In Adult Patients With Diabetic Macular Edema Are Intravitreal Bevacizumab Injections More Effective Than Laser Therapy at Improving Best-Corrected Visual Acuity?

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In Adult Patients with Diabetic Macular Edema are Intravetrial Bevacizumab Injections more Effective than Laser Therapy at Improving Best-Corrected Visual Acuity?

Heather Bladek, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 20, 2013
Abstract

**Objective:** The objective of this selective EBM review is to determine whether or not in adult patients with diabetic macular edema intravitreal bevacizumab injections are more effective than laser therapy at improving best-corrected visual acuity.

**Study Design:** Review of three English language non-blinded randomized control trials from 2010 and 2012.

**Data Sources:** Non-blinded randomized control trials comparing intravitreal bevacizumab injections to macular laser therapy found using Pubmed and EBSCOhost web databases. All articles were published in peer-reviewed journals.

**Outcomes Measured:** The primary outcome of best-corrected visual acuity (BCVA) was measured using the Early Treatment of Diabetic Retinopathy Study (ETDRS) protocol and visual acuity charts and Snellen visual acuity charts at 6, 12, and 24 months in their respective studies.

**Results:** When comparing macular laser therapy to intravitreal bevacizumab injections the patients receiving the injections had a statistically significant ($P > 0.05$) increase in BCVA at 1, 12, and 24-month time points. At 24 months the proportion of patients who gained 10 or more letters was 49% for the bevacizumab group and 7% in the laser therapy group.

**Conclusion:** Although macular laser therapy is the current standard of care for diabetic macular edema (DME), it has been proven to produce inferior clinical outcomes alone when compared with intravitreal bevacizumab injections and other monoclonal antibodies. Long-term use of bevacizumab should be considered as an initial treatment modality for DME to not only halt vision loss, but restore vision as well.

**Key Words:** DME & Bevacizumab & Laser Therapy
Introduction

Type II diabetes is a metabolic disorder characterized by inappropriate hyperglycemia due to the occurrence of insulin resistance at a cellular level and ultimately inadequate insulin secretion from the pancreas. The cornerstone of treatment consists of strict glycemic control via insulin or oral agents as well as aggressive hypertension and hyperlipidemia treatment and monitoring. When diabetes is poorly controlled it can lead to an array of micro and macro vascular complications including retinopathy, neuropathy, and coronary artery disease.

One such complication, diabetic macular edema, occurs when there is retinal thickening due to micro vascular changes compromising the blood-retinal barrier. This causes an increased permeability of the capillaries leading to leakage of plasma into the surrounding retina causing edema. \(^1\) Vascular endothelial growth factor (VEGF) and other inflammatory markers such as cytokines also play a role in retinal edema. \(^1\)

Diabetes is a leading cause of blindness, with diabetic retinopathy becoming the leading cause of preventable blindness in the United States. This amounts to countless visits to primary care providers per year and an increase in specialist appointments with DME patients encountering the ophthalmologist 7.9 times per year. \(^4\) This translates into a 31% increase in healthcare costs for this patient population already heavily burdened by their chronic condition. \(^3\) The overall result is increased health care spending is illustrated by data that the total estimated cost of diabetes in 2012 was $245 billion. \(^2\)

The current treatment paradigm for diabetic macular edema is to optimize glycemic and hypertensive control to preserve visual acuity and begin laser photocoagulation therapy when ophthalmic exam reveals abnormalities. Laser therapy is
initiated when the disease process is clinically significant classified by retinal thickening and hard exudates on funduscopic exam.\textsuperscript{8} Adjunct medications include intravitreal triamcinolone acetonide injections, anti-VEGF therapy in the form of monoclonal antibodies, and intravitreal corticosteroid injections.\textsuperscript{8}

Currently laser photocoagulation therapy is the standard of care, but this procedure only halts further vision loss from the time of diagnosis, which is usually after significant damage has occurred. Other treatment modalities are aimed at restoring vision lost prior to diagnosis and can be utilized earlier in the disease process to reclaim visual acuity and quality of life.

**Objective**

The objective of this systematic review is to determine whether or not in adult patients with diabetic macular edema intravitreal bevacizumab injections are more effective than laser therapy at improving best-corrected visual acuity.

