0.3 or 0.5 mg	Ranibizumab (n = 133) Ranibizumab + laser (n = 132) Laser (n = 131) On day 1, injection of ranibizumab 0.5 mg, continued monthly until stable vision was achieved. As of month 3, 1 injection per month was continued if stable vision was not yet achieved	Aflibercept 2q4 (n = 136/154) Aflibercept 2q8 (n = 135/151) Laser (n = 132/154) Aflibercept 2 mg every 4 weeks or 2 mg every 8 weeks after 5 initial monthly doses (from baseline to week 16)
Mean change in BCVA letter score from baseline	Month 12 Ranibizumab: 6.8 Ranibizumab + laser: 6.4 Laser: 0.9	Month 24 Ranibizumab 0.3 mg: 12.5/10.9 Ranibizumab 0.5 mg: 11.9/12.0 Sham: 2.6/2.3	Month 12 Ranibizumab: 6.6 Ranibizumab + laser: 6.4 Laser: 1.8	Week 52 Aflibercept 2q4: 10.5/12.5 Aflibercept 2q8: 10.7/10.7 Laser: 1.2/0.2
Mean change in CRT/ CFT / CRST / CST from baseline ( $\mu\text{m}$ )	Month 12 Ranibizumab: -118.7 Ranibizumab + laser: -128.3 Laser: -61.3	Month 24 Ranibizumab 0.3 mg: -250.6/-259.8 Ranibizumab 0.5 mg: -253.1/-270.7 Sham: -133.4/-125.8	Month 12 Ranibizumab: -134.6 Ranibizumab + laser: -171.8 Laser: -57.2	Week 52 Aflibercept 2q4: -195.0/-185.9 Aflibercept 2q8: -192.4/-183.1 Laser: -66.2/-73.3
SAEs	Non-ocular SAEs Ranibizumab: 20% Ranibizumab + laser: 14.2% Laser: 13.6%	Any SAEs Ranibizumab 0.3 mg: 5.6/9.6% Ranibizumab 0.5 mg: 11.9/5.6% Sham: 10.6/9.4%	Non-ocular SAEs Ranibizumab: 10.5% Ranibizumab + laser: 9.8% Laser: 14.1%	Non-ocular SAEs Aflibercept 2q4: 23.0% Aflibercept 2q8: 22.3% Laser: 22.6%

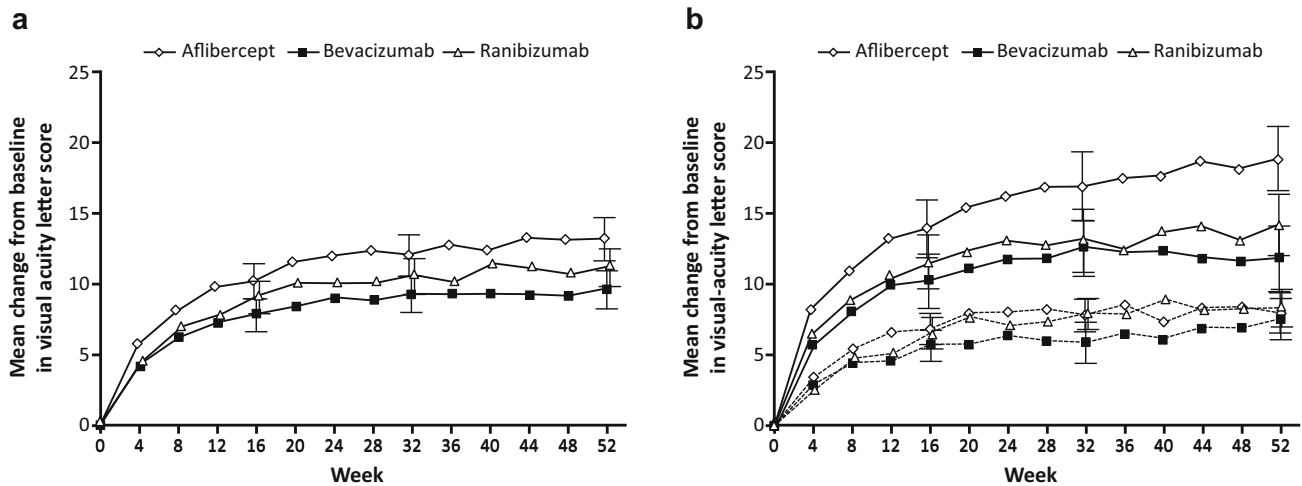
DME diabetic macular edema, BCVA best-corrected visual acuity, CRT central retinal (subfield) thickness [RESTORE], CFT central foveal thickness [RISE/RIDE], CRST central retinal subfield thickness [REVEAL], CST central (optical coherence tomography) subfield thickness [VIVID/VISTA], SAE serious adverse event

cardiovascular events was found in the arms receiving the highest and most frequent doses [105], suggesting that anti-VEGF agents have to be used carefully in patients with poor health status.

