Lucentis and Avastin in Diabetic Retinopathy

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Declarations

- I have received research funding and consultancy fees from Novartis UK, Bayer UK, Allergan, Pfizer and Alimera.

- I have sat on the NICE appraisal panels representing RCOphth and RNIB.
Lucentis and Avastin – what you need to know

- What are they?
- Similarities but important differences
- How are they given?
- Indications for use DR?
- What is the evidence?
- A case example
- Future developments.
What are they?

- Lucentis = ranibizumab
- Avastin = bevacizumab
- Both are humanised monoclonal antibodies against vascular endothelial growth factor (Anti-VEGF)
  - *mab* = *monoclonal antibody*
  - *zu* = *humanised*
VEGF (VASCULAR ENDOTHELIAL GROWTH FACTOR)

- VEGF protein important in repair of tissues
- VEGF in vivo promotes angiogenesis and increased permeability of retinal blood vessels
- Deregulated, abnormal VEGF expression is found in tumours, retinal disorders etc
- VEGF A is important isoform
Lucentis and Avastin – similar but important differences.

<table>
<thead>
<tr>
<th></th>
<th>Ranibizumab</th>
<th>Aflibercept</th>
<th>Bevacizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Size</strong></td>
<td>48 kDa(^{25})</td>
<td>97-115 kDa(^{27})</td>
<td>149 kDa(^{30})</td>
</tr>
<tr>
<td><strong>Structure</strong></td>
<td>Antibody fragment</td>
<td>Recombinant fusion protein</td>
<td>Full-length antibody</td>
</tr>
<tr>
<td><strong>Target</strong></td>
<td>All VEGF-A isoforms(^{26})</td>
<td>All VEGF-A isoforms, VEGF-B and placental growth factor(^{27})</td>
<td>All VEGF-A isoforms(^{30})</td>
</tr>
<tr>
<td><strong>Half-life in humans</strong></td>
<td><strong>Ocular</strong> 9 days(^{25})</td>
<td>Unknown 4-5 days(^{28,29})</td>
<td>6.7 days(^{31})</td>
</tr>
<tr>
<td></td>
<td><strong>Systemic</strong> ~2 hours(^{25})</td>
<td>20 days(^{30})</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ranibizumab</th>
<th>Bevacizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LUCENTIS</strong></td>
<td>AVASTIN</td>
</tr>
<tr>
<td>Developed for ocular use only</td>
<td>Developed for bowel cancer</td>
</tr>
<tr>
<td>Given by intravitreal injection</td>
<td>Given by intravitreal injection</td>
</tr>
<tr>
<td>Licensed for eye use</td>
<td>Unlicensed for eye use</td>
</tr>
<tr>
<td>NICE approved</td>
<td>Not appraised by NICE</td>
</tr>
<tr>
<td>Expensive drug c.£420</td>
<td>Cost variable £5-100</td>
</tr>
<tr>
<td>Extensive evidence</td>
<td>Extensive use but limited evidence</td>
</tr>
<tr>
<td>Safety data and post marketing surveillance programme.</td>
<td>Limited safety data; no post marketing surveillance</td>
</tr>
<tr>
<td>No safety concerns</td>
<td>Probably equally effective as ranibizumab</td>
</tr>
<tr>
<td></td>
<td>Some safety concerns</td>
</tr>
</tbody>
</table>
Bevacizumab concentration in the vitreous and the aqueous humor of the noninjected left eye after intravitreal injection of 1.25 mg/0.05 mL bevacizumab into the fellow eye. Values at day 0 indicate background levels of bevacizumab detection in control animals.

