Neovascular AMD

Neovascular (wet) AMD:
Development of CNV

New abnormal blood vessels proliferate and penetrate Bruch’s membrane

Neovascular (wet) AMD:
Development of Disciform Scar

CNV is accompanied by fibrous tissue leading to permanent destruction of outer retina

Neovascular (wet) AMD:
Development of CNV

New blood vessels leak blood and fluid

Can you have CNVM with 20/20?

In the CAPT: (with annual FA)
1052 patients enrolled
282 eyes of 225 patients developed CNVM
Half of CNVMs were subfoveal
25% of CNVMs were found in both eyes

And, 10% per year X 5 yrs develop CNVM in the fellow eye

Occult CNVM with 20/20

Only 1 eye had CNVM develop in the area of the laser treatment.


Neovascular AMD

- Central fibrovascular scar (▶)
- Subretinal Lipid (→)
- SRF (**)

Development and Progression of AMD

Early
- Drusen
- Neovascular AMD
- Hemorrhage
- Detachment of RPE
- Disorganization of RPE
- Macular edema

Late
- Choroidal neovascularization
- Subretinal hemorrhage
- SRF
- Lipid
- RPE

Risks for CNVM & GA (CAPT)

Complications of Age-related macular degeneration (laser-reduction of drusen)

- 1052 participants -10 or more large drusen (125 µ) and visual acuity of 20/40 or better in each eye.
  - Choroidal neovascularization developed in 141 observed eyes and 141 treated eyes.
  - Among eyes free of GA at baseline, endpoint GA developed in 61 observed eyes and in 58 treated eyes.

Risks for GA (CAPT 2008)

- older age (RR, 6.39 [95% CI, 1.64–24.9] for 79 years vs. 50–59 years)
- greater retinal area covered by drusen (RR, 5.10 [95% CI, 2.57–10.1] for 25% vs. 10%)
- RPE depigmentation (RR, 2.64 [95% CI, 1.26–5.33])
- focal hyperpigmentation RR, 10.4 [95% CI, 4.51–24.0] for 250 µ vs. none

Risks for CNVM (CAPT 2008)

- older age (RR, 2.81 [95% CI, 1.33–5.94] for 79 years vs. 50–59 years)
- cigarette smoking (RR, 1.98 [95% CI, 1.16–3.39] for current vs. never)
- focal hyperpigmentation (RR, 1.84 [95% CI, 1.22–2.76] for 250 µ vs. none).
**Stages of Neovascularization**

Step 1: Elaboration of the angiogenic signal

Step 2: Activation of vascular endothelial cell proteinases to degrade the basement membrane (2a) and the extracellular matrix of interstitial tissue (2b)

Step 3: Stimulation of vascular endothelial cell migration

Step 4: Stimulation of vascular endothelial cell proliferation

Step 5: Formation of capillary lumen

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**PED in AMD**

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**AMD Treatments – Laser Photocoagulation**

- Macular Photocoagulation Study Group (MPSG) parameters
  - Extrafoveal (> 200 μl)
  - Juxtafoveal (1-199 μl)
  - Subfoveal

- Well-circumscribed vessels identified at FA (Classic, discrete CNVM) were treated and vision loss was reduced compared to age-matched controls

*Occult vessels are ill-defined at FA (ineligible for treatment): clinical picture may by a combination of the 2.

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**Laser Photocoagulation: MPS Trial**

- Thermal laser:
  - Non-selective
  - Destroys CNV
  - Causes collateral damage

---

**Laser photocoagulation**

Photo courtesy Mark McGuire, OD (UABSO ’83)
**AMD Treatments – Laser Photocoagulation**

- **MPSG results summary**
  - 3-6 mo following treatment, treated eyes may have worse VA (ave: 3 lines) than untreated eyes (ave: 2 lines) but progress faster
  - At 2 years post-treatment, treated eyes average 1.5 lines better VA
  - 2 years post-treatment, treated eyes are less likely to show >/= 6 lines than untreated eyes

- **Laser Photocoagulation – example**
  - Immediate post-op
  - S/P 6 months
  - No leakage from treated area

