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CURRENT AND EMERGING THERAPIES IN DIABETIC MACULOPATHY

Ophthalmology

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KEYWORDS

INTRODUCTION:

DIABETIC RETINOPATHY(DR) is one of the leading causes of blindness in middle aged population[1].An estimated 346 million people are affected by diabetes worldwide in 2011, and the number of people with diabetes is expected to double from 2005 to 2030.[2]Diabetic macular edema (DME) is the most frequent cause of vision loss related to diabetes. 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, which showed an approximate 50% reduction in the rate of moderate vision loss at 3 years following laser photocoagulation compared to no treatment.[3]. But nowadays the intra-vitreal pharmacotherapies has revolutionized the management in DMEand several recent randomized clinical trials have shown improved effectiveness of these drugs compared to focal/grid laser.[4-6]

Defination And Criteria Of Diabetic Maculopathy:

Diabetic maculopathy consist of macular edema and ischemia. Majority of diabetic maculopathy occur in Non Insulin Dependent Diabetes Mellitus (NIDDM) [7], Macular ischemia is more frequent in Insulin Dependent Diabetes Mellitus (IDDM) [8], after 20 years of known diabetes, the prevalence of diabetic macular edema (DME) is approximately 28% in both type 1 and type 2 diabetes [9]

Diabetic macular edema is defined as retinal thickening within 2disc diameter of the center of macula. It can be broadly classified as:

1. FOCAL EDEMA: area of retinal thickening less than 2disc diameter not affecting the center of macula
2. DIFFUSE EDEMA : 2 or more disc diameter thickening not affecting the center of macula.

CLINICALLY SIGNIFICANT MACULAR EDEMA (CSME):

ETDRS defined CSMEas edema satisfying any 1 of the following 3 criteria:

1. Any retinal thickening within 500micron meter of the center of macula
2. Hard exudates within 500 micron meter of the center of macula with adjacent retinal thickening
3. Retinal thickening at least 1 disc diameter in size any part of which is within 1 DD of the center of macula

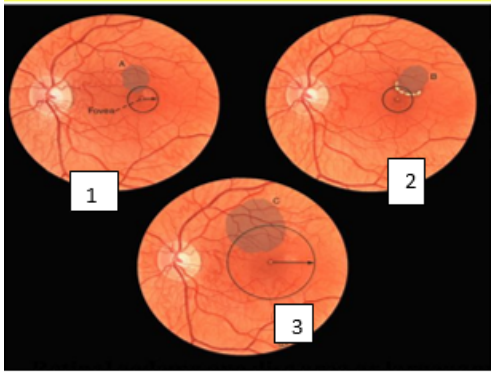


Fig: Showing The 3 Criterias For Csme As Described By Etdrs:

MANAGEMENT GUIDELINES:

- Management of patients with DR with macular edema includes:

ASSESSMENT OF DISEASE SEVERITY:

- **Record of comorbidity** like diabetic nephropathy or neuropathy, hypertension ,anaemia , dyslipidemia etc.
- **Full ocular examination**: vision, pressure (IOP), refraction, dilated fundus examination.
- **Seven-field stereo photograph** of posterior retina as suggested by ETDRS for macular edema evaluation.

Three specific examinations that have replaced the stereo photographs are:

- **Slit lamp biomicroscopy(with +78D or +90D).**
- **Fluorescein angiography.**
- **OCT.**

MANAGEMENT CONSIDERATIONS

- MEDICAL THERAPY:
- TREATMENT PROPER
- Retinal laser.
- Intravitreal anti-VEGF.
- Intravitreal corticosteroids.
- Newer pharmacotherapies

MEDICAL THERAPY:

Medical treatment should focus on optimizing glycaemic (HbA1c < 7) and hypertensive control and lowering lipid levels as demonstrated by the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) [11,12]. Anaemia and nephropathy should also be controlled These issues are best managed by primary care physicians and internists.

TREATMENT PROPER:

LASER THERAPIES:

The Early Treatment Diabetic Retinopathy Study (ETDRS) set the guidelines for the treatment of diabetic macular edema. The study found that laser reduced the risk of moderate visual loss from diabetic macular edema by 50%.[13]Laser spot of 100microns, Power of 100Mw, and at duration of 100ms is recommended. The slit lamp delivery method with a macular contact lens is preferred. The laser spots are placed as shown in (Figure 2). The fovea avascular zone(FAZ) is spared.

