**Name of journal: *World Journal of Ophthalmology***

**ESPS Manuscript NO: 17182**

**Manuscript Type: Editorial**

**Curing diabetic retinopathy: Is a strategy emerging?**

Stewart MW. Curing diabetic retinopathy: Is a strategy emerging?

**Michael W Stewart**

**Michael W Stewart,** Department of Ophthalmology, Mayo Clinic Florida, Jacksonville, FL 32224, United States

**Author contributions:** Stewart MW solely contributed to this manuscript.

**Conflict-of-interest** **statement:** Michael W Stewart, MD has served on advisory boards for Allergan and Regeneron, as a consultant for Boehringer-Ingelheim, and his employer has received research support from Allergan and Regeneron.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Correspondence to: Michael W Stewart, MD,** Department of Ophthalmology, Mayo Clinic Florida, 4500 San Pablo Rd., Jacksonville, FL 32224, United States. [stewart.michael@mayo.edu](mailto:Stewart.michael@mayo.edu)

**Telephone:** +1-904-9532232

**Fax:** +1-904-9537040

**Received:** February 22, 2015

**Peer-review started:** February 22, 2015

**First decision:** June 3, 2015

**Revised:** June 23, 2015

**Accepted:** August 13, 2015

**Article in press:**

**Published online:**

**Abstract**

Diabetic macular edema (DME) is the leading cause of blindness among working aged individuals of industrialized countries. The Early Treatment of Diabetic Retinopathy Studies (ETDRS) demonstrated that timely laser photocoagulation significantly decreases vision loss from DME, thereby establishing laser as standard- of- care for over 2 decades. Unfortunately, only a minority of patients treated in the ETDRS experienced significant improvements in visual acuity (VA), leaving researchers to look for more effective interventions. The recently introduced drugs (ranibizumab, aflibercept) that prevent the binding of vascular endothelial growth factor (VEGF) to its trans-membrane receptors produce superior improvements in VA over laser, either when administered as monotherapy or when combined with as-needed supplemental macular laser photocoagulation. The pivotal phase III trials featured monthly (ranibizumab, aflibercept) or bimonthly (aflibercept) injections of each drug for 2 years during which a significant number of patients experienced improved diabetic retinopathy severity scores. The need for anti-VEGF injections dropped significantly after 2 years in both the RISE/RIDE and DRCR.net Protocol I trials indicating that VEGF production had diminished. These data let to the FDA approval of both ranibizumab and aflibercept for the treatment of diabetic retinopathy complicated by DME. Physicians may now treat vision-threatening DME with ranibizumab or aflibercept while simultaneously improving DR and possibly achieving long-term regression.

**Key words:** Diabetic macular edema; Ranibizumab; Aflibercept; Diabetic retinopathy; Vascular endothelial growth factor

**© The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Drugs that prevent the binding of vascular endothelial growth factor (VEGF) produce greater gains in best corrected visual than can be achieved with laser photocoagulation. The recently completed pivotal phase III trials showed that regular injections of ranibizumab and aflibercept over 2 years also improved the severity of diabetic retinopathy. Both drugs have now been approved for the treatment of diabetic retinopathy (DR) in patients with diabetic macular edema (DME) thereby allowing physicians to consider VEGF inhibition to improve DR in patients with vision threatening DME.

Stewart MW. Curing diabetic retinopathy: Is a strategy emerging? *World J Ophthalmol* 2015; In press

The widespread use of drugs that bind vascular endothelial growth factor (VEGF) has reduced the incidence of blindness from neovascular age-related macular degeneration (nAMD) by up to 50%[1], thereby leaving diabetic retinopathy (DR), which had long been the leading cause of blindness in working-age individuals of industrialized nations, into the leading overall position. Diabetic retinopathy is the result of a complex set of biochemical abnormalities and histopathological changes, and though the exact cause of diabetic retinopathy is not completely understood, evidence from the large Diabetes Control and Complications Treatment Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) implicates poor blood glucose control in patients with both type 1 and type 2 diabetes[2,3]. Elevated blood glucose interferes with hexosamine flux, the polyol pathway, protein kinase C, and advanced glycation endproducts, each of which halts electron transport through the mitochondria, limits oxygen utilization, and causes tissue ischemia[4]. Ischemia stabilizes the cell’s natural oxygen sensor, hypoxia-inducible factor-1α, and upregulates VEGF synthesis. VEGF induces swelling, growth and migration of vascular endothelial cells, abnormalities that are potentiated by other conditions such as systemic arterial hypertension and elevated blood lipids.