- **Laser Photocoagulation – limitations**
  - Only 10-15% of CNVM’s are sufficiently small to be delineated by FA (eligible)
  - 50% of successfully treated CNVM’s will leak within 2 years (vigilant monitoring)
  - Some “eligible” lesions are subfoveal

  *need alternative treatment options*

**PDT Outcomes (TAP-1)**

- **Indications for traditional photocoagulation**
  - Subfoveal location
  - Well-demarcated boundaries
  - “Classic” CNVM presentation
  - Small size

- **Alternative treatment (PDT) developed due to limitations of laser photocoagulation**
**AMD Treatments**  
Photodynamic Therapy (PDT)

- Alternative to thermal laser photocoagulation of subfoveal CNVM's
  - Applied in tumor treatments...
  - Partial selective destruction of new choroidal blood vessel growth by nonthermal-radiation (red / near-IR; peak 689 nm.) and
  - Production of ROS's identified by IV-administered photosensitizer (verteporfin)

**PDT with Verteporfin**  
(Visudyne® clinical process)

- Partial selective destruction may spare RPE and photoreceptors & allow recanalization
- Degree of destruction of CNVM may be related to dosing of verteporfin and light energy
- Implications for retreatment frequency and intervals


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**Visudyne® Therapy**  
A Two-Step Process

**Step 1**  
10 Min infusion

**Step 2**  
83 sec activation

---

**Determining GLD and Treatment Spot Size**

- Determine size of lesion on photographic image
- Calculate actual GLD on retina
- Add 1000 µm to allow a 500 µm border around lesion
- Treatment spot should be no closer than 200 µm to edge of optic disc
Determining GLD and Treatment Spot Size

- Determine size of lesion on photographic image
- Calculate actual GLD on retina
- Add 1000 µm to allow a 500 µm border around lesion
- Treatment spot should be no closer than 200 µm to edge of optic disc

Follow-up

- Follow-up visits after a treatment should be scheduled at least as often as every 10–14 weeks
- Fluorescein angiography is required to determine whether leakage has recurred
- Retreatment is often necessary during the first 2 years

Retreatment

Patients are retreated as often as every 10–14 weeks if:
- Evidence of leakage from classic or occult CNV
- No serious adverse events believed to be associated with prior therapy

Early phase of angiogram showing recurrent leakage within a hypofluorescent region 3 months after Visudyne therapy

Photodynamic Therapy (PDT)

Baseline: Subfoveal SRF; Classic and occult CNVM; Late leakage

S/P: 3 mo. Reduced SRF; late leakage; progression nasally

S/P: 12 mo. (w/3 re-bx.) Reduced SRF; late leakage

Vision Outcomes

<table>
<thead>
<tr>
<th>Change in Visual Acuity*</th>
<th>3-Month Follow up</th>
<th>12-Month Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Verteporfin (N = 422)</td>
<td>Placebo (N = 389)</td>
</tr>
<tr>
<td>+6-line increase</td>
<td>1 (0.3)</td>
<td>0 (0.6)</td>
</tr>
<tr>
<td>+5-line to +6-line increase</td>
<td>8 (2.0)</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>+1-line to +5-line increase</td>
<td>80 (19.4)</td>
<td>22 (5.7)</td>
</tr>
<tr>
<td>No change</td>
<td>150 (36.0)</td>
<td>67 (17.4)</td>
</tr>
<tr>
<td>-1-line to -5-line decrease</td>
<td>102 (24.3)</td>
<td>55 (14.6)</td>
</tr>
<tr>
<td>-5-line to -9-line decrease</td>
<td>52 (12.3)</td>
<td>32 (8.7)</td>
</tr>
<tr>
<td>-6-line decrease</td>
<td>16 (4.0)</td>
<td>25 (6.5)</td>
</tr>
</tbody>
</table>

No. (%) of Patients

<table>
<thead>
<tr>
<th></th>
<th>3-Month Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>+6-line increase</td>
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* More (1 & 4, respectively) verteporfin eyes than placebo gained > 6 lines of vision