### Choice of agents

In the Protocol T study, bevacizumab, ranibizumab, and aflibercept were compared head-to-head, and all three were confirmed to be effective in patients with center-involved DME (Fig. 8a) [78]. The improvement in visual acuity at

1 year was significantly greater in patients in the aflibercept group who had an initial visual acuity of 20/50 or worse than in their counterparts in the bevacizumab and ranibizumab groups, but in patients who had an initial visual acuity of 20/32–20/40 there was no significant difference between the treatment groups in terms of improvement (Fig. 8b) [78]. At 2 years, however, patients in the aflibercept group who had a baseline visual acuity of 20/50 or worse showed greater improvement of visual acuity when compared with patients receiving the other agents, but there was no significant advantage to aflibercept over ranibizumab [106].



**Fig. 8** Mean changes in visual acuity over time in the DRCR.net Protocol T study. **a** Overall changes. **b** Changes according to baseline visual acuity: solid lines indicate a baseline visual acuity of 20/50 or worse, and dashed lines indicate a baseline visual acuity of 20/32–20/40. The number of eyes assessed at each 4-week interval ranged from

195 to 224 in the aflibercept group, 188–218 in the bevacizumab group, and 188–218 in the ranibizumab group. Bars indicate 95% confidence intervals. Reproduced with permission from Wells et al. [78]. Copyright © 2017 Massachusetts Medical Society. All rights reserved

There were no significant differences between the bevacizumab, ranibizumab, and aflibercept groups in rates of Anti-Platelet Trialists' Collaboration (APTCL) events (a cluster endpoint of serious adverse events, hospitalization, death, or major cardiovascular events) at 1 year [78]. By 2 years, APTCL events had occurred in 5% of patients in the aflibercept group, 8% of patients in the bevacizumab group, and 12% of patients in the ranibizumab group [106].

The recent survey of Japanese retinal experts revealed that anti-VEGF agents were the most frequently used first-line therapy for center-involved diffuse macular edema, regardless of visual acuity [15]. More than half the respondents reported using bevacizumab, ranibizumab, or aflibercept according to the needs of individual patients with DME [15]. Approximately 60% of respondents reported that their choice of agent would be based on the 1 year results of the Protocol T study, and most reported that the main factor affecting their choice of drug was its effectiveness in patients with a visual acuity of less than 20/40 in the evaluation at 1 year [15].

Based on the results of the Protocol T study, the American Society of Retina Specialists Anti-VEGF for Diabetic Macular Edema Comparative Effectiveness Panel considers that patients with worse visual acuity at initiation of treatment would derive greater benefit from aflibercept at 1 year [107]. On the other hand, when visual acuity is good, bevacizumab might be the agent of choice because of its cost-effectiveness. The panel concluded that ophthalmologists should choose from the three anti-VEGF agents on a patient-by-patient basis [107]. It should be noted that there are differences between Japan and the US in terms of

treatment settings and costs of each agent when extrapolating data from the US to clinical practice in Japan.

### Treatment regimens

In Japan, the package inserts for ranibizumab and aflibercept recommend that during the loading phase ranibizumab should be administered at doses of 0.5 mg (“preferably administered as one injection per month until achieving stabilization of visual acuity”) and aflibercept at doses of 2 mg (“administered once per month for a total of 5 administrations”). Most retinal experts in Japan consider stability of central retinal thickness and/or visual acuity to be the parameters indicating stabilization of disease activity during anti-VEGF monotherapy in the loading phase [15]. In the Phase II (DA VINCI) study, aflibercept 2 mg was administered on three occasions at 4-week intervals during the loading phase. When patients did not receive aflibercept for 4 weeks after the last dose (week 12 from the initial dose), a mild decrease in visual acuity and a slight increase in central retinal thickness were observed at week 16 [108]. In the VIVID/VISTA studies [9], aflibercept 2 mg was administered every 4 weeks for a total of five doses; however, similar changes were not observed.

In the Japanese survey of retinal experts, more than 70% of respondents administered anti-VEGF agents PRN in the maintenance phase and 50% considered the treat-and-extend regimen to be ideal [15]. The recently reported RETAIN study compared a treat-and-extend regimen and a PRN regimen with respect to changes in BCVA. It was found that the treat-and-extend regimen was not inferior to

the PRN regimen and the number of clinical visits between achieving a stable BCVA and assessment at month 24 was smaller in the treat-and-extend group (median 8) than in the PRN group (median 18) [96].

When asked about the maximum number of injections of anti-VEGF monotherapy they would administer before switching to combination therapy or other treatment options, 23% of retinal experts in the Japanese survey reported that they would administer at least 3 injections and 18% at least 5 injections; approximately 40% reported no specific number of injections [15]. A retrospective analysis of Medicare claims' data in the US for 2008–2010 showed that the average annual number of anti-VEGF injection claims per patient with DME was 4.2 [109].

### Treatment of persistent DME

The post hoc exploratory analyses of the Protocol I study shows that approximately 40% of patients had persistent DME (central subfield thickness  $\geq 250$   $\mu\text{m}$  on time-domain OCT) at 24 weeks after initiating treatment with ranibizumab but that this rate decreased after 3 years of treatment [110]. Even in patients whose DME persisted for 3 years, 42.5% had a visual acuity improvement of  $\geq 10$  letters [110].

