

Anti-VEGF and diabetic macular oedema (Audit)

Western eye hospital

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ST1

Objectives

- Identify adherence of anti-VEGF treatment regime for diabetic macular oedema (DMO)
- How many new and current patients are on anti-VEGF injections treatment for DMO?
- Avastin Vs Lucentis at WEH
- How many AMD patient are receiving anti-VEGF under diabetic service?

Treatment standard DMO

CSMO	Centre involving	Visual acuity	Phakic/pseudophakic	OCT	Treatment options
Yes	No		Either		Photocoagulation
Yes	Yes	Normal, or minimally reduced by macular oedema (>78 letters).	either		Photocoagulation or observe if the source of leakage is very close to fovea and there are no other treatable lesions suitable or safe to laser (Level C)
Yes	Yes	VA in region of 78-24 letters	Phakic	> 250µm central subfield thickness	Intravitreal anti-VEGF treatment with or without laser for eyes unresponsive to other treatments, intravitreal fluocinolone implant may be considered, but bearing in mind the potential side-effects
Yes	Yes	VA 78-24 letters	pseudophakic	> 250µm central subfield thickness	intravitreal anti-VEGF treatment , OR Intravitreal triamcinolone (preservative-free) with or without adjunctive laser may also be considered . (Level A) OR intravitreal fluocinolone implant may be considered if available, and eye unresponsive to other treatments (level A)
Yes	Yes	< 24 letter	Pseudophakic	> 250µm central subfield thickness	Observation may be appropriate, especially if longstanding and no response to previous laser, or if considerable macular ischaemia . Otherwise may consider anti-VEGF treatment or intravitreal steroid after careful consultation and consent.

Bevacizumab (Avastin)

- Humanised monoclonal antibody from DNA recombinant Chinese hamster ovary cells
- Available as 100mg or 400mg vials at 14mg/ml and 16.5mg/ml concentrations respectively
- Angiogenic factor VEGF causes increased permeability of the blood retinal barrier involved in neovascularisation.

Avastin

- Licensed for the treatment of cancer:
 - Metastatic Ca colon, breast, Lung (NSCLC), RCC, ovarian
- Unlicensed for any other uses (IVT)
- Supplied in 100mg or 400 mg vials (€242.66 and €924.40 respectively)
- Diluted and aliquoted into individual doses by second supplier (not manufacturer)
- Each IVT injection 1.25mg (3 month shelf life)
- Outbreaks have been reported

Avastin and DMO

- Certain PCT commissioning groups support or permit the use of Avastin
- USA survey shows Avastin to be favoured (2008) mainly on cost effectiveness.
- Avastin versus sham/laser shows better improvement in VA and CMT
- Injected at 0, 6 and 12 weeks.
- RCT are small (n=62-130)

Ranibizumab (Lucentis)

- Humanised monoclonal antibody fragment produced from E.Coli recombinant DNA
- 10mg/ml solution for injection (0.23ml vial)
- Indication and licensed for:
 - Neovascular (wet) AMD
 - Diabetic macular oedema
 - Macular oedema secondary to branch/central RVO
 - Choroidal neovascularisation secondary to pathological myopia

