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Does Ranibizumab Improve Best Corrected Visual Acuity in Adults with Diabetic Macular Edema Compared to Those without Ranibizumab?

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ABSTRACT

Objective: The objective of this selective evidence based medicine (EBM) review is to determine whether or not ranibizumab improves best corrected visual acuity (BCVA) in adults with diabetic macular edema compared to patients who do not receive ranibizumab

Study Design: The selective review examined best corrected visual acuity values reported from published, primary literature sources that examined the efficacy of ranibizumab in diabetic macular edema

Data Sources: Two double blind randomized controlled trials and one case control study were selected and reviewed

Outcomes Measured: Best corrected visual acuity (BCVA) as measured from Early Treatment Diabetic Retinopathy Study visual acuity charts, which were converted to dichotomous data to determine treatment effects. Adverse events were also considered in this selective review to determine safety of this therapeutic intervention.

Results: Mean BCVA improvements were 10.3, 9, and 13 with all p-values < 0.05 compared to statistically significant decline in acuity in control arms. Adverse event rates were notably higher in therapeutic arms but only a minority was serious adverse events (SAE).

Conclusion: All reported increases in BCVA suggests that indeed ranibizumab is an effective therapeutic option for diabetic macular edema but requires continued investigation to further elaborate its safety profile outside a controlled research setting

Key Words: Ranibizumab, Lucentis, diabetic macular edema, diabetic retinopathy, macular edema, VEGF inhibitors

Diabetic macular edema (DME) is a common manifestation of diabetic retinopathy, causing blurred vision due to the edema of the macula. In a diabetic patient, poorly controlled hyperglycemia triggers several cascades of pathologic mechanisms. One such pathway both induces the apoptosis of pericytes that surround retinal vessels as well as thickens the basement membrane of the very same vessels, which allows microaneurysms to occur and the leaking of plasma in the retinal layers to include the macula. Though the eye is capable of tolerating a certain volume of leaked fluid in the retina, hyperglycemia and retinal ischemia also trigger the release of vascular endothelial growth factor (VEGF). VEGF is a key signaling protein that promotes a pathologic angiogenesis; the body increases the vasculature in the retina, which is prone to the same microaneurysms and leaking. A combination of neovascularization and porous vessels leads to the rapid accumulation of plasma fluid, leading to diminishing visual acuity.

Epidemiology

Diabetes mellitus and its complications have a regrettably high impact and prevalence in the United States; therefore physician assistants will undoubtedly encounter, diagnose, and treat this disease. In 2010, the CDC estimated that approximately 25.8 million individuals suffered from diabetes mellitus in the United States.[1] Of these diabetics, nearly 100% of type 1 diabetics and approximately 60% of type 2 diabetics are projected to develop diabetic retinopathy over the course of 15 to 20 years.[2] In light of its incidence, it is imperative for physician assistants and other healthcare providers to prepare themselves to be able to identify and treat this condition accurately and effectively.

Likewise, diabetic retinopathy has a significant impact on the patient and social welfare programs. In a study comparing Medicare reimbursements to diabetics without and with macular edema, the investigators found that Medicare paid an additional $2,892 per Medicare beneficiary

with diabetic macular edema within the first year of diagnosis.[3] At three years following the diagnosis, Medicare reimbursed on average an additional $8,312 per Medicare beneficiary with diabetic macular edema.[3] While the cost to the federal government is clear, it may also be surmised that the cost to the patient rises as well with co-pays, deductibles, and associated logistical costs (e.g. transportation).

Diabetic retinopathy also substantially affects the time spent by both provider and patient. In another study examining the impact of this manifestation of diabetic retinopathy, it was estimated that patients with diabetic macular edema have three times more ophthalmologic visits than those who do not, with approximately 3.9 visits per year.[4] With an estimated prevalence of 2 million suffering diabetic retinopathy in the United States[2], this comes out to approximately 8 million healthcare visits in the United States per year.

Current & Future Therapies

With the impact of diabetic retinopathy & macular edema established, the logical questions to investigate are what is known about the disease and what can be done to combat it. As described earlier, much is already known about the etiology and pathophysiology of diabetic macular edema; however the elusive piece of the puzzle is curative therapy.

