Journal of Diabetes and Its Complications 30 (2016) 545–553

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: www.jdcjournal.com

A multimodal approach to diabetic macular edema

Adrian Au [a], Rishi P. Singh [b,*]

[a] Case Western Reserve School of Medicine, 2109 Adelbert Rd. Cleveland, OH 44106
[b] Cole Eye Institute, Cleveland Clinic Foundation, 9500 Euclid Ave, Cleveland, OH 44106

ARTICLE INFO

Article history:
Received 5 August 2015
Received in revised form 7 November 2015
Accepted 9 November 2015
Available online 14 December 2015

Keywords:
Diabetic retinopathy
Diabetic macular edema
Anti-VEGF
Laser photocoagulation
Corticosteroids

ABSTRACT

Diabetic retinopathy is a common complication of uncontrolled diabetes. A complication is diabetic macular edema, which is the leading cause of blindness in patients with diabetic retinopathy. Historically, management of these conditions was laser photocoagulation with regulation of blood pressure, blood sugar, and cholesterol. The initial studies demonstrated that this treatment regimen prevented further visual deterioration but did not improve visual acuity. Novel studies identifying the presence of vascular endothelial growth factor (VEGF) in the eye with accompanying elucidation of diabetic pathophysiology allowed for the development of alternative therapies, namely antibodies against VEGF and corticosteroids. These two therapies revolutionized the management of diabetic macular edema by not only preventing vision loss, but also improving overall vision. In this review, we outline the major breakthroughs and underlying thought processes of the paradigm shifts that have occurred in management of these conditions. Further, we present how the evolving role of anti-inflammatory and anti-VEGF therapies, in a combinatorial approach, may provide further permutations to optimize treatment.

1. Introduction

Diabetic retinopathy (DR) is the most common complication of diabetes, affecting one in three diabetics (Center of Disease Control National Center of Chronic Disease Prevention & Health Promotion Division of Diabetes Translation, 2015). In 2005, 5.5 million patients were affected with diabetic retinopathy, with the expectation that it would triple by 2050 to 16 million (Saaddine et al., 2008). With the prevalence of diabetes in 2013 estimated at 24.4 million in the United States and 382 million worldwide, it comes as no surprise that diabetes continues to be the leading cause of blindness in the United States (International Diabetes Foundation, nd). Although advancements in systemic management for diabetes have made major strides, management of diabetic retinopathy has remained poor.

Diabetic retinopathy is characterized by progressive bilateral damage to retinal blood vessels. It has four stages that extend from microaneurysms (either background retinopathy or mild nonproliferative retinopathy) to extensive abnormal blood vessel growth (proliferative retinopathy). Early in the disease, patients may not experience any symptomology. However, poor management of risk factors – hyperglycemia, chronically elevated hemoglobin A1C (HbA1c), hypertension and hyperlipidemia – can cause disease progression (Yau et al., 2012). Subsequently, patients can experience blurry vision, decrease in visual acuity, metamorphopsia, or other visual complaints. If left untreated, patients become incurably blind.

Vision loss in patients affected with diabetic retinopathy commonly manifests as fluid accumulates beneath the macula, the central portion of the retina responsible for high visual acuity. This occurs in all disease stages secondarily to incompetent blood vessels causing diabetic macular edema (DME) or in end stage disease when abnormal blood vessels grow (proliferative retinopathy). As a result, targeted therapy has been directed at limiting the damaging effects of poor vasculature integrity. The main goals of treatment are to: 1) manage risk factors to minimize the effects of systemic diabetes on retinal vasculature, 2) reduce fluid accumulation, and 3) prevent the consequences of fluid disrupting the retina. As the leading cause of blindness in patients with DR is DME, we will specifically outline and discuss the evolution of multimodal management of DME in this review.

2. Evolution of treatments

Historically, the treatment of DME was focused on vision stabilization. The 1985 landmark Early Treatment of Diabetic Retinopathy Study (ETDRS) established glycemic control, blood pressure regulation, and macular laser photocoagulation as standard

Conflicts of interest:
Au: none.
Singh: consulting fees: Alcon Laboratories, Genentech, Regeneron, Allergan, ThromboGenics, Shire; contract research: Genentech, Regeneron, ThromboGenics.

