Debate Pro: Intravitreal injections for “nontractional” diabetic macular edema

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Retina consultant Watany Eye Hospital

Why are we debating?

- Before 2005 we had only 2 tools to treat DME:
  - Burn the macula: Destructive thermal laser.
  - Invade the macula: invasive vitrectomy!!!
Why are we debating?

- The retina society had all the time to prove that vitrectomy is the solution!!!!
- From 1992 (H. Lewis) till 2005 (first off label of avastin) !!!!

Why are we debating?

- The era of Pharmacologic treatment with intravitreal agents is relatively young (10 years) but why it happened and why we needed it?
Why are we debating?

- Because vitrectomy is not effective enough!
- Because we understand the cycle of DME more thoroughly!
- Because intravitreal agents are effective!

Why vitrectomy is not good enough?
Why vitrectomy is not good enough?

- In 2015, vitrectomy has only a limited role in the treatment of most cases of nontractional diabetic macular edema (DME).

Why vitrectomy is not good enough?

- The DRCR.net evaluated the use of vitrectomy for DME in a prospective multicenter cohort study (n= 241).
Why vitrectomy is not good enough?

- Unfortunately, however, in the primary cohort (n=87) in these eyes with “vitreomacular traction”, which one might think would have the best results—the visual acuity results were disappointing!!!

Why vitrectomy is not good enough?

The authors concluded that:
- 28% to 49% of eyes similar to those in the study were likely to have improvement of visual acuity
- 13% to 31% were likely to experience worsening!!
Why vitrectomy is not good enough?

- A subset analysis showed that peeling of the epiretinal membrane (ERM) and internal limiting membrane (ILM) was associated with thinning of the retina.

Why vitrectomy is not good enough? DRCR.net **conclusion**

- The role of vitrectomy compared with other approaches in the management of DME **remains uncertain** because the potential benefits and risks have not been clearly defined in the context of long-term, adequately sized, randomized clinical trials.
Am I too biased … ? Let us look more carefully

Studies supporting Vitrectomy study involving 27 eyes
Studies supporting Vitrectomy study involving 332 patients

LONG-TERM FOLLOW-UP OF VITRECTOMY FOR DIFFUSE NONTRACTIONAL DIABETIC MACULAR EDEMA

Conclusions: Pars plana vitrectomy with and without internal limiting membrane peeling appears to be beneficial in eyes with diffuse nontractional diabetic macular edema and its effectiveness is maintained long term.

Results: Postoperative follow-up ranged from 12 to 170 months (mean, 74.0 months). Five year follow-up data were available for 356 (71.8%) of 496 eyes. Mean preoperative best-corrected visual acuity significantly increased from 0.19 (20/105) to 0.32 (20/63) at 1 year after surgery (P < 0.0001), and 0.30 (20/67) at the final visit (P < 0.0001). The final best-corrected visual acuity improved in 256 (52.7%) of the 486 eyes, remained unchanged in 152 eyes (31.3%), and worsened in 78 eyes (16.0%). Postoperative major complications included neovascular glaucoma in 19 eyes (3.9%), recurrent vitreous hemorrhage in 10 eyes (2.1%), hard exudate deposits in the center of the macula in 21 eyes (4.2%), and glaucoma in 22 eyes (4.5%).

Studies supporting Vitrectomy
Studies supporting Vitrectomy

- 50% success rate in the best scenario... and you call this success!!!

Still am I biased???
Studies Not supporting Vitrectomy

They concluded: in the presence of DME with large intraretinal cysts > 390 microns and an enlarged FAZ, the patient should not be treated with vitrectomy with ILM peeling, because this may induce a “floor effect” or, in other words, a subfoveal atrophy, and subsequent visual deterioration.

