CURRENT CONCEPTS IN MANAGEMENT OF DIABETIC MACULAR OEDEMA

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INTRODUCTION

Diabetic macular oedema is a multifactorial major cause of blindness worldwide. The disease involves breakdown of blood retinal barriers and oxidative stress. It involves the release of various growth factors including vascular endothelial growth factor.Control of systemic comorbidities like hypertension and dyslipademia play an important role. Ophthalmic treatments include monotherapy or a combination therapy of laser and intravitreal pharmacologic treatments like intravitreal Triamcinolone Acetonide, Dexamethasone or Fluocinolone implants, anti VEGFs like ranibizumab, bevacizumab or Aflibercept. Following FDA approval ranibizumab and aflibercept have become the first line of therapy. Anti VEGF therapy has changed the entire management of diabetic macular oedema. Focal laser treatment is still a preferred method of treatment for non center involving macular oedema. The Early Treatment Diabetic Retinopathy Study (ETDRS) showed that focal photocoagulation in eyes with macular oedema (Figure 1) showed considerable improvement. The high intensity of laser burns used in ETDRS was associated with enlarged scarring, restricted visual fields and development of choroidal new vessels.

Intravitreal anti VEGFs have shown good results with minimal side effects. They have shown a mean visual improvement of 8 to 10 ETDRS letters.[1] Intavitreal injections need to be repeated every month. Intravitreal steroid implants have been considered where anti VEGFs fail to show desired results. Steroids are now being used as primary line of therapy also, since macular oedema in diabetics has been shown to be a result of various inflammatory factors apart from VEGFs, lie interleukins and chymotrypsins.[1]

MORPHOLOGICAL PATTERNS ON OCT IN DME

1. **DIFFUSE RETINAL THICKENING** appears as areas of increased retinal thickness with areas of reduced intraretinal reflectivity compared with retina without thickening (Figure 2A).
2. **DIABETIC CYSTOID MACULAR OEDEMA** appears as ovoid areas of low reflectivity separated by highly reflective septae that represent intra retinal cystoid like cavities (Figure 2B).
3. **POSTERIOR HYALOID TRACTION** Tangential traction exerted by the posterior hyaloids on the retina can be seen as a highly reflective band on the retinal surface.
4. **SEROUS RETINAL DETACHMENT NOT ASSOCIATED WITH POSTERIOR HYALOID TRACTION** A dark accumulation of sub retinal fluid is seen beneath the dome shaped elevation of the retina is seen. A highly reflective band which represents the outer surface of the detached retina, differentiates SRF from intra retinal fluid (Figure 2D).
5. **POSTERIOR HYALOID TRACTION AND TRACTIONAL RETINAL DETATCHMENT** PHT is seen as highly reflective signal arising from the inner retinal surface. TRD is seen as an area of low intensity signal underlying the highly reflective border of detatched retina. TRD often takes on a peaked configuration (Figure 2C).

MANAGEMENT GUIDELINES

A good metabolic control is mandatory for all patients undergoing treatment. Treatment starts with comorbidities like control of blood pressure, dyslipidemias etc.A thorough ocular examination including vision, intra ocular pressure, slit lamp examination, dilated fundus examination,+90 D examination, OCT and FFA are done.