**Methods**

All three studies selected for this review focused on a population of adult patients greater than 40 years of age with a diagnosis of diabetic macular edema. The interventions under investigation are repeated intravitreal bevacizumab injections versus the comparison group of laser photocoagulation therapy. The outcome measured in all three studies was best-corrected visual acuity. Two of the studies utilized the Early Treatment of Diabetic Retinopathy Study (ETDRS) protocol, which is the gold standard for visual acuity measurement for clinical trials. The third study used a traditional Snellen visual acuity chart and the results were reported in logMAR notation. All three studies chosen for this review were non-blinded randomized controlled trials.
The author completed a search during the time period of January through February of 2013 using Pubmed and EBSCOhost web databases. The key words used during the search were “Diabetic Macular Edema” and “Bevacizumab” and “Laser Therapy”. All three articles were published in English between 2010 and 2012 in peer-reviewed journals. The studies were selected based on their relevance to the clinical question posed and focused on outcomes that were patient oriented (POEMS; patient outcome evidence that matters). Only articles that investigated laser therapy and intravitreal bevacizumab injections were utilized and had to exclude other treatment modalities.

Inclusion criteria include studies that were randomized, controlled, prospective, and focused on patient oriented outcomes (POEMS). Exclusion criteria were trials with patients less than 18 years of age, macular edema due to causes other than diabetes, and primary measurements of disease oriented outcomes (DOE’s). Summary of statistics reported or used include P-values, RBI, ABI, NNT, paired t-test, and change from baseline.
Table 1: Demographics and Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th># Pts</th>
<th>Age (yrs)</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>W/D</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michaelides (2010)</td>
<td>RCT</td>
<td>80</td>
<td>40-86</td>
<td>M or F ≥18 yo, DM, (BCVA) in the study eye between 35 and 69 ETDRS letters at 4 mm, DME with CMT on OCT ≥270 micrometers, at least 1 prior MLT</td>
<td>Macular ischemia, macular edema due to a cause other than DME, any tx for DME in preceding 3 months, significant extraocular disease, A1c&gt;11%</td>
<td>2</td>
<td>Laser therapy or intravitreal bevacizumab injections</td>
</tr>
<tr>
<td>Rajendram (2012)</td>
<td>RCT</td>
<td>80</td>
<td>40-86</td>
<td>M or F ≥18 yo, DM, (BCVA) in the study eye between 35 and 69 ETDRS letters at 4 mm, DME with CMT on OCT ≥270 micrometers, at least 1 prior MLT, no anti-VEGF tx in fellow eye in previous 3 months</td>
<td>Macular ischemia, macular edema due to a cause other than DME, any tx for DME in preceding 3 months, significant extraocular disease, A1c&gt;11%</td>
<td>19</td>
<td>Laser therapy or intravitreal bevacizumab injections</td>
</tr>
<tr>
<td>Solaiman (2010)</td>
<td>RCT</td>
<td>42</td>
<td>42-72</td>
<td>CSME with CMT on OCT ≥350 micro meters, no hx injection, surgical intervention, or laser therapy</td>
<td>Macular ischemia, history intraocular surgery in the previous year, opacity of the optical media as cataract or vitreous hemorrhage</td>
<td>0</td>
<td>Laser therapy or intravitreal bevacizumab injections</td>
</tr>
</tbody>
</table>

Outcomes Measured

In all three studies the primary outcome measured was best-corrected visual acuity. In two of the studies the Early Treatment of Diabetic Retinopathy Study (ETDRS) protocol was chosen which uses an ETDRS visual acuity chart that has a more linear progression than standard eye charts. The visual acuity results were reported in letter
count notation. The third study utilized a traditional Snellen chart and reported their results in LogMAR notation.

Results

Two of the randomized controlled trials, 12 and 24-month data reports for the “BOLT Study”, evaluated the efficacy of intravitreal bevacizumab injections versus macular laser therapy in adult patients with clinically significant diabetic macular edema with the use of dichotomous data. The third trial made the same comparison with the use of continuous data.