Vision Outcomes

(3- and 12-month F/U)

- More (1 & 4, respectively) verteporfin eyes than placebo gained > 6 lines of vision
- There was no change in vision in the same % of eyes [3-mo: 32.8, 32.4; 12-mo: 21.6, 16.4]
- A > 6-line decrease occurred in approximately twice as many placebo as treated eyes [3-mo: 4.5, 11.1; 12-mo: 14.7, 23.7]
Vision Outcomes (12-month F/U)

- Loss of < 15 letters [3 lines] (p<.001)
  - 246/402 (61%) verteporfin-treated eyes
  - 96/201 (46%) placebo-treated eyes

- Greatest benefit when area of classic CNVM >50% of total lesion area
  - 67% vs. 39% (verteporfin) lost >15 letters


TAP results at 2 years (TAP-2)

- Entry criteria:
  - Subfoveal CNVM ≤5400 µl
  - Classic presentation
  - BCVA: 20/40-20/200

- Primary outcome measures
  - Evidence of leakage at FA
  - # lines of vision lost (< = 15 letters ≥ 3 lines)


TAP example

- SRF in color photo; note elevation

- Early and late angiograms showing hypofluorescence secondary to hemorrhage; and stippled hyperfluorescence corresponding to occult NV

TAP – 1st Outcomes @ 24 months

- Placebo-controlled trial
  - 54% (121/225) lost > 15 letters (verteporfin eyes)
  - 67% (76/114) lost > 15 letters (placebo eyes)

  - 30% (67/225) lost > 30 letters (V)
  - 47% (54/114) lost > 30 letters (P)
**TAP – Subgroup Outcomes @ 24 months**

- Placebo-controlled trial w/ *occult* CNVM
  - 55% (91/166) lost > 15 letters (V)
  - 68% (63/114) lost > 15 letters (P)
  - 30% (48/166) lost > 30 letters (V)
  - 47% (43/114) lost > 30 letters (P)

**TAP – Secondary Outcomes**

(12 and 24 mo.)

- Verteporfin group favored (*occult* or *classic*)
  - Final VA (better than 20/200)
  - VA improvement from baseline
  - Less likely development of classic CNVM
  - Less likely progression of classic CNVM

- Other factors favoring Tx.
  - (occult CNVM; favors Tx.)
  - Small (<4 DA)
  - VA worse than 20/50

**TAP @ 5 years**

n= 320; 193 competed

- The 3-year extension of the TAP study revealed:
  - No new safety concerns
  - An average of 2 additional treatments were applied over the 3 years
  - ~ 1/3 of patients had lost 3 lines of vision by the 2-year mark and only 37% had lost 3 lines by year 5. (classic CNVM)
  - Mean change in VA similar at 24 and 60 mo. (-1.5, -1.6)
  - Overall stability between years 2 and 5.

**Verteporfin risk**

- 4% of patients may experience severe vision loss (> 20 letters within 1 week of treatment)

- Examples…
**Management of Clinically Relevant Adverse Events**

- **Extravasation**
  - Avoidable with proper precautions

- **Infusion-related back pain**
  - No adverse sequelae known at this time
  - Resolves within a short time
  - 50 mg infusion of benadryl is prophylactic

(Tornambe PE. Using intravenous diphenhydramine to minimize back pain associated with photodynamic therapy with verteporfin. Arch Ophthalmol 2002; 120: 872)

**Management of Clinically Relevant Adverse Events (con’t)**

- Photosensitivity reactions
  - Treat as sunburn (sunscreen is ineffective)
  - Avoidable with proper precautions

- Acute severe vision decrease within 7 days
  - Observation, no retreatment recommended

**Example**

- **S/P 7 D**
  - Arrows outline SRF
  - Corresponding hypofluorescence

- **S/P 12 mo.**
  - Fibrosis w/ subretinal hemorrhage and hyperfluorescence
  - (loss of 20 letters in 7 days; N1 @ 1 yr)

- SRF w/leakage throughout and late staining
Alternative applications of Photodynamic Therapy (PDT)

