Review Article

Evidence-based review of diabetic macular edema management: Consensus statement on Indian treatment guidelines

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The purpose of the study was to review the current evidence and design a diabetic macular edema (DME) management guideline specific for India. The published DME guidelines from different organizations and publications were weighed against the practice trends in India. This included the recently approved drugs. DME management consisted of control of diabetes and other associated systemic conditions, such as hypertension and hyperlipidemia, and specific therapy to reduce macular edema. Quantification of macular edema is precisely made with the optical coherence tomography and treatment options include retinal laser, intravitreal anti-vascular endothelial growth factors (VEGF), and implantable dexamethasone. Specific use of these modalities depends on the presenting vision and extent of macular involvement. Invariable eyes with center-involving macular edema benefit from intravitreal anti-VEGF or dexamethasone implant therapy, and eyes with macular edema not involving the macula center benefit from retinal laser. The results are illustrated with adequate case studies and frequently asked questions. This guideline prepared on the current published evidence is meant as a guideline for the treating physicians.

Key words: Diabetic macular edema, diabetic retinopathy, evidence, intravitreal injections, laser

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Diabetic retinopathy (DR), the leading cause of visual disability in diabetics, is an important complication of diabetes mellitus (DM).[1-5] The reported prevalence of DR in India ranges from 17.6% to 28.2%.[6-9] With this prevalence, the number of people with DM is expected to increase from current 67 million to 79.4 million and patients with DR would increase to 22.4 million in another two decades.[5] The potential economic and social burden of DM and DR demands definite needs for an effective screening strategy, accurate case detection, and treatment effective for both DM and DR.

While the natural course of DR ranges from a mild stage, nonproliferative DR (NPDR) to a severe stage, proliferative DR (PDR), the visual acuity may not follow the same natural course. There could be reduction in vision, the vision-threatening DR (VTDR), at any stage of the disease. In a recent study of retinopathy status at presentation in self-reported type 2 diabetics in a tertiary eye care facility, 73.7% patients reported in NPDR stage though only 51% had good vision (>20/60) (submitted for publication). Likewise, diabetic macular edema (DME) could occur at any stage of retinopathy though it invariably manifests more commonly in the NPDR stage. A recent meta-analysis of 35 population-based studies of diabetics worldwide indicated that about one-third of diabetic individuals had some degree of DR, and fewer than 10% had either DME or PDR. This means that a substantial number of individuals with underlying diabetes do not progress to overt VTDR. However, these are at a risk of conversion and need regular follow-up.[10]

Diabetic Macular Edema Treatment Over Years

Focal and/or grid laser has been the mainstay of treatment in clinically significant DME.[11,12] In the early treatment DR study (ETDRS), immediate laser treatment irrespective of type of DME reduced the incidence of moderate visual loss by approximately 50% at all-time points (5% in immediate photocoagulation subgroup vs. 8% in deferred group at 1 year; 7% vs. 16%, respectively at 2 years; 12% vs. 24%, respectively at 3 years). Over many years, there have been substantial advances in understanding the pathophysiology and pathobiology of DME. Two advances that have significantly influenced our understanding of DME and treatment are the modern imaging tools such as the optical coherence tomography (OCT)[13] and newer therapeutics such as intravitreal anti-vascular endothelial growth factors (VEGFs).[14] At the same time, availability of various options and precise measurement of outcome has challenged us to design the therapeutic intervention best suited for an individual. This calls for a treatment algorithm as a guideline for care of patients with DME.

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Review of Treatment Options

Laser photocoagulation

It has been the mainstay of treatment since the ETDRS. While laser treatment increased the probability that a patient might have visual improvement, the number of patients actually manifesting substantial improvement was disappointingly small.[12]

Case 1[15]

A 68-year-old man, type 2-diabetic for 22 years and earlier treated with laser for DME, returned with complaints of the recent reduction in vision. The affected right eye had visual acuity of 20/30, N12. Fundus examination showed hard exudates temporal to fovea and previous photocoagulation marks; fluorescein angiography showed diffuse macular edema nasal to fovea, confirmed with OCT (highest edema, 506 µm corresponded to the fluorescein angiography). He received grid laser photocoagulation 2 times at an interval of 4 months. At 3 months following the second laser treatment, his vision improved to 20/20, N6, and the central foveal thickness reduced to 173 µm (this treatment was done in the year 2003 before the newer therapies were available) [Fig. 1].

Anti-vascular endothelial growth factors treatment

Current evidence suggests that anti-VEGF therapy reverses visual impairment.[16] Currently, 2 VEGF-bindings drugs are approved for treatment of DME—ranibizumab (Lucentis®; Novartis) and aflibercept (EyeLea®; Bayer). Pegaptanib sodium (Macugen®; Pfizer) has been earlier used and currently bevacizumab (Avastin®; Roche) has been tried. Evidence for DME treatment with anti-VEGF therapy is largely based on Phase II and Phase III randomized clinical trials [Table 1].

Pegaptanib[17]

A Phase II and III multicenter, double-masked, sham-controlled, parallel study group evaluated 1 and 2 years efficacy of intravitreal pegaptanib sodium 0.3 mg injection in center-involved DME. Treatment was administered every 6 weeks during the 1st year and as needed during the 2nd year. At 1 year, 36.8% of patients gained >10 letters in the pegaptanib group compared to 19.7% in the sham group; this increased to 38.3% and 30%, respectively in the 2nd year.

Case 2

A 64-year-old male, known type 2 diabetic for 6 years, earlier treated with laser photocoagulation for macular edema, presented with 20/70, N8 in the left eye. The fundus showed a small circinate ring of exudates at the macula. The fluorescein angiography (leaking microaneurysms) and the OCT (289 µm) confirmed macular edema. This eye was treated with laser, but macular edema worsened (345 µm). The treatment was changed to intravitreal triamcinolone acetonide (IVTA) 4 mg, but vision reduced (20/160) and macular edema worsened further (406 µm). The treatment was switched to intravitreal pegaptanib sodium injection. His vision improved to 20/50 and macular edema reduced to 157 µm following two injections of pegaptanib sodium and cataract surgery, done 26 months after triamcinolone injection [Fig. 2].