Neuroretinal dysfunction is the earliest manifestation of diabetic retinopathy but retinal vascular changes are much easier to detect. Capillary endothelial damage disrupts the blood-retinal barrier with loss of pericytes, thickening of the capillary basement membrane, and upregulation of intercellular adhesion molecule (ICAM-1). The induced margination of leukocytes closes capillaries, exacerbates ischemia, and further amplifies VEGF production, thereby leading to vascular and stromal proliferation.

Fibrovascular proliferation characterizes the most advanced form of diabetic retinopathy and though fibrosis does not regress, pre-fibrotic vascular changes are reversible. Timely, effective pan-retinal photocoagulation involutes neovascular vessels, reverses vascular dilation, and resolves retinal hemorrhages, but unfortunately it causes permanent loss of the peripheral visual field. Though substituting one pathologic condition for another may constitute a therapeutic success (a post-laser scarred retina is much preferred over a traction retinal detachment) true reversal of retinopathy with complete restoration of visual function never occurs.

VEGF may improve oxygen delivery to ischemic tissues by dilating retinal vessels, so retinal specialists have long recommended that anti-VEGF therapy be administered with caution to eyes with capillary non-perfusion for fear of worsening ischemia. But as a pluripotential cytokine, VEGF causes other retinal vascular changes that worsen blood flow. VEGF narrows capillary lumens by causing vascular endothelial cells to swell and blocks lumens by upregulating ICAM-1, which marginates leukocytes. Therefore, VEGF’s net effect is to decrease overall capillary perfusion and worsen the severity of the retinopathy.

The incorporation of anti-VEGF drugs into diabetic treatment algorithms has been slow, but encouraging results from the recent ranibizumab (Genentech®, S. San Francisco, CA/Roche, Basel, Switzerland) and aflibercept (Eylea®, Regeneron, Tarrytown, NY) registration trials[5,6], as well as phase III trials with the dexamethasone delivery system (Ozurdex®, Allergan, Irvine, CA) and the fluocinolone acetonide insert (Iluvien®, Almera, Alpharetta, GA)[7,8], promise to further increase the use of intravitreal pharmacotherapy in patients with diabetic macular edema (DME). These phase III registration trials met their primary endpoints – proportion of eyes improving by at least +15 letters – as well as several secondary functional and morphologic endpoints. Visual acuity (VA) improvements following macular laser photocoagulation average +2 to +3 ETDRS letters over 2 years, but improvements of +10 to +12 letters are achieved with monthly injections of ranibizumab and aflibercept. Macular edema significantly improves after the first injection, followed by slower additional gains with continued monthly therapy[5,6]. Visual acuity and macular thinning does not further improve after one year, but extension studies show that these gains stabilize through 5 years despite a decreasing frequency of injections[9].

Important secondary findings included improvements in average Early Treatment of Diabetic Retinopathy severity scores[5,6]. More eyes treated with ranibizumab than sham/laser experienced 2-level (37.8% to 40.9% *vs* 23.4% to 24.3%) and 3-level improvements (11.3% to 15.4% *vs* 2.6% to 4.0%) in ETDRS severity and fewer experienced 2-level (0.9% to 4.3% *vs* 8.9% to 9.6%) and 3-level (0.8% to 1.7% *vs* 3.2% to 4.3%) worsening[10]. At the 2-year point in VIVID and VISTA more aflibercept-treated patients compared to sham/laser experienced 2-level (33.8% and 29.1% *vs* 14.3%) improvements in ETDRS severity scores[6]. Though only a subset of the RISE/RIDE cohort was followed from years 3 through 5 with as-needed injections, decreased treatment frequency did not worsen DR scores. These results suggest that VEGF blockade not only improves the retinopathy through 2 years but it reverses the underlying pathophysiologic processes responsible for DR development.

How VEGF blockade improves DR severity despite a decreasing treatment frequency after 2 years is not known. Anti-VEGF drugs bind only soluble VEGF and prevent it from activating the trans-membrane receptor VEGFR2 but do not directly inhibit VEGF synthesis. However, these drugs dampen VEGF amplification by inhibiting ICAM-1 synthesis and the resultant margination and activation of leukocytes. Since activated leukocytes synthesize VEGF and initiate a self-sustaining, positive feedback loop, binding diffusible VEGF actually decreases overall VEGF production. Downregulated VEGF together with other as yet unidentified factors may permanently shut down VEGF synthesis and reverse retinopathy in some patients.

Drug developers are now working to expand the indications for anti-VEGF therapy by focusing on eyes at risk of DME-mediated vision loss. Ranibizumab was recently approved for the treatment of fovea-threatening DME due to DR[11] and Regeneron will launch a phase III aflibercept trial for eyes at risk of vision loss due to DR - those with moderate non-proliferative DR or early posterior segment neovascularization. The hope is that intravitreal aflibercept every 8 or 16 wk will prevent adverse outcomes - diabetic macular edema and high-risk proliferative diabetic retinopathy - by stabilizing or improving the severity of DR. If this trial produces successful results with an acceptable safety profile, it is easy to imagine subsequent trials that target lower risk retinopathy.