The results of a recently published retrospective study show that central macular thickness was significantly reduced in patients with persistent DME who were converted from ranibizumab or bevacizumab (at least 4 consecutive injections) to aflibercept (at least 2 injections afterwards) [111]. Although there was a trend of improved visual acuity and a decrease in intraocular pressure, these changes were not significant [111].

The respondents in the Japanese survey of retinal experts indicated that their choice of treatment for persistent DME after multiple anti-VEGF injections and/or laser therapy was vitrectomy (73%), steroids (20%), or a switch to another anti-VEGF agent (7%) [15]. However, there is still no definitive evidence concerning the treatment of patients who do not respond positively to anti-VEGF therapy.

### Perspectives

In Japan, two anti-VEGF agents were approved in 2014 for DME, and these agents are now recognized as first-line therapy for the treatment of center-involved diffuse DME. The loading regimen for anti-VEGF monotherapy has been determined based on visual acuity in large-scale clinical studies. However, in everyday clinical practice, the loading regimen is frequently determined according to anatomical parameters, and there is not yet a consensus regarding this regimen. In the maintenance phase, anti-VEGF therapy is most commonly administered PRN in Japan; however, there are no established criteria for retreatment in the

clinical setting. Most retinal experts consider that in the maintenance phase a treat-and-extend regimen is preferable. Therefore, further accumulation and evaluation of evidence is required. As macular edema sometimes persists even after anti-VEGF agents are administered in the early stage, there is need for more research to discover effective treatment options for these cases. There is still no consensus regarding treatment of patients who are refractory to anti-VEGF agents, specifically whether to continue treatment beyond refractoriness, switch agents, or proceed to a surgical treatment. Currently, anti-VEGF therapy is mainly used for the treatment of DME; however, there are unmet needs to be addressed for the long-term maintenance of visual acuity.

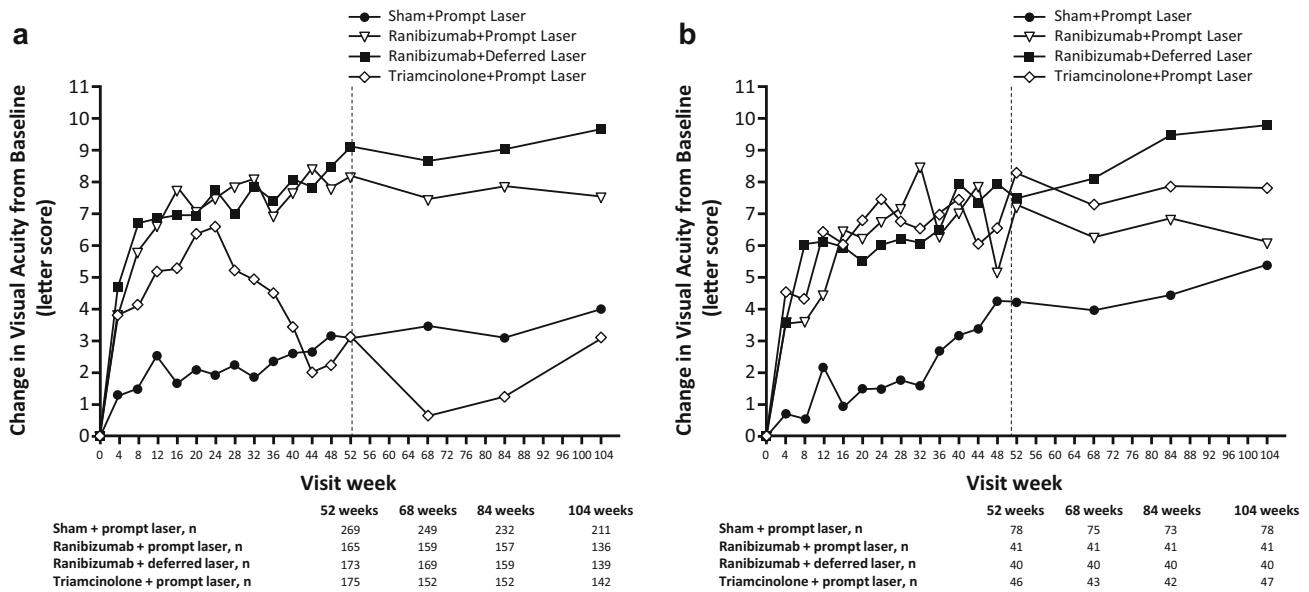
### Steroids for DME

Intravitreal triamcinolone acetonide is now approved in Japan for use in patients with DME. Compared with no treatment, a single intravitreal injection of triamcinolone acetonide 4 mg significantly improved BCVA and central macular thickness in Japanese patients with macular edema associated with non-proliferative diabetic retinopathy at week 12 [112]. Although intravitreal implants of fluocinolone acetonide and dexamethasone have been approved for DME in Europe and the US [113, 114] they have yet to be approved in Japan.

Sub-Tenon's injection of triamcinolone acetonide is often used off-label in Japan [115–117], and a clinical study for a drug approval application (JapicCTI-132139) is has been submitted.

