ECRONICON OPEN ACCESS

EC OPHTHALMOLOGY
Short Communication

Recent Trends in the Management of Diabetic Macular Edema

Ahmed Darwish[1,2]*

[1]*Professor of Ophthalmology - Vitreo-Retinal Consultant at Ain Shams University, Egypt*
[2]*Vitreo-Retinal Consultant at Dhahran Eye Specialist Hospital (DESH) KSA, Saudi Arabia*

***Corresponding Author:** Ahmed Darwish MD, Professor of Ophthalmology – Vitreo - Retinal Consultant at Ain Shams University, Egypt and Vitreo-Retinal Consultant at Dhahran Eye Specialist Hospital (DESH) KSA, Saudi Arabia.

Received: March 10, 2018; **Published:** May 21, 2018

Diabetic maculopathy is the commonest cause of blindness due to retinopathy from diabetes. It accounts for a large percentage of blindness particularly in type 2 diabetic patients. A cross-sectional study identified that the prevalence of diabetic maculopathy was 15% for type 1 patients and 23% for type 2 patients. Furthermore, of those patients who had background retinopathy the prevalence of maculopathy was remarkably high, 42% in type 1 patients and 53% in type 2 patients. Maculopathy carries a very high risk of loss in central vision; its direct relationship is shown in various studies, indicating a decrease in visual acuity (VA) with increasing severity of diabetic maculopathy [1].

It is recommended that in order to diagnose diabetic macular edema (DME) a base line fluorescein angiography (FA) together with OCT and fundus biomicroscopy should be done [2].

Base line predictors for a good treatment response with regards to high vision gains include less subretinal fluid (SRF) and intraretinal cystoid spaces(IRC) and no vitreomacular traction (VMT) [3]. Also, absence of disruption or disorganization of the inner retinal layers [4] and inner and outer photoreceptor segments and/or external limiting membrane [5] are important predictors for a good final visual outcome.

A thin subfoveal choroid at base line may predict bad visual acuity after therapy [6]. When diagnosed and treated, it is recommended to monitor disease activity on a monthly basis with OCT even if no treatment is needed in order to identify morphological changes as early as possible [2].

When managing diabetic macular edema it is important first to modify and control systemic risk factors. Control of hyperglycemia is critical to minimizing risk of onset and progression of diabetic retinopathy. The benefits of better glycemic control for reducing risk of retinopathy progression have been demonstrated in multiple randomized controlled clinical trials, [7-12]. Control of hypertension is also beneficial in lowering risk of progression of diabetic retinopathy, as demonstrated in the UKPDS [13,14]. The ETDRS data suggest that lipid lowering may decrease the risk of hard exudate formation and associated vision loss in diabetic retinopathy [15,16].

Treatment paradigms for DME have evolved considerably over the past several years, in the setting of a number of pivotal clinical trials. The efficacy of focal/grid laser photocoagulation for treatment of DME was established in the ETDRS. At 3 years, eyes with mild or moderate NPDR plus macular edema at baseline treated with immediate focal/grid laser photocoagulation showed an approximately 50% decrease in the rate of moderate vision loss [17]. The benefits of focal/grid laser photocoagulation have been highlighted by more recent clinical trials following the ETDRS [18]. In the era of anti VEGF injection, laser is clearly not the standard of care anymore. Relative indications include laser application especially to the vasogenic subform of DME, which is clinically characterized by the presence of focally grouped microaneurysms (MA) and leaking capillaries. A further indication is represented by eyes affected by DME with CRT less than 300um [2,19].

Subthreshold grid laser treatment can be helpful in eyes with higher visual acuity affected by early diffuse DME, in order to avoid the collateral thermal diffusion and the consequent chorioretinal damage and as a less expensive option [20].

Micropulse diode and yellow 577um lasers with a low intensity/high density application for diabetic macular edema was found to be as effective as conventional photocoagulation but without any evidence of laser induced retinal damage or adverse effect at the time of treatment or anytime thereafter [21-25].

Various VEGF antagonists have been developed for ophthalmic uses, including bevacizumab, a humanized murine monoclonal antibody binding VEGF-A; ranibizumab, a humanized murine monoclonal antibody fragment, also binding VEGF-A; pegaptanib sodium, an aptamer specifically inhibiting the VEGF-A 165 isoform; and aflibercept, a human fusion protein incorporating ligand-binding elements from VEGF receptors and the Fc region of an IgG1 molecule [26-28].