Ranibizumab

Results of several randomized trials using ranibizumab are available. They include comparison with sham injection (RESOLVE,[18] RISE, and RIDE[19]), comparison with laser treatment (READ-2[20] and RESTORE[21]), and comparison with prompt and deferred laser (DRCR.net Protocol I[22]). All these studies have shown that intravitreal ranibizumab monotherapy is superior to laser monotherapy or intravitreal triamcinolone and that additional laser (prompt or deferred) combined with intravitreal ranibizumab does not necessarily increase vision in DME.

Case 3

A 50-year-old male, diabetic for 7 years and hypertensive for 15 years, presented with decreased vision in both eyes for 4 months that was not responding to conventional laser therapy. The best-corrected visual acuity (BCVA) was 20/60, N36 in the right eye and 20/20, N6 in the left eye. The OCT confirmed center involved cystoid macular edema in the

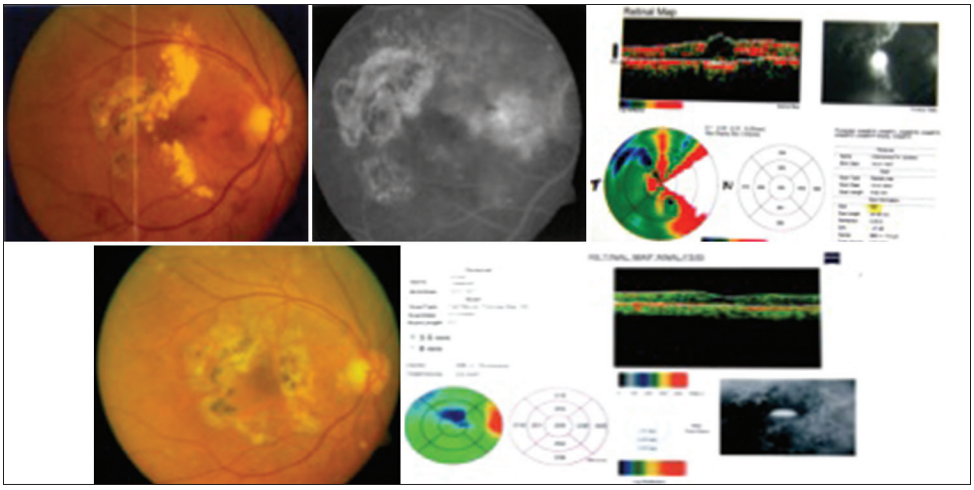

Figure 1: Top panel – Left - The right eye fundus on presentation – exudates and laser marks temporal to fovea (VA 20/30, N12). Middle - Corresponding fluorescein angiogram shows macular edema predominantly nasal to fovea. Right - Corresponding optical coherence tomography shows center-involved macular edema. Bottom panel – Left - Fundus after two sittings of laser treatment at interval of 4 months; there was complete resolution of exudates and newer laser marks are seen nasal to fovea. Right - Corresponding optical coherence tomography shows resolution of edema

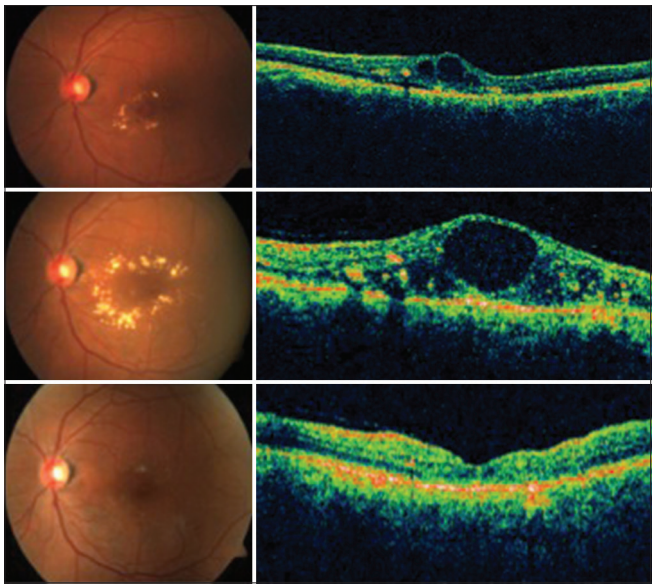

Figure 2: Top panel – Left - Fundus at presentation-circinate retinopathy at macula. Right - Cystic macular edema on optical coherence tomography (VA 20/70, N8; central macular thickness 289 μm). Middle panel – Fundus and optical coherence tomography following laser and one intravitreal triamcinolone. Circinate ring and macular edema increased (VA 20/160; central macular thickness 406 μm). Lower panel – Fundus and optical coherence tomography following two injections of pegaptanib sodium and cataract surgery (VA 20/50; macular thickness 157 μm)

right eye. After 2 intravitreal ranibizumab, vision improved to 20/30, N6; the macular edema regressed and was maintained thereafter [Fig. 3].

Bevacizumab

The bevacizumab or laser therapy, a Phase II single center 2-year study, compared intravitreal bevacizumab with laser therapy. At 2 years, more patients in the bevacizumab group gained > 10 and > 15 letters compared to laser monotherapy.[23]

Case 4

A 51-year-old male, diabetic for 25 years, presented with decreased vision in both eyes for 2 years. His BCVA was 20/50, N12 in the left eye. The left OCT showed center-involving cystoid macular edema. Following three consecutive monthly injections of bevacizumab, vision improved to 20/30, N6 with complete resolution of cystoid edema [Fig. 4].