Pharmacokinetics of intravitreal bevacizumab (Avastin®) in rabbits

Christos I Sinapis,¹ John G Routsias,² Angelos I Sinapis,¹ Dimitrios I Sinapis,¹ George D Agrogiannis,³ Alkistis Pantopoulou,¹ Stamatis E Theocharis,⁴ Stefanos Baltatzis,⁵ Efstratios Patsouris,⁶ and Despoina Perrea


Avastin is systemically absorbed and appears in circulation after intravitreal injection
Potential systemic worries with anti-VEGF’s

- We know from AMD….Both drugs are safe but…
- Increase risk of CVA, Myocardial Infarction and Arterio-Thrombotic effects
- In view of systemic absorption of more concern in Avastin
- Increased risks of untoward gastro-intestinal events with Avastin.
- What about in diabetic patients?
- Long term safety issues in diabetic patients-cardiovascular/cerebrovascular events. No significant adverse safety signals to date
How are anti-VEGF’s given?

- Intravitreal injection of drug is most effective way of delivering drug to retina.
- Given in a clean room with local anaesthesia drops
- Safe and effective

Potential risks:
- Endophthalmitis 1 in 1000
- Haemorrhage intraocularly – rare
- Cataract from lens trauma – rare
- Systemic side effects – probably rare
How effective are they?

- Clinical trials
- A case report
The Diabetic Retinopathy Clinical Research Network

Randomized Trial Evaluating Ranibizumab Plus Prompt or Deferred Laser or Triamcinolone Plus Prompt Laser for Diabetic Macular Edema

Supported through a cooperative agreement from the National Eye Institute and the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services EY14231, EY14229, EY018817
Study Rationale

To determine if anti-VEGF therapy alone or in combination with laser, or if triamcinolone in combination with laser, might result in improved outcomes compared with laser alone for treatment of DME, the DRCR.net designed a clinical trial to evaluate 3 treatment modalities for DME in comparison with focal/ grid laser:

- Intravitreal ranibizumab+prompt (within 1 week) focal/grid laser
- Intravitreal ranibizumab + focal/grid laser deferred for at least 24 weeks
- Intravitreal triamcinolone+prompt (within 1 week) focal/grid laser
Mean Change in Visual Acuity at Follow - up Visits

Values that were ±30 letters were assigned a value of 30.

P-values for difference in mean change in visual acuity from sham+prompt laser at the 52-week visit:
- ranibizumab+prompt laser <0.001;
- ranibizumab+deferred laser <0.001;
- triamcinolone+prompt laser =0.31.
PT — “the case of the diabetic groundsman”

- 63 year old, male, caucasian, head groundsman at a local prep. school
- Type 2 diabetes for 15 years
- Reasonably well controlled with Gliclazide, Metformin.
- HbA1C 7.5-8.2
History

- 2007 noted that he could not judge distances well and crashed mower into cricket pavilion
- Headmaster slightly concerned – parents had reported seeing mower being driven erratically – Head suggested a visit to optometrist.
- Vision was 6/36 right, 6/7.5 LE
- Had diffuse DMO RE>LE
- Referred to HES
Previous laser to both maculae—difficult to get good response – gradual deterioration
<table>
<thead>
<tr>
<th>Date</th>
<th>Right eye</th>
<th>Left Eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nov 2007</td>
<td>DMO – refractory to laser – vision problems RE IVTA (1)</td>
<td>Stable</td>
</tr>
<tr>
<td>Mar 2008</td>
<td>RE IVTA (2) Some improvement in OCT after first IVTA but not much change after second. Vision 6/24</td>
<td>Stable</td>
</tr>
<tr>
<td>Sep 2008</td>
<td>Raised IOP RE</td>
<td>Glaucoma diagnosed and drops</td>
</tr>
<tr>
<td>April 2009</td>
<td>IOP uncontrolled and field loss worse – RE trab.</td>
<td>LE diffuse DMO worse – laser 6/12</td>
</tr>
<tr>
<td>August 2009</td>
<td>RE stable – cupped pale disc, glaucoma stable but cataract noted. Still DMO</td>
<td>LE vision 6/18 DMO worse</td>
</tr>
<tr>
<td>Sep-Nov 2009</td>
<td></td>
<td>LE treated with [Avastin] a 3 injections – vision improves to 6/12 DMO better</td>
</tr>
<tr>
<td>Jan –Dec 2010</td>
<td>RE stable – listed for cataract op</td>
<td>LE deteriorating vision 6/12 part at best</td>
</tr>
<tr>
<td>May -2011 – Jan 2013</td>
<td>RE 6/60</td>
<td>LE 6/9, CRT = 320um</td>
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</table>
## RELIGHT study design