### Benefits and risks

DME is a consequence of the chronic inflammatory state caused by diabetes. Expression of VEGF and other permeability/inflammatory factors can be decreased by steroids [118, 119]. In the Protocol I study, visual acuity continued to improve in the triamcinolone (+ prompt laser) group until week 24 but decreased thereafter. There was no significant difference between the triamcinolone (+ prompt laser) group and the sham (+ prompt laser) group at the 1-year and 2-year visits (Fig. 9a) [10, 120]. Elevated intraocular pressure and need for cataract surgery were significantly more common in the triamcinolone (+ prompt laser) group than in the ranibizumab (+ prompt laser) group and the sham (+ prompt laser) group [10, 120]. In pseudophakic eyes, triamcinolone (+ prompt laser) was more effective than sham (+ prompt laser) and as effective as ranibizumab (+ prompt laser) (Fig. 9b); however, triamcinolone (+ prompt laser) had a greater risk of increased intraocular pressure [10, 120]. In addition, the



**Fig. 9** Mean changes in visual acuity over time in the DRCR.net Protocol I study. **a** Changes using all available data: *P* values (analysis of covariance) for the difference in mean change in visual acuity when compared with the sham + prompt laser group ( $n = 211$ ) at the 104-week study visit: 0.05 for the ranibizumab + - prompt laser group ( $n = 136$ );  $< 0.001$  for the ranibizumab + deferred laser group ( $n = 139$ ); and 0.57 for the triamcinolone + prompt laser group ( $n = 142$ ). **b** Changes in eyes

that were pseudophakic at baseline for the cohort that completed a 2-year visit: *P* values (analysis of covariance) for the difference in mean change in visual acuity when compared with the sham + - prompt laser group ( $n = 78$ ) at the 104-week study visit: 0.83 for the ranibizumab + prompt laser group ( $n = 41$ ); 0.15 for the ranibizumab + deferred laser group ( $n = 40$ ); and 0.53 for the triamcinolone + prompt laser group ( $n = 47$ ). Reproduced with permission from Elman et al. [120]

incidence of endophthalmitis is reported to be significantly higher with intravitreal injections of a steroid than with intravitreal injections of an anti-VEGF agent [121].

The results of the exploratory analysis of the Protocol I data show that ranibizumab was more effective than triamcinolone in preventing progression of retinopathy in patients with non-proliferative diabetic retinopathy, but both agents were effective in preventing progression of retinopathy in patients with proliferative diabetic retinopathy [122].

Approximately 50% of the respondents in the Japanese survey of retinal experts reported using steroids (by intravitreal injection and off-label sub-Tenon’s injection) and the other 50% reported using anti-VEGF agents in patients with DME that persisted after vitrectomy with no improvement in visual acuity [15]. A retrospective analysis in Japan reports that patients with a history of vitrectomy had significantly fewer recurrences or persistence of DME after an off-label sub-Tenon’s triamcinolone injection, but those who underwent microaneurysm photocoagulation or subthreshold micropulse diode laser photocoagulation combined with a sub-Tenon’s triamcinolone injection were at increased risk of recurrent or persistent DME [123]. In pseudophakic eyes, steroid injections and anti-VEGF injections may be similarly effective for improving visual acuity and decreasing retinal thickening [120], but it is not clear how these patients fare in the long term [102]. Steroid

injections seem to be most effective for pseudophakic patients with proliferative diabetic retinopathy.

**Perspectives**

The risk of concurrent elevated intraocular pressure, cataract, and endophthalmitis should be assessed before using steroids. The role of steroids in patients after vitrectomy and in those refractory to anti-VEGF agents should be evaluated in the future. In Japan, a clinical trial of sub-Tenon’s injection of triamcinolone acetonide is underway with the aim of receiving approval to market the drug for DME. Sub-Tenon’s injection requires delicate manipulation, so it might carry a risk of procedure-related complications. Hence, a standard procedure should be established and attention paid to it. Steroids have a variety of physiological actions that anti-VEGF agents do not possess. These will be important considerations in future applications of steroids.

**Laser photocoagulation for DME**

**Focal (direct)/grid laser**

Laser photocoagulation of the macular area has become standard therapy for DME (CSME) since a report on focal

(direct)/grid laser use in the ETDRS in 1985 [61]. Focal (direct) laser photocoagulation involves direct treatment of focal fluorescein leaks, and is used for discrete points of retinal hyperfluorescence or focal leakage (most are microaneurysms) identified by FA [61, 124]. Grid laser photocoagulation is delivered to thickened areas of the retina showing capillary dropout (in early-phase FA) and/or diffuse fluorescein leakage (often observed in the areas with capillary dropout in late-phase FA), and is applied in a grid pattern [61, 124].

