MALAYSIAN SOCIETY OF OPHTHALMOLOGY

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THE ROLE OF INFLAMMATION IN DME

At a recent continuing medical education event organized by Allergan, several leading experts gathered to share recent clinical updates, including treatment strategies for the management of DME.

PREVALENCE AND BURDEN OF DME IN MALAYSIA & CURRENT MANAGEMENT

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Diabetic macular edema is the accumulation of excess fluid in the macula area of the retina that can lead to vision loss. It is caused by the breakdown of the blood-retinal barrier that results in leakage of fluid and proteins into the macula, causing the macula to swell, which in turn affects visual function.[1,2]

Diabetic macular edema can occur at any stage of diabetic retinopathy. It is the most common cause of vision loss among people with diabetic retinopathy and about half of all people with diabetic retinopathy will develop DME.[3] A local study found that among diabetes patients who had follow-up at a Malaysian eye clinic, 51.6% had diabetic retinopathy while 26.7% had DME.[4]

Diabetic macular edema carries significant socioeconomic impact. Increasing loss of visual acuity not only affects patients' quality of life, but also impacts work-related productivity and healthcare-related costs.[5–7]

The Ministry of Health Malaysia DME guidelines serve as a framework to guide physicians in the diagnosis and management of this condition. Briefly, anti-vascular endothelial growth factor (anti-VEGF) treatment helps to improve visual acuity and avoids vision loss. Laser treatment will still have a role in selected patients, ie, those without access to anti-VEGF treatment, with persistent DME despite anti-VEGF treatment, or with DME that involves the centre of the macula but with good/excellent visual acuity where the role of laser serves as an option instead of observation or anti-VEGF therapy. Corticosteroid therapy may benefit patients with persistent DME despite anti-VEGF therapy, where it is thought that corticosteroids can address the inflammatory cascade involved in the pathogenesis of chronic edema in persistent DME.[1]

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INFLAMMATION IN DIABETIC RETINOPATHY: A NEW PARADIGM

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Inflammation is important in the pathogenesis of common vitreoretinal disorders including DME. Apart from VEGF, a host of inflammatory mediators are present at sites of macular edema including cytokines, chemokines, angiotensin II, prostaglandins, matrix metalloproteinases, interleukins, selectins, vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and inflammatory cells (macrophages and neutrophils).[8]

Leukocytes also play a role in increasing vascularpermeability, alongside VEGF. Mediated via adhesion molecules (selectins and integrins) expressed by the vascular endothelium, leukostasis—the accumulation leukocytes before adhesion to the endothelium—contributes to the disruption of tight junctions and breakdown of the blood retinal barrier.[8] A preclinical study by Mizuno et al[9] not only demonstrated this phenomenon, but also the therapeutic value of using corticosteroids to inhibit this process.

Corticosteroids also appear to exert anti-inflammatory effect by down-regulating inflammatory stimuli, increase the levels of tight junctions between endothelial cells to lessen vessels leakage, and possess angiostatic activity through the inhibition of VEGF.[10,11]

The differences between anti-VEGF monotherapy and corticosteroid therapy in reducing inflammatory stimuli in DME have been demonstrated in several human studies.

- ***Comparing intravitreal injection of triamcinolone or bevacizumab, Sohn et al[12] found that the corticosteroid therapy was associated with greater reduction in foveal thickness, as well as significantly decreased levels of inflammatory and angiogenic cytokines. On the other hand, only a more decreased level of aqueous VEGF was observed in the anti-VEGF arm vs the corticosteroid arm.***

- ***In the BEVORDEX (Bevacizumab or Dexamethasone Implants for DME) study,[13] dexamethasone implant achieved similar rates of visual acuity improvement compared with bevacizumab, with superior anatomic outcomes and fewer injections (Figure 1). Elevation of intraocular pressure and the incidence of cataract were more frequent with dexamethasone implant vs bevacizumab, but these were recognizable and treatable.***

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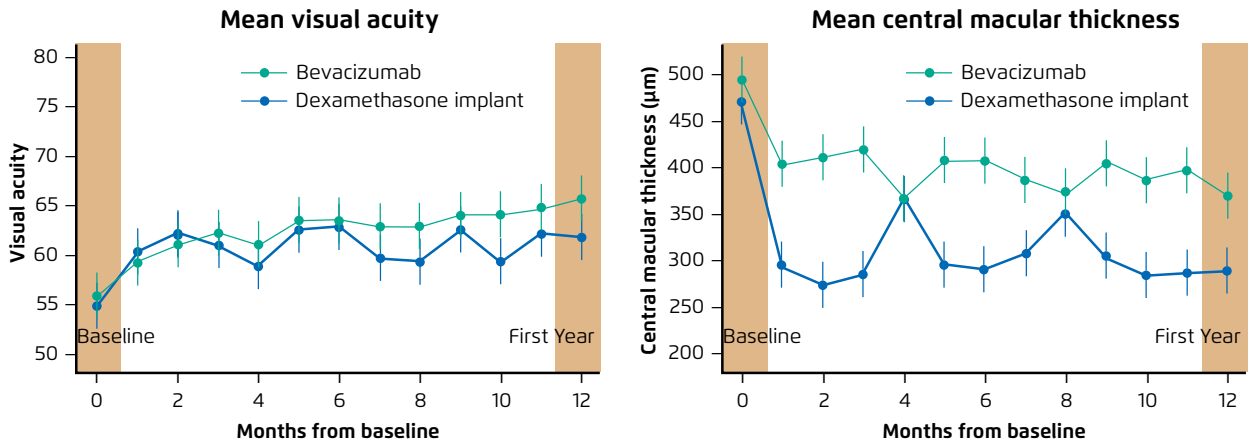
Figure 1. Dexamethasone implant achieves similar rate of visual acuity improvement with superior anatomic outcomes[13]



