Ocular Anti-VEGF Therapy for Diabetic Retinopathy: Overview of Clinical Efficacy and Evolving Applications

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Ocular anti-vascular endothelial growth factor (VEGF) therapy represents one of the most significant advances in modern medicine. The introduction and widespread use of ocular anti-VEGF therapy for age-related macular degeneration heralded a new era in the treatment of vascular and exudative diseases of the retina. Its expanding indications now include diabetic macular edema and proliferative diabetic retinopathy, two vision-threatening forms of diabetic retinopathy. It is widely anticipated that ocular anti-VEGF therapy could spark a dramatic shift in the treatment paradigm for diabetic retinopathy. However, despite its clear efficacy shown in clinical trials, the dynamic landscape of evolving medical, ethical, and economic issues related to this new treatment suggests significant challenges ahead. In this article, we provide a discussion of this topic as part of this two-part Bench to Clinic narrative. Here, our Clinic contribution provides an overview of the current evidence from clinical trials on anti-VEGF therapy for diabetic retinopathy, and highlights the hopes and fears of this new treatment from clinical and public health standpoints. In the Bench narrative that precedes this contribution, Simó et al. provide an overview of the role of VEGF in the pathogenesis of diabetic retinopathy.

Ocular anti-vascular endothelial growth factor (VEGF) therapy represents one of the most significant advances in modern medicine. The swift and widespread uptake of this new therapy into clinical practice for treating age-related macular degeneration has saved sight for millions worldwide (1). In fact, national blindness registries are already showing declining incidence of blindness related to age-related macular degeneration, coinciding with the advent of anti-VEGF therapy (2). Despite its clear efficacy, however, the safety, cost, and substantial burden upon the health care system of this new treatment have generated heated debates in many countries (3).

Now, it is widely anticipated that the use of ocular anti-VEGF therapy will be extended to treat the vision-threatening forms of diabetic retinopathy (4), which affect an estimated 28 million people around the world (5). In this two-part Bench to Clinic narrative, the Bench article by Simó et al. (6) reviews the pathophysiological role of VEGF in diabetic retinopathy and the molecular characteristics of antiangiogenic agents currently used. Here in the Clinic article, we provide an overview of the current evidence from clinical trials on anti-VEGF therapy for diabetic retinopathy, and highlight the hopes and fears of this new treatment from the clinical and public health standpoints.

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EPIDEMIOLOGY AND NATURAL HISTORY OF DIABETIC RETINOPATHY

As a global concern, diabetes affects more than 360 million individuals worldwide. This number is expected to exceed half a billion by 2030 (7). About one in three individuals with diabetes has signs of retinopathy, and among these, one-third may have diabetic macular edema (DME) or proliferative diabetic retinopathy (PDR), two vision-threatening forms of diabetic retinopathy (4). A recent pooled analysis of 35 population-based studies in developed countries estimated that more than 90 million individuals have diabetic retinopathy, with about 21 million having DME and 17 million having PDR (5).

In the Wisconsin Epidemiologic Study of Diabetic Retinopathy, about three in four participants developed retinopathy over a 10-year period, and for participants with retinopathy, about two-thirds developed more severe retinopathy and one in five developed PDR (4). In terms of progression, diabetic retinopathy progresses from nonproliferative to proliferative retinopathy in stages. Nonproliferative diabetic retinopathy (NPDR) is classified as mild, moderate, and severe forms. About 5% mild NPDR, 20% moderate NPDR, and 50% severe NPDR may progress to PDR within 1 year (4).

In developed countries, DME has now overtaken PDR as the more common vision-threatening form of diabetic retinopathy, particularly among patients with type 2 diabetes. In the National Health and Nutrition Examination Survey, DME was shown to be twice as common as PDR in the U.S. (8). The 10-year incidence of DME has been reported to be 20% in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (9). Although DME is usually correlated and accompanied with increasing severity of retinopathy, it may also run an independent course and develop even at the early stage of diabetic retinopathy.