DRCR.net conducted a study comparing two laser photocoagulation techniques for the treatment of DME, i.e., modified ETDRS photocoagulation (using burns that are lighter and less intense than those originally specified in the ETDRS) and a mild macular grid laser technique (application of mild and widely spaced burns throughout the macula, avoiding the foveal region), and found modified ETDRS grid photocoagulation to be superior to mild macular grid laser photocoagulation for decreasing retinal thickening [125]. Approximately 70% of the retinal experts in Japan responded that they used focal laser treatment, and approximately 20% used medical treatment in combination with focal/grid laser as the first-line therapy for center-involved macular edema with an obvious leakage point [15]. The most common distance between the center of the macula and the point of leakage when applying focal laser was 750  $\mu\text{m}$  or more (approximately 50% of respondents) followed by 500  $\mu\text{m}$  or more (approximately 30%) [15]. Laser photocoagulation was initially applied for lesions located 500  $\mu\text{m}$  or more from the center of the macula in the ETDRS [61].

### Benefits and risks

Improvement of edema in response to focal laser treatment may result from occlusion of leaking microaneurysms. Grid laser photocoagulation to areas of capillary dropout/non-perfusion reduces the oxygen demand of ischemic retinal cells, leading to long-term suppression of ischemia-induced overexpression of VEGF [126]. Other indirect effects have been suggested, including changes in the biochemical processes occurring in the retinal pigment epithelium [127]. According to ETDRS report number 1, the proportion of eyes that lost 15 or more letters on the ETDRS visual acuity chart in the immediate photocoagulation group (12%) was lower than that in the deferred photocoagulation group (24%) at 3 years [61].

The ETDRS study of photocoagulation reports that vision loss due to subretinal neovascularization and atrophic creep (enlargement of the laser scars) may occur after laser treatment [128, 129]. However, with advances in laser technology, such as subthreshold diode micropulse laser photocoagulation and short-pulse lasers, damage to

the normal retina is prevented and both accuracy and treatment time are improved [130–133].

### Combination with an anti-VEGF agent

Approximately 90% of the respondents in the survey of retinal experts in Japan reported using a combination of anti-VEGF injections and focal laser treatment, although variations were observed in the proportion of patients treated with combination therapy. The timing of the laser therapy was most commonly after anti-VEGF therapy [15].

The results of a 5-year follow-up of the Protocol I study showed that the improvements in visual acuity were quite similar between the ranibizumab + prompt laser group and the ranibizumab + deferred laser group for eyes with a baseline visual acuity letter score  $\geq 66$  (approximately 20/50 or better), but significantly better in the ranibizumab + deferred laser group for eyes with a baseline visual acuity letter score  $\leq 65$  (worse than about 20/50) [101]. For focal DME, however, the results from the REVEAL study conducted in Asian patients showed that the change in BCVA letter score at month 12 was + 4.9 letters in the ranibizumab monotherapy group compared with + 7.8 letters in the focal/grid laser + ranibizumab group [8]. In addition, the proportion of patients with a maximum treatment-free interval of 3 months or more was 38.3% in the ranibizumab monotherapy group and 50.8% in the focal/grid laser + ranibizumab group [8]. Combined laser therapy would be an option for management of focal DME, especially when attempting to extend the anti-VEGF retreatment intervals to reduce the total number of intravitreal anti-VEGF injections required. The findings of an ongoing multicenter trial in Japan (UMIN000012549) suggest that short-pulse focal/grid laser photocoagulation could reduce the number of intravitreal ranibizumab injections required to resolve macular edema [134]. However, further investigations are needed.

### Panretinal photocoagulation

In the survey of retinal experts in Japan, approximately 50% of respondents used a combination of anti-VEGF therapy with panretinal (or targeted retinal) photocoagulation in more than half of eyes with DME of patients who received anti-VEGF agents in the late phase of pre-proliferative diabetic retinopathy, and more than 80% reported that they performed panretinal/targeted retinal photocoagulation after anti-VEGF injections [15, 135].

In the Protocol J study performed by DRCR.net, patients with severe non-proliferative or proliferative diabetic retinopathy with center-involved DME received ranibizumab, triamcinolone, or sham injection (each combined with focal/grid laser) prior to panretinal photocoagulation. The

mean  $\pm$  standard deviation changes in visual acuity letter score were significantly better in the ranibizumab ( $+ 1 \pm 11$ ) and triamcinolone ( $+ 2 \pm 11$ ) groups when compared with the sham group ( $- 4 \pm 14$ ) in the short term (at the 14-week visit), suggesting that the risk of worsening of existing macular edema and associated loss of visual acuity following panretinal photocoagulation can be reduced by administration of intravitreal ranibizumab or triamcinolone [136].

In a study by Takamura et al., patients were enrolled if they had visual acuity of 20/40–20/320 and leakage from capillary retinal vessels and microaneurysms corresponding to DME and non-perfused areas identified on FA. The patients received bevacizumab after focal/grid laser and were then randomized to receive either targeted retinal photocoagulation for ischemic lesions or no additional laser therapy. Central retinal thickness decreased in both treatment groups in the month following anti-VEGF injection. Central retinal thickness then increased gradually in the group without targeted retinal photocoagulation but not in patients who received additional targeted retinal photocoagulation, indicating that targeted retinal photocoagulation may prevent recurrence of macular edema. These results suggest that residual retinal ischemia after focal/grid laser treatment and panretinal photocoagulation is involved in the pathogenesis of DME [135]. However, further evidence needs to be accumulated to elucidate the exact mechanism.

