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MANAGEMENT OF DIABETIC MACULAR EDEMA (DME)

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Diabetes mellitus (DM) is a chronic metabolic disease that can cause multiple organ damage. The prevalence of diabetes among Malaysians is expected to increase every year. In 2011, the National Health and Morbidity Survey (NHMS) had predicted an increase in the prevalence of DM among Malaysians to 21.6% by year 2020.[1] This made DM a major public health concern in the country. DM is related to both macro- and microvascular complications, such as stroke, heart attack, renal failure, amputation and last but not least, blindness.

Diabetic retinopathy is one of the serious complications of DM. The NHMS 2011 showed that 20.7% of diabetic patients have unknown status of diabetic retinopathy.[1] The undiagnosed diabetic retinopathy among Malaysians is a worrying condition to our country, as it can potentially cause blindness.

Diabetic macular edema (DME) is a serious early ocular morbidity in diabetic retinopathy. It commonly causes visual impairment in diabetic patients.

There are various treatment modalities for DME. The current treatment options include laser photocoagulation, intravitreal anti-vascular endothelial growth factors (VEGF) and corticosteroids injection. Over the past few years, research and studies have started to focus on the role of anti-VEGF in the management of DME. The use of anti-VEGF is strongly related to the underlying pathophysiology of DME. The thickening of basement membrane and loss of pericytes secondary to hyperglycaemia lead to breakdown of blood retinal barrier. This causes an increase in vascular permeability and fluid is accumulated in the macula. In the early development of DME, the main drive of macular edema is due to hypoxia and upregulation of VEGF. Anti-VEGF helps to improve vision and reduce macular edema.

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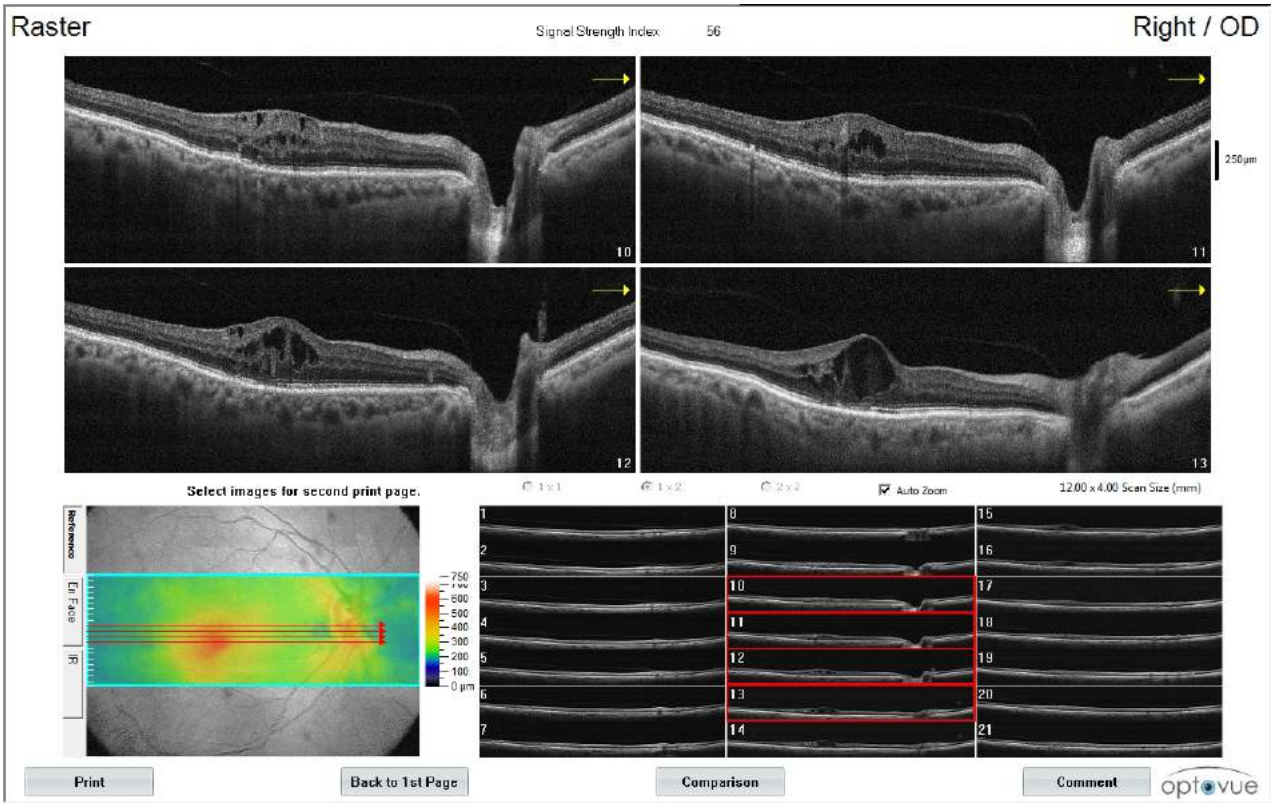
There are many well-designed randomised controlled trials that have shown the benefits of anti-VEGF in the management of DME: the RISE/RIDE studies[4] of Ranibizumab (Lucentis, Genentech); the BOLT study[5] of Bevacizumab (Avastin, Genentech) and the VIVID/VISTA studies[6] of Aflibercept (Eylea, Regeneron).