There is evidence to suggest a decline in the incidence and risk of progression for diabetic retinopathy over the last three decades (4,10). The incidence of visual impairment among people with diabetic retinopathy has also halved, likely as a result of a lower risk of DME and PDR among patients with recently diagnosed diabetes (10). These encouraging findings reflect improvement in the systemic management of retinopathy risk factors over time for a range of reasons, such as better devices for self-monitoring of glycemic levels and administration of insulin, new and effective hypoglycemic medications, and increased public awareness of the need for glycemic and blood pressure control through educational and screening programs. Despite these advances in diabetes care, it remains uncertain whether such a declining trend in the incidence of diabetic retinopathy will persist in the context of expanding diabetes epidemic worldwide, particularly in developing countries where intensive diabetes management and public health resources remain limited (11).

CURRENT STRATEGIES FOR MANAGEMENT OF DIABETIC RETINOPATHY

Systemic management of hyperglycemia, hypertension, and dyslipidemia remains the most important and effective strategy for preventing the development and progression of diabetic retinopathy (4). For many decades, retinal laser photocoagulation has been the standard ocular treatment for DME and PDR (4,10). The primary goal for most patients receiving laser therapy is to preserve any useful vision or to prevent adverse sequalae of PDR. Reversal of vision loss is uncommon. In addition, laser therapy is associated with significant ocular side effects due to its inherent destructive nature to the retina. Without timely laser therapy, however, patients may develop blinding neovascular complications, such as vitreous hemorrhage and tractional retinal detachment, leading to the need for surgical intervention (vitrectomy).

Over the last decade, intraocular administration of pharmacological agents (e.g., steroid and anti-VEGF agents) has been evaluated as a new treatment modality for DME and PDR (4,10). Delivery of these agents is achieved by direct injection into the vitreal cavity, a procedure that is usually performed in office setting by ophthalmologists using aseptic technique and topical anesthesia. Although intraocular injections of long-acting steroids (e.g., triamcinolone) have demonstrated ability to reduce DME and improve vision, these beneficial effects appear to be short-lived, and long-term visual outcome was generally not better than conventional laser therapy (4). Furthermore, repeated use of intraocular steroid injections is associated with significant ocular side effects (e.g., cataract, glaucoma). Nevertheless, there are certain advantages in using intraocular steroids (e.g., possibly longer-acting and relatively cheap compared with most anti-VEGF agents). Its use might therefore be beneficial for selected patients, such as those who have had previous cataract surgery, or as an adjunctive therapy prior to laser (12,13).

OCULAR ANTI-VEGF THERAPY FOR DIABETIC RETINOPATHY

The introduction and widespread use of ocular anti-VEGF therapy for age-related macular degeneration, with publication of major clinical trials (1), heralded a new era in the treatment of vascular and exudative diseases of the retina. The expanding indications for ocular anti-VEGF therapy, given via an injection into the vitreal cavity, now include DME and PDR.

Efficacy

As shown in the accompanying Bench article by Simó et al. (6), VEGF has long been a therapeutic target for diabetic retinopathy. In recent years, there has been a surge of clinical trials investigating the use of anti-VEGF therapy for DME (Table 1) (14–16). These trials provide robust evidence that intraocular administration of anti-VEGF agents is better than laser therapy both in preserving and in improving vision for patients with DME. Among the four anti-VEGF agents (ranibizumab, bevacizumab, pegaptanib, and aflibercept), ranibizumab has been the one most thoroughly tested. In randomized controlled trials that used ranibizumab injections, up to 46% of patients improved vision (vs. 18% with laser alone; by three lines or more on vision chart), and only 4% or less lost more vision (vs. up to 20% with laser alone). The studies also suggest that, compared with laser therapy alone, ranibizumab injections were more effective when used as a monotherapy or in combination with laser therapy in treating DME

Table 1—Major recent randomized controlled trials of ocular anti-VEGF therapy for DME

Trial	Number of study participants/eyes	Anti-VEGF agent	Results		Follow-up (months)
			Gained vision*	Lost vision*	
RISE and RIDE (42)	377	Ranibizumab	34–46 (12–18)	2–4 (9–10)	24
DRCRnet (13)	854	Ranibizumab (+ laser)	28–30 (15)	2 (8)	24
READ-2 (43)	126	Ranibizumab (+/− laser)	23 (17)	3 (6)	24
RESOLVE (44)	151	Ranibizumab (+/− laser)	32 (10)	3 (20)	12
RESTORE (45)	345	Ranibizumab (+/− laser)	23 (8)	1–3 (8)	12
BOLT (46)	80	Bevacizumab	32 (4)	0 (14)	24
Macugen 1013 (47)	207	Pegaptanib (+/− laser)	23 (15)	3–4 (6–9)	24
da Vinci (20)	176	Aflibercept	46 (11)	—	12

*, % of patients with ≥3-line vision gain or loss (vs. with laser therapy alone).