- Clinical study (13 non-AMD patients)
  - Infusion: 10 min IV
  - Irradiation: 30 min @ initiation of infusion
  - Increasing light dosage (50–150 J/cm²) at 1-wk, for up to 4 treatments
- Follow-up was 12–43 weeks


Alternative applications of Photodynamic Therapy (PDT)

- Treated disorders included:
  - ocular histoplasmosis
  - pathologic myopia - Results
    - Increase in mean VA = 2.6 lines
    - Most improvement was among those with worst VA (20/200 – 20/800; 6–9 lines)
    - Most cases showed improvement (FA) in leakage

Pathologic myopia – single Tx.
59 W/M, 20/800

Pathologic myopia – S/P 1 wk.
59 W/M, 20/800

Pathologic myopia – S/P 4 wks.

Pathologic myopia S/P - 12 wks.
59 W/M, 20/100
**AMD Treatments – Prophylaxis**

- Complications of AMD Prevention Trial
  - Laser treatment –applied in a grid to areas of large or numerous drusen (at-risk group)
  - Follow-up for > 5 years; fellow eye as control
- IR diode laser trial among patients with CNVM in one eye and bilateral drusen
- Choroidal Neovascularization Prevention Trial (1994-1999) found the risk of moderate prophylactic treatment increased vs. untreated fellow eye

**Intravitreal Corticosteroids**

- Have an inhibitory effect on:
  - Angiogenesis
  - Fibrotic activity
  - Inflammatory reactions
  - By reducing the migration and activation of inflammatory cells
- Stabilize:
  - Endothelial and basement membranes
  - Reduce vascular permeability and vascular leakage
- Inhibit vascular endothelial growth factor (VEGF)

---

**PDT and IVTA**

- 30% Improved vision with PDT & IVTA
- 16% Improved vision with PDT alone
- 25 Patient study
- No control group
- VisTA study underway

**IVTA Injection: Conclusions**

- Because of the antiangiogenic effect found 3 months after injection, IVTA has become an adjunctive treatment to PDT for CNV
- Risks of IVTA include:
  - Elevated IOP
  - Cataract progression
  - Pseudo-endophthalmitis
  - Endophthalmitis (rare)

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**Antiangiogenic Research**

- Folkman postulated new vessels (angiogenesis) contributed to tumor growth in cancer
- This stimulated antiangiogenic research in other fields such as ocular neovascularization
- Avastin for colorectal cancer now approved in 2004
- VEGF now a hot topic in CNV

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**Figure 4. Steps in neovascularization.**
VEGF in pathologic ocular neovascularization

VEGF is implicated in
- Neovascular AMD (NV-AMD)
- Diabetic retinopathy (DR)
- Retinal vein occlusion (RVO)
- Retinopathy of prematurity (ROP)
- Corneal neovascularization (KNV)
- Iris neovascularization (INV)

Summary

- VEGF and neovascularization are linked in experimental models (cornea, iris, retina, choroid)
- VEGF is necessary and sufficient to produce pathologic neovascularization
- Based on animal models
  - Preferential role of VEGF$_{164(165)}$ suggested in pathologic neovascularization
  - Blocking VEGF$_{164(165)}$ inhibits abnormal vessel growth while sparing normal vessels
AMD Medications

- Intravitreal anti-VEGF Injection:
  - Macugen (Eyetech)
  - Avastin (Genentech)
  - Lucentis (Genentech)


CATT (Comparison of AMD Treatments Trial)

<table>
<thead>
<tr>
<th>Arms</th>
<th>Assigned Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Active Comparator Lucentis® on a fixed schedule of every 4 weeks for 1 year; at 1 year, re-randomization to Lucentis® every 4 weeks or to variable dosing.</td>
<td>Drug: ranibizumab • 0.5 mg (0.05 mL) intravitreal injection</td>
</tr>
<tr>
<td>2: Experimental Avastin® on a fixed schedule of every 4 weeks for 1 year; at 1 year, re-randomization to Avastin® every 4 weeks or to variable dosing.</td>
<td>Drug: bevacizumab • 1.25 mg (0.05 mL) intravitreal injection</td>
</tr>
<tr>
<td>3: Experimental Lucentis® on a variable dosing schedule for 2 years; i.e., after initial treatment, monthly evaluation for treatment based on signs of lesion activity.</td>
<td>Drug: ranibizumab • 0.5 mg (0.05 mL) intravitreal injection</td>
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<td>Drug: bevacizumab • 1.25 mg (0.05 mL) intravitreal injection</td>
</tr>
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Estimated Primary Completion Date: December 2010 (Final data collection date for primary outcome measure)