Despite these encouraging results physicians need to be careful when using anti-VEGF therapy in eyes with DME and widespread retinal non-perfusion. Regular anti-VEGF injections may successfully resolve macular edema while simultaneously preventing the development of retinal neovascularization or neovascular glaucoma. Stopping injections, however, might precipitate rapid growth of neovascularization and blinding complications. Anti-VEGF therapy may open the door for curing retinopathy but predictable, dramatic, and permanent improvements will probably require combination therapy with inhibitors of angiopoietin 2, integrins, or platelet derived growth factor added to a regimen of regular anti-VEGF injections.

The anti-VEGF era began by treating vision loss due to diabetic macular edema but this encouraging journey now has us thinking that we can not only prevent vision loss but perhaps even reverse and cure DR.

**REFERENCES**

1 **Bloch SB**, Larsen M, Munch IC. Incidence of legal blindness from age-related macular degeneration in denmark: year 2000 to 2010. *Am J Ophthalmol* 2012; **153**: 209-213.e2 [PMID: 22264944 DOI: 10.1016/j.ajo.2011.10.016]

2 The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. *Diabetes* 1995; **44**: 968-983 [PMID: 7622004]

3 **Stratton IM**, Kohner EM, Aldington SJ, Turner RC, Holman RR, Manley SE, Matthews DR. UKPDS 50: risk factors for incidence and progression of retinopathy in Type II diabetes over 6 years from diagnosis. *Diabetologia* 2001; **44**: 156-163 [PMID: 11270671]

4 **Brownlee M**. Biochemistry and molecular cell biology of diabetic complications. *Nature* 2001; **414**: 813-820 [PMID: 11742414]

5 **Nguyen QD**, Brown DM, Marcus DM, Boyer DS, Patel S, Feiner L, Gibson A, Sy J, Rundle AC, Hopkins JJ, Rubio RG, Ehrlich JS. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology* 2012; **119**: 789-801 [PMID: 22330964 DOI: 10.1016/j.ophtha.2011.12.039]

6 **Korobelnik JF**, Do DV, Schmidt-Erfurth U, Boyer DS, Holz FG, Heier JS, Midena E, Kaiser PK, Terasaki H, Marcus DM, Nguyen QD, Jaffe GJ, Slakter JS, Simader C, Soo Y, Schmelter T, Yancopoulos GD, Stahl N, Vitti R, Berliner AJ, Zeitz O, Metzig C, Brown DM. Intravitreal aflibercept for diabetic macular edema. *Ophthalmology* 2014; **121**: 2247-2254 [PMID: 25012934 DOI: 10.1016/j.ophtha.2014.05.006]

7 **Boyer DS**, Yoon YH, Belfort R, Bandello F, Maturi RK, Augustin AJ, Li XY, Cui H, Hashad Y, Whitcup SM. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. *Ophthalmology* 2014; **121**: 1904-1914 [PMID: 24907062 DOI: 10.1016/j.ophtha.2014.04.024]

8 **Pearson PA**, Comstock TL, Ip M, Callanan D, Morse LS, Ashton P, Levy B, Mann ES, Eliott D. Fluocinolone acetonide intravitreal implant for diabetic macular edema: a 3-year multicenter, randomized, controlled clinical trial. *Ophthalmology* 2011; **118**: 1580-1587 [PMID: 21813090 DOI: 10.1016/j.ophtha]

9 **Elman MJ**, Ayala A, Bressler NM, Browning D, Flaxel CJ, Glassman AR, Jampol LM, Stone TW. Intravitreal Ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: 5-year randomized trial results. *Ophthalmology* 2015; **122**: 375-381 [PMID: 25439614 DOI: 10.1016/j.ophtha.2014.08.047]

10 **Brown DM**, Nguyen QD, Marcus DM, Boyer DS, Patel S, Feiner L, Schlottmann PG, Rundle AC, Zhang J, Rubio RG, Adamis AP, Ehrlich JS, Hopkins JJ. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. *Ophthalmology* 2013; **120**: 2013-2022 [PMID: 23706949 DOI: 10.1016/j.ophtha.2013.02.034]

11 Genentech press release regarding ranibizumab approval for the treatment of diabetic macular edema in patients with diabetic retinopathy. [accessed 2015 Feb 20]. Available from: URL: http://www.roche.com/media/store/releases/med-cor-2015-02-09.htm.

**P-Reviewer:** Chaqour B, Korpanty G, Peng SM **S-Editor:** Ji FF **L-Editor: E-Editor:**