In Michaelides et al 80 eyes were stratified according to BCVA and randomized into treatment and comparison groups. All participants had no clinically significant differences at baseline with regards to demographic characteristics, BP, HbA1c, BCVA, and retinopathy grading. Only duration of DME varied between the two groups with mean duration in months of 162 in the bevacizumab group and 177 in the laser group. In the laser arm 38 eyes underwent macular laser treatment at baseline and were followed every four months with a final visit at 12 months. Patients received an average of 3 laser treatments of which the decision was made at each follow up visit to treat if clinically indicated according to ETRDS guidelines. In the bevacizumab arm 42 eyes underwent injections at baseline, 6 and 12-week time points. Follow up was done every 6 weeks with subsequent injections guided by OCT-based protocol with patients receiving an average of 9 injections. At each follow up BCVA was measured.

In this study dichotomous data was utilized with intention-to-treat analysis. The relative benefit increase (RBI), absolute benefit increase (ABI), and numbers needed to treat (NNT) were calculated using efficacy rates from the bevacizumab and laser therapy
arms of the trial. These values we derived from experimental event rate (EER) and controlled event rate (CER) using clinical success percentages defined as gaining greater than 10 ETRDS letters from baseline. These results are summarized in Table 2. All statistical analysis was performed with a confidence interval (CI) of 95%. The bevacizumab group not only had a higher clinical success rate, but also at the 12-month time point the mean change in BCVA yielded a P value of 0.002. Two patients in the laser arm did not complete the 12-month follow up, however their 32-week data was carried forward in the intention-to-treat analysis.

Table 2: Treatment versus Control Improvement in BCVA – 12 Month

<table>
<thead>
<tr>
<th></th>
<th>CER</th>
<th>EER</th>
<th>RBI</th>
<th>ABI</th>
<th>NNT</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% patients gaining &gt;10 letters</td>
<td>0.079</td>
<td>0.31</td>
<td>2.92</td>
<td>0.23</td>
<td>4.3</td>
<td>0.01</td>
</tr>
</tbody>
</table>

In Rajendram et al, the same 80 eyes from Michaelides et al were continued to a 24-month time point. Fifteen patients did not enter the second year of the study, therefore demographic and health characteristics were compared among the remaining participants to assure there were still no significant differences. In the laser arm 37 patients received an average of 1 additional treatment and were followed up at 4-month intervals. In the bevacizumab arm 28 patients received an average of 1 additional intravitreal injection and were followed up at 6-week intervals. The decision to undergo re-treatment was guided by the same protocols as the previous study and BCVA was measured at each follow up.

The same intention-to-treat analysis with dichotomous data was carried through to the 24-month time point. Experimental event rate (EER) and controlled event rate (CER) were calculated using clinical success percentages defined as gaining greater than 10
ETRDS letters from baseline. The results are summarized in Table 3. All statistical analysis was performed with a confidence interval (CI) of 95%. In the bevacizumab group at 2 years the percentage of patients with visual improvement was 49% compared to 7% in the laser group, continuing the trend from the previous study. The change in BCVA from baseline was a mean gain of 8.6 letters for the bevacizumab group versus a mean loss of 0.5 letters in the laser group reaching statistical significance (P = 0.05).

Table 3: Treatment versus Control Improvement in BCVA – 24 Month

<table>
<thead>
<tr>
<th>% patients gaining &gt;10 letters</th>
<th>CER</th>
<th>EER</th>
<th>RBI</th>
<th>ABI</th>
<th>NNT</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.07</td>
<td>0.49</td>
<td>6</td>
<td>0.42</td>
<td>2.4</td>
<td>0.001</td>
</tr>
</tbody>
</table>

In Solaiman et al 62 eyes were randomized into treatment and comparison groups. Among all participants, demographic characteristics of average age, duration of diabetes, BCVA, and extent of macular edema were similar between the two groups. Only stage of retinopathy varied significantly with 5 participants in the laser group with nonproliferative diabetic retinopathy (NPDR) versus 6 with proliferative diabetic retinopathy (PRD). In the bevacizumab group similar trends were noted with 6 participants diagnosed with NPDR versus 5 with PDR. In the laser arm 19 eyes underwent 1 laser therapy treatment at baseline and were follow up at 1, 3, and 6 month intervals. In the bevacizumab group 21 eyes received one intravitreal injection at baseline and were followed up at the same time intervals. BCVA was measured at all visits.