Recently, the DRCR.net compared bevacizumab (1.25 mg), which remains a popular off-label option, ranibizumab (0.3 mg), and aflibercept (2 mg) for treatment of fovea-involving DME in eyes with visual acuity of 20/32 to 20/320. The treatment effect was similar among the three drugs for eyes with baseline visual acuity letter score ≥ 69 (approximately 20/40 or better) and demonstrated superiority of aflibercept for eyes with baseline visual acuity letter score < 69 (20/50 or worse). Corresponding improvements in retinal thickness mirror the changes in visual acuity [29].

Three- and five-year follow up in a few trials demonstrated continued benefit of VEGF antagonist therapy in the setting of further treatment when warranted and has not revealed any new safety concerns [30,31]. The frequency of treatment also appears to decrease with time [31].

In an attempt to have a guide line for whether anti VEGF treatment will give anatomical and functional benefit for treated patients with DME and hence to be continued or stopped, a post hoc analysis explored the relationship between early retinal anatomical response (after 12 weeks) and long term anatomical and visual outcomes (weeks 52 and 156) in eyes treated with ranibizumab plus prompt or deferred laser in Protocol I study. It was found that a strong (> or = 20%) CRT reduction at week 12 was associated with greater long-term improvement in best corrected visual acuity [32].

Injectable corticosteroids and sustained-release formulations for intraocular use have been evaluated for efficacy in DME.

The first corticosteroid to be tested in large clinical trials for treatment of DME was triamcinolone acetonide, (TA) administered by intravitreous injection [33-35]. Sustained-release inserts designed for intraocular delivery of fluocinolone acetonide and dexamethasone have been developed and have been recently approved for treatment of DME [36-39].

Corticosteroids are well known to promote cataract and to elevate IOP in some eyes, Dexamethasone, however, is less lipophilic than TA or fluocinolone acetonide and does not accumulate to the same extent in the trabecular meshwork and lens; therefore, there may be reduced risk of IOP increases and cataract progression with dexamethasone [40].

There is ample evidence for efficacy of various corticosteroids in treatment of DME, but none has shown superiority to intravitreous injection of VEGF antagonists or focal/grid laser photocoagulation when used as monotherapy. However, these medications can be very useful in select circumstances, particularly for DME refractory to other therapies in pseudophakic eyes without glaucoma or ocular hypertension. The need for less frequent administration is a present advantage over existing VEGF antagonists, but frequent follow-up is still necessary to monitor for intraocular pressure elevation and glaucoma [40]. Steroids can therefore be considered as a first - line treatment for patients not willing to come for monthly injections in the first 6 months of therapy. They can also be used as a first line therapy in patients who have a history of a major cardiovascular event as these patients were excluded from all major anti-VEGF trials [2].

It is preferred to use dexamethasone first. Fluocinolone may be appropriate for non-steroid responders with chronic macular edema that is not responsive to other treatments. Since TA is not approved and causes more increase in IOP and cataract, it should be used only in patients who cannot get approved agents for this indication [2].

A number of small case series have reported benefit of vitrectomy in the setting of demonstrable vitreomacular traction and epiretinal proliferation in DME [41-44]. Differences in patient populations, definition of clinically significant vitreoretinal traction, surgical approach, use of laser and medications as adjunct treatment, outcome measures, and follow-up, alongside the customary limitations and biases of retrospective studies, make it difficult to assess the efficacy of surgery [40]. It is, however generally agreed that the presence of antero-posterior traction may be an indication for pars plana vitrectomy (PPV) in eyes with DME. Tangential traction due to an epiretinal membrane or hyaloid membrane should be considered only when the response to anti-VEGF or dexamethasone implants is incomplete [2].

Results of case series evaluating vitrectomy for DME even in the absence of any visible vitreoretinal traction have been mixed, with some reports suggesting efficacy and others not [45-49]. Two very small randomized trials showed no evidence for significant benefit [50,51]. In the absence of any data from large, well-designed clinical trials, efficacy remains uncertain at best and, weighed against well-known risks of surgery, does not typically warrant vitrectomy for this indication alone [40].

