Ranibizumab: A Review of Its Use in the Treatment of Diabetic Retinopathy in Patients With Diabetic Macular Edema

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Abstract

Objective: To evaluate the pharmacotherapy role of ranibizumab, a vascular endothelial growth factor (VEGF) inhibitor, for the treatment of diabetic retinopathy (DR) in patients with diabetic macular edema (DME). **Data Sources:** PubMed, Science Direct, Google Scholar, and ClinicalTrials.gov searches (January 2000-May 2015) were conducted for articles published in English, and limited to clinical trials using the key words ranibizumab, DR, DME, anti-VEGF, and DR treatment. **Study Selection and Data Extraction:** Following PubMed, Science Direct, Google Scholar, and ClinicalTrials.gov searches, 4 clinical trials were identified and included in this review. Phase III/IV studies evaluating the clinical efficacy of ranibizumab versus placebo, ranibizumab versus laser, and ranibizumab versus other anti-VEGF agents were selected and evaluated. **Data Synthesis:** Ranibizumab administered to patients with DME for 12 to 36 months improved and prevented worsening of visual acuity. At month 36 the ranibizumab-treated eyes had a >2 or >3 step DR improvement compared with the sham crossover eyes. Ranibizumab was also found to be superior to laser treatment. Patients receiving ranibizumab gained 6.0 letters, improved tritan and protan color contrast thresholds, and demonstrated improved retinal sensitivity versus the subjects receiving laser treatment who lost 0.9 letters. When ranibizumab was compared with other anti-VEGF agents (aflibercept, pegaptanib, and bevacizumab), it was not always demonstrated to be significantly superior. **Conclusion:** Ranibizumab has been shown to be safe and efficacious for use in the treatment of DR in patients with DME. Thus, it is an alternative treatment approach to laser photocoagulation therapy.

Keywords

diabetes, adult medicine, clinical pharmacy, clinical trials, clinical pharmacology

Introduction

The diabetes burden continues to increase and affects more than 29 million individuals in the United States according to a recent Centers for Disease Control and Prevention statistics. This is significant because diabetes is the leading cause of new cases of blindness among individuals between the ages of 20 and 74 years.¹ Diabetic retinopathy (DR) is a microvascular complication and is the predominant diabetic eye condition.² It was estimated that more than 30% of adults aged 40 years or older had DR with or without macular edema between 2005 and 2008, which could lead to vision loss.¹

Diabetic retinopathy encompasses the damage to the retinal capillary bed due to consistently elevated blood glucose and high advance glycation end products, leading to retinal ischemia. Studies have associated the hypoxia caused by the retinal ischemia to the activation of the vascular endothelial growth factor (VEGF), which triggers growth of ocular blood vessels.³⁻⁵ Diabetic macular edema (DME) is a common cause of vision impairment in patients

with DR.⁶ DME is characterized by retinal swelling due to build-up of fluid and proteins in the macula of the eye.^{7,8} Besides the metabolic control of hyperglycemia, hypertension, and hyperlipidemia, the mainstay treatment approach in the management of DR and DME has included early eye screening and retinal photocoagulation laser therapy.^{3,9} The limitations of the photocoagulation laser therapy is its inability to improve visual acuity and associated side effects of peripheral and night vision loss.^{10,11} Other available therapies for DR and DME include intravitreal steroids and vitrectomy. However, the intravitreal steroids may cause cataract formation, increased intraocular pressure, and lead to infection, while vitrectomy has been associated with postoperative

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Table 1. Anti-VEGF Drugs: FDA-Labeled Indications and Non-FDA-Labeled Indications.

Generic	Brand	FDA-Labeled Indication	Non-FDA-Labeled Indications
Ranibizumab ¹⁶	Lucentis	<ul style="list-style-type: none"> • Diabetic macular edema 	<ul style="list-style-type: none"> • Choroidal retinal neovascularization, secondary to pathologic myopia
Aflibercept ¹⁷	Eylea	<ul style="list-style-type: none"> • Diabetic macular edema—Diabetic retinopathy • Exudative age-related macular degeneration • Macular retinal edema—Thrombosis of retinal vein 	<ul style="list-style-type: none"> • None known to date
Bevacizumab ¹⁸	Avastin	<ul style="list-style-type: none"> • Diabetic macular edema • Diabetic macular edema—Diabetic retinopathy • Exudative age related macular degeneration • Macular retinal edema—Thrombosis of retinal vein • Cervical Cancer • Glioblastoma multiforme of brain • Metastatic colorectal cancer • Metastatic renal cell carcinoma • Nonsquamous non-small cell lung cancer • Ovarian cancer 	<ul style="list-style-type: none"> • Age-related macular degeneration, secondary to choroidal neovascularization • Branch retinal vein occlusion with macular edema • Central retinal vein occlusion with macular edema • Choroidal retinal neovascularization, secondary to pathologic myopia • Diabetic macular edema • Diabetic retinopathy • Epistaxis—Osler hemorrhagic telangiectasia syndrome • Neovascular glaucoma; adjunct • Ovarian cancer • Retinopathy of prematurity • Diabetic macular edema
Pegaptanib ¹⁹	Macugen	<ul style="list-style-type: none"> • Age-related macular degeneration, neovascular (wet) 	