In the Protocol S study performed by DRCR.net, the effects of panretinal photocoagulation and an anti-VEGF agent (ranibizumab) on proliferative diabetic retinopathy were compared using the change in visual acuity at 2 years as the primary outcome. The anti-VEGF agent was demonstrated to be non-inferior to panretinal photocoagulation. Peripheral visual field loss and vitrectomy were significantly more common in the panretinal photocoagulation group [137]. Anti-VEGF therapy seems to be a theoretically reasonable treatment alternative for patients with proliferative diabetic retinopathy, although patient preference should be considered, given that panretinal photocoagulation may be less costly and require fewer clinic visits than anti-VEGF therapy.

## Perspectives

Although laser photocoagulation was found to be inferior to anti-VEGF therapy in terms of improvement in visual acuity and its inability to prevent leakage from the perifoveal capillaries, it is still an important treatment option for DME in clinical practice in Japan and is believed effective in maintaining improved visual acuity. Therefore, combination therapy using laser and anti-VEGF agents, which can prolong the interval to recurrence of macular

edema and the interval between anti-VEGF injections, should be investigated. It is also important to evaluate minimally invasive laser treatment, such as the subthreshold micropulse laser and short pulse laser/pattern scan laser, which are expected to cause no atrophic creep after a long period, as well as a navigation system to enable safer and more accurate laser photocoagulation. Further long-term investigations are required, and evidence needs to be accumulated regarding the effects of laser photocoagulation in DME, including the use of these new technologies.

## Vitrectomy for DME

### Purpose and mechanism

The role of vitrectomy in the treatment of DME remains to be fully elucidated. However, in clinical practice, there is a good deal of evidence suggesting that vitrectomy effectively restores retinal function and significantly decreases DME. Lewis et al. report that vitrectomy was effective in eyes with macular edema associated with a thickened and taut posterior hyaloid membrane [82]. Tachi et al. enrolled DME patients without a thickened hyaloid membrane and state that vitrectomy was effective in eyes without posterior vitreous detachment (PVD) [83]. Some studies point out that the outcome does not depend on the presence or absence of PVD [138, 139]. Terasaki et al. found that vitrectomy was effective in reducing foveal thickness and improving macular function also for DME without visible vitreomacular traction, although macular function recovered slowly compared to the anatomical recovery [140]. Various working mechanisms for the effectiveness of vitrectomy are reported. For example, vitrectomy relieves retinal traction, increases intraocular  $O_2$  partial pressure, and induces clearance of chemical mediators such as VEGF, and can therefore serve as an effective treatment for DME [141, 142]. However, according to the recent trend following introduction of anti-VEGF agents, candidates for vitrectomy include those with vitreomacular traction and those with an epiretinal membrane detected by OCT in current clinical practice.

### Outcomes

Although the precise mechanism by which vitrectomy decreases retinal thickness is still unclear, there are many reports that vitrectomy decreases macula edema and can improve visual acuity [82, 83, 138–140, 143–149]. A high level of evidence comes from DRCR.net Protocol D [146], a prospective cohort study of patients who underwent vitrectomy for DME. In that study, retinal thickening was reduced by vitrectomy in more than 80% of eyes with

vitreomacular traction, and 28–49% of eyes were estimated to have improved visual acuity while 13–31% were estimated to have worse visual acuity [146]. Similarly, a long-term study (with follow-up of 12–170 months) reports that long-term visual acuity improved in 52.7% of eyes with non-tractional DME after vitrectomy but deteriorated in 16% of eyes [144]. While improvement of BCVA after anti-VEGF therapy can be confirmed from a relatively early stage, following vitrectomy it is much slower. Approximately 3–4 months are required for macular edema to stabilize and for visual acuity the period is 12–24 months; however, the effects are maintained for a longer period [144, 150, 151].

A possible cause of decreased vision after vitrectomy is accumulation of hard exudates [152]. Another possible reason is patient selection bias, given that vitrectomy is performed in eyes with persistent DME that is refractory to other less invasive treatments and in which vitrectomy might not be effective. In selected patients earlier vitrectomy may achieve a better outcome. Factors such as a thickened hyaloid membrane, PVD, and traction are thought to be related to the outcomes. However, without adequate data from randomized controlled trials, the indication for vitrectomy in eyes with DME but no visible traction cannot be determined.

## Complications

Vitrectomy seems effective for DME but is associated with certain complications, including cataracts, retinal tear, retinal detachment, and neovascular glaucoma [146, 153]. Neovascular glaucoma is a severe complication following vitrectomy. In the long-term follow-up data reported by Kumagai et al., the rate in 486 eyes followed over 12–170 months of neovascular glaucoma was 3.9% and of glaucoma 4.5% [144]. Another group reports the incidence of neovascular complications to be 4.6% [153], suggesting that it is important to evaluate ischemic states and monitor patients on a monthly basis in the clinic. Complications such as cataracts are preventable. In Japan, cataract surgery is combined with vitrectomy to eliminate the visual loss that occurs with progression of cataract. For this reason, vitrectomy for DME seems to be more widespread in Japan than in the US. In view of the risk of complications, use of vitrectomy as a first-line therapy for DME has been limited. We need to balance the benefits and risks of vitrectomy for DME to decrease the complication rates seen in previous decades.

