Mini Review
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Trends in treating chronic persistent diabetic macular edema

Abstract

Chronic persistent diabetic macular edema responds poorly to intravitreal Anti-VEGF treatment, due to dominance of inflammatory cytokines in the pathogenesis, optical coherence tomography is important tool to evaluate structural changes and visual prognosis in diabetic macular edema. Multiple studies showed the efficacy of intravitreal steroids treatment and intravitreal Anti-VEGF agents may reduce the risk of visual loss in cases of chronic persistent diabetic macular edema. When optical coherence tomography shows signs of disorganization of inner retinal layer and interruption of ellipsoid zone in light of diabetic macular edema that responds poorly to Anti-VEGF treatment then switching to intravitreal steroids recommended.

Keywords: diabetic macular edema, optical coherence tomography, vascular endothelial growth factor, best corrected visual acuity, visual acuity, disorganization of the retinal inner layers, external limiting membrane

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Abbreviations: DME, diabetic macular edema; OCT, optical coherence tomography; VEGF, vascular endothelial growth factor; BCVA, best corrected visual acuity; VA, visual acuity; DRIL, disorganization of the retinal inner layers; ELM, external limiting membrane

Introduction

Diabetic macular edema (DME) induced by increasing vascular leakage due to thickened basement membrane, thus will lead to early reduction of vision in working age group,[1] DME previously treated with laser and intravitreal steroids (triamcinolone acetonide) in the pre Anti-VEGF era; however, intravitreal Anti-VEGF injection gained popularity due to easy administration, safe profile and good efficacy. Chronic persistent DME presents as long-standing DME usually more than 18 months, which features diffuse pattern, OCT may show photoreceptor layer loss, and usually responds poorly to Anti-VEGF. Usually response to Anti-VEGF treatment is poor when OCT fails to show reduction of retinal thickness of less than 10% or/and BCVA improvement after six injections, then DME deemed as chronic, and treatment should be changed to intravitreal steroids, because inflammatory mediators are the main driver of DME.

Pathology in a nutshell

In the early course of DME, vascular endothelial growth factor (VEGF) plays major role in the pathogenesis of DME, along with inflammatory cytokines, but in the chronic course, inflammatory cytokines govern the process of pathogenesis and VEGF may not have a significant role.[2] The chronic inflammatory process of DME lead to diffuse edema and damage to photoreceptors which presented as ellipsoid zone in optical coherent tomography (OCT), another feature is a chronic large disorganization of the retinal inner layers (DRIL) is another contributing factor to bad visual prognosis.

The importance of optical coherence tomography in DME evaluation

OCT is the gold standard of evaluating macular thinking in diabetic patients, when studying OCT for DME there are several things we have to pay attention to:

i. The presence of vitreomacular abnormality

ii. The location of the edema

iii. Changes in macular morphology and the presence of Disorganization Retinal Inner Layers(DRIL)

iv. DRIL identified as each 299-µm increase in the extent of DRIL over a four-month period was associated with a 1-line decrease in visual acuity at eight months along with or without demolishing boundaries between retinal layers.[3]

Nevertheless, an independent factor in reduced VA is the disruption of the photoreceptor inner segment/outer segment layer, because it reflects damage to the photoreceptors, which may reflect chronic macular edema, along with a diffuse pattern. However, some biomarkers detected on OCT can predict good response to dexamethasone intravitreal implant such as absence of hyper-reflective foci, sub macular fluid, and intact ellipsoid zone. Hence, DME morphological changes on OCT such as presence of intraretinal Cysts, sub retinal fluid, demolishing boundaries between retinal layers, and disruption of ellipsoid zone along can predict poor visual prognosis especially when DRIL is central and accompanied with ELM disruption.[4]

Clinical trials for persistent diabetic macular edema

Numerous clinical trials, evaluated the efficacy of various Anti-VEGF agents, however about 40% of cases are deemed as non-responsive to Anti-VEGF after 4-6 injections, those cases best treated with intravitreal steroids, another important finding that late reduction of central macular thickness may lead to anatomical improvements with limited visual benefits due to permanent functional damage of the macula.