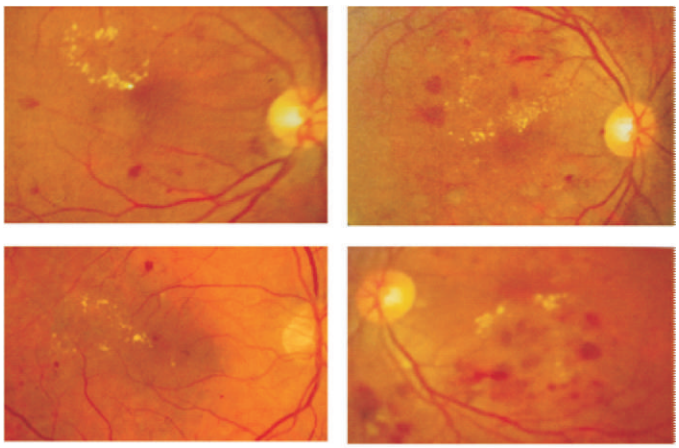

Figure 1 : Clinically significant macular edema

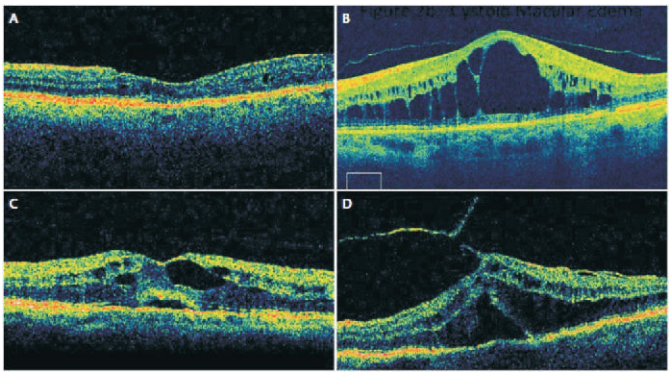

Figure 2 (A) : Diffuise retinal thickining
(B) : Cystcid macluar edema
(C) : Sub macular fluid with noPHT
(D) : DME with PHT

Several randomized control trials have evaluated the role of laser, anti VEGF intravitreal injection and intravitreal corticosteroid implant. They carry various levels of evidence. Laser therapy is done in non center involving DME and intravitreal anti VEGF /corticosteroid implant in non center involving DME. At the same time blood pressure levels of 130/80 or lower and hbA1c levels of less than 7 mg/dl are known to prevent progression of retinopathy.[2]

Five major groups have published guidelines for treatment of diabetic macular oedema –the American guidelines, the European guidelines, the Canadian guideline, International Council of Ophthalmology guidelines and the Asia pacific guideline.[2] All of them have inferred that the mainstay of treatment of DME has shifted from laser to intravitreal anti VEGFs and intravitreal dexamethasone implants. All guidelines mentioned initial loading doses of anti VEGF injection and repeat monthly injections till there is clinical improvement and macula is dry on OCT.[2]

In the care of DME two clinical tests –documented visual acuity with and without correction,measurement of IOP and two diagnostic tests FFA and OCT are of great importance. Both RESTORE STUDY and DRCR.net have considered anti VEGF monotherapy. RESTORE study recommends [3] loading doses of ranibizumab, then suspend treatment if vision is stable, continue treatment if it is not, restart treatment if DME worsens after initial stabilization. DRCR.net also recommends [3] loading doses followed by further injections till the macula becomes dry, then suspend therapy and continue if oedema recurs. Other three guidelines, the Canadian, the European and the Asia Pacific Guidelines recommend a combination therapy of intra vitreal injection and laser for non- centre involving DME and Ranibizumab monotherapy for centre involving DME.[2]

Retinal photocoagulation produces its beneficial effect by the following mechanisms :

1. Destruction of metabolically active cells and thus decreasing the ischaemic drive and secretion of angiogenic factors.
2. Reduction of total oxygen demand and improving intra retinal oxygen delivery.
3. Vasoconstricive effect and hence decreased exudation.
4. Facilitation of PVD induction.

Anti VEGF injection regimes

The RISE and RIDE trials established the superiority of anti VEGF injections over focal laser.[3] These studies were designed to establish treatment superiority over focal laser. They were modeled after earlier studies where monthly injections were given for the treatment of DME.

The advantages of monthly treatment was that it lead to rapid visual acuity improvement and the gain was maintained for atleast 3 years. The other main advantage was regression of diabetic retinopathy(DR).With monthly treatment patients experienced regression of 2 or more steps in DR score.

Disadvantages of monthly treatment included financial cost to the patients and insurers. Patients had to spend lot of time travelling to office every month. Family members had to share this cost further increasing the indirect burden.

PRN TREATMENT

In contrast to the monthly injections in monthly treatment, in PRN protocol anti VEGF injections are administered on the basis of presence of DME on fundus examination and on OCT.

PRN regime required frequent visits to the clinic to monitor the disease and treat if required.In DRCR.net protocol 1 the average number of visits were 13 in the first year,which decreased in the subsequent years.The advantage was a robust increase in visual acuity followed by stabilization and a decrease in the number of injections over time. However, the burden of visits still existed.[3]

TREAT AND EXTEND PROTOCOL

Based on the above responses most retina surgeons are shifting to treat and extend protocol over the past years. In this regimen the physician administers intra vitreal injection at each visit, but instead of a fixed monthly interval, the length of the interval varies depending on disease activity. On presentation, eyes are often treated monthly until macular edema resolves or until there is no further improvement in macular edema or visual acuity. As soon as the eye is deemed to have no edema, stable visual acuity, or stable macular thickness on OCT over several visits, a baseline has been established. The treatment interval is then extended by 1 to 2 weeks at a time, as long as vision and macular edema remain stable. If macular edema recurs or the visual acuity decreases, the interval is shortened by 1 to 2 weeks until the eyes return to their baseline.