* Corresponding author at: 9500 Euclid Avenue, Desk i32, Cleveland, OH 44195. Tel.: +1 216 445 9497.
E-mail address: singhr@ccf.org (R.P. Singh).

http://dx.doi.org/10.1016/j.jdiacomp.2015.11.008
1056-8727/

of care (Early Treatment of Diabetic Retinopathy Study, 1985). The intent of laser photocoagulation was to reduce leaky micro-aneurysms and inhibit extravasation of fluid into the macula, thereby preventing degradation of vision. The study demonstrated that laser photocoagulation decreased the risk of visual acuity loss in patients with clinically significant DME (CSDME) by 50%. Subsequent studies found that laser photocoagulation stabilized visual acuity with minimal or delayed improvements (DRCR.net et al., 2010; Nguyen et al., 2012; Scott et al., 2009). The study defined two primary outcomes as a way to establish efficacy of the treatment arm: retinal thickness and best-corrected visual acuity (BCVA). For the purposes of this review, we will report primarily on the latter as a functional evaluation of visual acuity in patients with diabetic retinopathy.

As pathophysiology of DME was uncovered, alternative therapies were developed to improve rather than stabilize vision. Studies have shown chronic exposure to hyperglycemia induces a cascade of anatomical and biochemical changes that affect micro-vascular architecture and retinal functionality (Antonetti et al., 2006; Cheung, Mitchell, & Wong, 2010; Curtis, Gardiner, & Stitt, 2009). Two mechanisms have primarily been implicated: increased production of vascular endothelial growth factor (VEGF), a pro-angiogenesis protein, and activation of inflammatory cascades involved in leukostasis and maintenance of vascular integrity (Antonetti et al., 2006; Cheung et al., 2010; Curtis et al., 2009; Kern, 2007). An important observation that catapulted VEGF as a primary therapy target was that VEGF was elevated intravitreally in DME and DR patients and the amount of VEGF correlated with severity of DME (Aiello et al., 1994 and Funatsu et al., 2003). VEGF has multiple isoforms, but VEGF-A is purported to be the primary isoform. When VEGF-A is bound to VEGF receptor 2 (VEGFR2), one of two protein-kinase activating receptors, it propagates its mitogenic, angiogenic, and permeability enhancing effects (Shibuya, 2006). Antibodies bound to VEGF inhibit activation of the VEGFR2 and ultimately prevent angiogenesis. In summary, alternative therapies, primarily focused on corticosteroids and VEGF, were investigated in clinical trials to not only stabilize but also improve vision.

The multifactorial pathogenesis of diabetic retinopathy lends itself to a multimodal approach to management. Utilizing anti-VEGF antibodies, corticosteroids, and laser therapy in a combinatorial fashion can provide optimized patient outcomes in comparison to monotherapy alone. Our evolving understanding of the cellular effects of diabetes on retinal integrity and vasculature will only increase the available tools to prevent diabetes-induced blindness. The purpose of this review is to provide context and describe the evolving role of anti-VEGF, corticosteroids, and laser therapy in the multimodal approach to diabetic macular edema and diabetic retinopathy.

3. Anti-VEGF therapy

Multiple clinical trials elucidated anti-VEGF in the reversal, stabilization, and prevention of future vision loss. We briefly outline the major clinical trials in Table 1 for the following three VEGF targeting drugs: ranibizumab (Lucentis), bevacizumab (Avastin), and aflibercept (Eylea).