<table>
<thead>
<tr>
<th>Month</th>
<th>0</th>
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<th>2</th>
<th>3</th>
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<th>5</th>
<th>6</th>
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<th>9</th>
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<tbody>
<tr>
<td>Treatment schedule</td>
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<tr>
<td>Ranibizumab 0.5 mg</td>
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<tr>
<td>Ranibizumab PRN</td>
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- Prospective, open-label, multicentre, single-arm, 18-month study to evaluate the efficacy and safety of ranibizumab 0.5 mg for the treatment of visual impairment due to DMO (N = 110)

- Retreatment criteria:
  - Residual central subfield retinal oedema (an OCT reading of ≥225 micrometers)
  - Increase in central subfield retinal oedema by >10% or 25 micrometers from the lowest in-study reading
  - No residual central subfield retinal oedema, but a total drop of 5 or more ETDRS letters from the in-study BCVA

BCVA, best-corrected visual acuity; PRN, pro re nata (as needed)
**Summary of key clinical results at month 12**

<table>
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<tr>
<th>Month</th>
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<th>6</th>
<th>7</th>
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<th>12</th>
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<tbody>
<tr>
<td>Treatment schedule</td>
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</table>

- **BCVA improved from a baseline mean of 62.6 letters to 67.8 letters at month 12**
  - Mean change: +5.2 letters
- **Patients received a median of 7 injections over 12 months (range, 3-9)**

BCVA, best-corrected visual acuity
Vision right eye 6/60. Laser ineffective.
Left eye ranibizumab

PT – what happened after RELIGHT?

<table>
<thead>
<tr>
<th>RE</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 Lucentis – treated when NICE approved Lucentis</td>
<td>12 further Lucentis – treated on compassionate grounds at end of study</td>
</tr>
<tr>
<td>Vision 6/24-6/60</td>
<td>Vision 6/9-6/18</td>
</tr>
<tr>
<td>Trab working; Field loss stable</td>
<td>Able to drive</td>
</tr>
</tbody>
</table>
What have I learnt from PT?

- Anti-VEGF’s are optimal standard of care if indicated
- Steroids have a role but significant side effects
- Campaign on behalf of our patients
- Clinical trials have an important role in getting access to new treatments for our patients and may enhance future management.
NICE Guidance

- NICE technology appraisals [TA274] Published date: April 2013
  
  *Ranibizumab is recommended as an option for treating visual impairment due to diabetic macular oedema only if:*

  - the eye has a central retinal thickness of 400 micrometres or more at the start of treatment **and**

  - the manufacturer provides ranibizumab with the discount agreed in the patient access scheme revised in the context of this appraisal.
Anti-VEGF’s in DMO – “a game changer”

- Patients with DMO assessed for diabetic care and control.
- Laser given if indicated – if focal leakage or exudate
- If laser ineffective or if CRT (central retinal thickness) > 400um eligible for ranibizumab
- Avastin – issues – unlicensed
- Aflibercept new alternative
- Steroids to be considered if anti-VEGF’s c/i, or if longer acting drugs needed.
Anti-VEGF’s in Proliferative Retinopathy

- Stops intra-ocular new blood vessel growth very effectively

- Have been used in patients with vitreous haemorrhage prior to vitrectomy surgery – make operation easier, less bleeding.

- May cause rapid contraction of retinal fibrous tissue – sudden retinal detachment has been reported

- Very effective in cases of neovascular glaucoma (NVI; rubeoosis iridis) because it stops nv growth in anterior chamber angle and buys time to give laser, sort out medication etc

- Currently Lucentis unlicensed for this- so Avastin used because its cheaper.
What does BARS stand for?

Barnes Akathisia Rating Scale