(17). In patients receiving combined ranibizumab and laser therapy, best long-term visual outcome could be achieved with initiation of injections followed by deferred laser therapy 6 months later (17). Unlike neovascular age-related macular degeneration, vision gain resulted from ranibizumab injections in patients with DME could be maintained with tapering of injection frequency over time (17,18). For example, the Diabetic Retinopathy Clinical Research Network (DRCRnet) suggests that the average number of injections in the first, second, and third year of treatment for DME was 9, 3, and 2, respectively, to maintain vision gained (17). Exploratory analysis of trial data demonstrated that ranibizumab injections could reduce risk of progression and increase likelihood of regression of diabetic retinopathy severity among patients with DME (19).

The evidence for the use of the other anti-VEGF agents is less robust due to the smaller number of trials with generally shorter follow-up. Nevertheless, all trials reported to date suggest a beneficial response to anti-VEGF agents for DME (Table 1). Being a synthetic fusion protein that has been specifically designed to act like an antibody, aflibercept may require less frequent injections and follow-up due to its longer half-life and durability (20). There is, however, a lack of data on comparative efficacy between aflibercept and ranibizumab injections.

Despite being an "off-label" therapy, intraocular bevacizumab injections are commonly used as a much more affordable alternative to ranibizumab. A small clinical trial recently compared the efficacy between ranibizumab and bevacizumab in treating DME. While demonstrating similar efficacy in reducing DME based on optical coherence tomography findings (primary outcome), results on visual outcome in this study were considered inconclusive due to inadequate power (21).

At present, the role of ocular anti-VEGF therapy for PDR is less clear, although nationwide studies by groups such as DRCRnet are under way to address this question. Exploratory analysis from DRCRnet provided the basis for further investigation into the role of intraocular anti-VEGF and steroid therapy in reducing risk of retinopathy progression (22). Preliminary data from the DRCRnet did not show significant short-term benefit of ranibizumab injections in reducing need for surgical intervention (vitrectomy) for PDR-related vitreous hemorrhage in the first 4 months. Nonetheless, positive effects were observed on secondary outcomes, including visual acuity improvement, increased laser completion rates, and reduced recurrent vitreous hemorrhage rates (23). Ongoing follow-up of these patients will hopefully offer more clarity in the value of anti-VEGF therapy for treating PDR. While anti-VEGF agents might be useful as a primary treatment, or adjunct to laser or surgical treatments for advanced PDR (24), its use has been reported to possibly accelerate the development or progression of tractional retinal detachment in a small percentage of cases (25).

Safety

Safety is paramount for any new treatment strategy. Although most clinical trials reported a favorable safety profile, data beyond 2 years of exposure for repeated intraocular anti-VEGF therapy are limited (17,26,27). Ocular safety concerns include cataract formation, infection (endophthalmitis), vitreous hemorrhage, and retinal detachment. The rates of serious sight-threatening complications are acceptably low, as shown in studies of not only patients with diabetic retinopathy, but also of patients with age-related macular degeneration (1,4,16).

However, the inherent study design of clinical trials hampers the ability to adequately assess systemic safety of rare but important events of interest (e.g., stroke, ischemic heart disease) because of potential selection bias and limited power. The basis of systemic safety concern roots from the known risk of serious adverse events associated with intravenous anti-VEGF therapy used in cancer patients, evidence of systemic absorption after intraocular anti-VEGF injections (28), and possible safety signals from large epidemiological studies of age-related macular degeneration (29–31). Potential adverse effects of systemic VEGF blockade that are particularly worrisome for diabetic patients include hypertension, proteinuria, impaired wound healing, and critical vascular responses to ischemia (32). These effects may amplify the cardiovascular risk among diabetic patients, particularly in those with retinopathy, who already have two- to threefold higher risk of stroke, coronary heart disease, and heart failure than those without retinopathy (33).

