Review Article :

TREATING DIABETIC MACULAR EDEMA – OVERVIEW

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Diabetes mellitus currently affects more than 170 million people worldwide and will affect an estimated 366 million by 2030 as predicted by WHO[1], with the most rapid growth in low- and middle-income countries, among populations of working age. India leads the world today with the largest number of diabetics in the world.

Diabetic macular edema (DME) is the most common cause of visual impairment in Diabetic retinopathy (DR) and is the leading cause of vision loss in working-age adults. DME is generally defined as retinal thickening or the presence of hard exudates within one disk diameter from the center of the macula secondary to diabetic retinopathy. It affects about 30% of patients with disease duration of more than 20 years and, if left untreated, >50% of patients lose >2 lines of visual acuity (VA) within 2 years.[2,3,4]There has been a lot large modulation in the treatment of DME till date, namely from laser then steriods to Anti VEGF and VEGF traps.

Laser DME Treatment Paradigms

Until the early part of 1980's there was no treatment available for DME.The first landmark, largest prospective randomised study the Early treatment Diabetic Retinopathy Study (ETDRS) trial found out found that grid macular photocoagulation decreased the risk of moderate to severe vision loss from DME by 50% compared to untreated controls over 3 years. [5] It also stated that modified grid laser, where a lighter burn is applied in addition to the targeted microaneurysm burn had better results. This became the standard of care for treating macular edema for over two decades. Nevertheless there were a group which did not respond to laser termed recalcitrant macular edema and a group (21%) in the DRCR.net protocol I study who achieved a 15-letter improvement at 2 years, suggesting a delayed benefit. More recent trials reported gains of only 0.9 letters and three letters for patients receiving laser monotherapy according to ETDRS guidelines.[6] There were failures of treatment, migration of laser burn towards center and frequently many achived modest visual gains therefore there was a search for unmet medical need for therapies that could restore VA in patients with DME.Although not fully elucidated, advances in understanding DME pathophysiology have launched the investigation of various pharmacological therapies, including those targeting vascular endothelial growth factor (VEGF), which is upregulated in eyes with DME,[7,8] and is a major mediator of increased retinal permeability.[9]

Pharmacological DME Treatment Paradigms

Corticosteroids were the first pharmacologic intravitreal treatment to be used for DME. Triamcinolone acetonide has been the most widely used and studied corticosteroid in the treatment of DME. [10-12] Intravitreal triamcinolone acetonide has been used for the treatment of DME for a number of years. The effects are often short-lived, requiring frequent retreatment with the main side effects being

cataract and glaucoma. In eyes with DME, use of both 2 mg and 4 mg doses resulted in over 50% of eyes gaining e"10 ETDRS letters (2 lines of Snellen VA),with the effects lasting for 16 and 20 weeks, respectively.[10] Eyes with laser photocoagulation behaved better in reference to ETDRS gain in BCVA as compared to triamcinolone. More recently, other formulations of corticosteroids have been studied and found to be effective in the reduction of DME, including a biodegradable dexamethasone implant (Ozurdex; Allergan, Irvine, CA), a time-released nonbioerodible surgically implantable reservoir of fluocinolone (Retisert; Bausch & Lomb, Rochester, NY), and a non-bioerodible injectable fluocinolone polymer (Iluvien;Alimera Sciences, Alpharetta, GA). [13-17]

A Phase 2 clinical trial evaluating the safety and efficacy of a 0.59mg surgically implanted fluocinolone acetonide intravitreal implant (Retisert) in eyes with DME found that VA gains of e"15 ETDRS letters occurred in 16.8%of implanted eyes at 6 months and 31.1% of eyes at 3 years, compared to 1.4% at 6 months and 20% at 3 years in the macular laser group. The incidence of elevated intraocular pressure and cataract formation was much higher in eyes receiving the implant with 33.8% requiring incisional glaucoma surgery and 91% requiring cataract extraction. [14]

A Phase 3 clinical trial evaluating the efficacy and safety of an intravitreally injected fluocinolone acetonide insert (Iluvien) in eyes with DME at low (0.2 5Øßg/d) and high (0.5 5Øßg/d)doses found VA gains at 3-years of e"15 ETDRS letters in 33%and 31.9% of study eyes. Of treated eyes, 26% required more than one treatment over the 3 year period. Cataract surgery was required in 83.8% of eyes in the treatment groups and elevated intraocular pressure was much higher in the treatment groups with 4.8% (low dose) and 8.1% (high dose), requiring incisional glaucoma surgery. [15,16]

A Phase 2 clinical trial evaluating the efficacy and safety of a surgically implanted intravitreal dexamethasone delivery system in eyes with DME found that a 700 5Øßg dose resulted in VA gains of e"10 ETDRS letters at 3 months after implantation in 33.3% of eyes and 30% of eyes at 6 months. In the 350 5Øßg group, e"10 ETDRS letter gains were seen in 21.1% and 19% at 3 and 6 months after implantation, respectively. There was no significant increase incataract development between treatment group but had higher incidence of elevated intraocular pressure, but no incisional glaucoma surgery was required in any of he the eyes. [17] A Phase 3 study of an injectable form of this biodegradable implant (Ozurdex) is currently ongoing.