Aflibercept

DA VINCI (DME and VEGF Trap-Eye: Investigation of clinical impact), a Phase II study, compared different doses of aflibercept (VEGF Trap) with laser over 1 year. At 1 year, more proportions of patients who received aflibercept gained >10 and >15 letters than those who received laser alone.[24] The Phase III parallel study, VIVID-DME and VISTA-DME, compared two doses of aflibercept (2 mg every 4 weeks, 2q4, and 2 mg every 8 weeks, 2q8) after initial 5 monthly injections with laser treatment; either dose of aflibercept was found superior to laser.[25]

The DRCR.net protocol T did a head-to-head comparison of ranibizumab, bevacizumab, and aflibercept in persistent

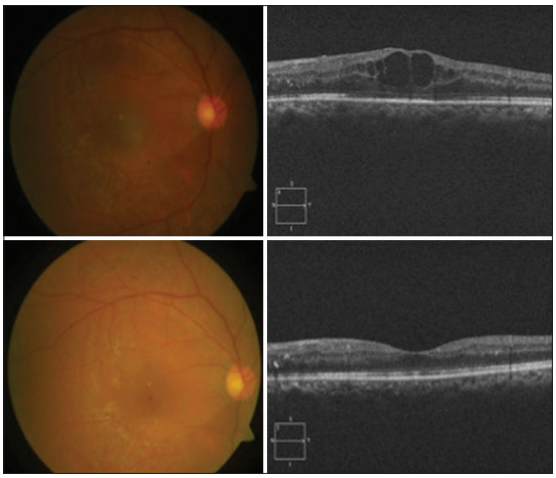

Figure 3: Top panel – At presentation: Left - Color fundus picture shows macular thickening; Right - Center involved macular edema (430 μm). VA 20/60, N36. Bottom panel – Postranibizumab treatment: Left - Color fundus picture with resolved macular edema; Right - Foveal thickness of 180 μm. VA 20/30, N6

DME.[26] This has shown that vision improved in DME following treatment with all three anti-VEGF molecules though the number of letters improvement was superior in intravitreal aflibercept (13.3 letters) compared to ranibizumab (11.2 letters) and bevacizumab (9.7 letters). This study further showed that visual gain in intravitreal aflibercept was better than ranibizumab when the initial vision was less. At 20/32–20/40 initial vision, the improvement in letter score gain in aflibercept was 8.0 letters and in ranibizumab 8.3 letters; in <20/50 initial vision, the improvement in aflibercept was 18.9 letters and in ranibizumab, 14.2 letters. At both situations, the visual letter gain in bevacizumab group was less (7.5 letters when initial vision was good and 11.8 letters when initial vision was not good).[26]

Intravitreal corticosteroids [Table 2]

Triamcinolone acetonide

Phase III DRCR.net study compared effects of 1 mg and 4 mg IVTA versus laser treatment. At 2 years, IVTA was not superior to laser treatment in DME.[27]

DRCR.net protocol I study evaluated patients receiving 0.5 mg ranibizumab combined with prompt or deferred laser versus 4 mg IVTA plus laser or laser only. At 1 year, visual gain of IVTA 4 mg plus prompt laser and sham injection plus prompt laser was similar.[28]

Case 5

A 57-year-old female, pseudophakic and earlier treated with retinal laser (panretinal and focal) and three injections of intravitreal ranibizumab in her left eye, presented with persistent cystoid macular edema in the left eye. Her BCVA was 20/60, N10. Fundus fluorescein angiogram (diffuse leakage) and the OCT (cystoid changes) confirmed macular edema. IVTA was injected in view of poor response to anti-VEGF. However, her intraocular pressure (IOP) increased to 42 mmHg on the first postoperative day and was subsequently controlled with two antiglaucoma medications. After 1 month, the IOP was 16 mmHg, and she was brought down to single antiglaucoma medication.

Table 1: Overview of selected anti VEGF RCTs in DME

Treatment	Study components	>10 letter gain	>10 letter lost	>15 letter gain	>15 letter lost
Pegatanib Phase I/III. 1 year Pegatanib 0.3 mg Vs Sham *n*=207	0.3 mg pegaptanib=107	38.3%	3.8%	23.4%	NA
	Sham=100	30.0%	9.0%	15.0 %	NA
RESOLVE Phase II. 1 year RBZ Vs Sham *n*=151	RBZ =102	60.8 %	4.9 %	32.4 %	2.9 %
	Sham=49	8.4 %	24.5%	10.2 %	20.4 %
RISE Phase III. 1 year Two doses of RBZ Vs Sham *n*=377	0.3 mg RBZ=125	62.7%	3.2%	44.8%	2.4%
	0.5 mg RBZ=125	62.4%	4%	39.2%	2.4%
	Sham=127	29.9%	16.6%	18.1%	10.3%
RIDE Phase III. 1 year Two doses of RBZ Vs Laser *n*=382	0.3 mg RBZ=125	59.2%	3.2%	33.6%	1.6%
	0.5 mg RBZ=127	64.5%	4%	45.7%	4%
	Laser=130	25.4%	13.8%	12.3%	8.4%
READ-2 Phase II, multicenter RBZ mono therapy /with laser Vs Laser alone n= 126	RBZ=28	46 %	NA	32 %	NA
	Laser=22	23 %		9 %	
	RBZ + Laser=24	38 %		21 %	
RESTORE Phase III study RBZ monotherpy/ with laser Vs Laser alone *n*= 345	RBZ=116	37.4 %	3.5%	22.6%	0.9%
	RBZ + Laser=118	43.2%	4.2%	27.9%	3.4%
	Laser=111	15.5%	12.7%	8.2%	8.2%
DRCR.net Protocol I. 5 years RBZ with Prompt Laser Vs RBZ with deferred Laser *n*=361(3 years)	RBZ + prompt laser=144	41%	11%	26%	2%
	RBZ + deferred laser=147	56%	5%	32%	3%
BOLT Phase II single center study BVZ Vs Laser. 2 year. *n*=65	Bevacizumab=37	49%	NA	32%	NA
	Laser=28	7%	NA	4%	NA
DA VINCI Phase II study 1 year Multidose Different time Aflibercept Vs Laser	0.5 mg q4. *n*=44	57%	NA	40.9%	NA
	2 mg q4. *n*=44	71%	NA	45.5%	NA
	2 mg q8. *n*=42	45%	NA	23.8%	NA
	2 mg PRN. *n*= 45	62%	NA	42.2%	NA
VIVID DME; VISTA DME Phase III parallel study 2 doses of aflibercept Vs Laser *n*=872. 1 year	VIVID. Aflibercept 2q4 VIVID Aflibercept 2q8 33.3%			32.4%	
	Vivid vs aser			9.1%	
	VISTA Aflibercept 2q4			41.6%	
	VISTA Aflibercept 2q8			31.1%	
	Vista Vs Laser			7.8%	
DRCR.net Protocol T. Phase III study 1:1:1 ratio 3 anti VEGF agents *n*=660. 1 year	Aflibercept 2.0 mg	Aflibercept 77%	Aflibercept 1%	Aflibercept 67%	Aflibercept 1%
	Bevacizumab 1.25 mg	Bevacizumab 60%	Bevacizumab 4%	Bevacizumab 41%	Bevacizumab 2%
	Ranibizumab 0.3 mg	Ranibizumab 69%	Ranibizumab 2%	Ranibizumab 50%	Ranibizumab 2%
	In general the mean improvement was 13.3 letters with aflibercept, 9.7 letters with bevacizumab and 11.2 letters with ranibizumab. There was more improvement with aflibercept when presenting vision was <20/50				