Abbreviations: VEGF, vascular endothelial growth factor; FDA, Food and Drug Administration.

complication of vitreous cavity hemorrhage.¹⁰⁻¹² However, recent clinical trials have reported significant visual improvement with minimal serious side effects in the use of anti-VEGF therapies for the treatment of DME.^{3,9,10}

Currently available anti-VEGF therapies include the following: pegaptanib sodium (Macugen, Eyetech Pharmaceuticals Inc, New York, NY, and Pfizer Inc, New York, NY), bevacizumab (Avastin, Genentech Inc, San Francisco, CA), ranibizumab (Lucentis, Genetech Inc, San Francisco, CA), and aflibercept (Eylea, Regeneron Pharmaceuticals Inc, Tarrytown, NY, and Sanofi Aventis Inc, Paris, France).^{3,13-15} These anti-VEGF therapies have varying Food and Drug Administration (FDA) approved indications, including neovascular age-related macular degeneration, macular edema, and/or DME, with the exception of bevacizumab, which is FDA approved for colon cancer but used off-label via intravitreal injection^{3,13-15} (see Table 1 for FDA-labeled and non-FDA-labeled indications).

More recently, in February 2015, ranibizumab was FDA approved for the new indication in the treatment of DR in patients with DME.¹³ The drug was designated by the FDA as breakthrough treatment and was reviewed expeditiously because of its reported substantial improvement over existing therapies for DR in patients with DME.²⁰

This has caused a paradigm shift in the approach of managing DR. In this article, we review the efficacy, safety, pharmacokinetics, pharmacodynamics, and clinical utility of ranibizumab in the treatment of DR in patients with DME.

Data Sources

PubMed, Science Direct, Google Scholar, and ClinicalTrials.gov searches (January 2000-May 2015) were conducted for articles published in English, and limited to clinical trials using the key words ranibizumab, DR, DME, anti-VEGF, and DR treatment. Following PubMed, Science Direct, Google Scholar, and ClinicalTrials.gov searches, 4 clinical trials were identified and included in this review. Phase III/IV studies evaluating the clinical efficacy of ranibizumab versus placebo, ranibizumab versus laser, and ranibizumab versus other anti-VEGF agents were selected and evaluated.

Pharmacology

Ranibizumab inhibits the activity of VEGF-A by binding and antagonizing the receptor site for the active form of the glycoprotein.²¹ VEGF-A plays an active role in the

pathogenesis of DME. In patients with diabetes, the levels are elevated in the vitreous and anterior chambers and correlate to the severity of DME.²² Thus, patients with diabetes have greater VEGF levels in ocular tissue than nondiabetics.²¹ VEGF acts on 2 receptor types; the first is a tyrosine kinase receptor that plays a role in angiogenesis, lymphangiogenesis, and hematopoiesis; and the other is a receptor that plays a role in activating neutrophils, which are found on the vascular endothelial cells, tumor cells, and within the nervous system.²¹ In DR and DME models, VEGF-A has been shown to cause neovascularization, vascular leakage, ocular angiogenesis, and vascular occlusion. The binding of ranibizumab to the VEGF receptors prevents endothelial cell proliferation, vascular leakage, and new blood vessel formation.¹⁴

Pharmacokinetics and Pharmacodynamics

The pharmacokinetic properties of ranibizumab have been evaluated in patients with DME, retinal vein occlusion, and age-related macular degeneration. Exposure to ranibizumab is similar in all 3 patient populations.²³ For DR in patients with DME, ranibizumab 0.3 mg (0.05 mL) is administered as intravitreal injection every 28 days.¹⁴ A phase III trial (RISE and RIDE) showed subjects who received ranibizumab had an apparent clearance (CL/F) of 24.8 L/day (patients had a median creatinine clearance of 65.2 mL/min).²³ The rate of systemic absorption (k_a rate of vitreous elimination) is 0.0969 L/day. The elimination half-life is reported as approximately 9 days.¹⁴ The apparent volume of the central compartment (Vd/F) is 2.77 L. Systemic exposure of ranibizumab is low, approximately 1:90 000 compared with vitreal concentrations. This would be favorable in patients receiving monthly injections, as it reduces the risk for systemic complications.²³