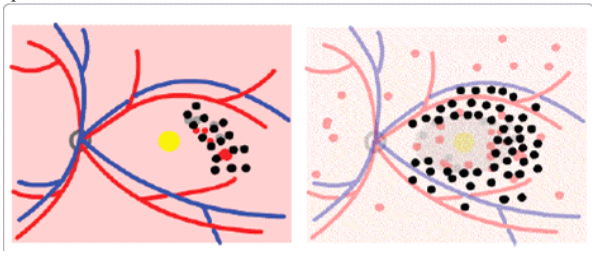


FIG 2: focal laser around the microaneyrysms and grid laser© pattern) around the FAZ

Complications of laser treatment include transient retina edema, accidental foveolar burns, paracentral scotomas, laser scar expansion, subretinal fibrosis and choroidal new vessles.

INTRAVITREAL STEROIDS AND ANTI-VEGFs:

Recently slow release steroids such as fluocinolone acetonide has been

implanted into the vitreous cavity with reduction in the macular edema and improvement in vision[13]. Complications of steroids such as cataract and raised intraocular pressure have limited their use. The Diabetic Clinical Research Network (DCRNet) in a randomised trial found that laser was superior to triamcinolone in the treatment of diabetic macular edema on the long term [14]. In June 2010, DCRNet compared the anti VEGF ranibizumab with laser and triamcinolone in a randomised trial and found ranibizumab(at a dose of 0.3mg) to be superior to both laser and triamcinolone either alone or in combination with laser [15]. The RESTORE study showed that Ranibizumab monotherapy or combined with laser provided superior visual acuity gain over standard laser in patients with visual impairment due to diabetic macular edema (DME) [16]. The RESOLVE Study and the READ 2 study also clearly showed that ranibizumab is effective in producing visual gain [17,18]. Bevacizumab (at a dose of 1.25mg) , an antiVEGF similar to ranibizumab has also been found to be superior to laser in The BOLT study [19].

Injection risk such as endophthalmitis should be borne in mind when intravitreal injection is administered.Macular edema with vitreo-macular traction has been shown by the DCRNet to benefit from vitrectomy[20]. The treatment of macular ischemia has been disappointing. AntiVEGF and laser treatments are contraindicated [21,22].

RECENT PHARMACOTHERAPIES:

As the current anti-VEGF therapies, although effective, have limitations in terms of frequent injections , treatment burdens, and complete efficacy in DME patients, novel therapies are being investigated.Strategies targeting molecules beyond VEGF are being explored along with novel drug delivery:

1. Cytokine inhibitors
2. Chemokine inhibitors
3. Kallikreinkinin inhibitor
4. Integrin Inhibitors
5. Mtor
6. ICAM-1
7. Nicotinic acetylcholine receptor
8. Renin-angiotensin system

CYTOKINE INHIBITORS:

***ANGIOPOIETIN-2*:** it is a family of growth factors that bind endothelial receptor tyrosine kinase Tie-2. It hastwo ligands Ang-1and -2 that bind to Tie-2. Ang-2 destabilizes blood vessels whereas Ang-1 stabilizes. Ang-2 is upregulated in retinas of diabetes, and increased Ang-2 leads to increased retinal vascular permeability. This pathway has been targeted in a recent ongoing clinical trial in DME patients.The combination of ANG-2 inhibitor and RBZ provided significant benefit over RBZ monotherapy in reduction of macular edema with a trend toward improved visual acuity in 3 months.[23]

***INTERLEUKINS*:** IL-6 is an important cytokine that has been consistent elevated in vitreous of patients with DME along with VEGF. A clinical trial using an intravitreal IL-6 antibody (EBI-029, Eleven Biotherapeutics,Cambridge, MA, USA) is being going on for its efficacy in DME patients.[24]

***TUMOR NECROSIS FACTOR*:** TNFα is an important cytokine that has been implicated in many inflammatory diseases including rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and Crohn's disease. A double-blind, randomized study in a small number of DME patients showed significant improved visual acuity and reduction in retinal thickness with intravenous infliximab(TNFα inhibitor) (5 mg/kg) intravenously.

Larger trials are needed to confirm the efficacy of these drugs in DME patients.[25]

CHEMOKINE INHIBITORS

The chemokine, CCL2, also known as monocyte chemotactic protein-1 (MCP

1) play an important role in vascular inflammation by inducing leukocyte recruitment and activation.This molecule is critical for monocyte trafficking and microglial activation in the retina seen in early diabetic retinopathy. An oral inhibitor targeting the receptors for chemokine, CCR2/CCR5 (Pfizer, USA), isbeing currently examined in an ongoing clinical trial in DME patients in comparison with intravitrealRBZ[26].