Lucentis in diabetic macular oedema

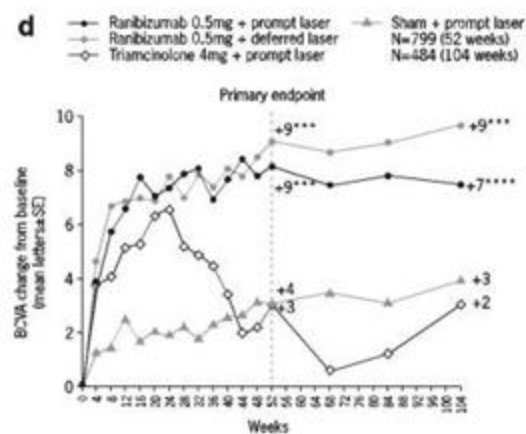
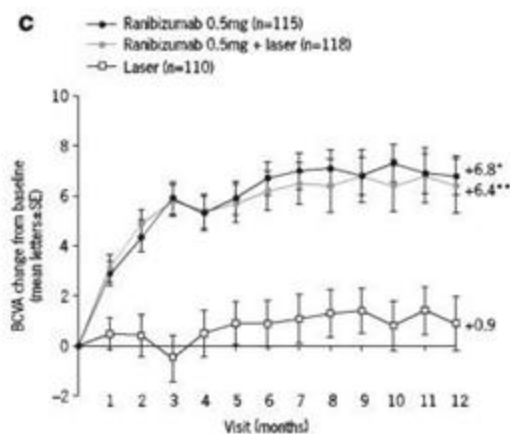
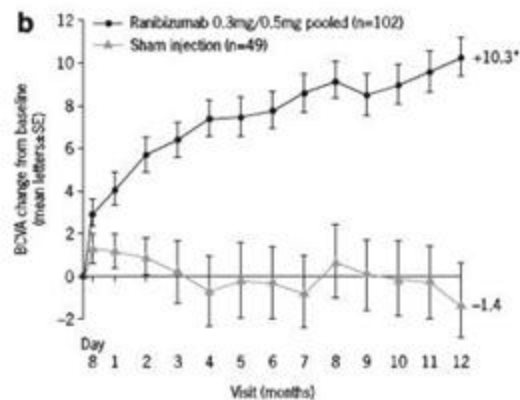
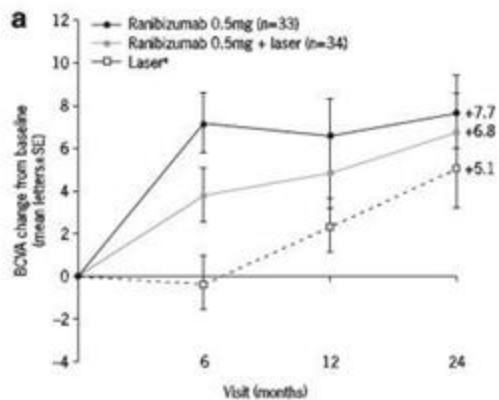
- 0.5 mg (500 μ m) single IVT injection (Novartis)
- 3 monthly injections with stable visual acuity during course of treatment.
- If after 3 months no improvement then further treatment is not recommended
- In 2011 NICE did not recommend drug as effective use of NHS resources
- Revised NICE review
 - Revised patient access scheme