In the D1 and D2 studies DR severity was assessed via fundus photography. Significant improvements were seen from baseline. Early Treatment Diabetic Retinopathy Study Retinopathy Severity Scores (ETDRS-RSS; test measuring visual acuity) at baseline ranged from 10 to 75.²⁴ At month 36 all ETDRS-RSS scores were greater than or equal to 60.¹⁴

Clinical Efficacy

A number of studies have been conducted to evaluate the clinical efficacy of ranibizumab versus placebo, and ranibizumab versus laser in DR. However, no studies have currently been done evaluating the clinical efficacy of ranibizumab versus other anti-VEGF agents for DR in DME. See Table 2 for a list of completed and upcoming trials evaluating the efficacy of ranibizumab for DR.

Ranibizumab Versus Placebo

The efficacy of ranibizumab versus placebo is supported by the data from the phase III, randomized double-masked, sham-controlled, multicenter clinical trials RISE and RIDE. Adults with DME were randomized to monthly 0.3 or 0.5 mg ranibizumab or sham injections. Patients who were receiving sham treatment were switched over to 0.5 mg ranibizumab during the third year. Baseline risk factors associated with developing proliferative diabetic retinopathy (PDR) were evaluated. PDR was analyzed using the Kaplan–Meier analysis. Main outcome measure during this trial was the change of ETDRS severity scale and clinical signs of progression to PDR. These outcomes were measured via photographic changes and defining events of PDR. Ranibizumab reported to be more efficacious than sham treatment. At month 36, the ranibizumab treated eyes had a ≥ 2 or ≥ 3 step DR improvement compared with sham/0.5 mg crossover. At month 36, 3.3% of the sham/0.5 mg, 25.0% of the 0.3 mg ranibizumab treated group, and 13.2% of the 0.5 mg ranibizumab treated group achieved a ≥ 3 step improvement. The authors concluded that ranibizumab administered to patients with DME for 12 to 36 months, compared with sham, can decrease DR severity and prevent worsening.³²

Ranibizumab Versus Laser

The efficacy of ranibizumab versus laser is demonstrated in the prospective, phase IV randomized, single-masked clinical trial LUCIDATE. The study population consisted of 33 eyes from 33 patients with center involving DME, having ETDRS scores of 55 to 79 letters at baseline. Subjects were randomized to either the ranibizumab group (receiving 3 initial loading doses of 0.5 mg ranibizumab and thereafter treatment every 4 weeks) of the laser treatment group (treatment every 12 weeks). The duration of the study was 48 weeks. Visual acuity, retinal sensitivity, color contrast sensitivity protan and tritan thresholds were reported at 12, 24, and 48 weeks. Pattern and full-field electroretinogram amplitudes, implicit times, and multifocal electroretinogram amplitude distribution were also reported. The authors of this study concluded that ranibizumab was superior to laser treatment as subjects in the ranibizumab group gained 6.0 letters, demonstrated improved tritan and protan color contrast thresholds, and improved retinal sensitivity versus the subjects receiving laser treatment who lost 0.9 letters.³³

Ranibizumab Versus Other Anti-VEGF

Currently, there are no data available for the efficacy of ranibizumab versus other anti-VEGF agents for DR in patients with DME; current data only exist for the efficacy

Table 2. Completed and Uncompleted Clinical Trials Evaluating the Efficacy of Ranibizumab for Diabetic Retinopathy.