Kallikrein-kinin inhibitor

Vitreous proteomics has shown increased levels of plasma prekallikrein and plasma kallikrein (PKal)levels in vitreous of DME patients. Intraocular activtion of the PKal-kinin pathway may contribute to increased retinal vascular permeability many patients with DME. A Phase II clinical trial using an inhibitor of PKal (Kalvista) has been completed in DME patients. A Phase II trial using the same inhibitor in DME patients is in progress.[27]

Integrin inhibitors

Integrin are cell surface receptors to the extracellular matrix immunoglobulin molecules. The early step of inflammation, leukostasis, or adherence of leukocytes to the endothelium is dependent on specific integrin on the endothelium. A Phase II trial using an integrin antagonist, Luminate , ALG-1001 (Allegro Ophthalmic, LLC, USA), is in progress in DME patients for comparison with BVZ and focal laser therapy.[28]

mTOR

Mammalian target of rapamycin (mTOR) is a tyrosine kinase that forms two different binding complexes, TORC1 and TORC2. Its activation controls the expression of over 60 genes, including VEGF.[29] Rapamycin (sirolimus) as well as the related drug everolimus inhibit the TORC1 mTOR complex. A recent phase I/II study of five adult patients demonstrated the safety of subconjunctival rapamycin for the treatment of DME.[30] Currently, a phase II dose-ranging study is underway for the treatment of DME.[31] Palomid 529 is another mTOR inhibitor that affects both TORC1 and TORC2. It is currently undergoing the phase I safety trials for the treatment of neovascular AMD with either intravitreal or subconjunctival injection.[32,33] Its safety and efficacy to treat DME has not yet been examined.

ICAM-1

As detailed above, ICAM-1, plays a critical role in leukostasis in diabetic retinopathy and its inhibition in animal models of diabetes blocks increased vascular permeability.[34] It exerts this action through binding with lymphocyte function antigen-1 (LFA-1). SAR 1118 is a LFA-1 inhibitor. In animal models of diabetes, topical administration of this drug has been shown to reach the retina and decrease leukostasis and breakdown of the BRB.[35] Further investigation is needed to determine if SAR 1118 or other ICAM-1 or LFA-1 inhibitors will be safe and effective for the treatment of DME.

Nicotinic acetylcholine receptor

Nicotinic acetylcholine receptors are ligand gated ion channels that are made up of following five subunits, α1-10, β1-4, γ, and ε (reviewed in[36]). Vascular endothelial cells contain nAChRs and can also produce acetylcholine. Nicotine has been shown to cause increased vascular permeability through activation of endothelial α7-Nicotinic acetylcholine receptors (nAChRs).[37] Campochiaro *et al*., recently published reports of a multicenter phase I/II clinical trial assessing the safety and efficacy of topical mecamylamine, a nonspecific nAChR antagonist, for the treatment of chronic DME.[38] In this study of 23 patients, 8 patients showed improvement, 9 showed equivocal results and 4 patients showed worsening that could be convincingly attributed to the drug used in this study. Mecamylamine may prove to be beneficial to a subset of patients with DME and more specific nAChR antagonist may provide more uniformly beneficial results.

Renin-angiotensin system

The components of the Renin-angiotensin system (RAS) have been identified in the retina (reviewed in[39]). The RAS appears to be upregulated in diabetic retinas and angiotensin II (ANG II) can directly stimulate the secretion of VEGF. Based on animal models, the renin inhibitor, aliskiren (Novartis, East Hanover, NJ, USA) may have beneficial effects on DME and DR.[40]Despite the potential of medications targeting the RAS, results of the Diabetic Retinopathy Candesartan Trials (DIRECT) were disappointing with regards to the effect of candesartan, an AT1 receptor blocker, on DME.[41,42]

CONCLUSION:

DME and VTDR(vision threatening DR) are important causes of vision loss in DR. Reduction of macular edema may cause improved vision.Laser treatment has been standard treatment since 1970s but now reserved for non-center involving macular edema.Based on several RCT, anti-VEGF therapy and implantable dexamethasone have been the new standard care in center-involved macular edema.Cost of care has not reduced. Till the newer less expensive

therapies are available anti-VEGF or implantable dexamethasone with or without laser will continue to be the treatment of choice in DME and VTDR.