The Malaysian Clinical Practice Guidelines for DME[7] recommended monthly intravitreal anti-VEGF injection for 6 months with a deferment of laser treatment for 6 months for fovea involving DME. If anti-VEGF therapy is not available in the practicing centre, focal/grid laser should be offered as alternative treatment.

The Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol I[8] has shown that the combination of anti-VGEF with prompt laser or deferral of laser for at least 6 months in DME cases offers a better visual outcome, compared to prompt laser alone. For non-central involving DME, macular edema can be observed until vision is threatened except in certain worrying conditions such as during pregnancy, worsening cataract or edema is rapidly extending towards the center of macula.[7] Switching anti-VEGFs between bevacizumab, ranibizumab or aflibercept can be helpful when there is a lack of response after multiple intravitreal injections of a single anti-VEGF agent. Aflibercept has shown possible better affinity and lesser risk of tachyphylaxis. All DME patients who are under treatment should be monitored with serial Optical Coherence Tomography (OCT). OCT helps to guide the management of DME and prognosticate the ocular condition.



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In long-standing DME, chronic inflammation is the main drive of macular edema. Chronic DME is usually refractory to anti-VEGF treatment. Corticosteroids therapy can be considered when there is a suboptimal response of DME to anti-VEGF treatment especially after 6 monthly injections. There are several choices of corticosteroids drug for DME such as steroid implant (Ozurdex®), Fluocinolone and Triamcinolone. Ozurdex® is the current distinguished corticosteroids implant in the treatment of retinal vascular disorders. It offers a slow release of the medication over a long duration. Studies such as PLACID[9], MEAD[10] and BEVORDEX[11] had shown the efficacy of Ozurdex® implant in treating DME. Its therapeutic effect can last up to 6 months. However, most studies found that its effect dissipates after 4 months of implantation. The treatment with Ozurdex® implant has significantly reduced the number of injection to the eye. This eventually reduces the risk of intravitreal injection related complications. Nevertheless, the treatment of corticosteroids is always associated with its well-known side effects such as steroid induced-glaucoma and cataract development. Hence, the selection of patient for steroids treatment is very crucial to prevent undesirable outcome.

Before the advent of anti-VEGF, focal or grid laser is the main standard care for DME. The Early Treatment Diabetic Retinopathy Study (ETDRS) trial had shown that laser treatment can prevent moderate visual loss, defined as a loss of 15 letters or 3 lines LogMAR visual acuity by 50% among those patients with clinically significant macular oedema (CSME).[2]

However, the down side of macular laser photocoagulation is the formation of scar on the retina which can expand and lead to poor vision.

Today, with the new sub-threshold diode micropulse (SDM) laser technology, laser is used to produce a therapeutic treatment to DME without causing a detectable scar on clinical assessment after treatment. The idea of SDM laser is to retain the benefits of conventional laser while minimizing the destructive effect to the retina.[3] The laser emission is divided into short repetitive pulses which lasted for 0.1 to 0.5 seconds. The “on” time is the duration of each micropulse while the “off” time allows heat dissipation to prevent collateral damage to the normal tissues and confined treatment to the retinal pigment epithelium. The major drawback of SDM laser is that there is a lack of reliable titration protocols to achieve reproducible sub-visible treatments. Hence, the reported treatment results are variable.[3] Laser treatment is typically applied directly on the microaneurysm within the thickened retina or grid laser on the thickened retina without microaneurysm.

Apart from treating DME secondary to vascular elements, the vitreomacular interface changes can also contribute to the pathology of DME. In the presence of vitreomacular traction or epiretinal membrane, vitrectomy is indicated to relieve the tangential traction.

We should always be vigilant in looking for factors such as macular ischaemia, scarring, disorganization of inner retinal layers (DRIL) and non-diabetic related macular edema.

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In fact, these factors likely affect the direction of our management in DME and reduce the burden of patients for treatment.

As with all mentioned options of treatment in DME, the success of managing DME still requires a good glycemic control (HbA1c <6.5%) and blood pressure control of less than 135/75.[12]

Ophthalmologists should always work hand-in-hand with the endocrinologist and primary health care physicians to ensure good response to the treatment and visual stabilization.

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