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Lucentis® (ranibizumab ophthalmic injection) for diabetic macular edema (DME)

Abstract

Objective: To review the efficacy, safety and pharmacologic parameters of ranibizumab (Lucentis®) intravitreal ophthalmic injection versus alternative agents in the management of diabetic macular edema (DME).

Data sources: Information was reviewed from: MEDLINE (January 2000-December 2015), both manufacturers of ranibizumab (Genentech and Novartis), and the United States (U.S.) Food and Drug Administration (FDA). The internet was searched using the following key terms: avastin, diabetic macular edema (DME), eye, injection, intravitreal, lucentis, microvascular, ophthalmic, pharmacologic, ranibizumab, and retinopathy.

Study selection and data extraction: All English-language articles and abstracts were evaluated for inclusion. Appropriate, randomized controlled trials in DME are included in this review.

Data synthesis: The safety and efficacy of ranibizumab intravitreal ophthalmic injection (0.3mg every 28days) versus (0.5mg every 28days) versus placebo was evaluated in two randomized, double-masked studies in patients with DME over 24-36months. Patients were between 21-91years old (mean age 62); all patients were eligible for additional types of treatment, if needed, beginningmonth three of the studies [i.e., macular laser treatment or pan retinal photocoagulation (PRP)]. Atmonth 24, compared tomonthly ranibizumab 0.3mg, no additional benefit was observed withmonthly treatment with the ranibizumab 0.5mg dose; therefore, outcomes measured inmonths 24-36 were ranibizumab 0.3mg vs. placebo and based on changes in visual acuity. They were defined as:

a. Gain of greater than or equal (>) to15 letters

b. Loss of less than (<) 15 letters visual acuity and

c. Mean change in visual acuity.

Conclusions: Ranibizumab (Lucentis®) intravitreal ophthalmic injection 0.3mg given every 28days was shown to be safe and effective for the management of diabetic macular edema (DME) and is the first and only FDA approved pharmacological choice. Ranibizumab received its fourth FDA indication for treatment of serious eye diseases in February, 2015. It is now approved for the treatment of diabetic retinopathy in those with DME.

Keywords: avastin, bevacizumab, diabetic macular edema, eye, injection, intravitreal, lucentis, micro vascular, ophthalmic, pharmacokinetic, ranibizumab, retinopathy

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Abbreviations: DME, diabetic macular edema; AMD, age--related macular degeneration; DR, diabetic retinopathy; RVO, retinal vein occlusion; BG, blood glucose; NME, new molecular entity; DCCT, diabetes control and complications trial; AACE, association of clinical endocrinologists; FBS, fasting blood sugars; ETDRS, early treatment diabetic retinopathy study

Introduction

On February 6, 2015, LUCENTIS (ranibizumab) received its fourth FDA approved indication for management of serious eye diseases since 2006. It is now approved for patients with diabetic retinopathy (DR) and diabetic macular edema (DME).[1] LUCENTIS received its first approval as a new molecular entity (NME) for the treatment of neovascular (wet) age-related macular degeneration (AMD) in June, 2006.[2] It was also the first drug in a new class of medication called the Anti angiogenic Ophthalmic Agents/Vascular Endothelial Growth Factor A (VEGF-A) Antagonists that year. Fouryears later in June, 2010 LUCENTIS received a second approval for use in macular edema following retinal vein occlusion (RVO).[3] In August, 2012, ranibizumab received its third indication.[4–6] It was developed by Genentech, Inc., and Novartis. Genentech supports the U.S. whereas Novartis backs utilization in the rest of the world.[7]

Pathophysiology of diabetic macular edema (DME)

Poorly controlled diabetes causes micro vascular complications like diabetic retinopathy (DR) and over 4.2 million people age 40 and older with diabetes currently have DR.[8] Nearly 0.7million have

advanced DR that possibly will lead to severe vision loss.[8] DME is an advanced complication of DR[7] and the estimated lifetime risk of developing DME is thought to be about 13%.[9–11] DR is the number one cause of new blindness among adults aged 20-74[12] and DME is of nearly equal risk.[9–11]

