



Treatment for diabetic macular oedema: looking further into the evidence

Noemi Lois

Wellcome-Wolfson Centre for Experimental Medicine, School of Medicine, Dentistry and Biomedical Sciences, Queen's University, Belfast, UK
Correspondence to: Noemi Lois, MD, PhD, FRCS(Ed), FRCOphth. Wellcome-Wolfson Centre for Experimental Medicine, Queen's University, 97 Lisburn Road, Belfast BT9 7BL, UK. Email: n.lois@qub.ac.uk.

Abstract: Throughout the years, people with diabetic macular oedema (DMO) have seen the number of options for their treatment increasing. Laser photocoagulation was the first of these and great experience is behind it; intraocular steroids followed and more recently anti-vascular endothelial growth factor (anti-VEGF) agents came to light. Ophthalmologists face now the dilemma of determining which may be the best therapeutic strategy for each particular patient based on best available evidence. This article summarises data available from randomised clinical trials (RCTs) on treatments for DMO and provides some facts about this condition and its treatments that need to be taken into consideration when treatment decisions are made.

Keywords: Diabetic macular edema (DME); diabetic macular oedema (DMO); anti-vascular endothelial growth factor (anti-VEGF); laser photocoagulation; randomised clinical trials (RCTs); retina; diabetic retinopathy

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Introduction

The number of people with diabetes has risen from 108 million in 1980 to 422 million in 2014 (1). Diabetic macular oedema (DMO) is a major sight-threatening complication of diabetes. Based on the estimated prevalence of DMO (~7% in diabetic patients) (2) there are at least 29.5 million people suffering from DMO worldwide. The prevalence of DMO increases with the duration of diabetes; it has been estimated that ~20% of diabetics will have DMO after 20 years of disease (2). The risk of developing DMO increases with poor glycemic control and with increased blood pressure and serum cholesterol levels (2). People diagnosed at age 30 or older with diabetes and who develop clinically significant macular oedema (CSMO), as defined by the Early Treatment Diabetic Retinopathy Study (ETDRS) criteria (see below), seem to have increased ischemic heart disease mortality (3).

Definition of DMO

Several definitions for DMO have been used over the years and should be taken into consideration when interpreting the results of published landmark randomised clinical trials

(RCTs) on treatments for DMO.

Thus, DMO has been classified as CSMO/non-CSMO, focal/diffuse, ischaemic/non-ischaemic, centre/non-centre involving DMO, tractional/non-tractional, or mixed. Until relatively recently, CSMO/non-CSMO was the most widely definition used. CSMO was considered when thickening at/or within 500 microns from the centre of the fovea or hard exudation at/or within 500 microns from the centre of the fovea with adjacent retinal thickening or thickening of 1 disc area or more if within 1 disc diameter from the centre of the fovea, was present (4).

Based on findings on fundus fluorescein angiography (FFA) and depending on the extension of the area of leakage at the macula DMO can be classified as focal, when focal leakage from microaneurisms is detected, or diffuse, when diffuse leakage from diffusely dilated capillaries and/or from retinal pigment epithelium (RPE) throughout the macula is observed (5). There is no clear consensus with regards to the differentiation between ischaemic and non-ischaemic DMO. Some refer to ischaemic DMO whenever on FFA there is disruption of the perifoveal capillaries; others would refer to ischaemic DMO whenever areas of ischaemia are