In these cases, the recommended therapeutic approach is with intravitreal anti-VEGF drugs!!
Studies Not supporting Vitrectomy
18 patients

In this prospective, comparative study of PPV with and without ILM peeling for diffuse clinically significant macular edema, structural improvement was seen but with limited visual improvement after ILM peeling.
Studies Not supporting Vitrectomy

24 eyes

**Conclusions:** Pars plana vitrectomy with ILM peeling was associated with a reduction in DME when measured by OCT in the majority of eyes, but visual acuity outcomes showed minimal improvement compared to baseline.

These results suggest the efficacy of PPV with ILM peeling for eyes with DME has not been well established and should be reserved for therapy with selected cases.
### Other Studies (No ILM peeling)

#### Table 3. Vitrectomy Without Peeling Internal Limiting Membrane, With or Without a Taut Hyaloid

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. Eyes</th>
<th>ILM Peel</th>
<th>Taut Hyaloid Complete</th>
<th>Partial</th>
<th>Persisted</th>
<th>Improved</th>
<th>Unchanged</th>
<th>Worse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ikeda</td>
<td>1989</td>
<td>3</td>
<td>No</td>
<td>No</td>
<td>100%</td>
<td>0</td>
<td>0</td>
<td>100%</td>
<td>0</td>
</tr>
<tr>
<td>Ferrari</td>
<td>1999</td>
<td>9</td>
<td>No</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>No</td>
<td>N/A</td>
</tr>
<tr>
<td>Yang</td>
<td>2000</td>
<td>14</td>
<td>No</td>
<td>N/A</td>
<td>100%</td>
<td>0</td>
<td>0</td>
<td>100%</td>
<td>0</td>
</tr>
<tr>
<td>Yamamoto1,2</td>
<td>2003</td>
<td>84</td>
<td>No</td>
<td>N/A</td>
<td>Pre-op 484 μm - post-op 225 μm</td>
<td>45%</td>
<td>40%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Patridge</td>
<td>2004</td>
<td>12</td>
<td>No</td>
<td>N/A</td>
<td>Pre-op 314 μm - post-op 280 μm</td>
<td>45%</td>
<td>40%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Yamamoto3,4</td>
<td>2004</td>
<td>19</td>
<td>No</td>
<td>N/A</td>
<td>Pre-op 510 μm - post-op 251 μm</td>
<td>Median 1</td>
<td>Median 1</td>
<td>&lt; ETDRS limit &lt; 20/30</td>
<td>0</td>
</tr>
<tr>
<td>Laik94</td>
<td>2001</td>
<td>21</td>
<td>Yes</td>
<td>No</td>
<td>100%</td>
<td>0</td>
<td>64%</td>
<td>14%</td>
<td>6%</td>
</tr>
<tr>
<td>Park95</td>
<td>2004</td>
<td>59</td>
<td>No</td>
<td>N/A</td>
<td>Pre-op 403 μm - post-op 302 μm</td>
<td>17%</td>
<td>83%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Beda10</td>
<td>2000</td>
<td>5</td>
<td>No</td>
<td>Yes</td>
<td>Pre-op 357 μm - post-op 311 μm</td>
<td>40%</td>
<td>45%</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>Lewis42</td>
<td>1982</td>
<td>13</td>
<td>No</td>
<td>Yes</td>
<td>Pre-op 67 μm - post-op 265 μm</td>
<td>40%</td>
<td>30%</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Harbour11</td>
<td>1986</td>
<td>10</td>
<td>No</td>
<td>7/Yes</td>
<td>60%</td>
<td>0</td>
<td>20%</td>
<td>0</td>
<td>60%</td>
</tr>
<tr>
<td>Pendrass12</td>
<td>2000</td>
<td>16</td>
<td>Yes</td>
<td>6/Yes</td>
<td>30%</td>
<td>45%</td>
<td>25%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Higuchi13</td>
<td>2006</td>
<td>3</td>
<td>Yes</td>
<td>No</td>
<td>Pre-op 64 μm - post-op 244 μm</td>
<td>66.7%</td>
<td>33.3%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Otani14</td>
<td>2002</td>
<td>7</td>
<td>Yes</td>
<td>No</td>
<td>Pre-op 622 μm - post-op 265 μm</td>
<td>67%</td>
<td>32%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Tachibana15</td>
<td>1996</td>
<td>54</td>
<td>No</td>
<td>N/A</td>
<td>98.9%</td>
<td>1%</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Notes:**
- ILM = Internal limiting membrane
- OCT = Optical coherence tomography
- N/A = Not available
- VA = Visual acuity
- ETDRS = Early Treatment Diabetic Retinopathy Study