Clinical and Public Health Implications

Despite improvements in diabetes care, the prevalence of diabetic retinopathy will likely continue to rise, due to population growth, aging demographics, and expanding diabetes epidemic worldwide.

There are 20 to 30 million individuals with DME in developed countries (5). These numbers may double by 2030. Thus, the demand for eye care service will profoundly increase if anti-VEGF therapy is adopted as the standard treatment for DME. Such demand is currently unmatched by the workforce supply of ophthalmologists, even in many developed countries. Alongside the actual procedure of the injection itself, the need for regular, sometimes monthly, follow-up and monitoring of treatment response adds further stress to most health care systems.

The economic burden, for both patients and the society, is a major concern. Even in the U.S, the economic impact is substantial. For example, over a million adults have neovascular age-related macular degeneration in the U.S, and the cost of providing ocular anti-VEGF therapy for these patients was $1.5 billion between 2008 and 2009 alone (34). With another million adults with vision-threatening diabetic retinopathy in the U.S. (8), the extent to which this additional financial burden will affect the health care system is bound to be significant. Cost-effectiveness analyses have shown that substantial cost savings (40–88%) could be achieved by individualized treatment strategies for DME (35). Assuming equivalent effectiveness and similar safety profiles between bevacizumab and ranibizumab injections, the use of bevacizumab confers much greater value among different treatment options for DME (36). This is due to the substantial cost differential between the two anti-VEGF agents. Ranibizumab is up to 40 times more expensive than bevacizumab in some countries. Although there is now evidence to suggest similar efficacy of ranibizumab and bevacizumab for treating age-related macular degeneration (37), quality data on the comparative efficacy and safety of these two agents for DME are still lacking.

Another major challenge relates to patient access to ocular anti-VEGF therapy in less developed or developing countries (e.g., India, China, South America), where the prevalence of vision-threatening diabetic retinopathy might increase the most in the upcoming years. Like any new and expansive therapies, accessibility is an inevitable problem due to disparities in health care availability, access, and quality entrenched internationally between developed and developing nations as well as within countries. There is no simple solution, but it should not be