Lucentis and DMO

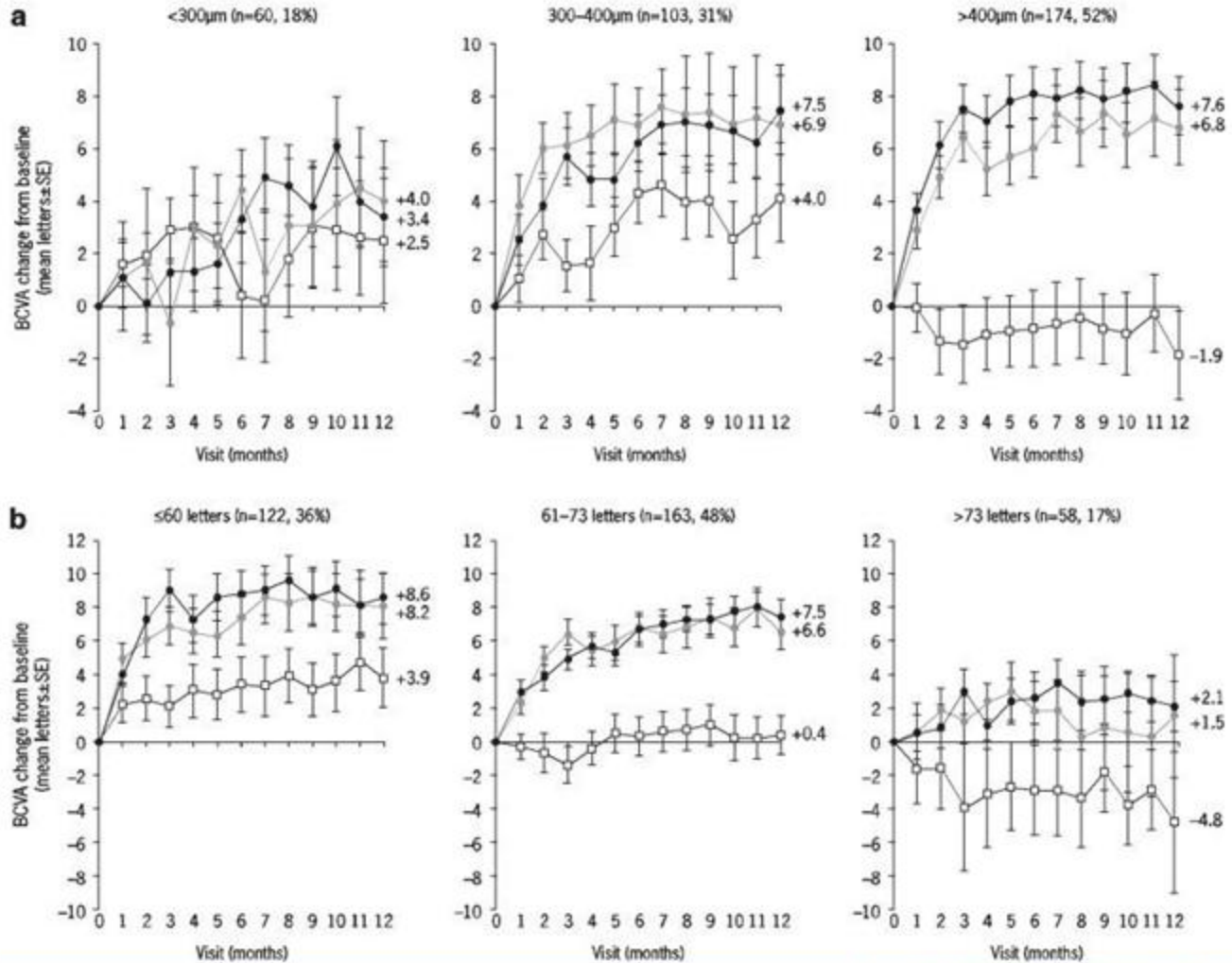
- NICE now recommends Lucentis since Feb 2013
 - Treatment option for DMO with visual impairment
 - If central macular thickness of $400\mu\text{m}$ from start of treatment **and**
 - The manufacturer supplier product with patient access scheme.
- Monthly review for first year
- Tx can be interrupted when VA stability is achieved
 - Defined as no documented VA improvement after 3 consecutive visits while on treatment

Why NICE changed their mind

- Recommendation based on 4 RCT
 - RESOLVE
 - RESTORE
 - READ-2
 - DRCCR.net
- RESTORE funded by Novartis
- No long term data
- No studies comparing to Bevacizumab



- Ranibizumab 0.5mg
- ▲ Ranibizumab 0.5mg + laser
- Laser



RESTORE trial Lucentis

- 345 patient with DMO + visual impairment
- Method: Ranibizumab, Ranibizumab + laser and laser alone.
- 37.4% Pts > 10 letter improvement in BCVA, 43.2% combined and 15.5 % laser alone (at 12 months).

Both are better than laser but are they safer?