Bibliography

1. Diabetic retinopathy Oxford diabetes library.

2. Schmidt-Erfurth U., *et al*. "Guidelines for the management of diabetic macular edema by the European Society of Retina specialists(EURETINA)". *Ophthalmological* 237.4 (2017): 185-222.

3. Gerendas B., *et al*. "Morphological parameters relevant for the visual and anatomic outcomes during anti-VEGF therapy of diabetic macular edema in the RESTORE trial". *Investigative Ophthalmology and Visual Science* 55 (2014): 1791.

4. Sun JK., *et al*. "Disorganization of the retinal inner layers as a predictor of visual acuity in eyes with center-involved diabetic macular edema". *JAMA Ophthalmology* 132.11 (2014): 1309-1316.

5. Shin HJ., *et al*. "Association between photoreceptor integrity and visual outcome in diabetic macular edema". *Graefe's Archive for Clinical and Experimental Ophthalmology* 250.1 (2012): 61-70.

6. Rayees N., *et al*. "Baseline choroid thickness as a predictor for response to anti-VEGF therapy in diabetic macular edema". *American Journal of Ophthalmology* 159.1 (2015): 85-91.

7. The Diabetes Control and Complications Trial Research Group., *et al*. "The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus". *New England Journal of Medicine* 329.14 (1993): 977-986.

8. Diabetes Control and Complications Trial Research Group. "The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial". *Diabetes* 44.8 (1995): 968-83.

9. UK Prospective Diabetes Study (UKPDS) Group. "Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34)". *Lancet* 352.9131 (1998): 854-65.

10. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complications Study Research Group. "Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus". *Journal of the American Medical Association* 287.19 (2002): 2563-2569.

11. Chew EY., *et al*. "Effects of medical therapies on retinopathy progression in type 2 diabetes". *New England Journal of Medicine* 363 (2010): 233-244.

12. "The effect of intensive diabetes treatment on the progression of diabetic retinopathy in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial". *Archives of Ophthalmology* 113.1 (1995): 36-51.

13. UK Prospective Diabetes Study (UKPDS) Group. "Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33)". *Lancet* 352.9131 (1998): 837-853.

14. UK Prospective Diabetes Study Group. "Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38". *British Medical Journal* 317.7160 (1998): 703-713.

15. Davis MD., *et al*. "Risk factors for high risk PDR and severe visual loss: ETDRS Report # 18". *Investigative Ophthalmology and Visual Science* 39.2 (1998): 233-252.

16. Rodrigues-Fontal M., *et al*. "Metabolic control and diabetic retinopathy". *Current Diabetes Reviews* 5.1 (2009): 3-7.

17. Early Treatment Diabetic Retinopathy Study Research Group. "Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1". *Archives of Ophthalmology* 103.12 (1985): 1796-806.

18. Diabetic Retinopathy Clinical Research Network. "A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema". *Ophthalmology* 115.9 (2008): 1447-1149.

19. Mitchell P., *et al*. "The RESTORE Study; Ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema". *Ophthalmology* 118.4 (2011): 615-625.

20. Stanga P. "Subthreshold retinal treatment with yellow 577 nm PASCL laser". *Retina Today* (2013).

21. Laursen ML., *et al*. "Subthreshold micropulse diode laser treatment in DME". *British Journal of Ophthalmology* 88.9 (2004): 1173-1179.

22. LuttrullJK., *et al*. "Long term safety, high resolution imaging , and tissue temperature modeling of subvisible diode micropulse photocoagulation of retinovascular macular edema". *Retina* 32.2 (2012): 375-386.

23. Ohkoshi K., *et al*. "Subthreshold micropulse diodelaser photocoagulation of DMEin Japanese patients". *American Journal of Ophthalmology* 149.1 (2010): 133-139.

24. Figueira J., *et al.* "Prospective randomized controlled trial comparing subthreshold micropulse diode laser photocoagulation and conventional green laser for clinically significant DME". *British Journal of Ophthalmology* 93.10 (2009): 1341-1344.

25. Vujosevic S., *et al*. "Subthreshold micropulse yellow laser versus subthreshold micropulse infrared laser in center involving DME : morphologic and functional safety". *Retina* 35.8 (2015): 1594-1603.

26. Michels S., *et al*. "Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration twelve-week results of an uncontrolled open-label clinical study". *Ophthalmology* 112.6 (2005): 1035-1047.