VEGF: Vascular endothelial growth factors, DME: Diabetic macular edema, RCT: Randomized Clinical Trial, RBZ: Ranibizumab

At 3 months, her BCVA was 20/60, N6, and there was complete resolution of macular edema in OCT. She had recurrence of macular edema, confirmed with OCT, 6 months after the IVTA injection. However, in view of earlier posttreatment IOP rise, she was again advised intravitreal anti-VEGF in the left eye [Fig. 5].

Fluocinolone acetonide

The fluocinolone acetonide in DME study, a 36-month Phase III study, examined efficacy and safety of fluocinolone acetonide compared with sham injection. At 3 years, there was better visual gain in eyes that received any dose of fluocinolone acetonide (0.2 µg/day and 0.5 µg/day).[29]

Dexamethasone

A larger parallel 3-year study, the Macular Edema: Assessment of Implantable Dexamethasone in Diabetes (MEAD) study, recorded improvement of vision with two different doses of implantable dexamethasone (22.2% eyes with 0.7 mg DEX implant and 18.4%

eyes with 0.35 mg DEX implant gained >15 letters). Cataract formation (67.9% eyes with 0.7 mg implant and 64.1% eyes 0.35 mg implant), reduction in central retinal thickness (111.6 μm with 0.7 mg implant and 107.9 μm with 0.35 mg implant), and >10 mmHg IOP increase (27.7% in 0.7 mg implant and 24.8% in 0.4 mg implant) were similar in both implants. The mean number of device injection over 3 years was 4.1 and 4.4 for 0.7 mg and 0.35 mg dexamethasone implant, respectively.[30]

Case 6

A 60-year-old female, not responding to both laser and anti-VEGF therapy, had gross cystoid macular edema and visual acuity of 20/80 in both eyes. She received dexamethasone implant (Ozurdex) in both eyes. At 5 months follow–up, her visual acuity improved to 20/32 in the right eye and 20/50 in the left eye without rise in IOP. Clinical examination showed resolution of macular edema and was confirmed on the OCT [Fig. 6].

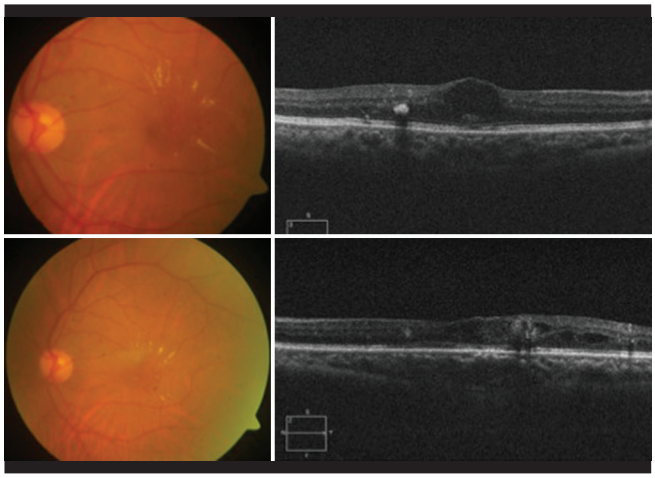

Figure 4: Top panel – At presentation: Left - Color fundus at presentation – few hard exudates, microaneurysms and area of retinal thickening. Right - Cystoids macular edema (326 μm). VA 20/50, N12. Lower panel – Postbevacizumab injections: Left - Color fundus picture shows resolved macular edema; foveal thickness reduced to 187 μm. VA 20/30, N6

Combination therapy (anti-vascular endothelial growth factors and laser)

DRCR.net protocol I studied the effect of prompt and deferred laser with intravitreal ranibizumab injection. Both 3-year[22] and 5-year reports[31] showed that deferred laser (deferred by 24 weeks after intravitreal ranibizumab) did not have any deterrent effect on the visual recovery. The mean change in visual acuity letter score from baseline to the 5-year visit was + 7.2 letters in the prompt laser group and + 9.8 letters in the deferred laser group. An improvement of >10 letters was achieved in 46–58% in prompt and deferred laser group, respectively, and an improvement of >15 letters was achieved in 27–38% in prompt and deferred laser group, respectively. In addition, from baseline to 5 years, 56% of patients in the deferred laser group did not receive laser. However, the mean numbers of intravitreal ranibizumab injections were higher in the deferred laser group (17 injections) than the prompt laser group (13 injections).[31]

Vitrectomy

The role of vitrectomy in the management of DME without vitreomacular traction is less clear. While vitrectomy with or without internal limiting membrane (ILM) peeling reduces macular edema, the visual gain is less consistent. However, vitrectomy reduces the macular edema and thus may reduce the number of anti-VEGF injections.