### Other Studies (ILM peeled)

#### Table 4. Vitrectomy With Internal Limiting Membrane Peeling

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. Eyes</th>
<th>ILM Peel</th>
<th>Taut Hyaloid Complete</th>
<th>Partial</th>
<th>Persisted</th>
<th>Improved</th>
<th>Unchanged</th>
<th>Worse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iwasaki</td>
<td>2005</td>
<td>20</td>
<td>Yes</td>
<td>No</td>
<td>Pre-op 57 μm - post-op 211 μm</td>
<td>50%</td>
<td>35.5%</td>
<td>15.5%</td>
<td></td>
</tr>
<tr>
<td>Aoki</td>
<td>2004</td>
<td>21</td>
<td>Yes</td>
<td>No</td>
<td>Pre-op 68 μm - post-op 271 μm</td>
<td>32%</td>
<td>43%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Dilger16</td>
<td>2004</td>
<td>60</td>
<td>Yes</td>
<td>N/A</td>
<td>Pre-op 553 μm - post-op 221 μm</td>
<td>42%</td>
<td>50%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Grandorfer17</td>
<td>2000</td>
<td>12</td>
<td>Yes</td>
<td>N/A</td>
<td>Pre-op 67 μm - post-op 221 μm</td>
<td>42%</td>
<td>50%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Kolacyzu13</td>
<td>2005</td>
<td>29</td>
<td>Yes</td>
<td>No</td>
<td>Pre-op 67 μm - post-op 221 μm</td>
<td>69%</td>
<td>17%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Kimura113</td>
<td>2005</td>
<td>21</td>
<td>Yes</td>
<td>No</td>
<td>Pre-op 58 μm - post-op 211 μm</td>
<td>67%</td>
<td>33%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Ruskatz22</td>
<td>2004</td>
<td>5</td>
<td>Yes</td>
<td>N/A</td>
<td>Pre-op 67 μm - post-op 221 μm</td>
<td>60%</td>
<td>20%</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>Recchia11</td>
<td>2005</td>
<td>11</td>
<td>Yes</td>
<td>N/A</td>
<td>Pre-op 67 μm - post-op 221 μm</td>
<td>91%</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Shah14</td>
<td>2006</td>
<td>38</td>
<td>Yes</td>
<td>No</td>
<td>Pre-op 486 μm - post-op 520 μm</td>
<td>Mean of 0.06 logMAR units</td>
<td>Mean of 0.06 logMAR units</td>
<td>Mean of 0.06 logMAR units</td>
<td>Mean of 0.06 logMAR units</td>
</tr>
<tr>
<td>Stobie15</td>
<td>2005</td>
<td>25</td>
<td>Yes</td>
<td>No</td>
<td>Pre-op 544 μm - post-op 284 μm</td>
<td>52%</td>
<td>32%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Yannoulez14</td>
<td>2005</td>
<td>12</td>
<td>Yes</td>
<td>No</td>
<td>Pre-op 498 μm - post-op 220 μm</td>
<td>50%</td>
<td>50%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Thomas15</td>
<td>2005</td>
<td>19</td>
<td>Yes</td>
<td>No</td>
<td>Pre-op 403 μm - post-op 330 μm</td>
<td>Mean of 0.06 logMAR units</td>
<td>Mean of 0.06 logMAR units</td>
<td>Mean of 0.06 logMAR units</td>
<td>Mean of 0.06 logMAR units</td>
</tr>
<tr>
<td>Jahn16</td>
<td>2004</td>
<td>33</td>
<td>Yes</td>
<td>No</td>
<td>Pre-op 71 μm - post-op 281 μm</td>
<td>55%</td>
<td>15%</td>
<td>30%</td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- ILM = Internal limiting membrane
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- VA = Visual acuity
- ETDRS = Early Treatment Diabetic Retinopathy Study
Other Studies (with and without ILM peeling)