Preliminary results of a comparison of Avastin and Lucentis for CNVM in AMD


- Design: prospective comparison
- Small study (n = 20; 13 (bev.*), 7 (ran.**))
- Short duration (6 mo.)
- Mean outcomes
  - Bevacizumab group gained 15 letters and had 35 uM decrease in CMT
  - Ranibizumab group gained 7 letters and had 102 uM decrease in CMT

*Bevacizumab = Avastin®
**Ranibizumab = Lucentis®

Macugen

Avastin

Avastin
Avastin

Lucentis

Lucentis (Ranibizumab)

- Lucentis is the “parent” full body molecule
- A recombinant humanized antibody fragment that binds to VEGF and inhibits all VEGF isoforms
- Several trials are ongoing for predominantly classic, minimally classic, and occult CNV
  - Some with concurrent PDT
  - Some without PDT
- Intravitreal injections of 0.3mg to 0.5mg, given monthly for up to 24 months

Lucentis

- 95% rate of stabilization
- 31%-40% gain 3 lines
- MARiNA & Anchor Study
- If not given every month, patients lose vision back to baseline (Pier Study)

Vision Results: Lucentis vs. Sham

- Study 1:
  - Lucentis 0.5 mg (n=240)
  - Sham (n=238)
- Lucentis – gained 6.6 letters
- Sham – lost 14.9 letters

Vision Results: Lucentis vs. PDT

- Study 2:
  - Lucentis 0.5 mg (n=139)
  - Verteporfin PDT (n=143)
- Lucentis – gained 11.3 letters
- PDT – lost 9.5 letters
Avastin

- First used intravenously to treat colon cancer
- Humanized antibody fragment that binds to all VEGF
- Large molecule that DOES penetrate retina
- No known toxicity to retina to date

Avastin

- 80 patient study – Avery et al 2006
- 36% gained 3 lines of vision
- 95% stable

Avastin

- 266 patient study – Spaide et al 2006
- 38% halved visual angle
- 20/184 → 20/100 at 3 months

First Avastin trial reported

Baseline CRT = 328 μ; VA = 20/200
S/P 4 wks: 209 μ; 20/80
S/P 8 wks (2 inj.): 181 μ; 20/40; stable @ 12 wks.

Avastin Treated Patient

Pre-Avastin  Post

Avastin (Intravenous for NV AMD)

- N = 18
- 24-week study
  - Initial IV infusion
  - 1-2 doses @ 2-week
- Results
  - VA improved @ 2 wks and was sustained @ 24 wks

Avastin (Intravenous for NV AMD)

Reduction in retinal thickness (OCT)


VA | CRT
---|---
20/80 | 539
20/20 | 212 (+ 12 wks)
20/20- | 240 (+20 wks)
20/32- | 370 (+ 24 wks. Re-Tx)
20/20 | 227 (+28 wks)

Avastin (intravitreal for PDR)

Regression of INV and NVD @ 6 weeks


VA | CRT
---|---
20/160 | 569
20/64 | 243 (+ 12 wks)
20/64 | 297 (+20 wks)
20/32- | 430 (+ 24 wks. Re-Tx)
20/20 | 261 (+28 wks)