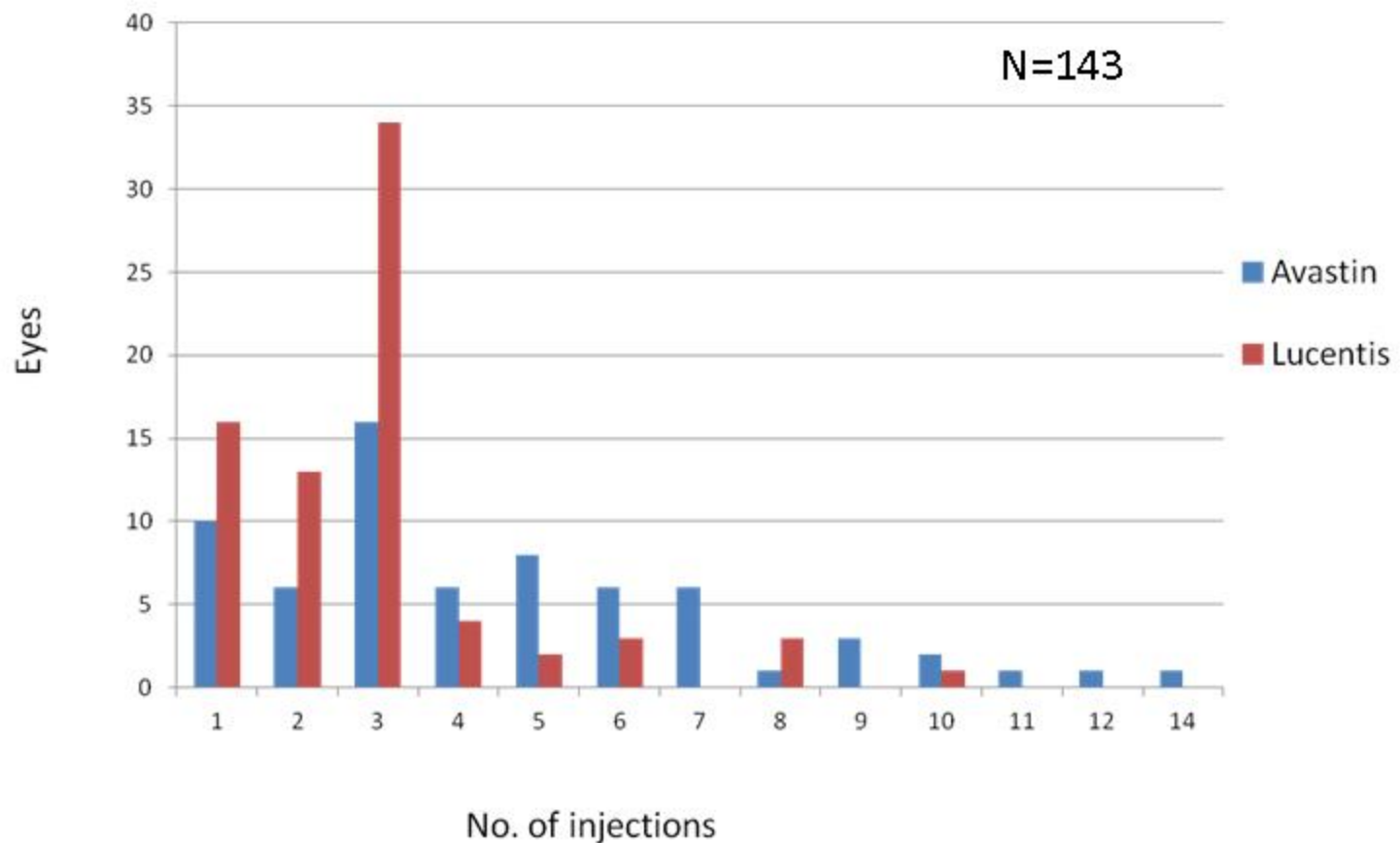
- Complications limited to eye
- Include
 - Vitritis
 - Vitreous detachment
 - Retinal haemorrhage
 - Minor: Pain, conj Hg, FB sensation, dry eye, bleph, raised IOP

Audit: Diabetic macular oedema

- 80 DMO patients receiving anti-VEFG injections
- 143 injections for DMO
- First IVT for DMO - Aug 2009
- 15 eyes with wet AMD (226 injections)