REFERENCES

1. World Health Organization Diabetes Fact Sheet Number 312. [cited in 2011]. Available from:http://www.who.int/mediacentre/factsheets/fs312/en/
2. The 14-year incidence of visual loss in a diabetic population. Moss SE, Klein R, Klein BE Ophthalmology. 1998 Jun; 105(6):998-1003.
3. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group.Arch Ophthalmol. 1985 Dec; 103(12):1796-806.
4. Elman MJ, Aiello LP, Beck RW, Bressler NM, Bressler SB, et al. Diabetic Retinopathy Clinical Research Network. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. (e35).Ophthalmology. 2010;117:1064–77.
5. Elman MJ, Bressler NM, Qin H, Beck RW, Ferris FL, 3rd, Friedman SM, et al. Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology. 2011; 118: 609–14.
6. Mitchell P, Bandello F, Schmidt-Erfurth U, Lang GE, Massin P, Schlingemann RO, et al. The RESTORE study: Ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology. 2011;118:615–25.
7. DasT, Rani A (2006) Diabetic Eye Diseases in Foundations of Ophthalmology.New Delhi, Jaypee: 54-55
8. Das T, Jalali S, Vedantam V, Majji AB (2003) Retinal vascular disorders.Clinical Practice of Ophthalmology. New Delhi, JP Brothers: 350
9. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL (1984) The Wisconsin Epidemiologic Study of Diabetic Retinopathy. IV.Diabetic macular edema. Ophthalmology 91: 1464–1474.
10. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group.Arch Ophthalmol. 1985 Dec; 103(12):1796-806.
11. Diabetes Control and Complications Trial Research Group (1993). The effectof intensive treatment of diabetes on the development and progression of long-term complications insulin-dependent diabetes mellitus. N Engl J Med 329: 977-986.
12. UK Prospective Diabetes Study Group: (UKPDS 38) (1998) Tight bloodpressure control and risk of macrovascular and microvascular complications in type 2 diabetes BMJ 317: 703–713.
13. Campochiaro PA, Hafiz G, Shah SM, Bloom S, Brown DM, et al. (2010)Sustained Ocular Delivery of Fluocinolone Acetonide by an Intravitreal Insert Ophthalmology 117: 1393-1399.
14. Diabetic Retinopathy Clinical Research Network (2008) A randomized trialcomparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema. Ophthalmology 115: 1447–1459.
15. Diabetic Retinopathy Clinical Research Network, Elman MJ, Aiello LP, BeckRW, Bressler NM, Bressler SB, et al. (2010) Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 117: 1064–1077.
16. Mitchell P, Bandello F, Schmidt-Erfurth U, Lang GE, Massin P, et al. (2011)The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology 118: 615-625.
17. Massin P, Bandello F, Garweg JG, Hansen LL, Harding SP, et al. (2010) Safetyand Efficacy of ranibizumab in diabetic macular edema (RESOLVE study): a 12 month, randomized, controlled, double –masked, multicenter phase II study. Diabetes Care 33: 2399–2405.
18. Nguyen QD, Shah SM, Heier JS, Do DV, Lim J, et al. (2009) Primary end point(Six months) Results of the Ranibizumab for edema of the mAcula in diabetes (READ-2) study. Ophthalmology 116: 2175-2181.
19. Michaelides M, Kaines A, Hamilton RD, Fraser-Bell S, Rajendram R, et al.(2010) A Prospective Randomized Trial of Intravitreal Bevacizumab or Laser Therapy in the Management of Diabetic Macular Edema (BOLT Study): 12-Month Data: Report 2. Ophthalmology 117: 1078-1086.
20. Diabetic Retinopathy Clinical Research Network Writing Committee, Haller JA,Qin H, Apte RS, Beck RR, Bressler NM, et al. (2010) Vitrectomy for Diabetic Macular Edema and Vitreo macular Traction. Ophthalmology 117: 1087-1093.
21. Chung EJ, Roh MI, Kwon OW, Koh HJ (2008) Effects of Macular Ischemiaon the Outcome of Intravitreal Bevacizumab Therapy for Diabetic Macular Edema. Retina 28: 957-963.
22. Richardson EC, Patel J, Hykin PG (2003) Reduced visual acuity followingstandard ETDRS macular laser for clinically significant macular edema. Eye 17: 431–433.
23. Macular Edema: The TIME-2 Trial