A treat-and-extend regimen has several potential advantages. Unlike with a PRN schedule, the clinician does not have to wait until macular edema is worse before treating the patient. Chronic macular edema can lead to irreversible vision loss, so preventing recurrence of edema can potentially preserve visual acuity in the long term.

A treat-and-extend regimen can also reduce the number of office visits without sacrificing visual acuity. One retrospective case series compared a visual acuity–guided PRN (VAPRN) protocol with an OCT-guided treat-and-extend (OCTAE) regimen in patients with DME treated with Ranibizumab.[3] At 1-year follow-up, there was no significant difference in visual acuity (+8.3 letters vs. +9.3 letters) in the VAPRN and OCTAE groups, respectively, although the VAPRN group required fewer injections (5.9 vs. 8.9) than the OCTAE group ($P < .001$).[3] It is not clear whether these visual acuity and OCT outcomes would be maintained over time.

In another retrospective series, the mean number of injections using a treat-and-extend regimen was 8.8 over a 2-year follow-up period with a mean injection interval of 11 weeks.

A multicenter randomized study recently compared Ranibizumab for the treatment of patients with DME administered in one of three regimens: monthly, or on a treat-and-extend basis either with or without macular laser administered at month 1 and again every 3 months based on microaneurysm leakage on fluorescein angiography.At 1 year, mean BCVA was not statistically significantly different among the three cohorts. Although there was no difference in BCVA among the groups, the number of injections required to achieve these visual acuity gains was significantly lower in both treat-and-extend groups compared with the monthly group (10.7 injections for treat-and-extend without laser, 10.1 injections for treat-and-extend with laser, and 13.1 injections for the monthly group; $P = < .001$).[3]

INTRAVITREAL STEROID IMPLANTS

Diabetic macular oedema has been shown to be a result of several inflammatory factors other than VEGF. Anti inflammatory effect of dexamethasone is rapid and may produce beneficial effects within a week of treatment. Steroid administration may reduce VEGF expression, attenuate leukostasis, and vascular leakage and decrease the production of proinflammatory cytokines. The fact that dexamethasone is able to improve DME symptoms in patients refractory to anti-VEGF suggests that in these cases inflammatory mediators may have a more important role than VEGF in disease development.[3]

Dexamethasone implant helps in improvement of visual acuity as also a decrease in CMT. The effect of dexamethasone implant lasts for 6 weeks.Very rarely repeat injections are required. Very few complications like cataract formation or raised intraocular pressure have been reported. Intravitreal steroid implant may be used as a primary line of therapy in DME patients who are pseudophakic or are waiting for cataract surgery. It is also recommended for all recalcitrant cases not responding to repeat intravitreal anti VEGF injections.[4]

PERIPHERAL ISCHAEMIA

Peripheral ischemia is an important finding in eyes with DME , which is highlighted even more by new technological advances in wide-angle fluorescein angiography. The modern approach suggests that treating this peripheral ischemia is a pivotal issue in DME therapy. Peripheral ischemia leads to up-regulation of VEGF and ablation of the periphery would result in down-regulation of VEGF. Peripheral laser photocoagulation enhances formation of posterior vitreous detachment (PVD) ,which enhances DME resolution.

To prevent immediate worsening of DME after peripheral laser, anti VEGF injection with or without steroid implant are given prior to laser photocoagulation. Photocoagulation leads to increased oxygen supply to the remaining retina, especially the area of macula. This results in retinal vasoconstriction and a decrease in DME, avoiding the need for both focal therapies of the posterior pole and repeated anti-VEGF injections.

CLINICAL SITUATIONS

1. **Macular oedema, center involved, good visual function**

   One should treat with anti VEGF therapy because the macular centre is involved. Patient might be reluctant as the vision is good in this case. While the discretion lies with the treating physician, one could consider just observation if the vision is good and the macular oedema non cystic. A good metabolic control is off course mandatory.[2]

2. **Macular oedema, centre involved, compromised visual function**

   Anti VEGF therapy or intravitreal dexamethasone is the treatment of choice. The patient should be counseled that he will have to return to the clinic for regular follow ups and further treatment if required. The risk of cardiovascular complications and development of cataract or raised intraocular pressure must be explained to the patient.

3. **Macular oedema with vitreomacular traction**

   Vitreous surgery with or without ILM peeling is the treatment of choice. Anti VEGF injections should not be used as they further worsen vitreo macular traction.

4. **Macular oedema, center involved, no vitreomacular traction**

Vitreous surgery may be considered only after exhausting all possible options.