3.1. Ranibizumab (Lucentis)

Ranibizumab, a FAB fragment with one targeted VEGF binding site, was the first VEGF therapy to be approved by the FDA for treatment of DME (Fig. 1). Two-phase II clinical trials, Safety and Efficacy of Ranibizumab in Diabetic Macular Edema (RESOLVE) and two-year outcomes of the ranibizumab for edema of the mAcula in Diabetes (READ-2), investigated the effectiveness of ranibizumab in the treatment of DME. In the RESOLVE study, patients were treated with ranibizumab or sham injection for their first three months with the option for dose doubling or rescue laser. RESOLVE showed ranibizumab improved BCVA by 10.3 ± 9.1 letters from baseline while sham injection decreased BCVA by 1.4 ± 14.2 letters (Massin et al., 2010). To determine whether ranibizumab was better than the standard of care, READ-2 compared ranibizumab versus laser photocoagulation versus a combination of ranibizumab and photocoagulation. Two-year follow up showed that patients on ranibizumab improved on average by 7.7, laser by 5.1, and combination by 6.8. Although not statistically significant, combination therapy required fewer injections during the second year, suggesting that laser therapy and ranibizumab helped reduce persistent or recurrent macular edema (Nguyen et al., 2010).

Four recent clinical trials established ranibizumab as a treatment for DME that lead to its FDA approval. 12 Month Core Study to Assess the Efficacy and Safety of Ranibizumab Intravitreal Injections (RESTORE) validated READ-2 findings by comparing ranibizumab monotherapy, laser alone, or a combination of the two. RESTORE showed significant improvement in patients treated with three monthly injections of ranibizumab (6.1 ± 6.43) or ranibizumab and laser therapy (5.9 ± 7.92) as compared to laser alone (0.8 ± 8.56) (Mitchell et al., 2011). Two concurrent clinical trials Study of Ranibizumab Injection in Subjects with CSDME and Center Involvement Secondary to Diabetes Mellitus (RISE and RIDE) further showed that at twenty-four months mean BCVA with monthly 0.3 mg ranibizumab injections steadily improved BCVA by 10.9-12.5 letters while patients with 0.5 mg ranibizumab and sham injections rose by 11.9-12.0 and 2.3-2.6 letters, respectively (Fig. 2). 0.3 mg became the preferred dosing as it maintained efficacy in treatment of DME but decreased the risk of systemic side effects, discussed later, in diabetics, a known at-risk population. Importantly, patients treated with ranibizumab were found to have reduced risk of diabetic retinopathy progression and regression of diabetic retinopathy in patients with DME (Nguyen et al., 2012).

The fourth clinical trial not only performed ranibizumab efficacy and safety, it evaluated whether corticosteroid treatment was beneficial. Diabetic Retinopathy Clinical Research Network (DRCR.net), a large multicenter cohort of specialists focused on diabetic retinopathy, performed Protocol I. They designed their clinical trial to resolve ranibizumab efficacy and determine relative importance of laser therapy for DME. In addition, they included triamcinolone, a corticosteroid therapy, previously shown to be superior to untreated diabetic retinopathy in ETDRS, but not superior to laser photocoagulation (DRCR.net, 2008). Patients were randomized to receive sham injections plus prompt laser, 0.5 mg ranibizumab plus prompt or deferred (>24 weeks) laser, or triamcinolone 4 mg plus prompt laser. Monthly therapy was administered until stabilization or lack of further improvement. The one-year BCVA mean change, similar to two-year outcomes, was significantly greater in the ranibizumab and prompt laser group (+9 ± 11) and ranibizumab and deferred laser (+9 ± 12) while triamcinolone and prompt laser (+4 ± 13) were comparable to the sham and prompt laser (+3 ± 13) population. The import of all these clinical trials established ranibizumab as a monotherapy with or without laser therapy for DME.

3.2. Bevacizumab (Avastin)

Bevacizumab differentiates itself from ranibizumab by being a full-length monoclonal antibody (as opposed to a Fab fragment like ranibizumab) and by having two VEGF binding sites that increase its affinity to VEGF. Bevacizumab and ranibizumab are both derived from the mouse monoclonal antibody for VEGF. DRCR.net in 2007 performed a study evaluating intravitreal bevacizumab with an additional bevacizumab, sham, or laser photocoagulation treatment at twelve weeks. At 12 weeks, treatment with 1.25 mg and 2.5 mg bevacizumab at two initial encounter and 6 week follow-up improved BCVA by +5 and +7 letters, respectively. This was a significant