AGE RELATED MACULAR DEGENERATION and VISUAL IMPAIRMENT

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Declarations

- Pharma sponsored research funding: Allergan, Bausch and Lomb, Novartis, Pfizer, CentreVue
- Advisory Board Memberships: Alcon, Alimera, Allergan, Bayer, Novartis, Pfizer, Santen, Thrombogenics
- Educational Travel grants: Allergan, Alimera, Bayer, Novartis, Pfizer
- Speaker Honoraria: Alimera, Allergan, Bausch and Lomb, Novartis, Pfizer
- Member MS Scientific Committee (Up to Apr 2015)
AGE-RELATED MACULAR DEGENERATION (AMD) and VISUAL LOSS

- AMD – commonest cause of severe visual impairment > 50 years

- Two types: Dry

  - Wet – CNV

Visual loss rapid and worse for wet AMD
Dry AMD

- The most common form of AMD
DRY AMD: GA
AMD: leading cause of sight loss in the UK

- AMD: 48%
- Cataracts: 5%
- Myopia: 2%
- Diabetic Retinopathy: 2%
- Retinitis Pigmentosa: 2%
- Diabetic Retinopathy: 2%
- Glaucoma: 11%
- Others: 28%
Risks for AMD

- Multi-factorial
- Genetic
- Environmental
Genetic Risks

- Mutations predispose to AMD, or protect

- CFH, HTRA1/ARMS2, CC2, CFB, CFHR

- Note: Genetic testing for AMD is not advised currently except for research purposes
AMD: Increased Risks

- Smoking
- Cardiovascular disease: hypertension, hyperlipidemia
- Antioxidant levels in blood
Risks for AMD Progression

- Large (soft) drusen >63u
- Hyperpigmentation
- Advanced AMD in one eye: GA, CNV
AMD Overview

- Age-related macular degeneration (AMD) represents a socio-economic burden\(^1\)
- The neovascular form of AMD is characterized by choroidal neovascularization (CNV) and is responsible for the majority of severe rapid vision loss\(^1\)
- AMD is associated with a 17–60% decrease in quality of life depending on the severity of vision loss\(^2\)
  - Visual disability is often accompanied by an increased risk of emotional distress and clinical depression\(^3\)
  - Loss of vision can also have financial implications\(^4\)

AMD: Consequences/Associated Risks

- Depression
- Falls and fractures
- Loss of independence
- Reduced health related quality of life
Very severe AMD is associated with a similar reduction in QoL to severe stroke.
The emotional and social effects of AMD

Impact of vision loss due to AMD

- Fear of total blindness
- Feeling isolated and helpless
- Depression

Psychological well-being

- Increased risk of injury due to falls

Physical well-being

- Forced to rely on caregivers
- Guilt

Lost independence

- Daily necessities: Driving, preparing meals, shopping, recognising faces

Daily activities

- Hobbies: Reading, gardening, embroidery, watching television

- Guilt
- Forced to rely on caregivers
- Depression
- Fear of total blindness
- Feeling isolated and helpless

Mitchell J, Bradley C. Health Qual Life Outcomes 2006;4:97
Dry AMD

- The most common form of AMD
- Causes the gradual death of photoreceptors in the macula
- RPE cell death precedes photoreceptor loss
- Slow and gradual loss of central vision
DRY AMD: GA
MAHALO: GA progression over 4 years
DRY AMD

- No proven treatment
- Prevention of progression to more advanced AMD by ocular nutritional supplements: Vit C (500mg), Vit E (400IU), Zinc (80 mg), Beta carotene (15 mg)
- Progression reduced by 25% in high risk groups in AREDS 1
- AREDS 2: Lutein, Zeaxanthin, Omega-3 Fatty acids
MAHALO Study: Lampalizumab

- Phase II Study
- Monthly intravitreal injection of lampalizumab (Roche)
- Fab of humanised Mab active against CFD
- Significant reduction in progression of GA by 20.4% in 18 months cf sham treated eyes
- Phase III study ongoing
DRY AMD: Future

- RPE transplantation

- Stem Cell therapies: Regeneration of photoreceptors and RPE

- Substances that reduce progression of degeneration
Wet AMD: Epidemiology Overview

- Wet (exudative) AMD accounts for between 10–15% of cases, but is responsible for around 80% of severe vision loss in AMD

- In the UK, in 2006, it was thought that there 26,000 new cases of wet AMD each year

- The prevalence of wet AMD is increasing with the ageing population: most recent estimate suggests much higher incidence: 44,000 new cases per year in the UK!