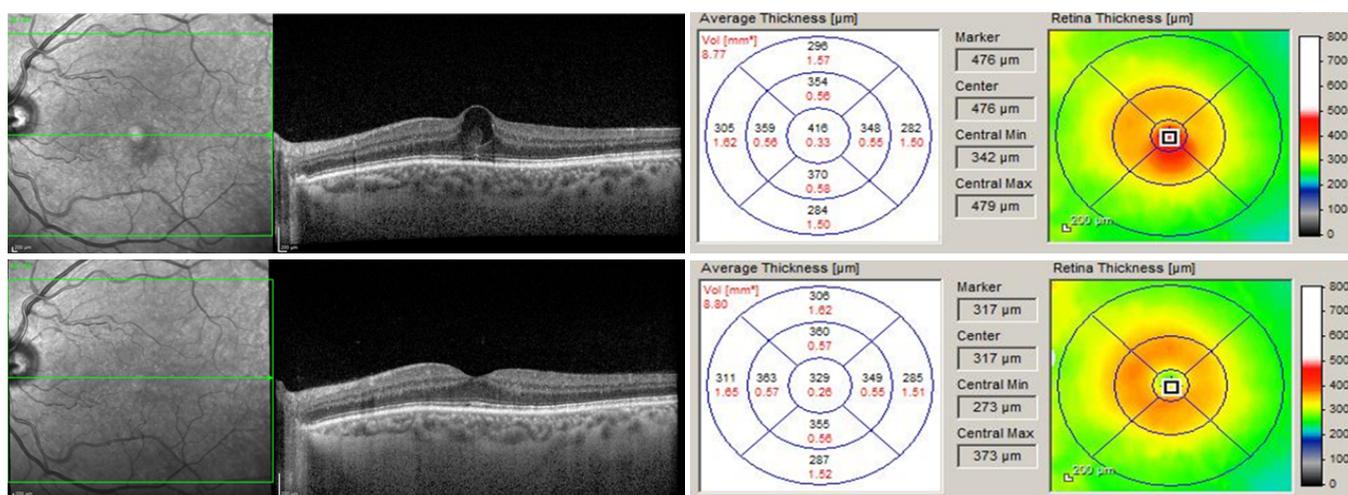


Figure 1 A diabetic patient presented in January 2015 with reduced vision in both eyes; optical coherence tomography (OCT) clearly demonstrated central involving diabetic macular oedema (DMO) (top row; left eye shown). The mean central subfield thickness was over 400 microns (top centre row); anti-VEGF therapy was planned to be undertaken on the following week, as per patient request. The patient failed to attend his appointment and did not return to clinic until June 2015. By then, complete resolution of the DMO was noted (bottom centre row and bottom row; left eye shown) with no change in the systemic status of the patient.

detected anywhere at the macula.

With the advent of optical coherence tomography (OCT) DMO was classified as centre or non-centre involving based on the presence or absence, respectively, of fluid at the centre of the fovea. Using also OCT, DMO was defined as tractional or non-tractional based on the presence/absence of a tractional component (either traction from an incompletely detached posterior hyaloid or from epiretinal membranes).

Given the different types of DMO and the different mechanisms for fluid accumulation, it would be extremely unlikely that a given treatment would be appropriate for all patients; a more personalised therapeutic approach would seem more appropriate for the treatment of patients with DMO.

Natural history

Although most cases of DMO will progress and fluid accumulation will worsen over time with subsequent visual loss, spontaneous resolution of DMO can occur (*Figure 1*). It has been suggested that spontaneous resolution of DMO may be observed in ~33–35% of patients (6). On this regard, it is interesting to note that in the sham arm of the RISE and RIDE RCTs, only 74% and 70% of patients, respectively, received macular laser suggesting that that ~30% of patients the DMO may have improved over the follow-up period requiring no treatment.

As it is not clear on whom DMO may resolve spontaneously, it is not possible to fully determine which patients could potentially be observed rather than treated.

Unlike in the ETDRS study, recently conducted RCTs evaluating new treatments for DMO (see below) included only patients with some degree of visual loss ($\leq 20/32$ or $\leq 20/40$) (7–10). However, not all patients with DMO will present with reduced vision. DMO, even when marked and centre-involving, may not cause immediate subjective or objective sight loss (*Figure 2*).

Furthermore, it is not clear when visual loss would ensue in a particular patient if DMO were to be left untreated and, importantly, when would sight loss become irreversible (*Figure 3*).