Current therapies focus on glycemic control and focal laser photocoagulation. Tight glycemic control in patients with diabetes mellitus is the most effective therapy, but this efficacy is lost as retinopathy progresses to advanced stages. This leaves focal laser coagulation as the mainstay of therapy for diabetic macular edema. Unfortunately this therapy is far from ideal; patients undergoing the procedure may expect a modest improvement in best corrected visual acuity (BCVA) by 30%, and up to 20% of those who receive laser photocoagulation will experience a worsening of their vision.[1]

The risks and limited efficacy of focal laser photocoagulation has driven the search for a more effective therapy that can help restore visual acuity in patients with diabetic macular edema. Ranibizumab (trade name Lucentis) is a result of such research. Ranibizumab is a monoclonal antibody, which inhibits VEGF-A and thereby prevents the angiogenesis of excessive, weak vasculature that would otherwise leak plasma into the retinal layers & macula. It is among the first generation of promising treatments that may help restore vision in those with diabetic macular edema but is also relatively new and requires further examination.

OBJECTIVE

Therefore the objective of this selective review is to determine whether or not ranibizumab improves BCVA in adults with diabetic macular edema.

METHODS

Criteria

To examine this question, this paper focuses on adults (age ≥ 18 years old) with a diagnosis of diabetic macular edema. Interventions that were considered in a literature search included intravitreal injections of ranibizumab, placebo injections, and focal laser photocoagulation, provided the study had at least one arm including ranibizumab as an intervention and one without. The quantifiable, objective outcome used was BCVA as assessed through the Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity chart. Types of studies considered were randomized controlled trials; however one study that was selected and included in data analysis was a case control study.

Data Sources

A search of English-language published, primary literature was performed through various, reputable search engines to include MedLine, PubMed, and Ovid. Key words used in the

search included: Lucentis, ranibizumab, diabetic macular edema, and diabetic retinopathy. A Cochrane systematic review regarding the efficacy of ranibizumab on visual acuity in diabetics with macular edema was found dating 2009; therefore only articles published following this date were considered in this review as part of the inclusion criteria. Exclusion criteria included the effects of ranibizumab on other similar ophthalmologic pathologies and studies using subjective metrics to gauge the efficacy of this novel monoclonal antibody.

Ultimately, three studies were selected: a double-blind randomized controlled trial conducted by Massin et al in 2010 (i.e. the RESOLVE study)[5], another double-blinded randomized controlled trial conducted by the Diabetic Retinopathy Clinical Research Network (DRCRN) in 2010[6], and a case control study led by Ozturk et al in 2011.[7]

Massin et al published the findings of a multicenter, phase II clinical trial on ranibizumab on its safety and efficacy on study participants with diabetic macular edema. The study was designed as a double-blinded, randomized control trial. The investigators randomized subjects into three arms: 0.3 mg intravitreal injections, 0.5 mg intravitreal injections, and sham treatment as the control group; they then measured best corrected visual acuity in their subjects at various time points to include 12 months following treatment. The study was selected for its quality design and large sample size from different sites.

The 2010 DRCRN study was a multicenter phase III clinical trial conducted as a double-blinded, randomized controlled trial. The investigators compared the following interventions in the study: (1) sham intravitreal injection followed by prompt (within 3-10 days of injection) focal laser photocoagulation; (2) 0.5 mg ranibizumab injection followed by prompt focal laser photocoagulation; (3) 0.5 mg ranibizumab injection followed by deferred (≥ 24 weeks) focal laser photocoagulation; and (4) 4 mg triamcinolone injection followed by prompt focal laser

photocoagulation. Though this selective review seeks to compare treatment of ranibizumab in those suffering diabetic macular edema with those who do not receive it, it was decided that only the first two interventions listed were truly comparable to be able to better attribute therapeutic effect (if any) of ranibizumab compared to placebo. Follow up was performed both at 1 year and 3 years following treatment. To ensure maximal consistency with the RESOLVE study, data points from the 1-year mark was examined in this review. This too was selected for its quality design and large sample size from different sites.