**Conclusion about PPV for DME**

- The large number of series evaluating the efficacy of vitrectomy (with or without ILM peeling) has yielded **conflicting results** suggesting vast gaps in our understanding of the mechanisms or which subgroups might benefit the most.
Conclusion about PPV for DME

- A significant reduction in foveal thickness has commonly not led to improvement in visual acuity
- indicating that even ILM peeling does not uniformly improve visual outcomes despite favorable anatomic results.

Conclusion about PPV for DME

- The natural history is not uniformly bad, and may parallel results of preliminary surgical series with 22% spontaneous improvement and only 17% deterioration at 1 year in 107 eyes.

Conclusion about PPV for DME

- The serious limitations of all published reports is the lack of a control group!!

Accordingly, only a randomized, controlled trial will clarify the role of vitrectomy or importance of ILM peeling in DME.
Conclusion about PPV for DME

- Until such time, caution is advised regarding visual improvement in patients undergoing vitrectomy for diabetic macular edema in the absence of preretinal traction.

What if vitrectomy fails to resolve DME?

- An unintended consequence of the procedure is that subsequent intravitreal pharmacologic treatment of posterior segment disease may be less effective in vitrectomized eyes !!!!
What if vitrectomy fails to resolve DME?

- Drug diffusion and clearance from the vitreous cavity is more rapid in vitrectomized eyes,
- limiting drug exposure to the retina and reducing treatment success and options.

This was proven in studies in rabbits and humans!!

Potential complications?

- Endophthalmitis,
- Retinal detachment, and proliferative vitreoretinopathy
- Vitreous hemorrhage.
- Progression of nuclear sclerosis

To wrap up Vitrectomy in nontractional DME

- Unpredictable visual success
- Compromise pharmacologic treatment if it fails.
- Potential vision threateneing complications
Intravitreal Pharmacologic agents and the cycle of DME

Algorithm
- The treatment algorithm for DME today may involve numerous options,
- starting with metabolic control
- and proceeding to injection of anti-VEGF agents,
- use of focal laser and scatter laser,
- and perhaps steroid injection
- or some other adjustment of the pharmacologic approach (with a different agent or more frequent application)
Level 1 evidence

- 5 studies that provide level I evidence for intravitreal ranibizumab, alone or in combination with other treatments for DME.
- DRCR (2), restore, rise, ride

Level 1 evidence (long term results)

- We now have 5-year follow-up data from a study by the Diabetic Retinopathy Clinical Research Network (DRCR.net) assessing pharmacotherapeutic treatments for DME in a randomized, prospective setting.
Long term results of Anti VEGF therapy

- Intravitreal Ranibizumab for Diabetic Macular Treatment: 5-Year Randomized Trial Results
  - Michael J. Elman, MD, Allison Ayala, MS, Neil M. Bressler, MD, David Browning, MD, Christina J. Flaxel, MD, Adam R. Glassman, MS, Lee M. Jampol, MD, Thomas W. Stone, MD, for the Diabetic Retinopathy Clinical Research Network

Long term results of Anti VEGF therapy and macular laser treatment
The average visual acuity gain at 1 year was maintained to 5 years concomitant with a progressively diminishing number of treatments.