Current treatments

Prevention

Ideally, preventing the development of DMO, rather than treating it once established, should be the best option to avoid sight loss. Given that only a small proportion of all patients with diabetes will develop DMO, identifying the people at higher risk for developing this complication would be essential to increase the likelihood for potential preventive treatments to be cost-effective. As stated above, people with poor glycemic control, hypertension and high

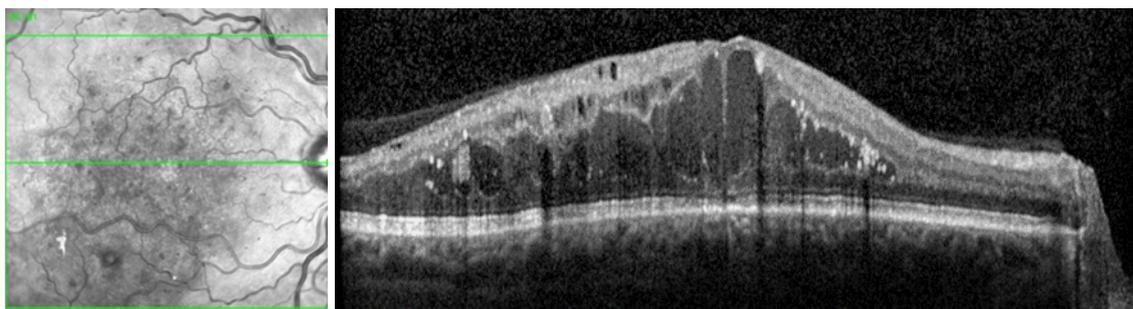


Figure 2 Optical coherence tomography (OCT) of the right eye of a patient with marked diabetic macular oedema (DMO). Although findings were symmetric in both eyes, the patient was asymptomatic and visual acuity was 6/6.

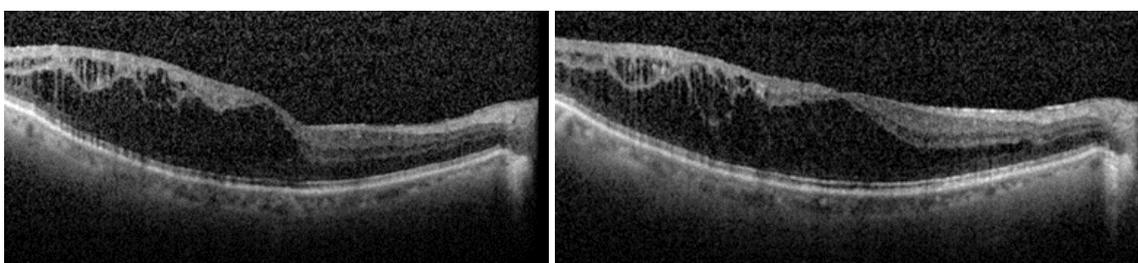


Figure 3 Optical coherence tomography scans of the left eye of a patient with diabetic macular oedema (DMO). In October 2014 central-involving DMO was noted in his right eye although he was asymptomatic with vision of 6/7.5 (left panel). Due to on-going problems which required vitreoretinal surgery in his left eye, the patient declined treatment of this right eye, which was his best-seeing eye. His vision remained stable at 6/7.5 at his last review in June 2016.

serum cholesterol are at higher risk of developing DMO; controlling these systemic risk factors should be sought, although may be difficult in some patients. Care should be taken, however, to avoid rapid changes (increase or decrease) in HbA1c and blood pressure as these may precipitate the development of DMO. Thus, at least in people with type 1 diabetes the risk of development of DMO requiring treatment was found to be reduced when changes in levels of HbA1c, systolic and diastolic blood pressure were kept within $\pm 0.5\%$, 10 and 5 mmHg, respectively, during a 6-month period (11). Indeed, it has been recommended that six-month changes in HbA1c should be kept below 2 percentage points to minimise progression to CSMO (11-12).

Scarce data is available with regards to other characteristics that may make patients more prone to develop DMO; research studies attempting to elucidate risk biomarkers are, thus, very much needed.