Ozturk et al performed a case control study examining the clinical records of patients with diabetic macular edema who received either ranibizumab or bevacizumab (a similar VEGF inhibitor) and compared improvement in BCVA. The study encompassed 29 eyes of 29 patients, and these patients received either 0.5 mg ranibizumab intravitreal injection or a 1.25 mg bevacizumab intravitreal injection. Both Snellen charts and ETDRS visual acuity charts were used to assess improvements in patient's vision. Due to the limited number of quality studies following 2009, this study was selected not only for its quality but its consistency in measuring outcomes following administration of ranibizumab.

Both the RESOLVE study and the 2010 Diabetic Retinopathy Clinical Research Network study reported mean changes in BCVA with 95% confidence intervals and its associated p-values. The RESOLVE study further reports relative risk values associated with the gain or loss of letters in BCVA. Ozturk et al reported mean & median changes as BCVA values with associated p-values.

Information regarding the inclusion and exclusion criteria as well as specific interventions of the selected studies is summarized in Table 1.

Table 1: Demographics and Characteristics of Included Studies

Study	Type	No. of Participants	Age	Inclusion Criteria	Exclusion Criteria	Withdrawn from Study	Intervention(s)
Massin et al (2010)	Double-blind, randomized control trial	151	63.6	• Age >18 years • Type 1 or type 2 diabetes mellitus • Hb_{A1C} levels that have not substantially fluctuated and are ≤12% • DME with center involvement in at least one eye	• Panretinal, focal peripheral laser photocoagulation within 6 mos • Previous grid/central laser photocoagulation (with exceptions) • Proliferative diabetic retinopathy in the study eye (with exceptions) • Unstable medical conditions (with exceptions) • Systemic corticosteroids within 4 mos • Use of corticosteroids more than 2 / week • Previous participation in a study on anti-angiogenic drugs • Any condition that may introduce confounding factors • Any condition that puts prospective subjects at substantial risk from the studied intervention • Ocular inflammation in either eye or history of cataract surgery in the study eye within 6 mos • Women of childbearing age without sufficient use of contraceptives, pregnant or nursing women	19	Monthly intravitreal injections of ranibizumab (Lucentis™) at 0.3 mg OR 0.5 mg OR sham treatment (pressure with blunt tip of syringe against anesthetized eyes.
Diabetic Retinopathy Clinical Research Network (2010)	Double-blind, randomized control trial	691	63 ± 10	• Best-corrected ETDRS visual acuity of 24 to 78 • Retinal thickening due to DME involving the center of the macula AND assessed to be the main cause of visual loss • Retinal thickness ≥250 µm	• Treatment for DME within the prior 4 months prior to recruitment into the study • Panretinal photocoagulation within the prior 4 mos or anticipated need within next 6 mos • Major ocular surgery within the prior 4 mos • Hx of open-angle glaucoma or steroid-induced IOP elevation • IOP ≥25 mmHg. • SBP >180 mmHg or DBP >110 mmHg • Any cardiac event requiring hospitalization within 4 months before randomization	44	• Sham injection plus prompt focal/grid photocoagulation • Intravitreal ranibizumab plus prompt focal/grid photocoagulation • Intravitreal ranibizumab with deferred focal/grid photocoagulation • Intravitreal triamcinolone plus prompt focal/grid photocoagulation
Ozturk et al (2011)	Case control study	29	56.18 ± 13.07	• Patients with type 1 or 2 diabetes mellitus (DM) • Age ≥ 18 years old • Received only 1 dose injection of bevacizumab and did not attend the scheduled repeated intravitreal bevacizumab injection regimen OR • Among them, patients who visited the retina service after at least 6 months and planned to receive monthly intravitreal ranibizumab injection for DME	• Application of any other intravitreal drug injection elsewhere during the study period • Panretinal, grid, or focal laser photocoagulation within 6 months of studied intervention • Presence of any other macular pathology • Any associated pathology requiring laser or surgical treatment • Intraocular surgery within 6 months of studied intervention • Intravitreal drug injection to the other eye not examined in the research within 6 months of study internvention • Did not attend the first 3 control visits.	0	Monthly intravitreal injections of ranibizumab at 0.3 mg OR 0.5 mg OR sham treatment (pressure with blunt tip of syringe against anesthetized eyes.

