Current Treatment Options for Diaebtic Macular Oedema

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Introduction

Diabetic macular oedema (DMO) is a complication of diabetes affecting the central part of the retina (called the macula) responsible for colour vision and perception of fine detail. The most central part of the macula is the fovea, which is responsible for sharp vision.

A Simplified Summary of the Anatomical, Physiological and Biochemical pathways that results in DMO

DMO occurs due to changes in retinal vascular calibre, reduced connective tissue around capillaries and changes in the vascular integrity at a cellular level due to raised blood sugar and hypoxia. This results in a breach of what is, in health, a watertight blood retinal barrier. Breakdown of this blood retinal barrier results in an increased production of vascular endothelial growth factor (VEGF), which is like a cellular "distress signal". Other cellular distress mechanisms come into play such as intracellular adhesion molecule 1 (ICAM -1) and down regulation of anti-inflammatory factors such as pigment epithelium derived growth factor (PEDF). All contribute further to the breakdown of the blood retinal barrier that results in what is seen clinically in M1 patients, exudates and micro-aneurysms. Exudates are solidified protein rich material that results from leakage of plasma constituents into the area, allowing a build-up of excess fluid (oedema). Fluid disrupts the anatomical organisation of the tightly packed receptors (mainly cones) in the fovea. This results in visual impairment and approximately 5.4% of diabetic patients are estimated to have reduced central vision due to the process described above (GE, 2012). The treatment strategies target one or more of the steps outlined in the DMO process.

LANDMARK TRIALS & CURRENT TREATMENT OPTIONS

Figure 1a – All the current treatments available for DMO.

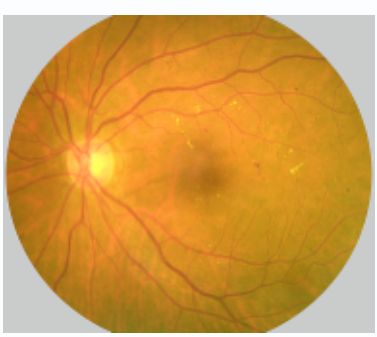


Figure 1b – Fundus photo of Left Eye with features of Diabetic Maculopathy.

Macular laser therapy using Argon laser was first line therapy prior to the discovery of anti-vascular endothelial growth factor (anti-VEGF) therapy. These treatments have also transformed the management of DMO as they have done for neovascular age related macular degeneration.

Macular laser treatment was the standard of care for sight threatening DMO and its efficacy in reduced risk of progression was evidenced by the ETDRS (Early Treatment of Diabetic Retinopathy Study) study. This was a landmark clinical trial showing a reduction in the risk of losing 2 lines on the Snellen chart by 50% in a 5 year period if laser was applied where signs of clinically significant macular oedema (CSMO) were seen (Ciulla TA, 2003).

Often a single treatment is not sufficient and laser does not reverse the visual loss experienced. At best it stabilises vision. The importance of systemic control cannot be emphasised enough for delaying progression and enhancing the prognosis with all therapies for DMO. Advice on optimal management of diabetes, diet modification, smoking cessation, lifestyle changes to increase physical activity and blood pressure control are important factors.

Ranibizumab (Lucentis, Genetech, San Francisco, CA, USA) (RBZ), an anti-VEGF agent is a humanised, recombinant monoclonal antibody fragment that binds all isoforms of VEGF-A. As described in the pathway above, VEGF is a critical stimulus in the pathogenesis of DMO (Nguyen QD T. S., 2012). The National Institute for Clinical Excellence (NICE) recommended its use in February 2012. In all NHS trusts in England and Wales, ophthalmologists will require NICE approval of efficacy and cost effectiveness in order to obtain the treatment. In fact, if a treatment is approved by NICE, it must be made available to all eligible patients within 3 months of the NICE guidance being issued. It was deemed efficacious and cost effective for DMO patients with a central macular thickness of greater than 400 microns on an OCT scan of the macula. The RISE study showed 44.8% receiving monthly 0.3mg RBZ and 39.2% on 0.5mg RBZ had > 15 letter gain and the matching groups in the RIDE were 33.6% and 45.7% respectively (Nguyen QD B. D., 2012). This was the first time a therapy resulted in an increase in vision for DMO patients.