Multitude of large clinical trials

- The randomized clinical trial Ranibizumab for Edema of the Macula in Diabetes (READ-2) and that of the Diabetic Retinopathy Clinical Research Network (DRCR.net) along with pivotal studies RESOLVE and RESTORE in >1000 patients have established the efficacy and safety of ranibizumab in DME.
Clinical example June 2011

July 2011
December 2013 / 13 months Rx free

Individualized PRN 10 injections/2.5 yrs
Multiple Anti VEGF agents

- Bevacizumab (Avastin). [BOLT trial]
- Ranibizumab (Lucentis).
- Aflibercept (Eylea). [DA VINCI, VIVID, and VISTA trials]
- DRCR.net Protocol T [head to head comparison]

Being refractory to one anti-VEGF agent does not mean will be refractory to other anti VEGF agents!

- Shift from Bevacizumab to Ranibizumab.
- Or from Ranibizumab to Bevacizumab.
- Or from Ranbizonab to Aflibercept
Comparison: Refractory to one agent and shifted to another agent

Safety
Safety

- From the literature available to date, there seem to be no greater systemic risks to DME patients receiving intravitreal anti-VEGF injections.

**SYSTEMIC SAFETY OF RANIBIZUMAB FOR DIABETIC MACULAR EDEMA**

Meta-analysis of Randomized Trials

**YASUKO YANAGIDA, MD, TAKASHI UEWA, MD, PhD**

**Results:** Six trials with 2,459 patients were included.

**Conclusion:** Ranibizumab for diabetic macular edema is considered safe when the patients are carefully selected based on systemic vascular conditions and it is used on a pro re nata basis. Further evaluation is necessary on more intensive use or on high-risk patients.

**RETINA** 34:629–635, 2014
Safety

- Ocular side effects including endophthalmitis and retinal detachment are very rare if proper injection technique is adopted.

Cost

- May be an issue with repeated injections.
- However, we do have a cheap and efficacious alternative…. Avastin or off label triamcinolone acetonide!
Other agents

We can use alternative agents

- DME is more than a VEGF driven disease—it is multifactorial.
- There is no doubt that inflammation plays an important role in DME especially chronic cases.
Multiple agents

- Anti VEGF agents
- Steroids
  - Triamcinolone acetonide
  - Fluocinolone acetonide.
  - Dexamethasone implant (Ozurdex)

Steroids

- It is not just the type of steroid that we choose,
- but the dose of the steroid as well as
- the stage of disease in which we use the steroid that determines its efficacy.
- The same steroid may have different effects depending on its dose and the pharmacokinetics of how it is delivered.
Steroids

- A bolus of a drug may work very differently than drug released in a sustained zero order or near zero order kinetics distribution.

DME cycle

- Early in the course of diabetes, hyperglycemia is present, and the inflammatory component starts the VEGF cycle.
DME cycle

- It is the chronic phase of DME where sustained-release steroids will have the biggest role in conjunction with debulking VEGF.
- Combination therapy may help us keep patients stable for long periods of time and achieve better visual results.

DME cycle

- 6/30/2011 – VA 20/60
  - Rx: Ozurdex
- 6 wks post Ozurdex
  - VA 20/40
Intravitreal drugs

- Now there is a treatment that has a good chance of substantially improving their vision.
- Superiority of Ranibizumab injection as monotherapy
- Anti-VEGF agents are the first-line treatment for center-involving DME worldwide.
- There is a reduction in treatment burden with injections over time.
- The DRCR.net Protocol T will provide us with some head-to-head data evaluating ranibizumab, bevacizumab, and aflibercept.

so if you have a patient with **nontractional** DME...
Subject him to surgery?

- Unpredictable results.
- No level 1 evidence!
- Unknown timing.
- Compromise future pharmacologic treatment
- Possible complications e.g. RD and vitreous hemorrhage
- Co-morbidities (cataract).
- Not every one can perform

OR inject intravitreal agent

- Level 1 evidence with long term results.
- Multiple agents acting on different pathways and chemokines.
- Different and flexible dosing regimen.
- Reversible and interchangeable.
- Anyone can do with short learning curve... can be done in any remote village.
- Effective and safe.
conclusion

- Diabetic macular edema is a medical multifactorial disease due to a metabolic disease and NOT a surgical problem.
- Vitrectomy should be considered only if there is evident traction.

Thank you!