Early Diagnosis is Critical for Saving Sight

- Wet AMD is the most serious form of AMD and can progress very quickly\(^1\)

- It is an aggressive disease, in which significant vision can be lost in a short time if untreated\(^2\)

- This has a huge impact on patient independence and quality of life\(^1\)

Visual Perception
AMD Patient
Visual Perception and Assessment in AMD

- VA reduction parallels exact location of lesion, and duration
- VA reduction in AMD esp nAMD is NOT linear
- Important to obtain VA measurement (Snellen Chart) appropriately recorded
Wet AMD

- Most aggressive form of AMD
- Results in 90% of all AMD registrations
- Caused by the formation of new blood vessels under the retina
- Blood vessels leak, bleed and scar
Natural Course of Neovascular AMD

Formation of New Vessels

New abnormal blood vessels proliferate and penetrate Bruch’s membrane.
New blood vessels leak blood and fluid.
OCT nAMD
Pathogenesis of neovascular AMD is heterogeneous

- The pathogenesis of CNV is highly complex and multifactorial

- Vascular endothelial growth factor (VEGF) is an essential component of the angiogenic cascade

- Anti-VEGF therapy in wet AMD results in significant vision stabilisation/improvement

VEGF in AMD

Vascular endothelial cell

- Proliferation
- Proteolysis
- Migration

 autres Angiogenic growth factors

VEGF

Pegaptanib Blocks Isoform VEGF 165

Ranib, Beva, Aflib Block All VEGF Isoforms

Basement Membrane
WET AMD: Current Treatments

- Pegaptanib (Macugen, Eyetech/Pfizer): Anti-VEGF165, anti-angiogenic and anti-permeability

- Ranibizumab (Lucentis, Genetech/Novartis): Similar to Macugen. Binds all isoforms of VEGF (121, 165, 189 etc)

- Bevacizumab (Avastin, Roche/Genetech): Similar to Lucentis. Developed for colorectal cancer, unlicensed for intraocular administration

- Afibercept or VEGF Trap (Eylea, Bayer) binds all VEGF isoforms and PIGF
ANCHOR mean change in VA

[Graph showing ETDRS letters over months for Verteporfin (n=143) and Ranibizumab 0.3 mg (n=140) and Ranibizumab 0.5 mg (n=139).]

+11.3
+ 10.7
+ 8.5
+ 8.1
-9.6
-9.8

*** p<0.0001 vs verteporfin

Data on file ANCHOR 24mo
ANCHOR mean change in VA

Verteporfin (n=143)  Ranibizumab 0.3 mg (n=140)  Ranibizumab 0.5 mg (n=139)

ETDRS letters

Month

+11.3

+8.5

-9.6

-9.8

20.5 letter benefit ***

17.9 letter benefit ***

*** p<0.0001 vs verteporfin

Data on file ANCHOR 24mo
Secondary endpoint: Mean change in VA over time

- **Sham**
- **Ranibizumab 0.3 mg**
- **Ranibizumab 0.5 mg**

ETDRS letters

**Visit (months)**

- **2**
- **4**
- **6**
- **8**
- **10**
- **12**
- **14**
- **16**
- **18**
- **20**
- **22**
- **24**

- **+7.2**
- **+6.5**
- **-10.4**
- **+6.6**
- **+5.4**
- **-14.9**

21.4 letter benefit *

20.3 letter benefit *

* * P < 0.0001

MARINA study
VIEW Studies: Mean Change in Visual Acuity Baseline to Week 96

ETDRS letters

Week

0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72 76 80 84 88 92 96

0 2 4 6 8 10 12 14

9.3 2q4
8.7 Rq4
8.4 2q8
8.3 0.5q4
7.9
7.6
7.6
6.6

Rq4
2q8
2q4
0.5q4
VIEW Studies: Mean Change in Central Retinal Thickness to Week 96

LOCF; Full analysis set; VIEW 1: OCTs mandatory at baseline, weeks 4, 12, 24, 36, and all visits weeks 52-96; VIEW 2: OCTs mandatory at all visits
Efficacy:

Mean change in visual acuity at 12 months

- Monthly bevacizumab was non-inferior to monthly ranibizumab (8.0-letter gain versus 8.5-letter gain, respectively)
- PRN bevacizumab was non-inferior to PRN ranibizumab (5.9-letter gain versus 6.8-letter gain, respectively)
Efficacy:

*Differences between study group pairs in mean VA change at 12 months*

- The comparison between PRN bevacizumab and monthly ranibizumab (also monthly bevacizumab) was inconclusive (failed to demonstrate non-inferiority).
- The number of injections for the PRN bevacizumab arm was 7.7 compared to 6.9 for the ranibizumab arm ($p = 0.003$)

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Difference in mean change in visual-acuity score (no. of letters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab monthly</td>
<td>Ranibizumab monthly</td>
<td>-3.9 -0.5 2.9</td>
</tr>
<tr>
<td>Bevacizumab PRN</td>
<td>Ranibizumab PRN</td>
<td>-4.1 -0.8 2.4</td>
</tr>
<tr>
<td>Ranibizumab PRN</td>
<td>Ranibizumab monthly</td>
<td>-4.7 -1.7 1.3</td>
</tr>
<tr>
<td>Bevacizumab PRN</td>
<td>Bevacizumab monthly</td>
<td>-5.7 -2.1 1.6</td>
</tr>
<tr>
<td>Ranibizumab PRN</td>
<td>Bevacizumab monthly</td>
<td>-4.5 -1.2 2.1</td>
</tr>
<tr>
<td>Bevacizumab PRN</td>
<td>Ranibizumab monthly</td>
<td>-5.9 -2.6 0.8</td>
</tr>
</tbody>
</table>
Efficacy:

*Mean change in total retinal thickness at fovea at 12 months*

- Mean decrease in retinal thickness (total foveal thickness) was significantly greater in the ranibizumab monthly group compared with all other treatment groups ($p = 0.03$)
Conclusions - Efficacy

- Monthly bevacizumab was non-inferior to monthly ranibizumab in mean VA change from baseline to Month 12

- PRN ranibizumab was non-inferior to monthly ranibizumab in mean VA change from baseline to Month 12

- PRN bevacizumab failed to demonstrate non-inferiority *versus* ranibizumab monthly and bevacizumab monthly
Conclusions- Efficacy (contd)

- A higher number of injections were required with PRN bevacizumab (7.7) compared to PRN ranibizumab (6.9)

- Differences in retinal thickness were significantly greater at 12 months with ranibizumab monthly treatment compared to other treatment groups
Combination Radiotherapy and Anti-VEGF

- Internal (Epiretinal) brachytherapy and ranibizumab

- Ocular posterior segment specific external beam delivery system: Oraya
Oraya Therapy™ & IRay® Stereotactic Radiotherapy System

Radiation targets rapidly proliferating tissues

- Endothelium (anti-angiogenic)
- Fibroblasts (anti-fibrotic)
- Inflammatory cells (anti-inflammatory)

• Beam spot measures 4.0 mm at fovea
• Minimal doses of radiation to optic disc & crystalline lens
• Minimal patient effective dose (equivalent to 1/10th of head CT scan)
Anti-PDGF in nAMD

- Ophthotech, Study ID OPH1001
- E10030, Anti-PDGF Pegylated Aptamer
- Combination with ranibizumab
- Phase II completed in March 2012
- 1:1:1 of
- 0.3mg E+Ran:1.5mgE+Ran:ShamE+Ran at 0, 48, 12, 16, 20 weeks
- Primary efficacy VA at 24 weeks
ESBA

- ESBA 1008 (AL-86810) is a humanised single chain (Fv) Ab fragment
- VEGF Inhibitor, blocks VEGF ligand receptor
- M Wt ~26kDa
- Intravitreal Injection
- Longer duration of activity compared to ranibizumab
- Phase 2
Suboptimal outcomes in nAMD

- Diagnosis
  - CNV- PCV
  - Other diagnosis
- Treatment frequency –under-treatment
  - Infrequent ff-up
- Unnecessary treatment withholding
PATIENT

Patient Education 2nd eyes given direct contact number

Optometrist

Guidelines
- Signs & symptoms
- Length of symptoms
- V/A >6 6/60

Eye Dept

A&E

By FAX or Email

Fast Track Macular Clinic
Or Medical Retina/Casualty
- Macular Treatment Centre or
- Local DGH

Treatment Centre

Dedicated Fax Number

Local Eye Unit

V/A LogMAR or Snellen
FFA
OCT

LVA
Assessment and support
Counselling
Registration

Ideals to aim for:
t = < 1 week from optom to Fast Track Clinic
t = < 2 weeks from Fast Track Clinic to Treatment

GP

By FAX or Email t=< 1 week

Local Eye Unit
SUPPORT and QUALITY

- Support and quality of service are essential and must not be compromised.
- Provision of counselling and liaison with LVA clinic are important.
- Eye Clinic Liaison Officer’s are useful and should be available.
- Monthly monitoring is crucial, although where and by whom can be varied according to patient characteristics and regional clinic structure.
AMD: REHABILITATION

► REGISTRATION as VISUALLY IMPAIRED
► COUNSELLING

► LVA - initial visit + continuing dialogue

► SUPPORT GROUPS AND SOCIETIES-Macular Disease Society, RNIB
Visual rehabilitation provides practical support that may impact QoL

Visual rehabilitation can include:
- optical devices such as specialized glasses, magnifiers, telescopes, adaptive computer technology and brighter lighting
- teaching patients how to cope and adjust to vision loss, possibly with the help of support groups
- raising awareness of resources such as talking books and special products designed for the visually impaired

Quality of rehabilitation services varies between regions

The optimum outcome for physicians is to restore the patient’s ability to take part in their favourite activities and hobbies (e.g. knitting or reading)

Summary

► AMD has a devastating impact on patient QoL
► Visual rehabilitation is associated with marked improvement in QoL
► Improvements in QoL correlate strongly with improved VA
► Treatment with anti-VEGFs is associated with significant improvements in NEI-VFQ-25 scores
► Patients with AMD may benefit from:
  • improvement and stabilization of vision with anti-VEGF treatment
  • provision of visual aids and learning skills for coping with low vision

VEGF, vascular endothelial growth factor
Thank You