

## Diabetic macular edema: Current management 2013

J Fernando Arevalo

J Fernando Arevalo, Retina Division, Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, MD 21287, United States

J Fernando Arevalo, The Vitreoretinal Division, The King Khaled Eye Specialist Hospital, Riyadh 11462, Saudi Arabia

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**Correspondence to:** J Fernando Arevalo, MD, FACS, Chief of Vitreoretinal Division, The King Khaled Eye Specialist Hospital, Al-Oruba Street, PO Box 7191, Riyadh 11462, Saudi Arabia. [arevalojf@jhmi.edu](mailto:arevalojf@jhmi.edu)

Telephone: +966-11-482-12343860 Fax: +966-11-482-1234727

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### Abstract

Diabetic retinopathy (DR) is the leading cause of vision loss of working-age adults, and diabetic macular edema (DME) is the most frequent cause of vision loss related to diabetes. The Wisconsin Epidemiologic Study of Diabetic Retinopathy found the 14-year incidence of DME in type 1 diabetics to be 26%. Similarly the Diabetes Control and Complications Trial reported that 27% of type 1 diabetic patients develop DME within 9 years of onset. The most common type of diabetes, type 2, is strongly associated with obesity and a sedentary lifestyle. An even higher incidence of macular edema has been reported in older patients with type 2 diabetes. Within the last 5 years, the use of intravitreal corticosteroids and intravitreal anti-vascular endothelial growth factor (VEGF) agents have come into clinical practice for the management of DME and several recent randomized clinical trials have shown improved effectiveness of ranibizumab compared to focal/grid laser. In this theme issue, we discuss the classification of DR and the treatment options currently available for the treatment of DME including corticosteroids, anti-VEGF agents, combined therapy, enzymatic vitrectomy (vitrealysis), and new therapies.

### DIABETIC MACULAR EDEMA

An estimated 347 million people are affected by diabetes worldwide in 2011, of those 138 million live in China and India and another 36 million in the United States and Russia. The number of people with diabetes is expected to double by 2030<sup>[1]</sup>. Diabetic retinopathy (DR) is the leading cause of vision loss of working-age adults<sup>[2]</sup>, and diabetic macular edema (DME) is the most frequent cause of vision loss related to diabetes. The Wisconsin Epidemiologic Study of Diabetic Retinopathy found the 14-year incidence of DME in type 1 diabetics to be 26%<sup>[3]</sup>. Similarly the Diabetes Control and Complications Trial (DCCT) reported that 27% of type 1 diabetic patients develop DME within 9 years of onset<sup>[4]</sup>. The most common type of diabetes, type 2, is strongly associated with obesity and a sedentary lifestyle. An even higher incidence of macular edema has been reported in older patients with type 2 diabetes<sup>[5]</sup>.

Argon laser photocoagulation has been the mainstay of treatment for macular edema since the publication of the results of the Early Treatment Diabetic Retinopathy Study (ETDRS), which showed an approximate 50% reduction in the rate of moderate vision loss at 3 years following laser photocoagulation compared to no treatment<sup>[6]</sup>. However, for patients with center involved macu-

lar edema, the risk of moderate vision loss at 3 years remained 15% with treatment<sup>[6]</sup>. Since the publication of ETDRS, the DCCT and United Kingdom Prospective Diabetes Study have demonstrated that tight glycemic and blood pressure control decrease the risk of microvascular complications of diabetes, including DR and vision loss<sup>[4,7-10]</sup>. As intensive blood pressure and blood sugar control have become the standard of care, visual outcomes have improved, but recent studies from the Diabetic Retinopathy Clinical Research Network indicate that even with the guidelines of tight glycemic and blood pressure control, 12%-13% of patients with foveal centered diabetic macular edema who undergo focal/grid laser lose 10 or more ETDRS letters after 2-3 years of follow-up. Additionally, with a baseline median vision of 20/50-20/63, only 36%-44% of patients gained 10 or more ETDRS letters at 2-3 years of follow-up, indicating the need for improved treatment modalities<sup>[11-13]</sup>. The outcomes may be even worse in developing countries where glycemic and blood pressure are poorly controlled.