Aflibercept (Eylea, Bayer PLC) is also licenced for DMO. It will be appraised by NICE in the summer of 2015. Aflibercept is a fully human recombinant fusion protein composed of the second Immunoglobulin domain of vascular endothelial growth factor (VEGF) receptor-1. The VIVID and VISTA trials are two randomised, multicentre double masked studies looking at three groups, 2mg Aflibercept every 4 weeks and sham laser, 2mg Aflibercept every 8 weeks after 5 initial monthly doses plus sham laser and laser plus sham injections (U, 2013). The primary endpoint in these studies was the change from baseline BCVA (letter score) at 12 months. The VIVID-DMO results for the three groups were +10.5 letters, +10.7 letters and +1.2 in the laser and sham injection group. The VISTA-DMO results for the same groups were +12.5, +10.7 and +0.2 letters.

Another Anti-VEGF called Bevacizumab (Avastin) has been used and the evidence is consistent although of lower impact. The most common does is 1.25 mg and it must be prepared in a pharmacy setting that can ensure safe supply. In the UK, supplies can be obtained from Moorfields and Liverpool & Aintree Hospitals. There are legal implications to using a non-licensed therapy when a licensed alternative exists, however due to the significant cost difference between Bevacizumab and Ranibizumab and the continuous need to find cost saving opportunities Bevacizumab is currently counted but surrounded in issues that have yet to be resolved at a policy maker or government level. The BOLT study compared Bevacizumab injections to macular laser and reported a median gain of +8 letters at 12 months follow up compared to +0.5 letters in the laser group. The median number of injections were 9 and laser treatment were 3 (Michaelides M, 2010).

TABLE 1:

Anti-VEGF therapies for DMO and their other indications for use.

	Ranibizumab	Aflibercept	Bevacizumab
Company	Genentech/Novartis	Regeneron/Bayer	Genentech/Roche
MOA	Anti-VEGF-A antibody fragment [1]	Anti-VEGF-A/PlGF/VEGF-B recombinant fusion protein[3]	Anti-VEGF-A full-length antibody[5]
Molecular structure			
Molecular weight	48 kDa[2]	97–115 kDa[3]	149 kDa[6]
Half-life in the human eye	9 days[1]	Unknown	6.7 days[7]
Systemic half-life	~2 hours[2]	2-6 days[4]	20 days[5]
Licensed indications	Wet AMD, visual impairment due to DMO, visual impairment due to MO secondary to RVO (BRVO and CRVO), visual impairment due to CNV secondary PM)[1]	Wet AMD, visual impairment due to MO secondary to CRVO[3] Metastatic colorectal cancer[8]	Metastatic colorectal cancer, metastatic breast cancer, non-small cell lung cancer, metastatic renal cell cancer[5]

Corticosteroids supress multiple pathways of inflammation and reduce damage to the blood retina barrier.

TABLE 2: Comparative Analysis of Corticosteroids.

Compound (Brand Name)	Intravitreal dose and duration	Estimated daily dose	Total dose	Procedure	Duration of Action	Status WRT to DMO
Triamcinolone Acetonide (kenalog)	4mg 3 months	44.4 micrograms/day	4mg	injectable	Approx. 3 mo	Off label
Fluocinolone Acetonide (Retisert)	0.59mg 30 months	0.6 micrograms/day initially 0.3-0.4 after 1 month	500 microgram	Incision and suture	2.5 years	Not licensed for DMO (only for non infectious uveitis)
Dexamethasone (Ozudex)	700 microgram 3-6 months	11.7 micrograms/day	750 microgram	injectable	Approx. 4 mo	Licensed for DMO NICE appraisal due April 15
Fluocinolone Acetonide (Illuvien)	0.5 microgram	0.5 or 0.2 micrograms/day	190 microgram	injectable	3 years	Licensed and NICE approved for pseudophakic patients
Adapted from Kane et al and Campochiaro						