ClinicalTrials.gov Identifier	Phase	Sponsor/Collaborator	Arms	Primary Outcome	Status
NCT0047333 ²⁵	III	Genentech, Inc	<ul style="list-style-type: none"> Ranibizumab 0.3 mg monthly intravitreal injection for 36 months Ranibizumab 0.5 mg monthly intravitreal injection for 36 months Sham intravitreal injection monthly for 24 months/crossover to ranibizumab 0.5 mg for remaining 12 months 	Percentage of patients who gained ≥ 15 letters in BCVA score from baseline at month 24	Complete
NCT01223612 ²⁶	IV	Moorfields Eye Hospital NHS Foundation Trust/Novartis	<ul style="list-style-type: none"> Ranibizumab 0.5 mg monthly Intravitreal injection 	Functional and anatomical change in the retina over 48 weeks	Complete
NCT00545870 ²⁷	III	Ursula Schmidt-Erfurth, MD/Medical University of Vienna	<ul style="list-style-type: none"> Modified ETDRS laser Bevacizumab 1.5 mg monthly intravitreal injection Ranibizumab 0.5 mg monthly intravitreal injection 	Change in macular edema and the absolute change in visual acuity; change of neovascularization	Complete
NCT01476449 ²⁸	II	Retina Vitreous Associates of Florida/Genentech, Inc	<ul style="list-style-type: none"> Monthly ranibizumab 	Mean change in ETDRS eye chart vision	Active and ongoing
NCT00931125 ²⁹	II	Attila Vajas/Semmelweis University	<ul style="list-style-type: none"> Treat and extend ranibizumab Vitrectomy with ranibizumab Vitrectomy without ranibizumab 	Efficacy of preoperative intravitreal treatment	Active and ongoing
NCT01489189 ³⁰	III	Diabetic Retinopathy Clinical Research Network/National Eye Institute (NEI) and Genentech, Inc	<ul style="list-style-type: none"> Anti-VEGF + deferred PRP 	Mean change in visual acuity from baseline to 2 years	Active and ongoing
NCT02005432 ³¹	IV	University of Sao Paulo/Rafael de Montier P. Barroso, MD, University of Sao Paulo	<ul style="list-style-type: none"> Prompt PRP SS-PRP MS-PRP IVR 	Fluorescein angiography leakage area	Active and ongoing

Abbreviations: BCVA, Best Corrected Visual Acuity; ETDRS, Early Treatment for Diabetic Retinopathy Study; VEGF, vascular endothelial growth factor; PRP, panretinal photocoagulation; SS-PRP, single shot photocoagulation; MS-PRP, multiple shoot photocoagulation; IVR, intravitreal ranibizumab.

in DME. The efficacy of ranibizumab versus another anti-VEGF agent was compared in a 2013 prospective randomized trial. This study compared best-corrected visual acuity (BCVA) and spectral domain optical coherence tomography (SDOCT) outcomes associated with intravitreal bevacizumab versus intravitreal ranibizumab for the management of DME. Sixty-three eyes with center involving DME were randomly assigned to receive 1.5 mg intravitreal bevacizumab or 0.5 mg intravitreal ranibizumab. There was a

significantly greater mean improvement in BCVA in the intravitreal ranibizumab group compared with the intravitreal bevacizumab group at weeks 8 ($P = .0318$) and 32 ($P = .0415$), with a trend toward significance at weeks 28, 36, and 40. A significant reduction in mean central subfield thickness was observed in both groups at all study visits compared with baseline ($P < .05$).³⁴

The efficacy of ranibizumab versus other anti-VEGF was also compared in the trial *Aflibercept, Bevacizumab, or*

Ranibizumab for Diabetic Macular Edema. This study evaluated aflibercept, bevacizumab, and ranibizumab for treatment of macular edema. Six hundred and sixty subjects were randomly assigned to receive intravitreal aflibercept 2.0 mg, bevacizumab 1.25 mg, or ranibizumab 0.3 mg. Each drug was administered every 4 weeks. Mean change in visual acuity after 1 year was the primary outcome. Visual acuity scores ranged from 0 to 100, with higher scores representing better visual acuity (a score of 85 represents 20/20 vision). The authors of the study concluded that intravitreal aflibercept, bevacizumab, and ranibizumab all improved vision in eyes with center-involved DME; however, the relative baseline effect depended on the baseline visual acuity. When baseline visual acuity loss was mild (letter score of 78-69), there were no apparent differences between the groups. At worst levels of baseline visual acuity (letter score less than 69), aflibercept was more effective at improving vision, compared with the other anti-VEGF groups. The mean improvement was 18.9 with aflibercept, 11.8 with bevacizumab, and 14.2 with ranibizumab.³⁵

Safety/Adverse Effects

Ranibizumab has been associated with endophthalmitis and retinal detachments, increase in ocular pressure, and thromboembolic events. Proper aseptic injection technique should be used when administering ranibizumab and early monitoring of infection should be in place to avoid endophthalmitis and retinal detachment.³⁶ Increase in ocular pressure has been associated with the administration of ranibizumab; therefore, pre- and postinjections should be monitored. Arterial thrombotic events (ATE) have also been reported with the use of ranibizumab.¹⁴ These events include nonfatal myocardial infarction, nonfatal stroke, and vascular death. The ATE rate at 2 years was 5.6% (14 out of 250). The stroke rate was 1.2% (3 of 250). At 3 years the ATE rate was 10.8% (27 out of 250) and the stroke rate was 2.0% (5 out of 250).³⁶ Fatalities in the first 2 years were 2.8% (7 out of 250) and at 3 years 4.4% (11 of 250). Even though the rate of these incidences are low, they cannot be excluded in patients with DR and DME who are taking anti-VEGFs.^{14,36}