Fenofibrate is an inexpensive drug to treat hypertriglyceridaemia. Two large RCTs, the fenofibrate intervention and event lowering in diabetes (FIELD) (13) and the Action to Control Cardiovascular Risk of Diabetes (ACCORD) (14) demonstrated the benefit of once-daily

orally administered fenofibrate on the treatment of people with type 2 diabetes and diabetic retinopathy, including reducing the progression of the disease and the need for laser treatment for DMO and proliferative diabetic retinopathy (PDR). Fenofibrate has been licenced in Australia for the treatment of diabetic retinopathy. Given its low cost, safety profile and its beneficial effects not only on retinopathy but also on other diabetic complications (15-17) fenofibrate seems an excellent preventive measure for people with diabetes and diabetic retinopathy.

Treatment

As with regards to prevention, control of risk factors including HbA1c, blood pressure and lipids should be sought in patients with DMO. Communication with general practitioners and endocrinologists seems essential to achieve this.

Current treatment options for DMO include macular laser photocoagulation, intravitreal (anti-vascular endothelial growth factor) anti-VEGF therapies and intravitreal steroids. Herein, important considerations with regards

to macular laser photocoagulation as well as anti-VEGF therapies for the treatment of DMO will be discussed. Although intraocular steroids are also a viable option on selected patients with DMO, as intravitreal steroids are not considered a first line therapy for the majority of patients, only few facts about this treatment modality will be presented.

Macular laser photocoagulation

The ETDRS = early treatment diabetic retinopathy study demonstrated that macular laser photocoagulation reduced the risk of losing ≥ 3 ETDRS lines by 50% at 3 years in people with diabetic retinopathy and DMO. However, a ≥ 15 letters improvement in vision was achieved only in $< 3\%$ of patients (4). As a result, it has been repeatedly stated in the literature that laser can reduce the risk of moderate vision loss but cannot improve vision in DMO. It is essential however, to consider that in the ETDRS study, the definition used for the diagnosis of DMO was “CSMO”. Patients with CSMO may not have centre-involving DMO and, subsequently, may not have reduced vision. Furthermore, as discussed above, not all patients with centre-involving DMO will have either reduced vision. Indeed, in the ETDRS, the great majority of participants [1,903/2,243 eyes (85%)] had a baseline visual acuity of $\geq 20/40$ at baseline (4). In contrast and for comparison, in recent landmark RCTs comparing laser with anti-VEGFs a baseline visual acuity of $\geq 20/40$ was observed in $\sim 20\text{--}50\%$ of eyes only (7-10). As lower levels of vision prior to treatment appear to be associated with larger improvements in vision following treatment (8), the higher levels of vision observed in the ETDRS may have resulted in a reduced chance for visual acuity improvement. In fact, recent trials have shown that laser treatment can improve vision in people with DMO. Thus, in people with centre involving DMO, vision improved by ≥ 10 letters in 32% and 44% of patients at 2 and 3 years, respectively (18,19). The question is then, who are the laser responders?

In the United Kingdom, the National Institute for Health and Care Excellence (NICE) appraised anti-VEGFs (ranibizumab and aflibercept) for the treatment of DMO (20,21). NICE found these treatments to be cost-effective compared with laser only in patients with centre involving DMO and central retinal thickness (CRT) $\geq 400 \mu$; in people with CRT < 400 microns laser treated dominated and, as a result, laser treatment is recommended for the treatment of these latter patients in UK. CRT, thus, may assist in the selection of patients with higher chance to respond to

laser treatment. On this regard, it is interest to note that in landmark trials comparing laser with anti-VEGFs the mean CRT at baseline was higher than 400 microns (405 μ in the DRCR.net protocol I, $> 460 \mu$ RISE & RIDE, 412–426 μ in RESTORE, $> 479 \mu$ VISTA & VIVID) (7,9,10,22). Laser photocoagulation may also be an appropriate option for patients with localised leakage on FFA. Other parameters that may make patients more suitable for laser treatment need to be elucidated. If DMO resolves following macular laser, recurrences are much less likely to occur than after anti-VEGF therapy and patients require to be seen much less often (follow-up intervals will be determined by the severity of the retinopathy) which is beneficial to patients, especially for those of working age who may find it difficult to take days off work to attend clinical appointments, and to health care providers, which are struggling to meet service demands.