27. Moshfeghi AA., *et al*. "Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration: twenty-four-week results of an uncontrolled open-label clinical study". *Ophthalmology* 113.11 (2006): 2002.e1-12.

28. Nguyen QD., *et al*. "A phase I trial of an IV-administered vascular endothelial growth factor trap for treatment in patients with choroidal neovascularization due to age related macular degeneration". *Ophthalmology* 113.9 (2006): 1522.

29. Diabetic Retinopathy Clinical Research Network. "Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema". *New England Journal of Medicine* 372 (2015): 1193-1203.

30. Brown DM., *et al*. "Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE". *Ophthalmology* 120.10 (2013): 2013-2022.

31. Elman MJ., *et al*. "Intravitreal Ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: 5-year randomized trial results". *Ophthalmology* 122 (2015): 375-381.

32. Dugel Pravin U., *et al*. "Association between early anatomic response to anti-VEGF therapy and long term outcome in diabetic macular edema. An independent analysis of Protocol I study data". *Retina* (2018).

33. Elman MJ., *et al*. "Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema". *Ophthalmology* 118.4 (2011): 609-614.

34. Beck RW., *et al*. "Three-year follow-up of a randomized trial comparing focal/grid photocoagulation and intravitreal triamcinolone for diabetic macular edema". *Archives of Ophthalmology* 127.3 (2009): 245-251.

35. Elman MJ., *et al*. "Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema". *Ophthalmology* 117.6 (2010): 1064-1077.

36. ILUVIEN - Fluocinolone acetonide implant. Package inserts. Full prescribing information (2014).

37. OZURDEX - dexamethasone implant. Package inserts. Full prescribing information. Updated 9/2014.

38. Campochiaro PA., *et al*. "Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema". *Ophthalmology* 118.4 (2011): 626-35.

39. Boyer DS., *et al*. "Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema". *Ophthalmology* 121.10 (2014): 1904-1914.

40. Schachat AP: Ryan's RETINA , sixth edition, chapter 50 (2018): 1160.

41. Dillinger P and Mester U. "Vitrectomy with removal of the internal limiting membrane in chronic diabetic macular oedema". *Graefe's Archive for Clinical and Experimental Ophthalmology* 242.8 (2004): 630-637.

42. Figueroa MS., *et al*. "Surgical and anatomical outcomes of pars plana vitrectomy for diffuse nontractional diabetic macular edema". *Retina* 28.3 (2008): 420-426.

43. Hartley KL., *et al*. "Pars plana vitrectomy with internal limiting membrane peeling for diabetic macular edema". *Retina* 28.3 (2008): 410-419.

44. Higuchi A., *et al*. "Pars plana vitrectomy with removal of posterior hyaloid face in treatment of refractory diabetic macular edema resistant to triamcinolone acetonide". *Japanese Journal of Ophthalmology* 50.6 (2006): 529-531.

45. Ikeda T., *et al*. "Vitrectomy for cystoid macular oedema with attached posterior hyaloid membrane in patients with diabetes". *British Journal of Ophthalmology* 83.1 (1999): 12-14.

46. La Heij EC., *et al*. "Vitrectomy results in diabetic macular oedema without evident vitreomacular traction". *Graefe's Archive for Clinical and Experimental Ophthalmology* 239.4 (2001): 264-270.

47. Recchia FM., *et al*. "Pars plana vitrectomy with removal of the internal limiting membrane in the treatment of persistent diabetic macular edema". *American Journal of Ophthalmology* 139.3 (2005): 447-454.

48. Rosenblatt BJ., *et al*. "Pars plana vitrectomy with internal limiting membranectomy for refractory diabetic macular edema without a taut posterior hyaloid". *Graefe's Archive for Clinical and Experimental Ophthalmology* 243.1 (2005): 20-25.

49. Yanyali A., *et al*. "Long-term outcomes of pars plana vitrectomy with internal limiting membrane removal in diabetic macular edema". *Retina* 27.5 (2007): 557-566.

50. Patel JI., *et al*. "Diabetic macular oedema: pilot randomised trial of pars plana vitrectomy vs macular argon photocoagulation". *Eye (London)* 20.8 (2006): 873-881.

51. Thomas D., *et al*. "A randomised controlled feasibility trial of vitrectomy versus laser for diabetic macular oedema". *The British Journal of Ophthalmology* 89.1 (2005): 81-86.

Volume 9 Issue 6 June 2018