The pathophysiology of DME has been best explained by comparing the human eye to a camera that still uses film that needs to be developed; the retina of the eye to film that gets put into the camera, and a person's vision to pictures being taken. In this manner, if the film is damaged before the pictures are taken wouldn't you expect the picture to be damaged when you develop it? The same consideration can be given to DME, there is damage to the retina, depending on the type, location, and extent of damage to the retina, the change in vision ranges from minimal to severe and can be temporary or permanent.[9–12]

Eye complications become more apparent as blood glucose (BG) abnormalities produce alterations in the microvasculature in the retina; the vessel walls become fragile, leak fluid, and form micro aneurysms. Fluid accumulates in the central part of the retina (the macula), which leads to DME. The macula has specialized nerve endings that detect color and necessary for daytime vision. As the injury progresses, blurring occurs in central or lateral vision from retinal thickening or hard exudates forming.[13] Vision loss progresses over severalmonths, and the ability to focus clearly becomes nearly impossible. Decreased oxygen delivery to the retina causes new blood vessel formation, leading to proliferative diabetic retinopathy (PDR). New blood vessel formation may sound like a good thing, but not in this situation. These new capillaries are unstable and rupture easily; which leads to more of this vicious cycle.[9–11] See Table 1 for the International Clinical Diabetic Macular Edema Disease Severity Scale.[14]

Table 1 International clinical diabetic macular edema disease severity scale[13]

Proposed disease severity findings observable upon dilated ophthalmoscope level	
Diabetic macular edema apparently absent	No apparent retinal thickening or hard exudates* in posterior pole
Diabetic macular edema apparently present	Some apparent thickening or hard exudates* in posterior pole
If diabetic macular edema is present, it can be characterized as follows	
Proposed Disease Severity Level	Findings Observable Upon Dilated Ophthalmoscopy
Diabetic macular edema(DME) present	Mild macular edema: some retinal thickening or hard exudates* in the posterior pole but distant from the center of the macula.
	Moderate macular edema: retinal thickening or hard exudates* approaching the center of the macula, but not involving the center.
	Severe macular edema: retinal thickening or hard exudates* involving the center of the macula.

*Hard exudates are a sign of current or previous macular edema. DME is defined as retinal thickening; this requires three dimensional assessments that are best performed by dilated examination by slit-lamp biomicroscopy and/or stereo fundus photography.

#Revised from the American Academy of Ophthalmologists, The Eye MD Association

Two conditions lead to DME and increase hydrostatic pressure within retinal capillaries: hypertension and fluid retention. Fluids inside these vessels are normally stable; however, in abnormal conditions they exert higher pressures that drive fluid from within the capillaries causing edema inside the macula.[9–11]

DME is classified into two categories:

A. Focal and

B. Diffuse.

This becomes relevant due to because of the initial type of management used; first line treatment for DME is laser photocoagulation and the type of laser used differs based on the type of DME.[8–11] Focal Diabetic Macular Edema (FDME) is caused by "foci or concentrations" of vascular abnormalities caused primarily by leaky micro aneurysms; whereas Diffuse Diabetic Macular Edema (DDME) is caused by dilated retinal capillaries.[9–11] The two types of laser photocoagulation treatment are: Focal and Grid. Focal Laser Treatment is used to treat FDME to close leaking micro aneurysms and Grid Laser Treatment to treat DDME and applied to areas of retinal thickening where there is diffuse leakage; grid laser treatment is used to produce a retinal burn of mild to moderate intensity.[9–11]

