THE ROLE OF anti-VEGF IN DIABETIC RETINOPATHY AND AGE RELATED MACULAR DEGENERATION

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INTRODUCTION

ANGIOGENESIS PROCESS

STIMULATION FACTOR ➔ ACTIVATED VEGF-RECEPTOR ➔ VASCULAR BASEMENT MEMBRANE PROTEOLYSIS

STABILIZATION & MATURATION OF NEW VESSELS ➔ INVASION & PROTEOLYTIC SURROUND MATRIX EXTRACELLULAR ➔ MIGRATION & PROLIFERATION

PERICITE & SMOOTH MUSCLE UNITED WITH NEW VESSELS
VEGF IS A KEY REGULATOR OF ANGIogeneSIS

- Stimulates proliferation, migration, survival of endothelial cells (preventing apoptosis)
- Activates degradation of endothelial cell basement membrane
- Promote vascular permiability
- Induces endothelial cell for vasodilatation
- Limphangiongenesis
- Tends to fibrous-scar formation
THE ANGIOGENIC CASCADE

- New vessels migration to formerly avascular space
- Vascular leakage and fragile
- Tendency to rupture and bleed

Progressive angiogenesis surround the macula
irreversible centre visual loss
What is VEGF

- Hypoxia causes upregulation of VEGF correlation with growth of new vessels
- Increased expression of VEGF-A found in RPE from surgically removed CNV membranes in AMD
- VEGF in the vitreous is elevated in cases progressing from NPDR to PDR, and Diabetic Macular Edema (DME)
VEGF in PATHOLOGIC PROCESS

- Tumor growth
- Rheumatoid arthritis
- Eye disease
  - PDR
  - AMD
  - Rubeotic eye
  - Corneal disease response
  - ROP
  - Vein occlusion

Ischemic/hypoxia, inflammation $\rightarrow$ generalized stimulation factors
<table>
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<th>Therapeutic Strategies</th>
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<tr>
<td><strong>Neutralization of VEGF activity</strong></td>
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<tr>
<td>• Ranibizumab anti VEGF monoclonal antibody fragment</td>
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<td>• Pegaptamib anti VEGF 165 optamer</td>
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<tr>
<td>• Bevacizumab : anti VEGF monoclonal antibody</td>
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<td>• VEGF trap : receptor decoy</td>
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<td><strong>Interference with VEGF receptor activity</strong></td>
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<td>• Inhibitor of receptor tyrosin kinase activity</td>
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<td>• Soluble VEGF receptor analogue</td>
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<td><strong>Degeneration of VEGF Si RNA</strong></td>
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CONTRA INDICATION FOR anti-VEGF THERAPIES

- Pregnancy and lactation
- Ophthalmic inflammation
- Driver and Machine Operator
- Young patient, young adult patient
The Role anti-VEGF in Diabetic Retinopathy

- Laser Photocoagulation is the gold standard for treatment of diabetic retinopathy
- Photocoagulation reduce risk of severe visual loss by >50%
- NV regression is temporary without laser, so the role of anti-VEGF treatment is adjunctive therapy in DR
- Timely laser P.C. for DR → Reduce visual loss by 95%
- Adequate PRP can be significantly regressed HRC (NVD, NVE) & ME

ETDRS
Bevacizumab and PDR

28/3/2006
Intravitreal bevacizumab

12/4/2006
Regression of NVD

16/8/2006
NVD reopened

Closure of NV is temporary without laser
Adjunctive treatment for PDR: Bevacizumab

VEGF blockade may accelerate fibrotic traction
Adjunctive anti-VEGF in PDR

- Any severe PDR
- PDR with DME
- PDR with NV unresponsive to laser
- PDR with opaque media (VH, cataract) preventing laser PRP
- All eyes with active NV and/or VH planned for VX
- PDR and Rubeosis iridis

Remember risk of accelerated fibrous tissue contraction
Adjunctive anti-VEGF in NPDR with DME

- Laser PC grid or focal Remains the primary treatment
- Anti-VEGF has an important role, to be modified by controlled trial evidence
  (some time requires multiple injection each 6 weeks)
LASER P.C. For DME

- Decreased risk of moderate visual loss
- Increased chance of moderate visual gain with minimal VF defect
- Reduce Retinal Thickening

