AREDS (Age Related Eye Disease Study)¹

**Purpose:** To assess the clinical course, prognosis, and risk factors of age-related macular degeneration (AMD) and cataract.

**Methods:** A prospective multicenter randomized clinical trial involving 3640 participants.

**Conclusions:** People at high risk of developing advanced stages of AMD lowered their risk by about 25% when treated with a high-dose combination of vitamin C, vitamin E, beta-carotene, and zinc. People with intermediate or advanced AMD in one eye only, the micro nutrients reduced risk of vision loss caused by advanced AMD by 19%. However if only early AMD, the supplements did not provide any apparent benefit.

AREDS 2 (Age Related eye disease study 2)

**Purpose:**
1. Whether oral supplementation with lutien (10mg/kg), zeaxanthin (2 mg/d) and / or omega -3 long chain polyunsaturated fatty acids (DHA, EFA) (1gm/d) will decrease the risk of progression to advanced AMD, as compared to placebo.
2. Evaluate the effect of eliminating beta carotene and reduced zinc from the original AREDS formulation on the development and progression of AMD.

**Methods:** 4000 patients were enrolled for the study from September 2006.

**Conclusion:** No over all additional benefit from adding omega 3 fatty acids or lutein and zeaxanthin to the formulation. However the study did find benefits in two sugroups of patients those not given beta carotene and those with very little lutein and zeaxanthin in their diets.

Macular Photocoagulation Study (MPS)²

**Purpose:** To evaluate if argon and krypton laser is of benefit in preventing or delaying loss of central vision in patients with Choroidal Neovascular Membrane (CNVM) due to AMD, presumed ocular histoplasmosis (POH), and idiopathic neovascular membranes (INVM)

**Method:** MPS consisted of 3 sets of Randomized Controlled Trial (RCTs).

a). **Argon Study:** Used argon blue-green laser photocoagulation on leaking abnormal blood vessels in CNVM outside the fovea [200 to 2500μ from center of Foveal avascular zone (FAZ)] in the three conditions: AMD, POH, and INVM

b). **Krypton Study:** To assess whether krypton red laser photocoagulation of CNVM lesions with posterior border 1 to 199μ from centre of FAZ is of benefit in preventing or delaying large losses of vision in patients with AMD, POH, and INVM.

c). **Foveal Study:** To assess whether laser photocoagulation benefits in preventing or delaying further vision loss in patients with new or recurrent CNVM under the centre of FAZ.

**Conclusions:**
- In all 3 arms, eyes with well-demarcated areas of classic CNV, defined by Fluorescein angiography, had a better visual prognosis when treated with laser photocoagulation versus observation. However subfoveal CNVM benefited more from laser treatment vs observation.
- Laser treatment for subfoveal CNV caused more visual loss in the immediate post laser period vs controls.
However, the amount of visual loss in control group at 1yr was same in treatment group. After 1yr, the control group exhibited more visual loss than the treated group.

**TAP (Treatment of AMD with Photodynamic therapy)**

**Purpose**
- To evaluate the efficacy of Visudyne therapy in patients with subfoveal CNVM secondary to AMD with predominantly classic CNV.

**Methods:**
609 patients with AMD and subfoveal CNV with a classic component and visual acuity (VA) between 6/12 and 6/60 underwent a 2:1 randomisation between treatment and control (sham treatment). Retreatment was applied to zones of persistent or new leakage at 3 monthly visits.

**Conclusions:**
- Visudyne therapy sustained VA, stabilized contrast sensitivity and preserved the quality of vision in patients with occult with no classic CNV.
- Benefit was most pronounced in smaller lesions (< 4 MPS DA: macular photocoagulation study disc area) or lower levels of visual acuity (< 20/50).
- Fewer patients developed the more aggressive classic component of CNV.

**VIP (Verteporfin in photodynamic therapy)**

**Purpose:**
To evaluate the efficacy of Visudyne therapy in occult with no classic CNVM or presumed early onset CNVM and good visual acuity.

**Methods:**
Patients of AMD, with subfoveal CNV lesions measuring no greater than 5400 μ in greatest linear dimension with either
- Occult with no classic choroidal neovascularization, BCVA score of at least 50 (Snellen equivalent approximately 20/100), and evidence of haemorrhage or recent disease progression; or
- Evidence of classic CNVM with a BCVA score of at least 70 (better than a Snellen equivalent of approximately 20/40); were assigned randomly (2:1) to verteporfin infusion (6 mg/m²) and light application with an reduced fluence (RF) rate (300 mW/cm²) for 83 seconds (light dose of 25 J/cm²) or b) an standard fluence (SF) rate (600 mW/cm²) for 83 seconds (light dose of 50 J/cm²) or c) to placebo infusion with RF or SF.

**Conclusions:**
- Visudyne therapy sustained VA, stabilized contrast sensitivity and preserved the quality of vision in patients with occult with no classic CNV.
- Benefit was most pronounced in smaller lesions (< 4 MPS DA: macular photocoagulation study disc area) or lower levels of visual acuity (< 20/50).
- Fewer patients developed the more aggressive classic component of CNV.