Illuvien (Alimera Sciences Inc. is an inert, non-biodegradable, micro-implant that provides sustained release Flucinolone Acetonide after being injected via a 25-guage proprietary inserter through a one-step self-sealing entry site on the sclera. It is a cylindrical tube (3.5mm in length and 0.37mm diameter) that can be placed with 14 others to make up 1 grain of rice. NICE approved its use for DMO in pseudophakic patients early in 2014. The FAME (A and B) study (Campochario P A, 2012) demonstrated the safety and efficacy of Illuvien in DMO. At 3 years follow up 28.7% receiving 0.2 micrograms and 27.8% receiving 0.5 micrograms per day showed >15 letter gain compared to 18.9% in the sham group. Development of cataract and raised intra-ocular pressure were the main complications. The rate of incisional glaucoma surgery was 4.8% in the low dose group and 8.1% in the high dose group and 0.5% in the sham group.

Ozurdex (Dexamethasone intravitreal implant, Allergan) has recently received its licence for use in DMO and will be appraised by NICE in April 2015. Until then any patient that is unresponsive to anti-VEGF therapy or unsuitable for both anti-VEGF and Illuvien may be considered for Ozurdex. An individual funding request would be needed to fund the treatment in the NHS setting.

The MEAD trial was the evidence base for the efficacy of Ozurdex in DMO (Boyer D.S, 2014). DMO patients (n=1048) with vision between 20/50 and 20/200 (Snellen equivalent 6/12 and 6/60) and a central macular thickness of >300 microns were randomised 1:1:1 to Ozurdex 0.7 mg, 0.35mg or sham implants. If re-treatment criteria were present, the patients received a further implant no more often than every 6 months. The primary outcome measure was gain in >15 letters from baseline to study end.

The mean number of treatments received over 3 years was 4.1, 4.4 and 3.3 with 0.7mg, 0.35mg and sham respectively. The percentage of patients with >15 letter gain was 22.2%, 18.4% and 12.0% (P<0.018). The mean average reduction in CRT was from baseline was greater with 0.7mg, -111.6 microns and -107.9 (0.35mg) and -41.9 (sham P<0.001). Rates of cataract related adverse events were 67.9%, 64.1% and 20.4% in the three groups (0.7mg, 0.35mg and sham). Increases in IOP were usually controlled with medication or no therapy. Only 2 patients in 0.7mg group and 1 patient in 0.35mg group required glaucoma incisional surgery.

TABLE 3: Summarising Results of Landmark Clinical Trials for Current Available Therapies for the Treatment of DMO.

Trial name	DMO Treatment	Method Notes	NICE status	Primary Endpoint	Headline result
RISE & RIDE	Ranibizumab (Lucentis)	0.3mg RBZ 0.5mg RBZ	NICE TA 274 April 2013	>15 letters from baseline at 12/12	RISE 44.8%, 39.2% RIDE 33.6%, 45.7%
VIVID & VISTA	Aflibercept (Eylea)	2mg every 4 weeks and sham laser, 2mg every 8 weeks after 5 initial monthly doses plus sham laser and laser plus sham injections	To be evaluated in Summer 2015	Mean increase in letters from baseline at 12/12	VIVID +10.5 letters, +10.7 letters and +1.2 (sham) VISTA +12.5, +10.7 and +0.2 (sham)
FAME	Fluocinolne Acetonide	Randomised 1:1:1 0.2:0.5:sham	NICE TA 271 January 2013 For pseudophakic patients DMo insufficiently responsive to available therapies	>15 letters from baseline 12/12	28.7% 27.8% 18.9% (sham)
BOLT	Bevacizumab (Avastin)	PRN Avastin injections (monthly review) compared to laser (every 3 months, if required)	Unlicensed world-wide use provides some evidence but legal implications in the UK prevent widespread use in NHS	Mean increase in letters from baseline at 12/12	+8 letters compared to +0.5 letters in the laser group
MEAD	Dexamethasone (Ozurdex)	Randomised 1:1:1 0.7:0.35 and sham Given not more often than 6 monthly when indicated	NICE to evaluate in Summer 2015	>15 letters from baseline at 3 years	22.2%, 18.4% and 12.0% (sham) (P<0.018)