Within the last 5 years, the use of intravitreal corticosteroids and intravitreal anti-vascular endothelial growth factor (VEGF) agents have come into clinical practice for the management of DME and several recent randomized clinical trials have shown improved effectiveness of ranibizumab compared to focal/grid laser<sup>[12-15]</sup>. In this theme issue, we discuss the classification of diabetic retinopathy and the treatment options currently available for the treatment of diabetic macular edema including corticosteroids, anti-vascular endothelial growth factor agents, combined therapy, enzymatic vitrectomy (vitrectomy), and new therapies.

Wu *et al*<sup>[16]</sup> give as the classification of diabetic retinopathy and DME. It is imperative that retina specialists, general ophthalmologists, internists, and endocrinologists learn to speak the same language in order to provide patients with the best care they deserve. Dhibi *et al*<sup>[17]</sup> review how corticosteroids have emerged as an alternative therapy for persistent DME or refractory to conventional laser photocoagulation and other modalities, due to anti-inflammatory, anti-VEGF and anti-proliferative effects. Many studies have demonstrated the beneficial therapeutic effect of corticosteroids with improvement to both retinal thickness and visual acuity (VA) in short-term on the treatment of DME. Peribulbar and intravitreal injections have been used to deliver steroids for DME with frequent injections due to the chronic and recurrent nature of the disease. Steroid-related side effects include elevated intraocular pressure, cataract, and injection related complications such as endophthalmitis, vitreous hemorrhage, and retinal detachment particularly with intravitreal steroid injections. In order to reduce the risks, complications, and frequent dosing of intravitreal steroids, intravitreal implants have been developed recently to provide a sustained release of corticosteroids and reduce repeated intravitreal injections for the management of DME. Stefanini *et al*<sup>[18]</sup> discuss the current status of the use of bevacizumab for the management of DME.

There is a strong evidence supporting that intravitreal bevacizumab injection has a good cost-effective profile in the management of DME and may be associated to laser photocoagulation; however, its clinical superiority regarding the duration of DME regression as well as the improvement of best-corrected VA compared to intravitreal ranibizumab and other intravitreal anti-VEGF therapies are still unclear and deserves further investigation. Moradi *et al*<sup>[19]</sup> review the treatment of DME using the first humanized monoclonal antibody targeting VEGF that has been FDA-approved for the use in the eye, ranibizumab. Krispel *et al*<sup>[20]</sup> discuss VEGF Trap-Eye (Aflibercept) for the Management of DME. Aflibercept presents a potential exciting new addition to the armamentarium of current VEGF antagonists available for the treatment of DME and other retinal vascular diseases. However, further studies are indicated to confirm the role, safety, and efficacy of aflibercept for DME. Diaz-Llopis *et al*<sup>[21]</sup> review their experience on enzymatic vitreolysis for diabetic retinopathy and DME. Enzymatic vitreolysis could be considered a good therapeutic alternative in diabetic retinopathy and macular edema. Finally, Al Shamsi *et al*<sup>[22]</sup> review new promising therapies for DME. The treatment of diabetic macular edema is rapidly evolving. The era of laser therapy is being quickly replaced by an era of pharmacotherapy. Several pharmacotherapies have been recently developed for the treatment of retinal vascular diseases such as diabetic macular edema. Several intravitreal injections or sustained delivery devices have undergone phase 3 testing while others are currently being evaluated. The results of clinical trials have shown the superiority of some of these agents to laser therapy. However, with the availability of several of these newer agents, it may be difficult to individualize treatment options especially those patients respond differently to various therapies. As such, more effort is still needed in order to determine the best treatment regimen for a given patient.

The etiology of DME is multifactorial. Therefore, the study of the important aspects of the pathogenesis and molecular pathways involved in the development of DME has led to the development of improved therapies for DME that have come into use in clinical practice. Additional promising therapeutic agents are currently being evaluated in clinical trials and additional molecular targets are being evaluated. Combined therapies targeting multiple pathways may yield synergistic treatment responses as several cytokines may be involved in the development of DME.

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