INDIAN DIABETIC MACULAR OEDEMA GUIDELINES [2]

One need not intervene in eyes with minimal vision reduction (20/20–20/25) irrespective of macular involvement. One should decide to treat with laser in noncenter-involving macular edema and anti-VEGF in center involving macular oedema.

Anti-VEGF therapy or implantable dexamethasone treatment becomes mandatory in center-involving DME with moderate to severe vision loss. Intervention when the vision is still good (>20/40) is likely to give better results. Because of possibilities of increased IOP and early cataract formation in phakic eyes associated with dexamethasone implant, the anti-VEGF injection is favored more often as the first line treatment. Anti-VEGF therapy should be continued till macular edema improves and vision is stable. A laser therapy (deferred laser) could be considered as it will reduce the number of injections; however, this is not evidence based.

Change of therapy is indicated in nonresponders or recalcitrant situation. The options are either change to another anti-VEGF or use implantable dexamethasone. Increase in IOP is a concern though the MEAD study has shown that the IOP rise in each treatment cycle is temporary and returns to baseline between two treatment cycles.

Finally, vitrectomy should be reserved for refractory cases not responding to any of the above-mentioned therapies. Vitrectomy is also necessary in eyes with documented vitreoretinal traction or when all options are exhausted . DRCR.net study has suggested that poor presenting vision and removal of epiretinal membrane are associated with superior visual gain following vitrectomy.[2]

REFERENCES

1. Ahmad M Mansour, J. (2019). Diabetic Macular Edema: From Old Concepts to New Therapeutic Avenues. [online] PubMed Central (PMC). Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5087101
2. Das T, Aurora A, Chhablani J, Giridhar A, Kumar A, Raman R et al. Evidence-based review of diabetic macular edema management: Consensus statement on Indian treatment guidelines. Ind J Ophthalmol. 2016;64(1):14.
3. Bryn Mawr Communications L. Retina Today - Intravitreal Anti-VEGF Injection Treatment Algorithms for DME [Internet]. Retina Today. 2019. Available from: http://retinatoday.com/2017/08/intravitreal-anti-vegf-injection-treatment-algorithms-for-dme
4. Edema M, Ameen Marashi M, Physician R. Retinal Physician-Management of Diabetic Macular Edema [Internet]. Retinal Physician 2019. Available from : https://www.retinalphysician.com/issues/2016/april-2016/management-of-diabetic-macular-edema
5. Pacella F, Ferraresi A, Turchetti P, Lenzi T, Giustolisi R, Bottone A et al. Intravitreal Injection of Ozurdex® Implant in Patients with Persistent Diabetic Macular Edema, with Six-Month Follow-Up. Ophthalmol Eye2016;8:OED.S38028.

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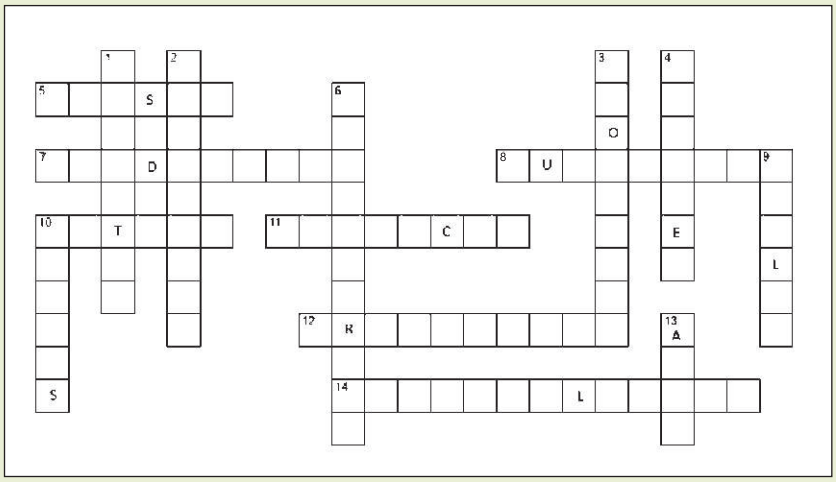

ACROSS
5 An eyelid disorder
7 Corneal graft rejection
8 A Retinopathy
10 A stereopsis test
11 An Ophthalmic instrument
12 An Aeging process
14 A scotoma

DOWN
1 An imaginary plane
2 A drug causing uveitis
3 A symptom
4 A line in Pterygium
6 Anti-Glaucoma
9 An inventor
10 An intraocular lens
13 A pupil

The correct answers can be mailed to editorupsos 2018@gmail.com