In the EDTRS, FFA was advised prior to laser photocoagulation to guide this treatment. FFA can delineate areas of leakage or non-foveal ischaemia that should be treated with laser as well as determine whether perifoveal capillary drop-out is present, in which case laser treatment may not be appropriate. However, data does not exist with regards to whether or not outcomes following macular laser are improved by the use of FFA; research into this area is needed. Of note, in most recent landmark trials evaluating anti-VEGFs for DMO FFA was not required to guide macular laser photocoagulation.

In recent years, micropulse, subthreshold laser has gained popularity as a treatment strategy for exudative macular disorders. Preliminary data available suggests that this type of laser may be superior to standard laser for the treatment of patients with DMO (23,24). In micropulse subthreshold laser a series of short laser pulses are applied (“micropulse”), instead of a continuous wave emission as used in standard laser, with no obvious retinal burn. Each pulse is separated from the next one by a long off-time; this off-time has the purpose of allowing the tissue to cool down, avoiding an increase in temperature in the retina, as it occurs when conventional laser is used. In this manner, a sublethal effect on the RPE is achieved with no or minimal retinal damage. Small case series and randomised trials including relatively small number of patients have shown that subthreshold tissue-sparing micropulse laser may have comparable or higher efficacy than standard laser, even in the absence of a visible burn, with reduced side effects (23-27). This laser may be easier to deliver as it can be applied to the entire macular area, obviating the need to determine areas of

Table 1 Proportion of eyes with ≥ 10 letter gain at 1 year in the Protocol T of the DRCR.net based on presenting vision ($\leq 20/50$ or $20/32-20/40$) (8)

Treatment	Initial VA (≥ 10 letter gain) (%)	
	$\leq 20/50$	$20/32-20/40$
Aflibercept-treated eyes	77	50
Bevacizumab-treated eyes	60	45
Ranibizumab-treated eyes	69	50

VA, visual acuity.

Table 2 Mean (\pm SD) visual acuity improvement following anti-VEGF treatment at 1 year in the DRCR.net Protocol T based on presenting vision (8)

Treatment	Initial VA	
	$\leq 20/50$	$20/32-20/40$
Aflibercept-treated eyes	18.9 ± 11.5	8.0 ± 7.6
Bevacizumab-treated eyes	11.8 ± 12.0	7.5 ± 7.4
Ranibizumab-treated eyes	14.2 ± 10.6	8.3 ± 6.8

Anti-VEGF, anti-vascular endothelial growth factor; VA, visual acuity; SD, standard deviation

leakage or retinal thickening. A large, adequately powered, pragmatic, multicentre, allocation concealed double-masked RCT is currently underway in the United Kingdom [diabetic macular oedema and diode subthreshold micropulse laser (DIAMONDS)] aimed at evaluating the clinical effectiveness and cost-effectiveness of diode subthreshold micropulse laser, when compared with standard threshold laser, for the treatment of patients with DMO) with a central retinal subfield thickness of (CST) of < 400 microns (EudraCT number 2016-003804-29). DIAMONDS will provide robust evidence for the management of patients with these milder forms of DMO.

Anti-VEGF therapy

Several RCTs have consistently demonstrated the value of anti-VEGFs for the treatment of patients with centre involving DMO (CSMO was not used to define DMO in these studies) and its superiority over laser treatment.

It is likely that, on average, around 50–60% of patients on anti-VEGFs would be expected to improve ≥ 2 ETDRS lines (≥ 10 letter gain) following this therapy (7–9,22). However, the proportion of people and the degree of improvement in vision seems to be dependent on the existing level of vision when treatment is initiated (Tables 1 and 2). Thus, the

recent protocol T of the DRCR.net demonstrated that a higher proportion of eyes with poorer levels of vision at presentation will experience visual acuity improvement (Table 1) (8). The degree of visual acuity improvement achieved seems to be also higher in eyes with poorer levels of vision (Table 2) (8).