**VISION trial (VEGF Inhibition Study In Ocular Neovascularisation)**

Vision-Year 1

**Purpose:**
To evaluate the usefulness of Pegaptanib in treating neovascular AMD. Entire spectrum of AMD, as encountered in clinical practice was included.

**Methods:**
Prospective, double-masked study, Phase 3, placebo-controlled trial. 1186 patients randomized to sham (0 mg), 0.3 mg, 1.0 mg, or 3.0 mg of drug. Intravitreal injections were given every 6 weeks.

The Primary endpoint was proportion of patients avoiding 3 lines / 15 letters (EDTRS) of vision loss at one year. Secondary endpoints were visual gain (>15 letters of vision) and/or mean change from baseline visual acuity.

**Results:**
- **Primary endpoint:** achieved by 70% of treated (0.3mg) vs. 55% of controls (p<0.001) representing a 27% increase in responders over controls.
- **Secondary endpoints:** Risk of severe loss of vision (>30 letters ETDRS) was seen in 10% of treated cases vs. 22% in control eyes. Visual gain (>15 letters of vision) was better in treated eyes at 6% (in 0.3mg), 7% (in 1.0 mg), 4% (in 3.0mg) vs. 2% of controls.
• Change in visual acuity defined as any gain in vision (>0 letters) was seen in 33% of treated vs 10% of control eyes.

**Conclusions:**

• Combined analysis for the Primary endpoint showed that Pegaptanib appeared to be efficacious at all doses tested (0.3mg, 1.0mg and 3.0mg). The FDA reviewed this data and approved the lowest dose of Pegaptanib, 0.3mg, for a broad label (all subtypes).

**Vision - Year 2**

**Purpose:**

• To evaluate the efficacy of one year of pegaptanib therapy vs. two years of pegaptanib therapy.

**Methods:**

• 1053 patients (out of 1186) continued in the VISION study for a second year.
• Patients in treatment arms were re-randomized to observation (i.e. treated for year one, observed for year two) OR continue Pegaptanib injections in the same dose group.
• Patients in the sham arm were re-randomized to receive Pegaptanib or continue to receive sham.

*Primary endpoint* was: Time until > 3 lines or 15 letters of vision was lost. Secondary end points were: Mean change in VA at week 102, proportion of eyes becoming legally blind (<6/60) and proportion of patients losing >15 letters at week 102.

**Conclusions:**

• Intravitreal injections of 0.3mg Pegaptanib are effective in treating exudative AMD.
• The therapeutic benefit is maintained regardless of lesion composition or size.
• Treatment benefit is greater for two years of sustained treatment rather than one year.
• Pegaptanib did not show statistically significant benefit among patients with occult disease or in lesions greater than 4 disc areas regardless of composition.
• Continuing visual benefit was observed in patients who were randomized to receive therapy with Pegaptanib in year 2 of the VISION trials when compared with 2 years usual care or cessation of therapy at year 1.

**Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA)**

**Purpose:**

• To evaluate the efficacy of Ranibizumab in CNVM

**Methods:**

Phase III, multi-centre, randomised, double masked, sham injection-controlled trial, involving 716 patients, who were randomised to intravitreal Ranibizumab 0.3 or 0.5mg or sham treatment once a month for 24 months

**Results:**

• Maintaining vision: Patients losing < 15 letters vision was seen in 95% (452/478) of treated vs. 62% (148/238) of control group (p<.0001)
• Improving vision: Gain of ≥ 15 letters was seen in 25% (59/238) of 0.3 mg Ranibizumab vs. 34% (81/240) of 0.5 mg of Ranibizumab versus 5% (11/238) of controls.

The difference between treated (both doses) and control in mean change in visual acuity from baseline was 17 letters. Visual acuity of > 6/12 at 12 months was seen in 40% (188/478) of treated vs. 11% (26/238) of control patients. At 12 months on an average 7 letters gained in treated group vs. 10.5 letters lost by control group.

**Conclusions:**

Intravitreal Ranibizumab 0.3 or 0.5mg was beneficial in arresting visual loss due to minimally classic or occult CNVM.

**Anti-VEGF antibody for the treatment of predominantly classic choroidal neovascularisation in AMD (ANCHOR)**

Comparing two different doses of Ranibizumab to verteporfin photodynamic therapy (PDT) in treating subfoveal neovascular macular degeneration.

**Methods:**

A Phase III, randomised, multi-centre double-masked active treatment-controlled trial. It enrolled 423 patients and randomised 1:1:1 to either PDT plus sham injection or to placebo PDT plus Ranibizumab (0.3 mg or 0.5 mg) monthly for 24 months. Fluorescein angiography was done every 3 months to determine the need for additional PDT or placebo PDT.

Inclusion criteria were patients with predominantly classic CNV and VA of 6/12 – 6/96. Primary endpoint was proportion of subjects losing <15 ETDRS letters at 1 year and secondary endpoint was change in VA from baseline.