VEGF-A is believed to be one of the major mediating factors associated with the development of DR and DME.VEGF is a proinflammatory mediator and plays a pivotal role in vascular permeability. It is well known that VEGF levels are higher in diabetic eyes than in normal eyes. [18] At present, there are 4 medications available that target VEGFA:pegaptanib (Macugen; Eyetech Pharmaceuticals, Palm Beach Gardens, FL, USA), bevacizumab (Avastin,Genentech,San Francisco, CA, US), ranibizumab (Lucentis; Genentech,San Francisco, CA, US), and aflibercept (Eylea; Regeneron,Tarrytown, NY).

Pegaptanib, a pegylated aptamer that targets the VEGF-165 isoform, when administered intravitreally every 6 weeks was found to be more efficacious than macular laser at 24months, with ETDRS letter gains of 6.1 and 1.3, respectively. [19] Intravitreal bevacizumab, a full-lengthrecombinant humanized antibody against all isoforms of VEGF-A, was found to be more effective than macular laser for persistent DME at 24 months, with ETDRS letter gains of 8.5. [20]

In August 2012, ranibizumab, a recombinant humanized monoclonal antibody

fragment that binds all isoforms of VEGF-A, was approved by the FDA for the treatment of DME at the 0.3mg dose, administered monthly via intravitreal injection. Treatment with ranibizumab resulted in over 39% of eyes with visually significant DME gaining e"15 ETDRS letters or more of vision compared to only 18% of control eyes (which were eligible for macular laser photocoagulation based on protocol specific criteria). The overall gain in VA with monthly ranibizumab injections was 10.9 and 12 ETDRS letters in the 0.3mg and 0.5mg groups, respectively,compared to a 2.3 letter gain in the control group. Results were sustained for 24 months with continued treatment. [21]

The most recent anti-VEGF agent which has been introduced is aflibercept, previously known as the VEGF-Trap-Eye. Aflibercept binds both VEGF-A and placental growth factors 1 and 2, is delivered via intravitreal injection and is currently under study for the treatment of DME. Initial one year results demonstrate that over 40% of eyes with visually significant DME gained atleast 3 lines of vision compared to 11.4% in the macular laser control group. [22]

Combination therapy for DME

Intravitreal pharmacothreapy has replaced macular laser photocoagulation as the gold standard in the care of DME.While it is quite successful in preventing vision loss from DME, and allowing for a significant number of people to realize a gain in VA, the burden of monthly intravitreal injections can become quite an encumbrance for patients,physicians, and the healthcare system as a whole due to high costs of medications, multiple physician visits, and potential complications from an invasive procedure.This has prompted for combination therapies with both laser and intravitreal injections so that allows for fewer treatments while maintaining VA gains. A large prospective,randomized, double-blinded study conducted by the Diabetic Retinopathy Clinical Research Network (DRCR) sought to answer this specific question. Eyes with DME were treated with focal macular laser photocoagulation alone, 0.5mg of monthly ranibizumab + prompt focal macular laser, 0.5 mg of monthly ranibizumab+ deferred focal macular laser (after week 24), or 4mg of quarterly triamcinolone acetonide+prompt focal macular laser. After the first year, intravitreal medications were only administered as needed based on clinical examination. At the end of the 2-year study, it was found that ranibizumab+ deferred focal macular laser was the superior treatment algorithm for eyeswith visually significant DME. [23]

Role of vitrectomy in DME

As vitreous humor is a concentration of factors affecting vascular permeability and the traction component on the macula it is thought to be a major culprit on DME. The role of pars plana vitrectomy in the management of DME is seen with mixed results. With a tractional component in the macula leading to DME, posterior vitreous detachment is has shown modest benefit.[24] Ocriplasmin (Jetrea; ThromboGenics, Belgium) is a serine protease which is injected into the vitreous causes vitreolysis and has a beneficial role in the treatment for DME.[24]

Conclusion

There has been an incredible advancement in the treatment of DME over the past 2-3 decades with the treatment paradigm changing from observation, macular laser photocoagulation to intravitreal pharmacologic therapies.Physician and patients are now pursuing gains in VA instead of maintenance or reduction in rate of visual loss from DME.Though there are numerous treatment options available and the future looks promising but the likely treatment of choice is perhaps a combination treatment. Thanks to advances in our understanding and increased treatment options for DME, we are now able to better manage this condition. While DME was often

blinding in the past, we now are able to provide many of our patients with excellent and sustained vision, thereby allowing them to continue to be a part of the workforce. The future is promising, but it must be kept in mind that DM is a systemic disease and optimal glycemic and BP control are of paramount importance in both preventing and delaying the progression of bothDR and DME. Communication and a team approach among primary care physicians, endocrinologists, and ophthalmologists will allow patients with DME to achieve and maintain long-term sustained VA gains.

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