Safety Profile

Retinal laser done properly is safe. The most serious and blinding risk of laser is inadvertent foveal burn. The other long-term side effects are central and paracentral scotoma,

Table 2: Overview of selected intravitreal corticosteroid in DME

Treatment	Study Components	>10 letter gain	>10 letter lost	>15 letter gain	>15 letter lost
DRCR.net. Phase III. 2 years Triamcinolone 1 and 4 mg Vs Laser	IVTA 1 mg =256	25%	28%	14%	20%
	IVTA 4 mg=254	28%	28%	17%	20%
	Laser=330	19%	19%	18 %	14%
DRCR Protocol I. Phase III RBZ + Laser Vs TA + Laser	IVTA 4 mg + Prompt Laser=188	21%	33%	14 %	8 %
	Sham + Prompt Laser=293	15%	28%	13 %	8 %
FAME. Phase III. 3 years 2 Fluocinolone acetonide (FA) doses Vs Sham. *n*=956	FA 0.2 μg /day. n= 185	NA	3.2%	28.7%	NA
	FA 0.5 μg/day. n= 375	NA	4%	27.8%	NA
	Sham=393	NA	16.6%	18.9%	NA
Implantable Dexa Phase III. 1 year 2 doses of Dexa implant Vs Observation *n*=171	700 μg dexamethasone=57	33.3%			
	350 μg dexamethasone=57	21.1%			
	Sham=57	12.5%			
MEAD. Phase III. 2 parallel studies; 2 doses of dexa implant Vs Sham *n*=1048. (Completed 607)	700 μg dexa=351 (225)		NA	22 %	NA
	350 μg dexa=347 (230)			18.4 %	
	Sham=350 (152)			12 %	
Champlain study Implantable Dexa in vitrectomized Eyes. *n*=55	7000 μg dexamethasone=57	30.4%			

DME: Diabetic macular edema, IVTA: Intravitreal triamcinolone acetonide, DRCR: Diabetic Retinopathy Clinical Research Network

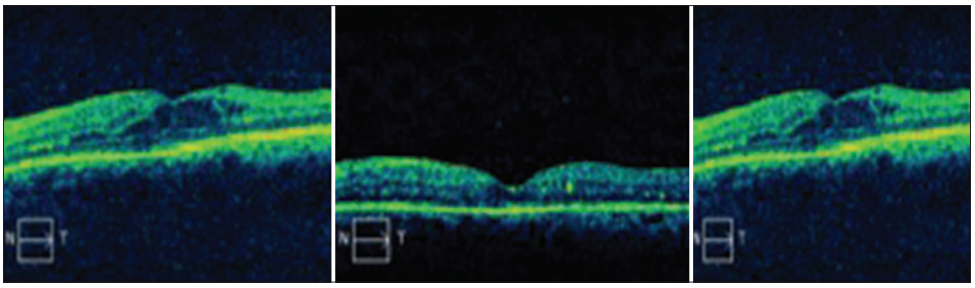

Figure 5: Optical coherence tomography. Left - Persistent macular edema after 3 intravitreal ranibizumab. Middle - Reduction of edema 3 months after intravitreal triamcinolone. Right - Return of macular edema at 6 months following intravitreal triamcinolone

Figure 6: Top panel – Fundus photograph of the right and left eye at presentation showing exudates at the macula. Middle panel – Optical coherence tomography of both eyes before Ozurdex injection showing macular edema both eyes and intraretinal exudates in the left eye (right). Lower panel – Postinjection - There was reduction of macular edema. The left eye intraretinal exudates have not reduced significantly

reduced color vision, and progressive enlargement of laser scars (laser creeps). The newer lasers such as pattern scan laser[32] and newer laser technique such as micropulse laser[33] minimize laser scar formation.

Anti-vascular endothelial growth factor

The most commonly reported ocular serious adverse event is endophthalmitis.[34] Adherence to proper aseptic measures is necessary to reduce or eliminate this serious adverse event. Patients with DM and higher glycosylated hemoglobin have a greater risk of cardiovascular disease.[35] Hence, the safety profile of anti-VEGF agents should be carefully considered, particularly when it is known that all patients will need several injections for several months and often time for a few years. Two head-to-head trials of ranibizumab and bevacizumab in age-related macular degeneration (AMD) and comparison of AMD treatment trial and alternative treatment to inhibit VEGF in age-related choroidal neovascularization did not show a significant difference in cardiovascular and systemic adverse events.[36,37]

The high incidence of early cataract and increased IOP following intravitreal corticosteroids compared with sham injection and laser treatment raises important concerns in clinical practice.[38]

Management of Guidelines

The management of patients with DR with macular edema begins with record of systemic comorbidities and proceeds to full ocular examination (vision, pressure, refraction, dilated fundus examination). Seven-field stereo photograph of posterior retina as suggested by the ETDRS is valuable for evaluation of macular edema, though three specific examinations have replaced the stereo photographs. They are slit lamp biomicroscopy (with + 78D or + 90D), fluorescein angiography, and OCT; they either qualify macular edema (slit lamp and fluorescein angiography) or quantify macular edema (OCT).

Several randomized control trials have evaluated three therapies—retinal laser, intravitreal anti-VEGF, and intravitreal corticosteroid in DME management. They carry various levels of evidence. Laser therapy in noncenter-involving DME and intravitreal anti-VEGF injection/dexamethasone implant carry level AI evidence (strong clinical outcome, strong evidence) and laser therapy in eyes that do not meet the anti-VEGF threshold carry level AIII evidence (good clinical outcome, insufficient evidence). At the same time, optimal maintenance of diabetes (HbA1c ≤ 7.0%) and blood pressure (<130/80 mmHg) known to prevent or delay progression of retinopathy also carry level AI evidence.

Five major groups have published guidelines for treatment of DME—the American guidelines,[21,39] the European guideline,[40] the Canadian guideline,[41] the International Council of Ophthalmology guideline,[42] and the Asia Pacific guideline.[43] All of them have inferred that the mainstay of treatment of DME has shifted from retinal laser to anti-VEGF treatment in most instances and concurrent use of dexamethasone implant (Ozurdex) at least in recalcitrant cases. All guidelines recommend initial loading dose of anti-VEGF, typically 3–5 injections, and continuation of therapy till there is clinical improvement and the fovea is dry (measured by OCT).