AMD Medicines Comparison

<table>
<thead>
<tr>
<th></th>
<th>How Often</th>
<th>Stabilized</th>
<th>≥ 3 Lines Gained</th>
<th>Long Term Safety Profile</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macugen</td>
<td>6 weeks</td>
<td>80%</td>
<td>12-20%</td>
<td>Excellent</td>
<td>$1000</td>
</tr>
<tr>
<td>Avastin</td>
<td>6-8 weeks</td>
<td>95%</td>
<td>36-38%</td>
<td>?</td>
<td>$50</td>
</tr>
<tr>
<td>Lucentis</td>
<td>4 weeks</td>
<td>95%</td>
<td>31-40%</td>
<td>Good</td>
<td>$2000</td>
</tr>
</tbody>
</table>

Other Management Strategies

- Other Nutrition and Supplement studies
  - Lutein*
- Interferon-α2
- Sub macular surgery
- External beam irradiation
- Thalidomide
- TTT (Transpupillary Thermo Therapy)
- ICG-guided laser treatment
- Retinal prostheses
- Gene therapy
- Low-dose Aspirin
- Blood-flow enhancement [Sildenafil citrate (Viagra®)]
- Hemofiltration (Rheotherapy)
- Intravitreal antiangiostatic steroids
- Intravitreal Anti-VEGF
**NV-AMD Trials**

- Evizon (Genaera) – Squalamine + PDT vs. PDT
- Sirna – vitreal injection anti-VEGF
- VEGF Trap (Regeneron) – intravenous anti-VEGF
- VisTA – Visudyne (PDT) + Triamcinolone
- Combrestatin A-4 phosphate (CA4P) – intravenous anti-VEGF
- Cand 5 – Vitreal injection of small RNA interface agent
- Squalamine (Genaera) – intravenous every 4 weeks anti-VEGF
- AG3340 (Agouron) – MMP inhibitor

**NV-AMD Trials (con’t)**

- AG 13958 - MMP inhibitor
- AdPEDF – single vitreal injection
- Brachytherapy (thesagenics) – 3 doses of radiation
- Submacular surgery trial – No Benefit
- Macular Translocation – small trial underway
- VEGF Trap
  - 95% Stable
  - 13 letter mean increase in VA

**Other Management Strategies**

- Submacular surgery
- External beam irradiation
- TTT (Transpupillary Thermo Therapy)
- ICG-guided laser treatment

**RPE Transplantation**

**Recent results**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Follow-up</th>
<th>VA</th>
<th>Late phase ICGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>2 days</td>
<td>14</td>
<td>CNVM leakage</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>2 months</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>76</td>
<td>6 weeks</td>
<td>13</td>
<td></td>
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<tr>
<td>4</td>
<td>81</td>
<td>4 weeks</td>
<td>9</td>
<td></td>
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<tr>
<td>5</td>
<td>93</td>
<td>3 weeks</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>10 weeks</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

**RPE Transplantation**

- 12 mo post-op
- Fixation on the patch
- 20/80 (20/200 pre-op)

**RPE Transplantation**

- Pre-op 20/200

- Late phase angiogram – no leakage
- Late phase ICGA – CNVM leakage!
RPE Transplantation

Post-op 20/64 (12 mo)

Uniform appearance to patch (SLO)

May have procedure to stabilize VA loss following PDT


Complications include PVR, RD (50% combined)

Modest results suggest caution in offering this treatment to patients


RPE Transplantation

No New Findings

Stem cell, autologous, and in vitro

Not rejecting

Vision gain minimal

RPE Transplantation

2 wks post-op – 20/80 VA

1 yr post-op – 20/160 VA

RPE transplantation (translocation)

Laser demarcation and excision of retina

Excision of underlying RPE and choroid

Patch grasped with forceps and inserted (sub retinal)

Viscous fluid for tamponade

**Autofluorescence**

* Transplanted RPE-choroid complex
  + normal retina


**Telescopic Technology**

- Implantable miniature telescope (IMT)
- 24° field (was 12° initially)
- 87% gained 3 lines of vision
- Average pre-op vision was 20/300

**IMT**

The telescope implant is only 4mm long and contains two wide angle glass microlenses.

**IMT**

Normal Eye
Central vision is focused on diseased macula.

**IMT**

 Implanted Eye
Central vision is rendered on central and peripheral retina.