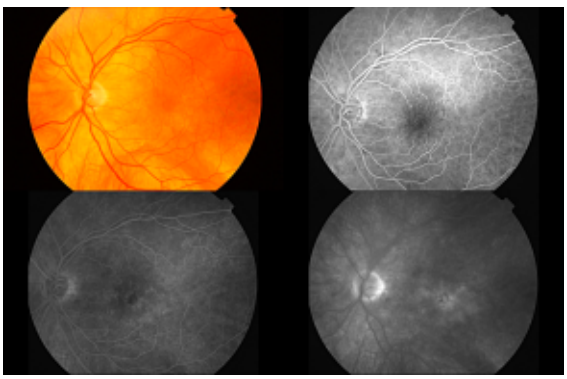


Figure 5.

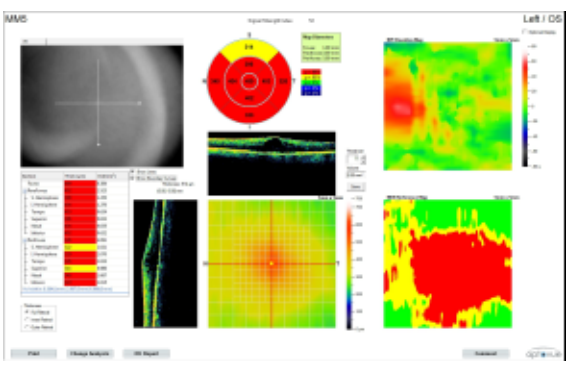


Figure 6.

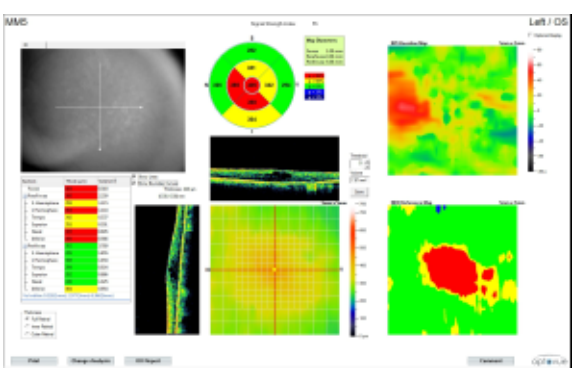
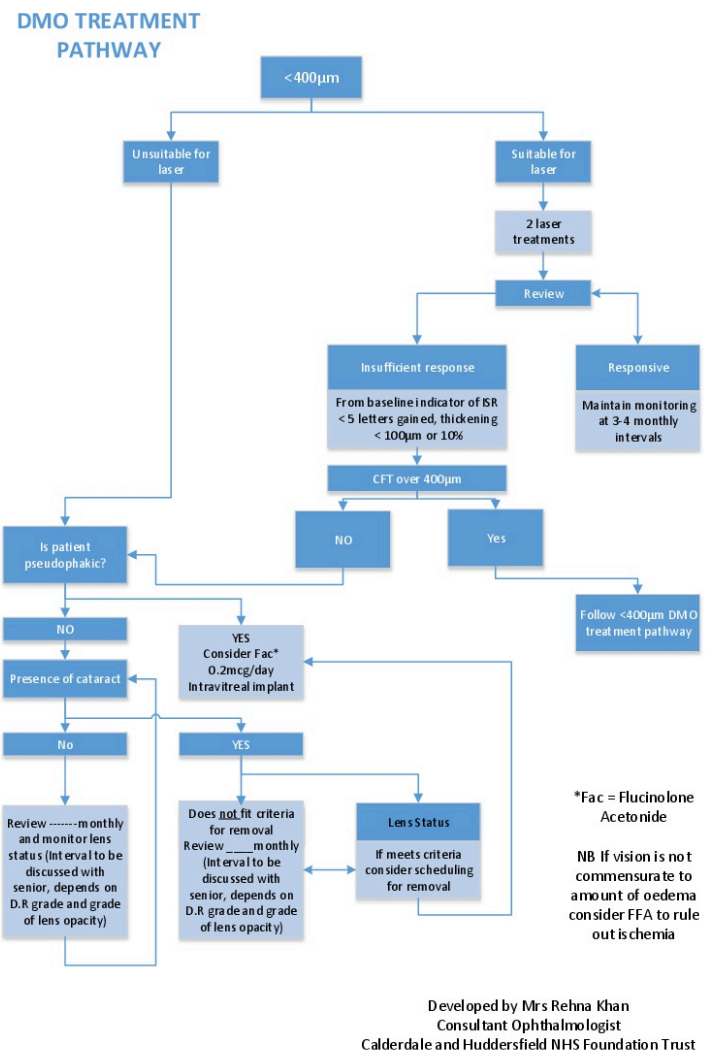