Continuous data was reported, but could not be converted to dichotomous data. At the 1 month follow up the mean improvement in BCVA from baseline was 38% calculated using a paired t test. A P value of < 0.05 was reported for the bevacizumab group with no significant differedenced noted in the laser group. At 3 months there was no
statistical significance in BCVA in either group and at 6 months both groups regress to approximately baseline values for visual acuity, all yielding a P value > 0.05. The results are summarized in Table 4. This data suggests that improvement in BVCA was transiently seen at only 1 month with intravitreal bevacizumab injections.

Table 4: Change Over Time in Mean BCVA

<table>
<thead>
<tr>
<th>Duration</th>
<th>Laser Therapy</th>
<th>Bevacizumab Injections</th>
<th>P-Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.84</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>1 month</td>
<td>0.83</td>
<td>0.52</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>3 months</td>
<td>0.75</td>
<td>0.71</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>6 months</td>
<td>0.85</td>
<td>0.82</td>
<td>P &gt; 0.05</td>
</tr>
</tbody>
</table>

Discussion

This systematic review analyzed three RCT’s to determine if intravitreal bevacizumab injections are more effective than laser therapy at improving BCVA in patients with DME. Overall the data demonstrates greater efficacy with repeated bevacizumab injections over laser therapy, which is the current standard of care. The data collected in two of the studies showed statistical significance at improving visual outcomes at 1 and 2 years.

Bevacizumab was first introduced as a treatment for various neoplastic processes, most notably colorectal cancer. Due to its mechanism of action as a VEGF inhibitor its use began unlabeled for age-related macular degeneration. Bevacizumab has various black box warnings related to intravenous administration, but they do not apply to the local ocular injections. Ophthalmic adverse events occur less than 2% of the time, most commonly vision loss due to endophthalmitis. There are no contraindications to this medications use, however the cost is significant at $761 per 4 mL without a generic available.
There were various limitations plaguing all three studies. All three trials recruited and tested a small sample of patients to investigate the treatment and comparison interventions. In Rajendram et al 15 patients did not wish to continue with the study illustrating the difficulty in maintaining a population over a long period of time that requires significant follow up. Another hindrance was the relatively short follow up period, ranging from 6 to 24 months, related to the disease process of macular edema. This decreases the strength of the finds in treatment of DME globally. Michaelides et al argues that due to the chronicity of DME intravitreal bevacizumab injections may be impractical. This is due to a combination of factors including cost and need for repeat injections to maintain positive visual outcomes. It is hopeful that the 24-month report showed a decreased frequency of injections was necessary to maintain visual acuity. This could aid healthcare providers in choosing this as a treatment option for patients thereby greatly increasing their quality of life.

Solaiman et al specifically had more limitations that the other trials. The study did not take into account cofounding factors such as degree of glycemic control, hypertension, and renal disease. All can impact the severity of DME, facilitate more rapid progression of the disease process, and indicate poor compliance practices with treatment regimens. Another factor limiting the strength of the results was that both the treatment and comparison groups had a disproportionate amount of patients with NPDR. This stage of retinopathy is less sensitive to VEGF dependent factors suggesting bevacizumab would be less therapeutic thereby placing that group at a disadvantage. This study also had deficits in validity due to its weak statistical analysis. It lacked a confidence interval,
specific P values were not calculated, and analysis was not performed on an intention-to-treat basis.

**Conclusion**

In conclusion, this systematic review of three RCT’s demonstrates that intravitreal bevacizumab injections are more effective than laser therapy at improving best-corrected visual acuity in adults with diabetic macular edema. The data collected in two of the studies showed statistical significance at improving and maintaining visual outcomes through to a 2-year time point. Laser therapy is the current standard of care and this new body of evidence suggests bevacizumab should be strongly considered for implementation early on in the disease process. Further studies are warranted to evaluate the synergistic effect of laser therapy combined with bevacizumab injections to improve visual acuity and halt further vision loss in this patient population.
References