Drug Interactions

Drug interaction studies have not been conducted in ranibizumab. When ranibizumab was combined with verteporfin photodynamic therapy, a small percentage of patients (11%) with neovascular age related macular degeneration developed serious intraocular inflammation.^{37,38}

Cost

The monthly administration of ranibizumab and the required evaluation and monitoring visits contribute to the health

care cost burden associated with intravitreal anti-VEGF treatment.³⁹ The wholesale acquisition costs of each single use 0.05 mL vial of ranibizumab varies according to the medication strength. The 0.3 mg and 0.5 mg doses are \$1170 and \$1950, respectively, for each monthly (approximately 28 days) intravitreal injection.⁴⁰ The outcome of cost-effectiveness analysis of ranibizumab in comparison with sham therapy, triamcinolone, and aflibercept showed greater gain in quality-adjusted life year, and/or financial value.⁴¹⁻⁴³ However, it is important to note that the cost-effectiveness analysis comparison between ranibizumab and aflibercept were based on the United Kingdom National Health Service model, thus may not apply in the United States.⁴³ The other anti-VEGF treatment that has been shown to improve DME is bevacizumab, and it is the cheapest available therapy with the monthly cost of \$50 per dose.⁴⁴ However, this agent is not FDA approved as an anti-VEGF therapy, and it is currently available in an intravenous injection formulation. Thus, if used off-labeled as an anti-VEGF therapy it must be compounded for intravitreal use.³ Thereby, clinicians must consider the potential associated risks of compounding intravitreal drugs including microbial contaminants and inconsistency of bevacizumab concentrations across drug samples when selecting an anti-VEGF therapy.⁴⁵

Dosage and Administration

Ranibizumab is supplied in a single-use glass vial that provides 0.05 mL for intravitreal injection in 0.3 mg (6 mg/mL solution) and 0.5 mg (10 mg/mL solution). The recommended monthly (approximately 28 days) dose for DME and DR in patients with DME is 0.3 mg administered via intravitreal injection. There is no adjustment needed for the geriatric population since notable efficacy and safety differences were absent during the clinical studies. In addition, renal dose adjustment is not necessary due to minimal systemic exposure of the drug. The drug should be administered monthly by a health care provider under controlled aseptic conditions to minimize infections via the use of sterile gloves, sterile drape, and sterile eyelid speculum. Each vial is to be used per eye treatment. In the event that both eyes need treatment, a new vial with changed syringe, gloves, drapes, eyelid speculum, filter, and injection needles should be used. Anesthesia and broad-spectrum microbicide should be administered prior to the drug administration.¹⁴ Other dosing regimens that have been used with ranibizumab besides fixed monthly dosing include as needed (PRN) and Treat-and-Extend (TAE).^{43,46} PRN dosing is administration of drug as needed based on the dryness of the macula, while TAE dosing involves the treatment with drug therapy until the macula is dry and minimal extension of treatment over time until there is recurrence.⁴⁷ The main premise behind the PRN and TAE schedules is to individualize therapy, reduce

cost, and reduce number of office visit for patients. In fact, Regnier et al demonstrated that ranibizumab TAE and PRN are both cost-effective options in the management of DME.⁴³

Patient Counseling

It is important to advise patients receiving monthly intravitreal ranibizumab injection to monitor and report the signs of endophthalmitis, which includes eye redness, sensitivity to light, eye pain, and vision changes. In addition, patients should be instructed to immediately report the signs and symptoms of myocardial infarction and stroke while on ranibizumab.¹⁴

Conclusions

The use of ranibizumab and other anti-VEGF would likely influence the management of DR. The recent FDA approvals of the 2 anti-VEGFs, namely, ranibizumab and aflibercept, via priority review process in the treatment of DR in patients with DME is significant. While laser therapy has been the mainstay therapy to delay vision loss, the advantage of anti-VEGF agents such as ranibizumab over the photocoagulation laser therapy is the improvement in visual acuity with minimal serious ocular adverse events. However, more studies are needed to assess the long-term efficacy and safety of this drug class.

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