Large, multi-center trials have been conducted in people with both types of diabetes showing that lowering BG to "near normal range" delays/prevents micro vascular complications (E.g. retinopathy). Normal fasting blood sugars (FBS) are between 70-99mg/dL (3.9-5.5mmol/dL); and people with diabetes have FBS between 70-130mg/dL (3.9-7.2mmol/dL).[13] The Diabetes Control and Complications Trial (DCCT) was the first landmark trial in type 1 diabetes that showed conclusively tight BG control was instrumental in preventing long-term micro vascular complications, like retinopathy in 1993.[13] In 1998, the United Kingdom Prospective Diabetes Study (UKPDS) presented comparable results in over 5000 people with newly diagnosed type 2 diabetes; this trial also showed the implication of strict blood pressure (BP) control.[14] An arm the Epidemiology of Diabetes Interventions and Complications (EDIC)[15] research study was published in 2010 that looked at the progression of retinopathy in adults and adolescents. This study concluded that prior glycemic control in the DCCT[13] was essential for the persistence of beneficial effects of glycemic control on retinopathy.

The American Diabetes Association (ADA) determined that an overall A1C goal for patients with diabetes should beless than (<) 7.0% [average blood glucose (BG) 154mg/dL=8.6mmol/L][10,11] The American Association of Clinical Endocrinologists (AACE) recommend a tighter A1C goal of 6.5% [BG140mg/dL=7.8mmol/L].[11] More or less stringent glycemic goals may be appropriate for individual patients. A1C goals should be individualized based on duration of diabetes, age, life expectancy, comorbid conditions, known cardiovascular disease (CVD) or advanced microvascular complications, hypoglycemia unawareness, and individual/patient considerations.[10,11] Is an A1C level the best measure of overall glycemic control? Or should providers use an estimated average glucose (eAG)? The debate continues. The eAG was introduced by the ADA in 2008. The following formula is used to calculate an eAG: eAG=.7 x A1C- 46.7.[10,16]

Adults with diabetes are recommended to have their BP less than 130/80mmHg; higher or lower systolic blood pressure (SBP) targets may be appropriate initially.[11,17,18] Blood lipid control is primarily based on low-density lipoprotein (LDL) cholesterol levels. In those with no obvious risk other than diabetes the recommendation is to

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lower the LDL-cholesterol (LDL-C) to a goal of less than 100mg/dL (<2.6mmol/L). In individuals with overt CVD, a lower LDL-C goal of less than70mg/dL (<1.8mmol/L), using a high dose of a statin, is an option. Once eye disease has progressed beyond early stages, other types of intervention/treatment measures may be necessary.[6,7,15]

Clinical pharmacology of ranibizumab

Vascular Endothelial Growth Factor (VEGF) causes neovascularization and leakage in models of ocular angiogenesis, vascular occlusion and contributes to pathophysiology of AMD, macular edema following RVO, and DME.[10,17–19] Ranibizumab (previously called rhuFabV2) is a monoclonal antibody fragment (Fab) that is derived from Escherichia coli *(E.Coli)*, a gram negative facultative anaerobic bacterium**;** it's molecular weight is about 48 kilo daltons and comes in a sterile, preservative-free, clear to pale-yellow solution single use glass vial, with 10mM histidine HCl, 10% α,α-trehalose dihydrate, 0.01% polysorbate 20, pH 5.5.[10,17–19] Its chemical formula is: $C_{2158}H_{3282}N_{562}O_{681}S_{12}$.[10,17–19]

Ranibizumab binds to active forms of subtypes of Vascular Endothelial Growth Factor (VEGF, specifically VEGF-A and the cleaved form, VEGF-110) and inhibits their biologic activity so they cannot act at their receptor sites (VEGFR1 and VEGFR2) on the surface of endothelial cells, reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation.[10,17–19] Ranibizumab was designed to deliver potent and durable intraocular VEGF an inhibition.[20] The clinical significance of this molecular design is unknown.

