World Journal of Ophthalmology

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DOI: 10.5318/wjo.v5.i4.142

World J Ophthalmol 2015 November 12; 5(4): 142-144
ISSN 2218-6239 (online)

EDITORIAL

Curing diabetic retinopathy: Is a strategy emerging?

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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.

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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: August 14, 2015
Published online: November 12, 2015

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 (DR) severity scores. The need for anti-VEGF injections dropped significantly after 1-3 years in both the RISE/RIDE and DRCR.net Protocol Ⅰ trials indicating that VEGF production had diminished. These data led to the FDA approval of both ranibizumab and aflibercept for the treatment of DR 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

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 (DR). Both drugs have now been approved for the treatment of 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; 5(4): 142-144 Available from: URL: http://www.wjgnet.com/2218-6239/full/v5/i4/142.htm DOI: http://dx.doi.org/10.5318/wjo.v5.i4.142

INTRODUCTION

The widespread use of drugs that bind vascular endothelial growth factor (VEGF) has reduced the incidence of blindness from neovascular age-related macular degeneration 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, in the leading overall position. DR is the result of a complex set of biochemical abnormalities and histopathological changes, and though the exact cause of DR is not completely understood, evidence from the large Diabetes Control and Complications Treatment Trial and the United Kingdom Prospective Diabetes Study 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 DR 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 DR 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]. VA 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 DR 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 3 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 - DME and high-risk proliferative DR - 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 or 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 DME but this encouraging journey now has us thinking that we can not only prevent vision loss but perhaps even reverse and cure DR.

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

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