Figure 7.

Figure 3: DMO treatment, patient pathway, - 400 microns

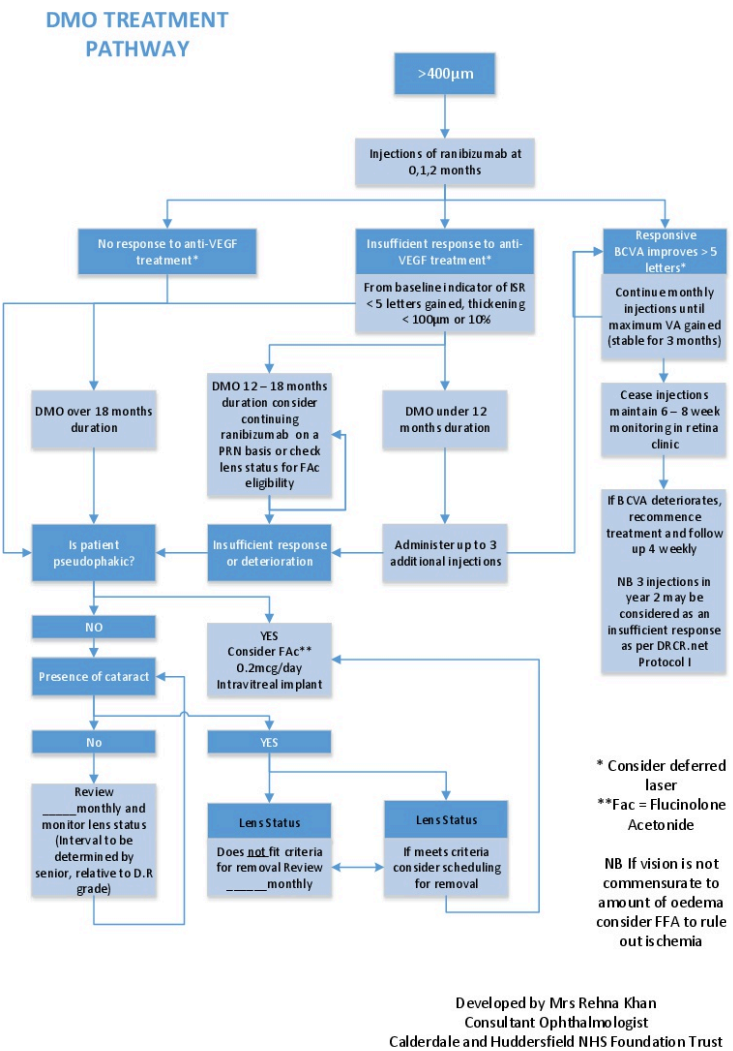


CLINICAL EXPERIENCE

The following case illustrates the steps in the patient treatment pathway shown above.