Pharmacokinetics/ pharmacodynamics of ranibizumab

See Table 2.[10,17–19]

Table 2 Pharmacokinetics and pharmacodynamics of ranibizumab[18–22]

Serum ranibizumab concentrations	**Low***
Serum ranibizumab concentrations	*Predicted to be about 90,000-times LOWER than vitreal fluid concentrations
Average vitreous elimination half-life(t½) [0.5mg dose]	Nine(9)days
Maximum Concentration Obtained(C_{max}) in the serum	Obtained after one day=0.79-2.90ng/mL*
Minimum Concentration Obtained(C_{min}) in the serum	Predicted to be between=0.07-0.49ng/mL*
Concentration needed to inhibit the biological activity of VEGF by 50%(assessed by in vitro cellular proliferation assay)	11-27 ng/mL*
Renal Impairment	No formal pharmacokinetic studies have been conducted; previous studies, patients had mild [50-80mL/min], moderate [30-50mL/min] and severe [less than 30mL/min] renal impairment where systemic clearance of ranibizumab was slightly lower, but not considered clinically or statistically significant.
Hepatic Impairment	No formal studies have been conducted. No dose adjustment is required.
Ethnicity	Experience is limited in groups other than the Caucasian population.
Elderly	Experience is limited in people over 65years of age
Pediatrics	Safety and efficacy has not been established in children or anyone less than18years of age.
Pregnancy/Childbearing/Fertility [Category C]	Studies in cynomolgus monkeys do not indicate direct or indirect harmful effects with respect to pregnancy or embryonic/fetal development. Due to its mechanism of action, ranibizumab must be regarded as potentially teratogenic. Therefore, women who wish to become pregnant and have been treated with ranibizumab, it is recommended to wait at least three months after the last dose of drug before conceiving a child. There is no data available on fertility.
Breastfeeding	No data; Breastfeeding is not recommended during use.
Carcinogenicity	No carcinogenicity data is available
Genotoxicity	No genotoxicity data is available
Pharmacodynamics	VEGF-Abinding to its receptors(VEGFR1 and VEGFR2) leads to endothelial cell proliferation, neovascularization, and vascular leakage. All of these thought to play a role in the progression of DME.

*Shows how low serum concentrations compared with levels needed for efficacy

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Clinical trials

Two parallel, double-blind, randomized, placebo-controlled studies led to the approval of ranibizumab for DME. Both were sponsored by Genentech.[10,19,20] The two studies RISE [A Study of Ranibizumab Injection in Subjects with Clinically Significant Macular Edema with Center Involvement Secondary to Diabetes Mellitus] and RIDE [A Study of Ranibizumab Injection in Subjects with Clinically Significant Macular Edema with Center Involvement Secondary to Diabetes Mellitus] were both Phase III clinical trials.

The primary outcome measure was to determine the proportion of subjects who gained at least15 letters in Early Treatment Diabetic Retinopathy Study (ETDRS) letters in best corrected visual acuity (BCVA) score compared with baseline in 24-months. This was not designated as a safety issue.[10,19,20] A total of 759 subjects were enrolled; selection criteria included: adult patients ≥18years (21-91years old; average age 62) with decreased vision due to DME; central subfield thickness (CST) ≥275 microns; study eye BCVA of 20/40 to 20/320; patients were included unless any of the following happened within threemonths of day 0: [anti angiogenic drugs in either eye, pan retinal photocoagulation (PRP), macular laser or intraocular steroids, cerebro vascular accident (CVA) or myocardial infarction (MI)]; A1C ≤12%.

Treatment protocol

Baseline throughmonth 24, 250 patients received ranibizumab 0.3mg, 252 received ranibizumab 0.5mg, and 257 received placebo injections everymonth. Macular laser was available per-protocol specified criteria throughmonth 24 Table 3. Duringmonths 25 through 36, subjects who previously received placebo injections were eligible to receivemonthly ranibizumab 0.5mg injections and subjects originally randomized tomonthly ranibizumab 0.3mg or 0.5mg continued to receive their assigned dose. Compared tomonthly ranibizumab 0.3mg, no additional benefit was observed withmonthly treatment with ranibizumab 0.5mg.[10,19] Visual acuity (VA) outcomes observed atmonth 24 in the subjects treated with ranibizumab 0.3mg were maintained with continued treatment throughmonth 36 in both DME studies. (See Table 3 for 24month outcomes).[10,19,20]