ETDRS
Patogenesis of Microvascular Occlusion in DR

- Capillaropathy
- Hematological changes
- Occlusion & Hypoxia
- Capillary leakage
The Role of VEGF in ME (Macular Edema)

- Microvascular occlusive process in macular area
- Blood Retinal Barrier (BRB) disruption
- Stimulate vascular permeability in the vascular arcade
Adjunctive anti-VEGF in NPDR with DME

- DME with vitreomacular traction, vitrectomy is indicated
- DME with widespread ischemia, VEGF blokade is contraindication
DIABETIC MACULAR EDEMA (DME)

DME with vitreo macular traction
- Vitrectomy is indication
- Laser or anti-VEGF may make worse

DME without traction
- Dx FFA:
  - Focal leakage
  - Diffuse leakage
  - Ischemia

Evaluating DME
- VA
- OCT
- FFA
Diabetic Maculopathy

- Focal
- Diffuse
- Ischemic
- CSME
Primary Grid or Focal Laser

- Depending on FFA
- As much ischemic area is safe

Combined laser and anti VEGF

- Significantly improved visual acuity in DME
VEGF blockade

2. Dry out Diabetic maculopathy before PRP to minimise further visual loss

Baseline
VA 20/300

1 Month after
VA 6/37.5
Anti-VEGF for Wet-Type AMD
EVALUATION FOR EXUDATIVE AMD

- **VA**
  - Decision for Rx, re-Rx

- **OCT**
  - Response to Rx, decision for re-Rx

- **FFA**
  - Diagnosis, activity

- **ICG**
  - Vascular sub-type

- **Color Fundus Foto**
  - Decision for Rx, re-Rx
**FLUORESCEIN ANGIOGRAPHY OF WET AMD**

- **Cart-wheel vascular pattern of classic CNV**
- **Choroidal Neovascularisation and other vascular lesions**
  - Sub-retina hge
  - Sub-RPE hge
  - Macular oedema
  - Subretinal fluid
  - Hard exudates
  - Pigment epithelial detachment
  - RPE damage
  - RPE atrophy
  - Photoreceptor atrophy

- **Fluorescence leakage and pooling**
- **Fluorescence staining, RPE window defect**
- **Blocked Fluorescence**

- **Fluorescein is 80% protein bound, therefore extravasates rapidly**
- **RPE up-take leading to poor visualisation of the sub-RPE vascular pattern**
POST 2 decades modality treatment of wet AMD

- MPS laser treatment
- Photodynamic therapy (PDT)
- Macular translocation
- TTT
- IV-TA
- Pneumatic Displacement
- Anti-VEGF
PROTOCOL:

Anti-VEGF management in exudative AMD (wet type)

Clinical Diagnosis
+/- Baseline OCT

Intravitreal anti-VEGF injections

Clinical evaluation
VA, OCT

Resolution

Observe

Recurrence

Residual
1. MARINA – TRIAL

Minimally classic or occult CNV  N = 716

2. ANCHOR – TRIAL

Predominantly classic wet AMD  N = 423

Both studies : 2 years, multicentre, double blind, randomized-trial

Ranibizumab (Lucentis) mono-Tx for wet type AMD could improve visual acuity, but combined therapy with PDT more effective for visual stabilization
Anti-VEGF combined with PDT adjunctive with pharmacologic agent

- Achieve better visual outcome
- Decrease growth of CNV
- Reduce the risk of vision disturbances
- Decrease number of treatments if compared with 2-monthly anti-VEGF mono-Tx
PCV and anti-VEGF

• Intravitreal Bevacizumab (Avastin) monotherapy had limited effectiveness for regression of PCV.

• PDT performed achieved complete resolution in 9 of 12 cases and partial resolution in the remaining 3 cases.

Barbazzetto IA 2009
CONCLUSION

The Role Anti-VEGF for DIABETIC RETINOPATHY

1. Optimizing metabolic control

2. Laser P.C. still gold standard (permanent)

3. Anti-VEGF is important role for adjunctive Tx, before & after laser P.C. or Vx, (temporer) to minimize further visual loss
CONCLUSION

The Role Anti-VEGF for AMD

1. PDT is primary therapy → Laser selected to pathologic endothel
   Physically (permanent) closes CNV

2. Anti-VEGF inhibits angiogenesis and vascular leakage (temporar) significantly promote visual recovery and visual stabilization.

3. Management of High Risk consideration (hypertension, smoking)