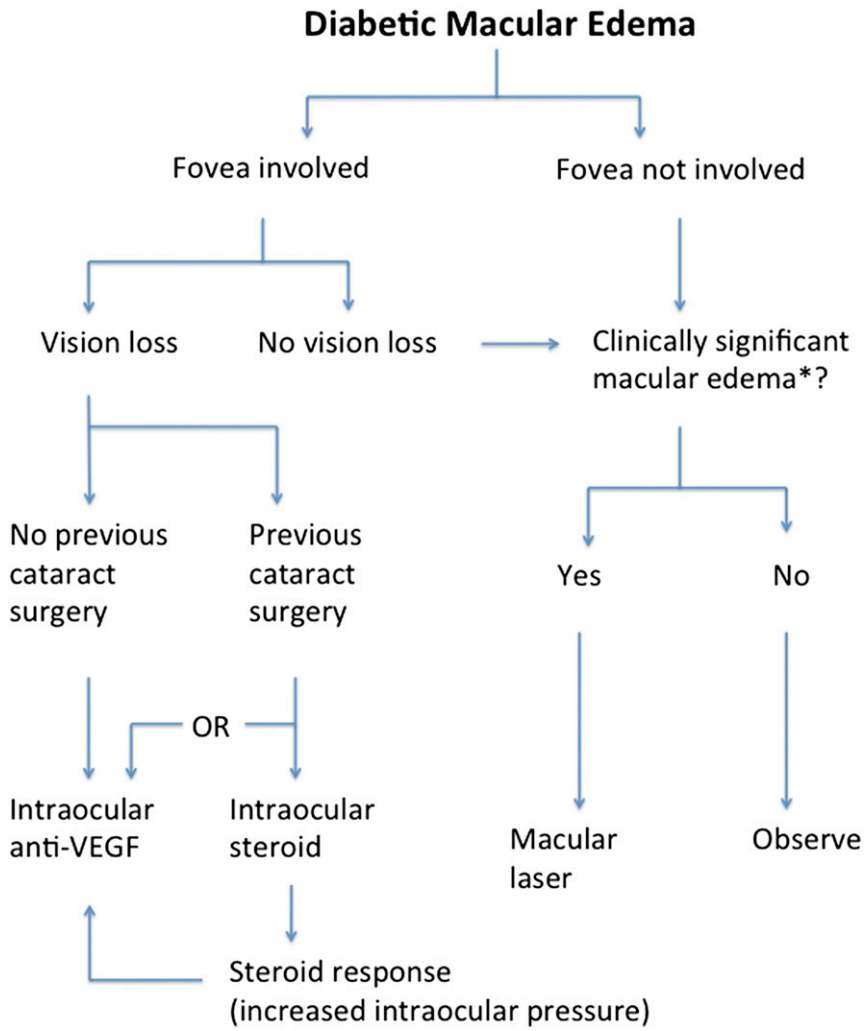

Figure 1—Clinical pathways for ocular treatments of DME. *Clinically significant macular edema is defined by the Early Treatment Diabetic Retinopathy Study (4).

the reason to overlook such issue. Rather, it should form the basis for more research in this uncharted area, and to endorse public health endeavors that aim to improve access and cost-effectiveness in the delivery of ocular anti-VEGF therapy to patients with vision-threatening diabetic retinopathy in these countries.

Unanswered Questions and Future Research

Although evidence supports the use of anti-VEGF therapy for treating diabetic retinopathy, several key questions remain unanswered. First, it is not a cure. Despite the possibility of reducing the number of anti-VEGF injections over time, repeated injections are required to maintain visual benefits for many patients. This is due to the relatively limited half-lives of the currently available anti-VEGF agents. While aflibercept may have longer half-life, there is a lack of evidence to date that it could be used less frequently than other anti-VEGF agents (e.g., ranibizumab) to achieve similarly favorable visual outcome. Hence, there is need for studies on comparative efficacy between the anti-VEGF agents, and an ongoing effort to discover new antiangiogenic agents with longer ocular half-lives or novel delivery mechanisms (e.g., ocular implants) to prolong the effects of anti-VEGF agents in the eye.

The use of optical coherence tomography (OCT) has allowed precise assessment of structural changes in DME in qualitative and quantitative manners (4). As a component of the diagnostic algorithms used in major clinical trials, OCT has in fact become an indispensible tool to manage anti-VEGF therapy for patients with DME (38). It also enables objective monitoring of treatment response. Specific patterns of morphological features on OCT have been proposed to predict visual outcome for patients with DME undertaking laser therapy (39,40). Less clear is the potential role of OCT in stratifying risk of progression and predicting therapeutic response to anti-VEGF therapy among patients with DME (41).

Combining anti-VEGF therapy with other existing or novel therapies targeting multiple pathophysiological pathways of diabetic retinopathy may further optimize visual outcome. Besides VEGF, several other mechanisms are important in the pathogenesis of diabetic retinopathy (e.g., inflammation, renin-angiotensin) (4). Therapies targeting these pathways (intraocular steroids, renin-angiotensin blockade) have been shown to have positive effects in treating diabetic retinopathy (4,10). The effects of combining these local and systemic treatments with ocular anti-VEGF therapy remain to be determined.

CONCLUSIONS

Visual impairment exerts considerable deleterious impact on quality of life and activities of daily living among patients with diabetic retinopathy. Importantly, visual impairment may also affect their ability to manage diabetes and other complications. Ocular anti-VEGF therapy has sparked a dramatic shift in the treatment paradigm for diabetic retinopathy (Fig. 1). Its indisputable efficacy shown in trials has already called for experts to revise clinical and therapeutic guidelines, recommending its use in some instances as the first-line primary therapy for DME (14). However, the dynamic landscape of evolving medical, ethical, and economic issues related to this new treatment suggests significant challenges ahead, with legitimate concerns regarding systemic safety, cost-effectiveness and sustainability of health care delivery. Furthermore, although ocular anti-VEGF therapy could substantially reduce visual impairment from diabetic retinopathy, ultimately it is not a cure. Only through a continuation of the critical ongoing efforts to understand pathophysiological mechanisms of diabetic retinopathy, and to find avenues to prevent diabetes, screen for early retinopathy, and optimize the management of systemic risk factors can we hope to remove diabetic retinopathy as "the leading cause of preventable blindness in working-aged people" (4), a finding that has persisted for more than half a century.

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