IVT	Injected eyes
Avastin	67
Lucentis	76
Total	143

Anti-VEGF injections frequency

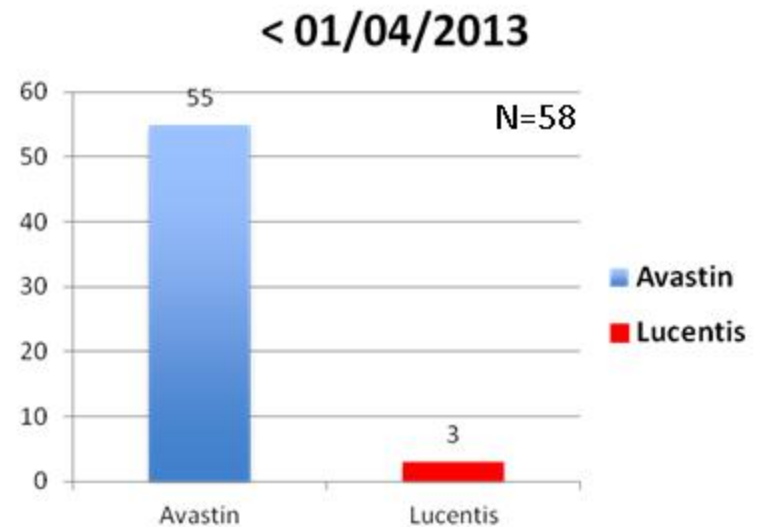


Diabetic service WEH

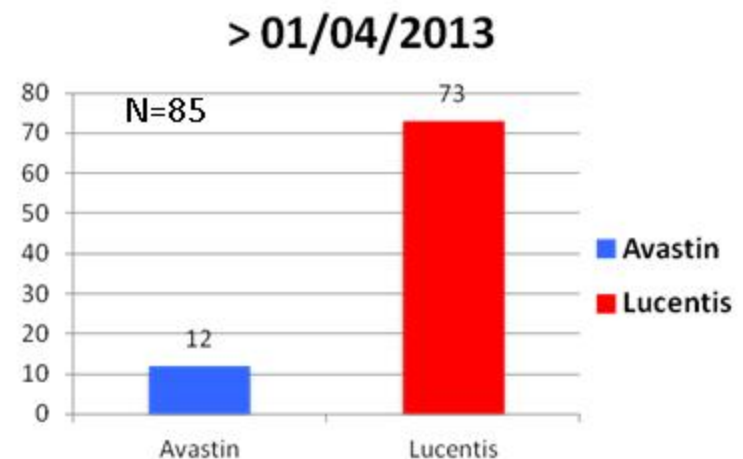
- 55% patient did not received further injections for more than 3 months since last injection (n=76)
- 22% of eyes started on bevacizumab were switched to ramibizumab
- 20 new patients in last 6 months (i.e not previously received any IVT treatment)
- First Lucentis under new guidelines given 05/05/2013
- 15 (20%) of patient starting Lucentis for DMO failed to complete dosing regime (i.e<3 doses after starting treatment within 1 month)

Comparison before and after NICE guidelines update

IVT	No. injections
Avastin	55
Lucentis	3
Total	58



IVT	No. injections
Avastin	12
Lucentis	73
Total	85



Ranibizumab Vs Bevacizumab

- Metanalysis for 5 RCTs matched
- 27 Vs 39 with OR 0.23 – 4.32 (0.95)
- Not credible difference in efficacy
- Direct head-to-head RCT needed (such as IVAN trial)

BMJ

BMJ 2012;345:e5182 doi: 10.1136/bmj.e5182 (Published 13 August 2012)

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RESEARCH

The relative clinical effectiveness of ranibizumab and bevacizumab in diabetic macular oedema: an indirect comparison in a systematic review

 OPEN ACCESS

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Unanswered questions

- Should we combine anti-VEGF with laser
- 3 and 5 year outcome data -> will it change our management
- What to do with non-responders?
- Are monthly follow-ups and increasing patient number manageable with current resources?
- Does Avastin still have a place in treatment of DMO?
- Why was Avastin never licensed for wet AMD/DMO?