Subjects in the placebo arms received ranibizumab 0.5mg beginning atmonth 25, and for last12months; these subjects achieved lesser VA gains compared to subjects who began treatment with ranibizumab at the beginning of the studies. A total of 582/759(77%) subjects completed the study.[10,19,20]

Recommended dosing of ranibizumab in DME

The recommended dose of LUCENTIS for DME is 0.3mg [0.05mL] of the 6mg/mL solution every 28days. LUCENTIS should be administered at least thirty minutes after the laser photocoagulation when given on the same day.[11,18–21]

Adverse Effects/drug interactions/contraindications in DME

People with diabetes are at potentially higher risk for vascular complications with VEGF inhibition. Overall complications and fatalities experienced are outlined in Table 4 (See Table 4 for Ocular/Systemic/Mortality data). Causes of death were typical of advanced complications of diabetes, however a relationship cannot be ruled out between those events and VEGF inhibition. As with all therapeutic proteins, there is the potential for an immune response in patients treated with LUCENTIS. The clinical significance of immunoreactivity to is unclear at this time.[17–20] No drug interaction studies have been conducted; LUCENTIS has been used adjunctively with verteporfin photodynamic therapy (PDT). However in AMD studies, 12/105 patients (11%) developed severe intraocular inflammation; in 10/12 patients this happened within 7days (±2days) after verteporfin PDT.[19]

LUCENTIS is contraindicated in patients with ocular or periocular infections or hypersensitivity to ranibizumab or any of the excipients in LUCENTIS.[19]

Table 3 Clinical Trials with Ranibizumab outcomes at Month [2411,18,20,22]

	Lucentis 0.3mg n=250	**Placebo N=257**
Received Macular Laser	37.6%(94)	72.0%(180)
Laser treatments received	0:62.4%(156)	0: 28.0%(72)
	1: 20.4%(51)	1: 26.1%(67)
	2: 7.2%(18)	2: 18.3%(47)
	3: 5.6%(14)	3:14.4%(37)
	4 or more: 4.4%(11)	4 or more: 13.3%(34)
Mean number of treatments(SD)	0.7(+1.3)	1.7(+1.7)
Received panretinal photocoagulation(PRP) laser	0.8%(2)	12%(30)

	Lucentis 0.3mg n=125 vs. Placebo n=130 (DME1=RISE)[11,20,22]	**Lucentis 0.3 n=125 vs. Placebo n=127 (DME2=RIDE)[11,20,22]**
Visual acuity		
Gain of greater than(>)15 letters in visual acuity	34% vs. 12% GAIN of 21% [95% CI, 11-30%]* ranibizumab 98%	45% vs. 18%; GAIN of 24% [95% CI, 14-35%]* ranibizumab 98%
Loss of less than(<) 15 letters in visual acuity	vs. placebo 92% LOSS of 7% [95% CI, 2-13%]* ranibizumab 10.9	vs. placebo 9% LOSS OF 8% [95% CI, 2-14%]* ranibizumab 12.5
Mean change in visual acuity(letters)	vs. placebo 2.3 Mean change: 8.5 [95% CI, 5.4-11.5]*	vs. placebo 2.6 Mean change: 9.6 [95% CI, 6.1-13.0]*

*Adjusted estimated based on stratified model; p<0.01

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Table 4 Adverse Effects of Ranibizumab.[11,20,22]