## Prognostic factors

Advances in OCT technology have allowed identification of the pathomorphology of DME in more detail.

Segmentation analysis of each retinal layer is useful for predicting the visual prognosis [154]. The visual prognosis after vitrectomy is associated with the integrity of the foveal photoreceptor layer as indicated by the IS/OS line on OCT images [155]. Murakami et al. report that the outer thicknesses in the temporal and inferior subfields were related to the postoperative visual acuity, although there was no significant association between postoperative visual acuity and pretreatment inner thickness in any subfield [156]. Kim et al. demonstrate an improvement in BCVA after vitrectomy in patients without an enlarged foveal avascular zone [157]. Multimodal preoperative evaluation of the macula will help to predict the outcome of vitrectomy.

Many studies show vitrectomy combined with peeling of the internal limiting membrane (ILM) to be an effective treatment for DME [143, 145, 147]. In a non-randomized, multicenter, clinical study conducted by the European Vitreo-Retinal Society, different treatments for DME were compared in 870 patients with a follow-up duration of 6 months to 2 years. In this study, vitrectomy with ILM peeling was more effective than anti-VEGF agents, steroids, or laser with regard to improvement of visual acuity; the proportion of  $\geq 3$ -line improvements was significantly higher for vitrectomy (55.2%) than for anti-VEGF agents (31.3%) [158]. Staining the ILM with triamcinolone achieved better improvement than non-peeling or staining the ILM with indocyanine green [143]. On the other hand, two research groups have recently reported finding no significant difference in long-term visual acuity [148], change in BCVA, or reduction of central macular thickness [149] using vitrectomy with ILM peeling versus vitrectomy with no ILM peeling. The necessity of routine ILM peeling is still a matter of debate. Routine treatment with anti-VEGF agents complicates the design of studies to investigate the efficacy of vitrectomy for DME itself.

Systemic factors have also been shown to affect the prognosis after vitrectomy [150, 159]. Decreases in foveal thickness after vitrectomy are associated with preoperative glycemic control and possibly, the removal of volume of vitreous gel [150].

## Management of recurrent macular edema after vitrectomy

Recurrence of edema may be an important reason to avoid the routine use of vitrectomy. One study demonstrates increased intravitreal concentrations of monocyte chemoattractant protein-1 following vitrectomy, suggesting that the inflammatory process may continue even after successful vitrectomy [160]. Creation of PVD is also reported to be an important consideration. Macular edema recurred in 2 cases with the remaining posterior vitreous



cortex attached after approximately 1 year [140]. Sawa et al. found that vitrectomy decreases the rate of recurrence of macular edema in patients with PVD [161]. Other surgical procedures might be related to the recurrence of edema.

Vitrectomy is reported to have the undesirable effect of increasing the clearance of ranibizumab and aflibercept in macaque eyes [162]. Another small retrospective study indicates that there was no change in BCVA or foveal thickness in the 6 months after injection of bevacizumab for DME in eyes with previous vitrectomy [163]. These data suggest that clearance of drugs is rapid and that drug half-lives are shortened in vitrectomized eyes. However, the results of an exploratory post hoc analysis of the Protocol I study indicates favorable functional and anatomical outcomes in vitrectomized eyes over 3 years of follow-up. There were no differences in the number of injections or laser treatment between eyes with and without previous vitrectomy during follow-up [164]. The volume of remaining vitreous might affect the effectiveness of anti-VEGF therapy after vitrectomy. There is limited evidence concerning the management of DME in patients with a history of vitrectomy [165, 166]. In Japan, sub-Tenon's capsule triamcinolone acetonide would be one option; however, injection of triamcinolone can cause an increase in intraocular pressure and/or HbA<sub>1c</sub> as a complication [167]. Additional research is warranted to determine the best management strategy.

### Patient selection

Vitrectomy can be an appropriate treatment choice for certain patients with DME even in the anti-VEGF era. If patients with diffuse DME have apparent vitreomacular traction, it is reasonable to perform vitrectomy to relieve it early before the photoreceptors in the fovea are damaged [146, 168]. Because it can have a long-lasting effect after a single procedure, vitrectomy may also be a useful treatment option for DME that persists despite anti-VEGF therapy [169, 170]. However, this group would include intractable cases, so the proportion of patients in whom vitrectomy will prove effective might be low.

More than 80% of respondents in the survey of retinal experts in Japan reported that vitrectomy is their first-line therapy for DME with apparent vitreomacular traction [15]. More than 70% of respondents felt that vitrectomy should be used to treat center-involved macular edema that persists without improvement after multiple anti-VEGF injections and/or laser therapy [15]. There may be VEGF-independent mechanisms involved in the development and persistence of macular edema [171].

Besides these patients, those who do not respond to anti-VEGF agents, those who have experienced cardiovascular/

cerebrovascular events during the preceding months, elderly patients with cataract, and those who need additional peripheral photocoagulation are thought to be good candidates for vitrectomy. Nevertheless, there is no consensus about the timing or indications for vitrectomy in patients with DME at this time.