Evidence suggests that optimal visual acuity outcome is seen with continuous anti-VEGF therapy up to 36 months.[14,15] However, this raises important safety concerns of the long-term use of anti-VEGF therapy. Several studies have reported the following adverse events associated with anti-VEGF therapy, ie, acceleration of geographic atrophy growth rate,[16,17] and increased risk of deaths and potentially cerebrovascular accidents.[15,18]

KEY TAKE-HOME MESSAGES:

1. Inflammation plays an important role in the pathogenesis of DME.

2. Anti-VEGF drugs and corticosteroids are effective in DME, but corticosteroid therapy appears to be more effective in addressing the inflammatory pathway of DME.

3. Long-term aggressive use of anti-VEGF therapy has important safety implications; consideration of total exposure to anti-VEGF therapy may be required in atrisk patients.

CASE STUDY: DIABETIC MACULAR EDEMA

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Ozurdex® is an intravitreal dexamethasone implant indicated for the treatment of adult patients with macular edema. To share his clinical experience in using Ozurdex®, Dr. Fong presented a case study of a 48-year-old male with a 5-year history of type 2 diabetes that was poorly controlled (HbA_{1c} 8.0%), who first visited him in 2012. He had bilateral phacoemulsification and implantation of intraocular lens 3 years ago for cataract. The patient's chief complaint was blurring of vision in the left eye with visual acuity

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of 20/50 (left) and 20/20 (right) that was treated with anti-VEGF therapy. Over the course of 2 years—between 2012 and 2014—this patient had worsening of diabetes control and he eventually needed dialysis. Due to macular thickening, the patient also received focal laser twice, numerous anti-VEGF therapy into both eyes, pan retinal photocoagulation (PRP) laser and subtenons triamcinolone injection. Despite all these interventions, his vision continued to deteriorate and the patient was not seen for 6 months due to follow-up defaults.

The patient returned in August 2014 with worsened vision. He was diagnosed with proliferative diabetic retinopathy and received PRP laser treatment. The patient's DME persisted despite the numerous anti-VEGF therapy and a decision was made to initiate Ozurdex® at follow-up in January 2015. Over the course of 2015, the patient received in total three and two Ozurdex® implants to the left and right eye, respectively, that helped to control his DME.

"This case study illustrates the efficacy of corticosteroid in persistent DME despite multiple anti-VEGF therapy in a patient with poorly controlled diabetes and renal failure. It also highlights the importance of inflammation in the pathogenesis of DME and the role of corticosteroids in addressing this," summarized Dr. Fong.

References: **1.** Ministry of Health Malaysia. Diabetic macular edema guidelines. Available at: http://mso.org.my/index.cfm?&menuid=12. Accessed 16 March 2016. **2.** Ciulla TA, et al. Diabetes Care 2003;26(9):2653–2664. **3.** US National Eye Institute. Facts about diabetic eye disease. Available at: https://nei.nih.gov/health/diabetic/retinopathy. Accessed 16 March 2016. **4.** Tajunisah I, et al. Med J Malaysia 2006;61(4):451–456. **5.** Gonder JR, et al. J Ophthalmol 2014;2014:939315. **6.** Shea AM, et al. Arch Ophthalmol 2008;126(12):1748–1754. **7.** Brook RA, et al. Presented at the 73rd Scientific Sessions of the American Diabetes Association. Chicago, Illinois. June 21–25, 2013. **8.** Ascaso JF, et al. Mediators Inflamm 2014;2014:432685. **9.** Mizuno S, et al. Invest Ophthalmol Vis Sci 2007;48(6):2831–2836. **10.** Sarao V, et al. Scientific World Journal 2014;2014:989501. **11.** Shamsi HN, et al. World J Diabetes 2013;4(6):324–338. **12.** Sohn JH, et al. Am J Ophthalmol 2011;152(4):686–694. **13.** Gillies MC, et al. Ophthalmology 2014;121(12):2473–2481. **14.** Elman MJ, et al. Ophthalmology 2012;119(11):2312–2318. **15.** Brown DM, et al. Ophthalmology 2013;120(10):2013–2022. **16.** Martin DF, et al. Ophthalmology 2012;119(7):1388–1398. **17.** Grunwald JE, et al. Ophthalmology 2015;122(4):809–816. **18.** Avery RL, Gordon GM. JAMA Ophthalmol 2016;134(1):21–29.