A female patient, age 77 who had an intraocular lens implant (pseudophakia) in both eyes, with type 2 diabetes presented at age 73 with significant diabetic maculopathy in the left eye (**Figure 5 & 6**). The vision in this eye was 6/24. At this time point macular laser was the only available treatment. She was treated with left macular laser and some improvement was noted. The left DMO recurred one year after macular laser (**Figure 7**). At this time point, Ranibizumab for DMO had been approved by NICE and the treatment was initiated as the central macular thickness was greater than 400 microns (NICE technology appraisal 274). The vision at this time was 71 letters in the left eye. She then had four intravitreal injections 1 month apart and **Figure 8** shows the central macular thickness.

Figure 4: DMO treatment, patient pathway, + 400 microns



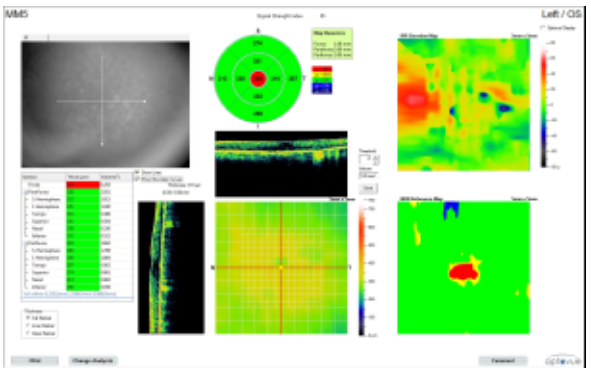


Figure 8.

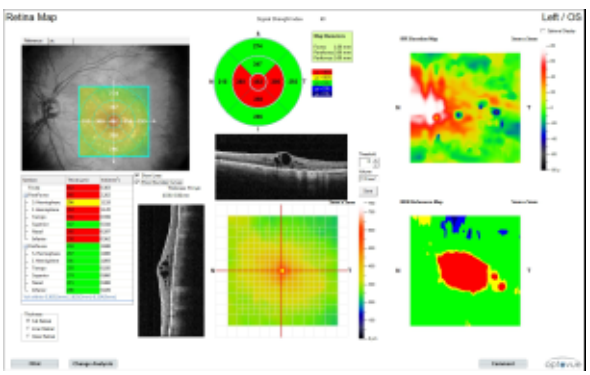


Figure 9.

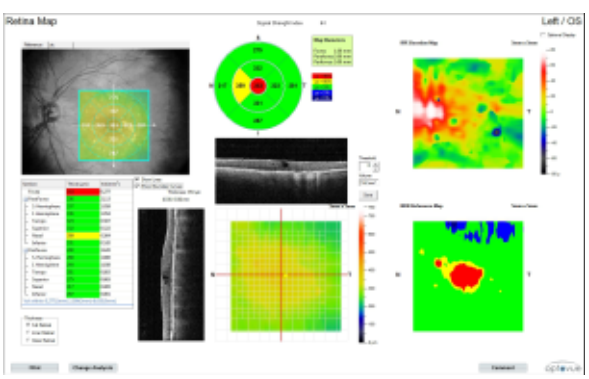


Figure 10.

Her vision was 70 letters. She then had no further injections until a recurrence was noted 3 months later. After a total of 5 Ranibizumab injections no significant reduction in central macular thickness was seen. At this time point Illuvien had become available (NICE TA 301) and as the patient had central macular thickness involving DMO that had failed other therapies and she was pseudophakic she met all the criteria. She had no risk factors for glaucoma and after a discussion of the risks and benefits of the implant, she opted to proceed with left Illuvien. Her vision at this time was 73 letters and **Figure 9** shows her OCT scan. She responded well and at her last review 6 months following the implant, she was 6/9 (81) letters and her central macular thickness was reduced (**Figure 10**).