OUTCOMES MEASURED

As previously stated, best-corrected visual acuity was measured in all three selected studies with the ETDRS visual acuity chart, an instrument that is similar to the Snellen chart and is used in clinical research assessing visual acuity. The chart, designed by Ferris et al in 1982[8], has become the gold standard in assessing visual acuity in clinical research studies[9] and defines with greater resolution the subtle differences of visual acuity that cannot be captured by the Snellen chart. This metric, known as BCVA, uses the total number of letters that a research subject can read in order to gauge their visual deficit. It can be read from a variety of distances depending on the size of the chart itself. As previously stated, best corrected visual acuity (BCVA) was the outcome measured in each of the three selected studies. In the RESOLVE study, investigators assessed BCVA of study participants at baseline, 1 month, and 12 months post treatment. Similarly, the 2010 Diabetic Retinopathy Clinical Research Network study and Ozturk et al had participants do the same with the ETDRS visual acuity chart.

RESULTS

Efficacy

In the RESOLVE study, at 12 months, the mean BCVA was 10.3 ± 9.1 letters improved from the baseline in patients receiving ranibizumab injections versus the 1.4 ± 14.2 letter decline in the control group ($p<0.0001$). For analysis purposes, continuous data was converted to dichotomous data, and a minimum improvement of 10 letters or more was considered therapeutic improvement in vision. Again at 12 months, 60.8% of individuals receiving the investigated drug experienced this level of improvement compared to the 18.4% of the control group experiencing this improvement. These values demonstrate a clear efficacy of the investigational new drug in the improvement of best corrected visual acuity.

The authors of the DRCRN study also reported treatment effects as continuous data, which was converted to dichotomous data for this selective review. Mean change in BCVA in study participants receiving ranibizumab and prompt photocoagulation at 12 months was a gain in 9 ± 11 letters while those in the control arm experienced a gain of 3 ± 13. The difference in mean change was reported to be a range of +3.2 to +8.5 with intravitreal ranibizumab injections at a 95% CI ($p < 0.001$). When comparing efficacy of ranibizumab versus control in the two prompt photocoagulation arms, approximately 50.8% of diabetics receiving ranibizumab enjoyed a 10 letter or more increase in BCVA compared to the 27.6% among the control group. Though both arms received focal photocoagulation, the relative benefit increase (RBI) clarifies the proportional effect of ranibizumab at an 84.1% increase. Additional figures on treatment effects follow in Table 2.

Ozturk and his colleagues performed a case control study, providing less substantial but nonetheless meaningful data. The study found pretreatment mean score to be 52.29 ± 17.76 and posttreatment scores to be 60.52 ± 18.44, with a median improvement from 53 to 66 ($p < 0.001$).

Table 2: Treatment Effects of Ranibizumab Injections in Diabetic Macular Edema Assessed by BCVA

STUDY	CER (%)	EER (%)	ABI (%)	RBI (%)	NNT (n)
RESOLVE Study	18.4	60.8	42.4	230	2.36 ≈ 3
2010 Diabetic Retinopathy Clinical Research Network Study	27.6	50.8	23.2	84.9	4.31 ≈ 5
2011 Ozturk et al*	n/a	n/a	n/a	n/a	n/a

* Data from case control study with limited results. Median BCVA improvement from 53 to 66 ($p < 0.001$)

Safety

As previously stated, the RESOLVE study also examined the safety profile of ranibizumab in study participants differentiating serious adverse events (SAE) and adverse events (AE) with subgroups of ocular events versus non-ocular events. Approximately 3.9% of subjects randomized into ranibizumab injections experienced ocular SAE (e.g. vitreous

hemorrhage) versus the 0% among those in the control arm. Seventy-eight (78.4) percent of study participants in the ranibizumab arms experienced ocular AE (i.e. eye pain, conjunctival hemorrhage, and increased intraocular pressure); fifty-seven percent of those in the control arm experienced the same ocular AE. Non-ocular AE and SAE demonstrated similar trends with a likelihood of these events to occur with those receiving ranibizumab. It should be noted that the investigators did not attribute all reported SAE & AE to the effects of the drug (e.g. only 60.7% experienced ocular AE attributed to ranibizumab by the investigators in contrast to the reported total 78.4 %). Additional harm effects are reported along with those of the other selected studies in Table 3.