**Retinal Microchip – No New Findings**

[Images of microchip]

**AMD Treatments - Investigational**

- **Submacular surgery** – currently under NEI trial
- Disadvantages
  - RPE damage pre-op
  - RD post-op
  - NO chance of VA improvement or stabilization (vs. observation)
- Advantage: reduced risk of severe VA loss (worse than 20/200) (vs. observation)
AMD Treatments - Investigational

- **External beam radiation therapy** (low-dose fractionated applications; based on sensitivity of vascular endothelium) – randomized trials show mixed results at 1-2 years; *failure in largest trial...*

  RAD Study Group. Ophthalmology 1999; 106:2239-47. (–) 
  Matshuhashi H. Jpn J Ophthalmol 2000;44:653-60. (?)

AMD Treatments - External beam radiation therapy (teletherapy)

- 203 patients with subfoveal CNVM and VA at least 20/200 [¼ served as controls (observation)]

  - Treatment group
    - 12 Gy of 6-mV photons in 6 fractions
    - Follow at 3,6,12,24 mo

  - Results (all NSS)
    - VA better in treatment group at all time points
    - Fewer treated patients had severe VA loss (> 6 lines)


AMD Treatments - TTT

- Treatment effects from TTT may be similar to those of PDT
- Vascular closure may result from hyperthermia (TTT)
- The vascular endothelium may be most sensitive to the effects of TTT

AMD Treatments - TTT

(72 W/M Choroidal MM)

<table>
<thead>
<tr>
<th>24 hr</th>
<th>3 mo</th>
<th>1 yr w/ recurrence</th>
<th>1 d S/P re-tx.</th>
<th>S/P 3 yr</th>
</tr>
</thead>
</table>

TTT

- May stabilize CNVM as well as PDT
  - VA 20/400 or better
  - Large (3000 to 6000u) spot size
  - Delivered over 60 sec
  - Results (n = 69 @ 6 – 12 mo)
    - 71% stable or improved
    - 29% lost at least 2 lines

AMD Treatments - Anecdotal

- **ICG-guided laser treatment**? Efficacy (principle is that ICG absorbs and fluoresces in the near IR) improving choroidal visibility

- Retinal transplantation and RPE transplantation – far from clinical acceptance

- Retinal translocation – some reported success but major complication is RD

---

AMD Treatments - Anecdotal

- **ICG Example** - 72 W/F 20/20 early AMD

  Prolonged choroidal filling (PCF) more evident on ICGA

  ![color](image1)
  ![FA (1 min)](image2)
  ![ICGA (1 min)](image3)

AMD Treatments - Anecdotal

- **ICG Example** 76W/F early AMD

  ![FA – 1 min](image4)
  ![ICGA 1 min](image5)

  20/30
  20/80
  X 12 mo

  NOTE: ↑ RPE atrophy, drusen, and PCF

---

AMD Treatments - Anecdotal

- **ICGA Example** – confluent drusen (20/20)

  ![PCF @ 1 min](image6)
  ![PCF @ 3 min](image7)
  ![PCF @ 8 min](image8)

  NOTE: ↓ Hypofluorescence; prolonged choroidal filling

---

ICGA prolonged choroidal filling phase (PCFP)

- 100 pts w/ Early AMD
  - 12 bilateral soft drusen
  - 88 unilateral late AMD

  PCFP defined as:
  - slow and patch choroidal
    - hypofluorescence @ < 1 min FA
  - reduced diffuse background fluorescence @ < 3 min ICGA)
ICGA – prolonged choroidal filling phase (PCFP) characteristics in AMD

- Results
  - Both FA (26%) and ICGA (32%) demonstrated PCFP
  - Clinically the best correlation with PCFP was RPE atrophy (28% of eyes w/PCFP, 6% w/o)

Results
- PCFP and fellow eyes with late AMD
  - Geographic RPE atrophy (25%)
  - Only 4% of eyes w/o PCFP had geographic atrophy in the [late AMD] fellow eye