More number of options has not necessarily helped in decision-making. There are uncertainties regarding treatment selection, initiation, frequency, and duration. The diabetics are usually younger in age relative to patients with AMD. They have longer life expectancy, and hence, they need longer duration of functional vision but without the side-effects of therapy such as cataract, glaucoma, and vitreoretinal traction.

Clinical Situations

We considered the following clinical situations while considering the Indian DME management guidelines for treatment of DME.

Macular edema, center not involved, good functional vision

Laser photocoagulation invariably works.[44] In our opinion, laser should be done at the earliest reduction of vision, at the stage of 20/25 if the systemic conditions (diabetes, blood pressure, and lipids) are under control [Fig. 7].

Macular edema, center involved, good functional vision

This situation raises dilemma. In theory, one should treat with anti-VEGF therapy because the macula center is involved. In practice, the patient may be reluctant to accept the treatment since functional vision is not impaired. While the discretion lies with the treating physician, one could consider observing if vision is good (20/20 or 20/20P) and the central macular edema is noncystic. Good metabolic control, of course, is mandatory.

Macular edema, center involved, compromised functional vision

Anti-VEGF therapy or intravitreal implantable dexamethasone is the choice. Three issues need consideration and a detailed discussion with the patient and the family: One, diabetic patients are already at an increased risk of cardiovascular complications; two, there is certain probability of increased IOP in patients receiving implantable dexamethasone and early cataract formation in phakic patients; three, there is a need to return to the clinic and compliance with ocular therapy till the eye is stable in addition to a need of life-long commitment for controlled systemic conditions. The final choice of choosing the specific therapy lies with the treating ophthalmologist.

Macular edema with vitreomacular traction

Vitreous surgery with or without ILM peeling is the recommended choice if the vision is < 20/40. Further injections may, in fact, increase the vitreomacular traction.

Macular edema, center involved, without vitreomacular traction

Vitreous surgery could be considered only after exhausting all available nonsurgical options.

Case 7

A 53-year-old male presented with NPDR in both eyes and clinically significant macular edema in the right eye. The right eye vision of 20/20, stable after focal laser. However, his vision decreased to 20/60 after cataract surgery 3 years later. Two injections of bevacizumab and one injection of triamcinolone (2 mg) in the right eye did not improve his vision. At this point, vitrectomy with ILM peeling was done; 4 months following vitreous surgery vision improved to 20/25 and macular edema reduced. Although vision improved in this eye, vitrectomy usually is not associated with a significant improvement in vision [Fig. 8].

Treatment Guidelines

In care of DME, two clinical tests (documented visual acuity with and without correction and measurement of IOP) and two diagnostic tests (fluorescein angiography and OCT) are of paramount importance. Both RESTORE study-[21] and DRCR.net based-guidelines[39] have considered anti-VEGF (ranibizumab) monotherapy. RESTORE study-based guideline recommends three loading doses of ranibizumab—suspend treatment if vision is stable; continue treatment when it is not; and restart treatment if DME worsens after initial stabilization. The DRCR.net study-based guideline has also recommended initial three loading doses of ranibizumab and monthly follow-up visits; continue treatment if DME is improving; suspend treatment if DME is not improving; and restart injection only DME worsens or recurs. The basic difference between the RESTORE and DRCR.net recommendation lies in treatment strategy following the loading doses—the RESTORE recommends suspending therapy for a while, and the DRCR.net recommends to continue therapy till there is improvement. The other three guidelines, the European guideline,[40] the Canadian guideline,[41] and the Asia Pacific guideline,[43] have considered both laser and anti-VEGF therapy laser for noncenter-involved DME and anti-VEGF (ranibizumab) monotherapy for center-involved DME. All guidelines recommend monthly injection for at least two consecutive visits or until the macula is normal, and treatment re-initiated if vision deteriorates due to DME until stability is achieved again. The Canadian guideline has considered intraocular corticosteroids as the second- or third-line of treatment after

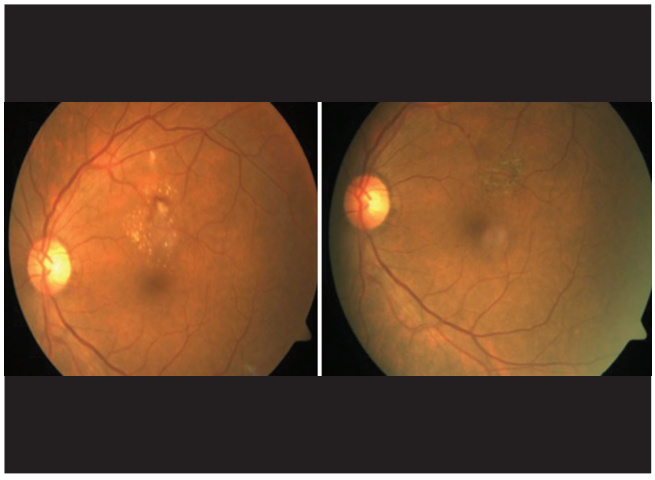

Figure 7: Left - Diabetic macular edema without center involvement. Right - Treated with laser (pattern scan laser) exudates resolved and edema subsided

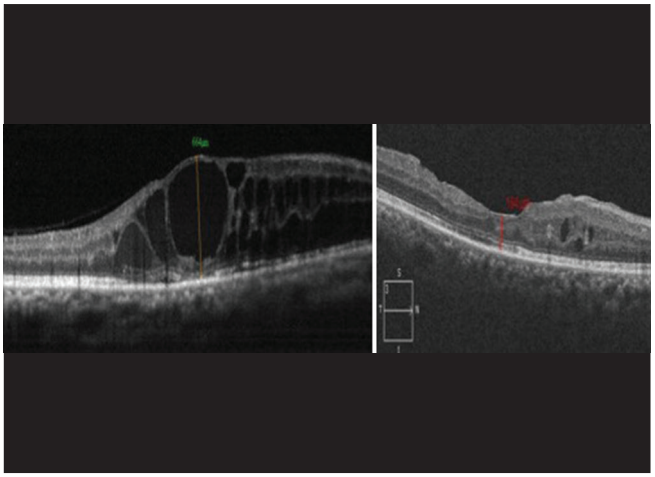

Figure 8: The optical coherence tomography before (left; 664 μm) and after (184 μm) vitreous surgery with internal limiting membrane peeling; visual acuity improved from 20/200 to 20/25 despite the presence of minimal cystic changes nasal to the fovea

other options (anti-VEGF and laser) are adequately explored and exploited.[41]