24. Treatment of Diabetic Macular Edema. Abstract, Association for Research in Vision and(ARVO) Meeting; 2014. Back to cited text no. 46
25. Sfikakis PP, Grigoropoulos V, Emfietzoglou I, Theodossiadis G, Tentolouris N, Delicha E, et al.Infliximab for diabetic macular edema refractory to laser photocoagulation: A randomized, doubleblind,crossover, 32-week study. Diabetes Care 2010;33:1523-8
26. A Phase 2, Multi-Center Study To Compare The Efficacy And Safety Of A Chemokine CCR2/5 Receptor Antagonist With Ranibizumab In Adults WithDiabetic Macular Edema
27. Kita T, Clermont AC, Murugesan N, Zhou Q, Fujisawa K, Ishibashi T, et al. Plasma kallikrein-kininsystem as a VEGF-independent mediator of diabetic macular edema. Diabetes 2015;64:3588-99
28. Allegro Ophthalmics Begins Phase 2 Clinical Trial of Luminate ® (ALG-1001) for the Treatment of Diabetic Macular Edema
29. Guertin DA, Sabatini DM. Defining the role of mTOR in cancer. Cancer Cell. 2007;12:9–22. [PubMed]
30. 56. Krishnadev N, Forooghian F, Cukras C, Wong W, Saligan L, Chew EY, et al. Subconjunctivalsirolimus in the treatment of diabetic macular edema. Graefes Arch ClinExp Ophthalmol. 2011;249:1627–33. [PMC free article] [PubMed]
31. 57. Dose ranging study of an ocular sirolimus (Rapamycin) formulation in patients with diabetic macular edema. [cited in 2011]. Available from: http://clinicaltrials. gov/ct2/ show/ NCT00656643 .
32. 58. Palomid 529 in patients with neovascular age-related macular degeneration. [cited in 2011]. Available from: http://clinicaltrials.gov/ct2/show/NCT01271270 .
33. 59. Phase I Study of Palomid 529 a Dual TORC1/2 Inhibitor of the PI3K/Akt/mTOR Pathway for Advanced Neovascular Age-Related Macular Degeneration (P52901) [cited in 2011]. Available from: http://clinicaltrials.gov/ct2/show/NCT01033721 .
34. Miyamoto K, Khosrof S, Bursell SE, Rohan R, Murata T, Clermont AC, et al. Prevention of leukostasis and vascular leakage in streptozotocin-induced diabetic retinopathy via intercellular adhesion molecule-1 inhibition. Proc Nat AcadSci U S A. 1999;96:10836–41.
35. Rao VR, Prescott E, Shelke NB, Trivedi R, Thomas P, Struble C, et al. Delivery of SAR 1118 to the retina via ophthalmic drops and its effectiveness in a rat streptozotocin (STZ) model of diabetic retinopathy (DR) Investig Ophthalmol Vis Sci. 2010;51:5198–204.
36. D'Hoedt D, Bertrand D. Nicotinic acetylcholine receptors: An overview on drug discovery. Expert OpinTher Targets. 2009;13:395–411. [PubMed]
37. 74. Abbruscato TJ, Lopez SP, Mark KS, Hawkins BT, Davis TP. Nicotine and cotinine modulate cerebral microvascular permeability and protein expression of ZO-1 through nicotinic acetylcholine receptors expressed on brain endothelial cells. J Pharma Sci. 2002;91:2525–38. [PubMed]
38. 75. Campochiaro PA, Shah SM, Hafiz G, Heier JS, Lit ES, Zimmer-Galler I, et al. Topical mecamylamine for diabetic macular edema. (e1).Am J Ophthalmol. 2010;149:839–51.
39. Wilkinson-Berka JL, Fletcher EL. Angiotensin and bradykinin: Targets for the treatment of vascular and neuro-glial pathology in diabetic retinopathy. Curr Pharma Design. 2004;10:3313–30. [PubMed]
40. 79. Wilkinson-Berka JL, Tan G, Binger KJ, Sutton L, McMaster K, Deliyanti D, et al. Aliskiren reduces vascular pathology in diabetic retinopathy and oxygen-induced retinopathy in the transgenic (mRen-2)27 rat. Diabetologia. 2011;54:2724–35. [PubMed]
41. 80. Chaturvedi N, Porta M, Klein R, Orchard T, Fuller J, Parving HH, et al. Effect of candesartan on prevention (DIRECT-Prevent 1) and progression (DIRECT-Protect 1) of retinopathy in type 1 diabetes: Randomized, placebo-controlled trials. Lancet. 2008;372:1394–402. [PubMed]
42. 81. Sjolie AK, Klein R, Porta M, Orchard T, Fuller J, Parving HH, et al. Effect of candesartan on progression and regression of retinopathy in type 2 diabetes (DIRECT-Protect 2): A randomized placebo-controlled trial. Lancet. 2008;372:1385–93