Clinical Trials for using steroids for persistent DME

TADMO study showed that intravitreal triamcinolone acetonide

can be effective in resolving macular edema in cases were deemed to be refractory, which are not responsive to laser therapy with beneficial effect persists for up to 2 years.[5] FAME study has compared two doses (0.5 & 0.2) of a fluocinolone acetonide intravitreal implant and sham injections in a patients persistent DME despite previous macular laser treatment, they concluded that percentage of patients with improvement of ≥15 letters from baseline are 31.9% (0.5 µg/d), 33.0% (0.2 µg/d), and 21.4% (sham).[6] Protocol U studied eyes with persistent DME, and visual acuity of 20/32 to 20/320 after at least three anti-VEGF injections, then injecting additional three monthly 0.3-mg Ranibizumab, after that compared continued intravitreal Ranibizumab alone with sham injection with Ranibizumab plus intravitreal dexamethasone implant. Protocol U concluded that adding intravitreal dexamethasone implant reduce central macular thickening and may increase intraocular pressure without improving visual acuity when comparing it to intravitreal Ranibizumab alone for persistent DME, however small group of patients that were pseudophakic enrolled in this study showed improved vision when comparing it to phakic patients.[7]

Clinical Trials for using Anti-VEGF for persistent DME

Along with Protocol U results that suggest continues Anti-VEGF intravitreal injection may lead to same visual outcomes when comparing it to intravitreal dexamethasone implant in patients with persistent DME. A secondary analysis from Protocol T concluded that development of persistent chronic DME was more in Bevacizumab group than in Aflibercept or Ranibizumab group, with more chances to resolve DME within 2 years in Aflibercept group; however continued Anti-VEGF therapy may lead to visual improvement and may prevent visual loss through 2 years of follow-up.[8]

Discussion

Recently, OZURDEX (0.7-microgram dexamethasone implant) has gained FDA approval for DME treatment, studies such as MEAD shown the efficacy and safety of Ozurdex especially in pseudophakic eyes with no history of glaucoma.[9] Many retinal physicians are using Ozurdex to resolve chronic diabetic macular edema when patients deemed as nonresponsive to Anti-VEGF after six monthly injections, as Ozurdex showed great effectiveness in such cases especially in pseudophakic patients, some patients are partially responsive to Ozurdex then a combined treatment with Anti-VEGF warranted in such cases. If repeated Ozurdex injections are needed then treatment with Iluvien (fluocinolone acetonide 0.19 mg implant) especially in cases that there is no tendency of increased intraocular pressure after multiple Ozurdex injections. Ozurdex and Lucentis do not have the same efficacy in chronic persistent DME, because of the dominance of inflammatory role in the pathogenesis and thus presented in Protocol U results as better reduction of macular thickness in combined group, where Ozurdex was the major contributor for macular thickness reduction more than Ranibizumab.

Protocol U, concluded similar visual outcome between adding OZURDEX or Ranibizumab alone, because of two major reasons, and first is cataract formation, because of short period of the study, and there is unknown visual prognosis after successful cataract surgery when compare it with Ranibizumab alone arm. Second, there is a lack of information about presence and duration of DRIL and status of ellipsoid on OCT in Ozurdex and Ranibizumab group, which play critical role in visual prognosis. Always check the status of glycemic control, when patient is not responding to treatment and if there is bad glycemic control then a consoling with endocrinologist is mandatory where HbA1C should kept under 7% with blood pressure control. A take home massage, do not waste time with Anti-VEGF if the patient not responding or poorly responding to treatment, especially when ellipsoid zone in danger and in the presence of DRIL. Pseudophakic eyes may benefit more when it comes to Ozurdex with chronic persistent DME, however thus should not discourage us to use it in Phakic eyes to resolve the DME and then cataract surgery can done later. In case that steroid is contraindicated or not available, then continuous Anti-VEGF may reduce the risk of visual loss, however starting DME treatment with Aflibercept may reduce the risk of development of chronic persistent DME.

Acknowledgment

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Conflict of interest

None.

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