With regard to safety in the 2010 DRCRN study, the investigators found no difference in the frequency of systemic, nonocular adverse events and serious adverse events; therefore only ocular AE & SAE are considered and examined in this review. The investigators also did not differentiate between an AE and SAE and, as in other studies, counted the number of events as opposed to the number of individuals experiencing these deleterious effects thereby altering the calculated RRI, ARI, and NNH. These calculated values, seen in Table 3, actually show negative values suggesting that ranibizumab intravitreal injections would actually reduce risk and harm to subjects without them.

Safety and adverse events were not addressed in the study conducted by Ozturk et al.

Table 3: Harmful Effects of Ranibizumab Injections in Diabetic Macular Edema Assessed by AE / SAE

STUDY	CER (%)	EER (%)	ARI (%)	RRI (%)	NNH (n)
RESOLVE Study (Ocular SAE)	0	3.9	3.9	n/a	25.6 ≈ 26
RESOLVE Study (Ocular AE)	57.1	78.4	21.3	37.3%	4.69 ≈ 5
2010 Diabetic Retinopathy Clinical Research Network Study (Ocular AE & SAE)	31	21	-32.3	-10	-10
2011 Ozturk et al†	n/a	n/a	n/a	n/a	n/a

† Adverse events not assessed or studied in this investigation

DISCUSSION

Before conclusively addressing whether or not ranibizumab is indeed effective restoring diminished sight in diabetics with macular edema, it is worthwhile to consider its flaws. For example, it should be noted that the two randomized controlled trials demonstrate the distinct possibility of worsening visual acuity. The RESOLVE study demonstrated that at least 7.8% experienced worsening visual acuity; the 2010 DRCRN study reported up to an 11% in subjects receiving ranibizumab and prompt focal photocoagulation. In clinical practice, these numbers may be high enough to warrant a great degree of caution in considering this treatment.

There are additional considerations to using ranibizumab as treatment for diabetic macular edema. During the analysis and writing of this selective review, the FDA recently approved its indication in the treatment of diabetic macular edema on 10 August 2012[10]; therefore its novelty and projected length of time being on patent is likely to keep the price high. As of 2006, a 0.5 mg dose of ranibizumab (wholesale price) cost $1,950 and likely has not changed substantially.[11] The FDA indication is for 0.3 mg per month, which would likely cost approximately $1,170. Although Genentech attempts to mitigate cost, it may be some time before health insurance companies become willing to cover any portion of these astronomical costs for its plan participants.

Ranibizumab also faces a competitor from the same manufacturer, bevacizumab (trade name Avastin) yet another VEGF inhibitor. Although the FDA does not approve its use in diabetic macular edema, studies such as the aforementioned Ozturk et al investigation have explored its off-label use with similar efficacy. Its cost ($17 to $50 per injection) also makes it substantially more appealing to prescribing practitioners.[11] As it stands, ranibizumab does not lack challenges in its future as a therapeutic option for diabetic macular edema.

CONCLUSION

Having considered the results of these studies and limitations of the drug itself, this selective EBM review concludes that ranibizumab is indeed effective in improving best corrected visual acuity in diabetic macular edema. This monoclonal antibody is not absolutely benign nor is it reasonably affordable by most individuals in the United States, but since curative therapy is lacking, ranibizumab and similar medications may represent the promise of eventual restored sight and pave the way for future generations of similar therapies.

The future direction of research will likely involve improved and more efficient means of engineering and compounding the medication in a manner that reduces costs and improves its safety profile since monoclonal antibody therapy remains costly,[13] which may prohibit patients and providers from accessing this effective therapeutic agent. Such research would fall under the purview of biomedical and biomedical engineering research to find cheaper methods of compounding and mass-producing ranibizumab.

Concurrent research should expand the inclusion criteria of previous clinical research studies and to begin minimizing exclusion criteria to establish a clearer safety profile. Since patients with diabetic macular edema will likely have other comorbidities, conducting clinical research in these populations with other chronic pathologic processes will clarify the boundaries in which providers may prescribe and administer this therapy. Until such research is complete, its use must be carefully monitored to ensure an efficacy consistency with prior phase II & III trials as well as fully determine its true safety profile as it is used outside a controlled setting.

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