**Results:**

• Maintaining vision: Patients losing <15 letters at 1 year was 94% in 0.3 mg Ranibizumab group vs. 96% in 0.5mg Ranibizumab vs. 64% in PDT group (p < 0.0001).
• Improving vision: Patients gaining ≥ 15 letters was 36% in 0.3 mg Ranibizumab, 40% in 0.5 mg Ranibizumab and 6% in PDT (p < 0.0001).
• On average, 9 and 11 letters were gained with 0.3 mg and 0.5 mg Ranibizumab respectively vs. 10 letters lost in PDT group (p<0.0001). Severe visual loss was seen in 13% of PDT group versus none occurred in Ranibizumab groups.

• Leakage on FFA decreased by 2 disc areas (DA) in Ranibizumab group and increased by 1/3 DA in PDT group (p<0.0001).

Conclusions:
Ranibizumab provided greater clinical benefit than verteporfin PDT in patients with ARMD with new-onset, predominantly classic CNVM. Rates of serious adverse events were low.

ProNTO (Prospective OCT Imaging of Patients with Neovascular AMD Treated with Intra-Ocular Ranibizumab)

Purpose: Whether dosing on the basis of fluid in the macula results in fewer injections but has similar visual acuity outcomes to a monthly dosing regimen.

Methods: 3 consecutive monthly injections of 0.5 mg Ranibizumab were given. Monitoring for anatomical and functional effects was done by OCT and FFA respectively. Injections were repeated only if required.

Results: After 1 year, the mean improvement in VA from baseline was 9.3 letters (p<0.001), and at 2 years it was 11.1 letters (p<0.001). Around 35% eyes gained at least 15 letters of VA at 1 year and 43% gained at least 15 letters at 2 years.

Conclusions: VA outcomes comparable with the outcomes from the phase III clinical studies, but fewer intravitreal injections were required.

Ongoing studies with Ranibizumab: FOCUS, PIER, HORIZON, PROTECT etc.

SANA trial- Systemic Avastin for neovascular AMD

Purpose: To evaluate the short-term safety of systemic bevacizumab and its effects on vision and subfoveal CNV in patients with neovascular AMD

Methods: single-center, uncontrolled clinical study. AMD patients with subfoveal CNV (N = 9) and best-corrected VA letter scores of 70 to 20 (approximate Snellen equivalent, 20/40-20/400). Patients were treated at baseline with an infusion of bevacizumab (5 mg/kg), followed by 1 or 2 additional doses given at 2-week intervals. Safety assessments were performed at all visits.

Conclusion: Significant improvement in VA and decreased retinal thickness (OCT) were seen. The systemic side effects led to the exploratory use of intravitreal injection of bevacizumab to treat CNV in AMD patients.

Comparison of ARMD treatment trials (CATT)

Purpose
• To evaluate effects of Ranibizumab (Lucentis) and Bevacizumab (Avastin) when administered monthly or as needed for 2 years
• To describe the impact of switching to as needed treatment after 1 year of monthly treatment.

Methods:
CATT enrolled 1200 participants aged 50 and older with subfoveal CNV secondary to AMD in at least one eye and visual acuity between 20/40 and 20/320, inclusive. CATT participants completed a total of 24 monthly study visits for 2 years.

All participants were assigned randomly to one of 4 treatment groups.

1) 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.
2) 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.
3) Lucentis on variable dosing for 2 years; i.e., after initial treatment, monthly evaluation for treatment based on signs of lesion activity.
4) Avastin on variable dosing for 2 years; i.e., after initial treatment, monthly evaluation for treatment based on signs of lesion activity.

Those who were assigned to fixed monthly dosing groups would receive treatment at every visit. Those assigned to variable dosing groups were evaluated for treatment at every visit. If lesion activity was seen, the participant received a study treatment.

Results:
• In same regimen for 2 years, mean gain VA was similar for both groups (bevacizumab and Ranibizumab). The difference in gain of VA was 1.4 letters (p= 0.21, not significant.)
• Mean gain was greater for monthly than for as needed treatment (difference 2.4 letters, p=0.046)
• The proportion of patients with 1 or more systemic serious adverse events was higher with bevacizumab than Ranibizumab.

Conclusion:
Ranibizumab and bevacizumab had similar effects on VA over 2 year period. Treatment as needed resulted in less gain in VA, whether instituted at enrollment or after 1 year of monthly treatment. No differences between the
two drugs in rates of death or arterio-thrombotic events was noted.

**VEGF Trap –Eye in Phase 3 trial**

**Purpose:**
Investigate efficacy and safety of Aflibercept in wet AMD.

**Results:**
- Phase 1 and 2 trials showed that monthly or bimonthly Aflibercept was not inferior to monthly Ranibizumab in preventing vision loss (< 15 letter loss). The visual gain and safety was comparable with the two treatments.

- Year 2 treatment involved monthly pro re nata (as needed) with required injections every 3 months and maintained vision gains from the first year, with an average of 4.2 injections of Aflibercept and 4.7 injections of Ranibizumab.

**References**
6. VEGF Inhibition Study in Ocular Neovascularization (V.I.S.I.O.N.) Clinical Trial Group. Year 2 efficacy results of 2 randomized controlled clinical trials of Pegaptanib for Neovascular Age-Related Macular Degeneration. Ophthalmology 2006 Sep; 113(9):1508.

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