India diabetic macular edema guideline [Fig. 9]

The Indian DME guideline has considered the new knowledge from clinical trials using aflibercept and dexamethasone implant. These therapies are recently the USA Food and Drug Administration (FDA) approved (between July and September 2014) and were not considered when other guidelines were prepared.

One need not intervene in eyes with minimal vision reduction (20/20–20/25) irrespective of macular involvement. One should decide to treat we suggest that laser (Case 1) be used in noncenter-involved macular edema and anti-VEGF in center-involved macular edema.

Anti-VEGF therapy or implantable dexamethasone treatment becomes mandatory in center-involved 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 with a belief that it will reduce the number of injection; 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[30] 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

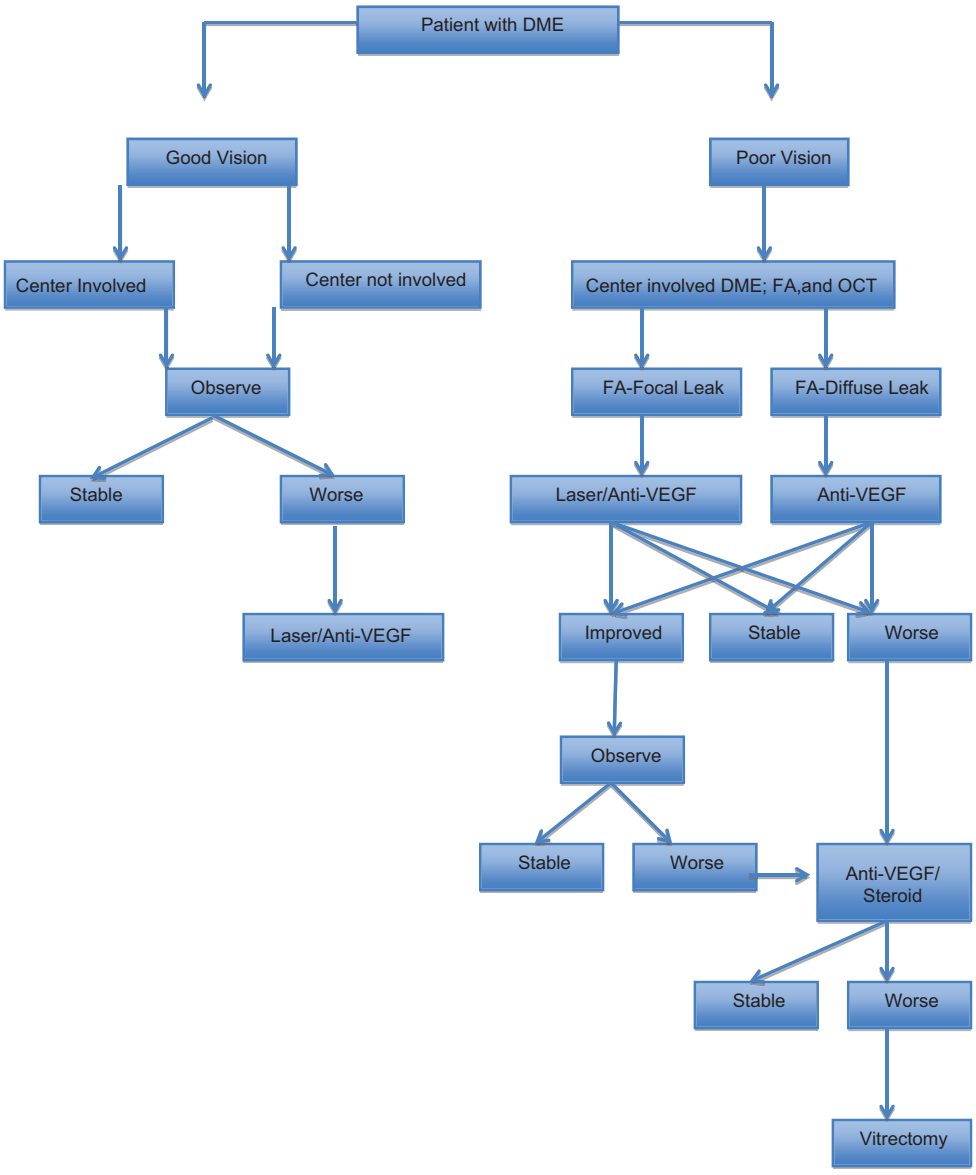

Figure 9: Diabetic macular edema treatment guideline

traction[45] or when all options are exhausted (Case 7). DRCR.net study has suggested that poor presenting vision and removal of epiretinal membrane are associated with superior visual gain following vitrectomy.[46]

Clinical Questions

Despite all the guidelines clinicians are required to answer several questions, either raised by the patients or colleagues, we considered some of them and answered them as per the current evidence.

Is laser therapy in diabetic macular edema redundant?

Laser therapy is the preferred mode of treatment in macular edema not involving the center (by fluorescein angiography and OCT) [Fig. 8].

What is the endpoint of anti-vascular endothelial growth factors therapy?

All studies using ranibizumab and aflibercept used a loading monthly injection of anti-VEGF before using it at longer intervals or when required (*pro re nata*). The published evidence suggests that most patients need more number of injections in year one, and then it reduces to next couple of years. The DRCR.net protocol has suggested that the OCT response of < 50 μ or unchanged visual acuity between two consecutive injections could be considered as an endpoint.