ICG-guided Laser-Activated Dye

Same patient imaged w/ OCT

RPE Transplantation

- Recent results

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Follow-up Time</th>
<th>Follow-up VA</th>
<th>Follow-up MVA</th>
<th>Follow-up Velocity</th>
<th>VA or MVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F 66</td>
<td>6 months</td>
<td>20/400</td>
<td>20/800</td>
<td>14 20/800</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>F 65</td>
<td>2 months</td>
<td>20/500</td>
<td>20/400</td>
<td>13 20/400</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>F 76</td>
<td>6 weeks</td>
<td>20/300</td>
<td>20/800</td>
<td>10 20/800</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>F 61</td>
<td>4 weeks</td>
<td>20/400</td>
<td>20/300</td>
<td>9 20/300</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>M 73</td>
<td>3 weeks</td>
<td>20/500</td>
<td>20/400</td>
<td>7 20/400</td>
<td>6</td>
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<tr>
<td>6</td>
<td>M 60</td>
<td>10 weeks</td>
<td>20/200</td>
<td>20/800</td>
<td>7 20/800</td>
<td>5</td>
</tr>
</tbody>
</table>


RPE Transplantation

- 12 mo post-op
  - Fixation on the patch
  - 20/80 (20/200 pre-op)


RPE Transplantation

- Pre-op 20/200


Late phase angiogram – no leakage

ICGA – normal filling

Late phase ICGA – CNVM leakage!

But...
RPE Transplantation

- Post-op 20/64 (12 mo)

- Complications include PVR, RD (50% combined)
- Modest results suggest caution in offering this treatment to patients


AMD Treatments – Anecdotal (con’t)

- Retinal prostheses (biocompatible silicon microelectronics) application may be to RP (VA limit is 20/400) rather than macular function (optobionics.com)

- Gene therapy – some progress in identifying the responsible gene; genetic modification in amenable cases

Low-dose aspirin and AMD risk

- Physicians Health Study (PHS)
- Aspirin arm intended to evaluate CVD risk reduction (325 mg every other day)
- Few (117/21216; 0.55%) developed AMD; and only 57 had VA < 20/30 - 5 years F/U
- Statistically non-significant 23% risk reduction among aspirin users vs. placebo


Viagra and AMD

- Choroidal blood flow increased ~ 30%
- Retinal circulation increased ~ 8%
- Contrast sensitivity increased ~35%


- BUT... Others have found no changes *


Viagra and AMD

- 9 males ages 51-85 (mean 71)
- single 100 mg dose or placebo
- 20/40 or better w/ early AMD
- No changes in VA, CS, CV, VF, PSRT within 8 hours of dosing

Hemofiltration

- Membrane differential filtration
- 40 patients (AMD); treatment group had 5 sessions over 21 wks
  - Mean ↑ (VA) 0.63 lines
  - Control group: 0.94 line ↓


Rheophoresis Pilot Study

- MIRA – 1
  - Multicenter Investigation of Rheophoresis for AMD
    - Age range 50-85
    - 20/40-20/100
    - Large soft drusen
  - 10 Rheo Group (10 Tx. [16 wks])
  - 10 Sham
  - 10 Observed
  - info@oculogix.com 727 784-2353

MIRA – 1 Outcomes [1 yr]

- VA
  - 7/20 Tx eyes improved by > 2.5 lines
  - 3/20 in each of the other groups had same ↑
- Subjective assessment positive for Tx group
  - Negative for placebo group
- QOL (VF-14) positive for 1/3 of Tx
- Rheo markers (total cholesterol, HDL cholesteral, IgA, fibriongen) all improved in Tx group; this correlated with improved VA

WWW.Oculogix.com/research.html

PERC study of Rheopheresis

- VA remained stable or improved after 18 weeks of treatment for 93 % (n = 30)
- 8 filtration treatments over a 10-12 week period
- Each treatment lasts for 2-4 hours and is administered by a nurse

Other Management Strategies

- Other Nutrition and Supplement studies
- Sub macular surgery
- ICG-guided laser treatment
- Retinal prostheses
- Gene therapy
- Low-dose Aspirin
- Blood-flow enhancement [Sildenafil citrate (Viagra®)]
- Intravitreal angiostatic steroids
- Intravitreal Anti-VEGF