Ocular events	**Ranibizumab 0.3mg n=250**	**Placebo n=257**
Any Ocular Adverse Event* [Most common: eye pain, intraocular inflammation, increased intraocular pressure(IOP) vitreous floaters, and conjunctival hemorrhage]	86.4%(216)	86.4%(216)
Cataract	28.0 %(70)	31.6%(79)
Glaucoma(excluding congenital)	2.8%(7)	22.4%(6)
Intraocular inflammation	3.6%(9)	3.2%(8)
Increased IOP	17.6%(44)	3.2%(8)
Iris neovascularization	0.4%(1)	6.8%(17)
Retinal detachment	0.4%(1) 0.4%(1)	0.8%(2)
Retinal neovascularization	0.8%(2)0.4%(1)	1.2%(3)
Systemic events		
Any Event(most common): [runny nose, headache, arthralgia, and bronchitis]	10.8%(27)	11.6%(29)
ATE bleeding/hemorrhage adverse events(AE)	2.8%(7)	2.8%(7)
Bleeding/Hemorrhage(CNS and CV)	1.2%(3)	1.2%(3)
Bleeding/Hemorrhage(non-CNS)	1.6%(4)	1.6%(4)
CHF	2.8%(7)	4.4%(11)
Fistulae(other)	0.4%(1)	0
Hypertension	1.2%(3)	0.4%(1)
Thrombolic event, arterial	5.6%(14)	6.8%(17)
Thrombolic event, venous	1.6%(4)	0.4%(1)
Morbidity or mortality		
Any Event	6.4%(16)	5.2%(13)
Deaths, overall	2.8%(7)	1.2%(3)
Vascular	2.0%(5)	1.2%(3)
Non-vascular	0.8%(2)	0
Unknown cause	0	0
MI, overall	3.6%(9)	3.6%(9)
MI, Fatal	0.8%(2)	0.8%(2)
MI, Non-fatal	2.8%(7)	2.8%(7)
CVA, overall	1.2%(3)	1.6%(4)
CVA, Fatal	0.4%(1)	0.4(1)
CVA, Non-Fatal	0.8(2)	1.2(3)
APTC events	5.6%(14)	5.2%(13)

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Formulary considerations

LUCENTIS is considered a specialty use item. The approved dosage, route, and interval for DME is 0.3mg (0.05 mL of the 6mg/mL formulation) given by intravitreal injection by an ophthalmologist every 28days. It should be stored in the refrigerator at (2°C -8°C), protected from light, kept in its carton, and shouldn't be frozen. An unopened box retains the manufacturer's expiration date, if refrigerated.[19–22] LUCENTIS is available in two dosage forms. It comes in single-use glass vial designed to provide 0.05mL for intravitreal injection. It is available as a 10mg/mL solution (LUCENTIS 0.5mg) and as 6mg/mL solution (LUCENTIS 0.3mg).[20]

LUCENTIS may be the only FDA-approved ophthalmic agent for DME; however that doesn't preclude the use of other products in disease state management.[19–22] Bevacizumab (Avastin®) is the product that is most commonly compared to LUCENTIS in the management of DME.[21] The two products are manufactured and marketed by the same pharmaceutical company, but is only FDA approved to treat metastatic colorectal, lung, breast, renal, and other types of cancers. Studies with bevacizumab 1.25mg and 2.5mg intravitreal in DME have shown a lesser response rate or more doses are needed to attain the same type of response seen with ranibizumab, but many ophthalmologists prescribe it because it is so much cheaper at only $55 per dose.[11,18–22] The major drawback to use in DME is there is no intravitreal dosage form commercially available; it must be prepared for intravitreal use from the intravenous formulation.[19–22]

Synthetic corticosteroids, like intravitreal triamcinolone acetonide (Triesence®), has beenused for ocular inflammatory conditions and visualization during vitrectomy; and pegaptanib sodium (Macugen®), an ophthalmic anti-VEGF agent for the treatment of choroidal neovascularization (CNV) from AMD.[10,19–22]

Conclusion

LUCENTIS (Ranibizumab) intravitreal ophthalmic injection 0.3mg is the first and only FDA approved pharmaceutical therapy for the management of DME. It is a specialty use medication and must be prescribed and used by highly trained physicians (i.e. ophthalmologists). It must be used under aseptic technique. The major advantage it has over other available agents is that it is FDA approved for use, so it is covered by Medicare. There is a commercially available product for intravitreal use; no other product is available in a commercially available able product. The major deterrent to use is the major cost per dose vs. other similar agents that require more time to prepare, but may work as well. Will cost prohibit its overall use?

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None.

Conflict of interest

Author declares that there is no conflict of interest.

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