Will topping with laser reduce number of anti-vascular endothelial growth factors injections?

Current evidence does not suggest such a benefit. In the DRCR.net study, ranibizumab plus deferred laser was superior in visual gain compared to ranibizumab plus prompt laser at the end of 5 years.[32]

What is the ideal situation for dexamethasone implant?

Evidence is accumulating to suggest that inflammation, in addition to VEGF, could also be playing a role in DR.[47,48] Dexamethasone is a glucocorticoid. It exerts its anti-inflammatory effects by influencing multiple signal transduction pathways, including VEGF. The corticosteroids action depends on the dosage: In high doses, it activates anti-inflammatory genes and in low doses, it suppresses activated inflammatory genes.[49,50] The dexamethasone implant has this characteristics mode of drug release profile – an initial phase of high concentration and the second phase of low concentration that helps in continued anti-inflammatory activity. Despite these benefits, the use of dexamethasone implant is restricted to recalcitrant cases only for the fear of inducing early cataract in phakic eyes and/or rise in IOP. However, pseudophakic eyes could be considered for primary implantable dexamethasone.

How does one shorten the treatment course?

There is no proven way of decreasing the treatment course. Good control of systemic conditions (blood glucose, blood pressure, and serum lipid) is some help definitely. Treat and extend regimen of ranibizumab treatment in AMD[51] reduced the number of patient visits, number of injection, and direct annual cost without compromising the final visual outcome. In the absence of a specific study, this information cannot be extrapolated to ranibizumab (and other anti-VEGF molecules) treatment in DME.

Practice Trends

Published evidence invariably influences the treatment pattern. The American Society of Retina Specialists, a large conglomeration of retina specialists both from and outside the USA, has been conducting a pattern and trend (PAT) survey on current vitreoretinal disease management issues among its members for several years. We have chosen five questions from the 2014 survey relevant for DME and selected matching questions in previous years, every 3-year apart from the year 2002. This was matched with a pilot study done in India, and the results are tabulated in Table 3.

The key PATs from the PAT survey are as follows:

- Center-involved DME, mild vision loss: Laser was preferred choice till 2011; slowly shifting to anti-VEGF therapy
- Center-involved DME, moderate vision loss: Laser with/without anti-VEGF preferred till 2011; trend shifting to anti-VEGF monotherapy
- Refractory DME: Intravitreal steroid is preferred since 2011
- Number of anti-VEGF in the 1st year: USA ophthalmologists tend to give more number of injections than the international community
- Decision-making diagnostic test in DME laser treatment: Fluorescein angiography continues enjoy the confidence.

Economy of Diabetic Macular Edema Care

DM is a life-long disease and hence requires life-long treatment. DME and VTDR, unlike cataract surgery or uncorrected refractive error (two common causes of blindness), also need many visits to the clinic and a longer period of treatment. In calculation of cost of resource usage in the USA (2000–2004), the care of DME was associated with a 31% higher cost in year 1 and 29% higher cost in year 3.[52] Most of these costs were due to diagnostic tests and treatment. The trend of care actually matches with the results of PAT survey. Between the year 2000 and 2004, the use of fluorescein angiography did not show much change, use of OCT increased from 18% to 40%, use of laser therapy decreased marginally from 38% to 30%, and use of intravitreal injection increased from < 1% to 10%. Average annual clinic visit was 3.9 times.

With the subsequent published evidences of beneficial effect of anti-VEGF and implantable dexamethasone therapy in DME (FDA approval: Ranibizumab – August 2012; aflibercept – July 2014, and implantable dexamethasone – September 2014) and the evidence of several injections or implant at least in the 1st year of treatment, it is expected that the number of clinic visits will proportionately increase. This is likely to add to additional costs of care.

Conclusion

DME and VTDR are important causes of moderate to severe vision loss in DR. This is precisely measured by fluorescein angiography and OCT. Reduction of macular edema may be associated with improved vision. Laser photocoagulation has been the standard of care in 1970s; currently, this is reserved for noncenter-involved macular edema. Based on several randomized control trials, anti-VEGF therapy and implantable dexamethasone have been the new standard of care in center-involved macular edema. While these therapies

Table 3: PAT Survey. Summary of some key questions and matching Indian survey

Question	2002	2005	2008	2011	2014	India
First line therapy in new phakic DME. VA 20/50						
USA			Laser. 82.2%	Laser. 43.3% Laser + anti VEGF 28.6%	Avastin 54% RBZ 38.5%	Ranibizumab 85.29% Bevacizumab 80.88%
Int					Avastin 38.5% RBZ 38.5%	
DME refractory to laser and Ranibizumab						
USA	Steroid 48%	90.9%	Vitrectomy 98.6%	Steroid 53.2%	Steroid 55.4% Another anti VEGF 19.7%	Implantable dexamethasone 79.41%
Int					Steroid 37.8% Another anti VEGF 18.7%	
Clinically significant DME; fluid on OCT. VA 20/25						
USA				Laser 68.3% Observe 10.3%	Anti VEGF 36.6% Laser 32.7% Observe 25.6%	Observe 83.82%
Int					Anti VEGF 43.2% Observe 28.4% Laser 20.5%	
Howe many anti VEGF injections in 1st year						
USA					7-9 inj. 46.5% 3-6 inj. 37.6%	1-2 inj,, OCT guided Rx 79.41%; 3 loading, PRN. 45.49
Int					7-9 inj. 29.7% 3-6 inj. 52.5%	
What diagnostic test guides in laser for DME						
USA		FFA. 56.2%			FFA. 66.5%	OCT. 89.71%
Int					FFA. 59.3%	FFA 64.71%

PAT: Pattern and trend, VEGF: Vascular endothelial growth factors, DME: Diabetic macular edema, OCT: Optical coherence tomography, RBZ: Ranibizumab

have promised for improvement in vision, the cost of care has not reduced. Till such time that newer less expensive therapies are available, anti-VEGF or implantable dexamethasone with or without retinal laser will continue to be the treatment of choice in DME and VTDR.

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Conflicts of interest

There are no conflicts of interest.

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