Many patients on anti-VEGFs, however, still require macular laser photocoagulation. Thus, in the DRCR.net protocol I, the proportion of eyes that required laser treatment in the ranibizumab + deferred laser arm increased over time, from 28% at 1 year to 42% at 2 years and 46% at 3 years (7,28,29). In the recently published DRCR.net protocol T study, laser treatment was needed in 41, 52 and 64% of patients receiving aflibercept, ranibizumab and bevacizumab, respectively, at 2 years and after a median number of ~ 15 injections (30).

Over a third of patients in the ranibizumab arms had still central retinal thickening after 3 and 5 years of treatment (29,31). The 5-year data presented by the DRCR.net, Protocol I, however, should be interpreted with caution as only $\sim 75\%$ of patients randomised to the ranibizumab arms and evaluated a baseline remained in the study at 5 years (31). It is also of interest to note that, in the RISE and RIDE, where patients received anti-VEGF injections (ranibizumab) monthly for 2 years, leakage, as determined on FFA, was present in a very high proportion of patients (74–83%) at 2 years (10). This may suggest that although increased VEGF levels are a very important mechanism responsible for the pathogenesis of DMO, it may not be the sole cue, at least in a proportion of patients. Alternatively, the persistent leakage observed at 2 years despite monthly injections of anti-VEGF may relate to a short lived action of anti-VEGFs and subsequent rebound increased permeability 4 weeks after the last injection.

A high proportion of patients (38–48%) in the ranibizumab arms in the DRCR.net Protocol I RCT were still receiving injections in year 5, indicating that a prolonged treatment course is required in many patients.

Importantly, reduced diabetic retinopathy progression has been consistently detected following the use of anti-VEGF agents (7,10); this may possibly reduce rates of PDR in patients under this therapy.

Intraocular steroids

Triamcinolone, dexamethasone and flucinolone have been used for the treatment of patients with DMO.

The Protocol I of the DRCR.net showed that in pseudophakic eyes, treatment with triamcinolone + prompt

laser achieved comparable visual benefit to Ranibizumab + laser (7). Importantly, triamcinolone + prompt laser seems to be more cost-effective than ranibizumab + laser (32). Triamcinolone, in its current formulation, however, is not licenced for intraocular use.

In UK dexamethasone and flucinolone have been appraised by NICE (33,34) for the treatment of DMO. Both have been recommended only for the treatment of pseudophakic eyes that do not respond to laser or anti-VEGFs.

Conclusions

Control of systemic risk factors, macular laser, anti-VEGFs and steroids can be used to treat patients with DMO. Treatment with fenofibrate should be considered to prevent the development of complications requiring treatment (DMO and PDR).

At least a third of patients will respond to laser treatment (very likely more if patients are selected for this treatment based on their characteristics e.g., those with localised leakage on FFA, those with <400 microns of CRT on OCT). Macular laser photocoagulation should be also performed in non-centre involving CSMO to prevent involvement of the centre and need for anti-VEGFs; the ETDRS study proved the value of laser under these circumstances. Laser should be also considered for patients with CSMO and normal or with minimal visual loss (>20/32) as data on anti-VEGFs is not available for this group but evidence from the ETDRS demonstrated a benefit of laser treatment.

In clinical practice it is expected that on average ~50–60% of patients will respond to anti-VEGFs with a ≥ 10 ETDRS letter improvement. Around 50% of patients will still require laser treatment and ~50% will still require injections 5 years on. The reduced progression of retinopathy observed in patients on anti-VEGF may lead to reduce rates of PDR in the future.

Licensed intraocular steroids (dexamethasone, flucinolone) may be considered as a second/third line therapy for people with DMO.

Ideally patients with DMO should be treated in a “personalised” manner, using the treatment preferred by the patient and the one that should provide the best chance to benefit her/him. Given that Health Services do not have infinite resources, not only the clinical effectiveness but also the cost-effectiveness of the treatments should be taken into consideration when selecting therapeutic strategies for patients.

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Footnote

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