### Perspectives

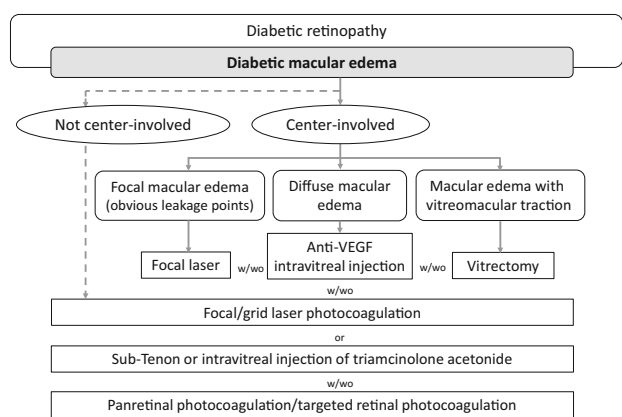
Vitrectomy is an invasive procedure but remains an important option for DME, especially in selected patients who do not respond to other treatments. Vitrectomy may become a safer option with the development of new technology, such as small-gauge instruments, wide-angle viewing systems, and safer dyes used for visualization of the vitreous and membrane. For increased efficacy, vitrectomy can be combined with laser, intravitreal anti-VEGF, or injection of steroids to compensate for the disadvantages linked to each treatment. Unfortunately, there is no randomized controlled trial with adequate statistical data to evaluate the effectiveness of vitrectomy. Given that there are many approaches to treatment of DME, a registration study reflecting real-world clinical practice would be necessary to evaluate the effectiveness of multidisciplinary treatment including vitrectomy.

### Conclusion

The advances in management of DME in recent years have been remarkable [2, 5, 11]. Anti-VEGF therapy will continue to play an important role in the treatment for DME, but there are still unmet needs, such as treatment for persistent DME, long-term maintenance of improved visual acuity, and safety concerns in high-risk patients. A multimodal approach has the potential to treat complex aspects of DME.

Based on the results of a survey of retinal experts in Japan [15] and the discussion in this paper, we propose a clinical practice algorithm for the management of DME in Japan (Fig. 10). Anti-VEGF agents are the first-line therapy for center-involved diffuse macular edema. Most experts choose focal laser treatment for patients with an obvious leakage point, and consider combination therapy with anti-VEGF agents. Further, most experts choose vitrectomy for DME with apparent vitreomacular traction. Use of steroids may also be considered in certain circumstances. Panretinal photocoagulation or targeted retinal photocoagulation is performed to reduce the production of VEGF in the ischemic area and to prevent progression of diabetic retinopathy after anti-VEGF injections.

It is important for management of DME in Japan to establish a multimodal approach to treatment, centered on



**Fig. 10** Proposed clinical practice algorithm for the management of diabetic macular edema in Japan. The first-line therapy is focal (direct) laser photocoagulation for center-involved macular edema with an obvious leakage point, intravitreal injection of an anti-vascular endothelial growth factor (VEGF) agent for diffuse macular edema, and vitrectomy for macular edema with apparent vitreomacular traction [15]

anti-VEGF therapy, and including steroid therapy, laser photocoagulation and vitrectomy. Future challenges concerning the development of a treatment guideline are summarized as follows: (1) optimization of the anti-VEGF injection regimen, that is, evaluation of a regimen which can maximize the improvement in visual acuity and reduce the burdens for both patients and physicians; (2) optimization of treatment by combining laser photocoagulation or vitrectomy with anti-VEGF agents; (3) optimization of treatment and management appropriate to specific pathological conditions; (4) accumulation of evidence for second-line therapy in patients refractory to first-line therapy; and (5) reinforcement of cooperation between ophthalmologists and physicians for appropriate systemic management, including prevention.

Considerable time will be required to address these challenges. Therefore, a consensus among experts is needed for the optimal management of DME, based on the current status of clinical practice in Japan.

**Acknowledgements** Medical writing and editing support was provided by Havas Worldwide Japan K.K.

**Conflicts of interest** H. Terasaki, Grants (Novartis, Pfizer, Santen, Wakamoto), Consultant fee (Bayer), Honorarium (Bayer, Novartis, Pfizer, Santen, Wakamoto), Writing fee (Santen); Y. Ogura, Consultant fee (Alcon, Janssen, Wakamoto), Speaker fee (Alcon, Baush Lomb, Bayer, HOYA, Kissei, Kowa, Novartis, Santen, Sanwa, Senju, Topcon); S. Kitano, Grant (Novartis); T. Sakamoto, Grant (Alcon), Consultant fee (Senju), Honoraria (Alcon, Bayer, Novartis, Santen, Senju, Wakamoto), Travel fee for lecture (Alcon, Bayer, Novartis, Santen, Senju, Wakamoto); T. Murata, None; A. Hirakata, Grant (Santen), Honorarium (Bayer, Novartis, Santen); T. Ishibashi, Consultant fee (Alcon, Bayer, Novartis, Santen, Senju, Wakamoto).

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