Q: Does anti-VEGF therapy promote macular atrophy in AMD?

What's macular atrophy and why should we care about it?

Disclosures

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F, financial support; R, recipient; C, consultant; P, patent

Macular atrophy progression
SEVEN-UP Study
n = 65 AMD patients

7 years after initiating ranibizumab treatment
• MA in all eyes
• MA growth in all eyes
• MA severity correlates with vision outcome
**what's macular atrophy?**

**Geographic atrophy**
- Dry AMD

**"Macular atrophy"**
- Exudative AMD
- Including anti-VEGF treated

loss of photoreceptors, RPE, choriocapillaris

- Unifocal or multifocal
- Parafocal or centrifugal
- Isolated atrophy

- Unifocal
- Central or centrifugal
- Atrophy + fibrosis, pigment

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**MARINA Trial**

2 year data

- Change in mean visual acuity from baseline
- FDA approval in the US for Lucentis: June 30, 2006

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**SEVEN UP Study: Design**

- 7-year outcomes in ranibizumab-treated patients from the ANCHOR/MARINA and HORIZON trials
- SEVEN UP Study

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Rofagha et al, Ophthalmology 2013, 120:2292-9
Bhisitkul et al, Ophthalmology 2016 (accepted)
SEVEN-UP: Visual Outcome
Compared to baseline entry into ANCHOR or MARINA
mean change in ETDRS letter score

MONTHLY INJECTIONS

SEVEN-UP: Visual Outcome
Compared to baseline entry into ANCHOR or MARINA
mean change in ETDRS letter score

Mean 4.2 inj/year

SEVEN-UP: Visual Outcome
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Mean 4.2 inj/year

SEVEN-UP: Visual Outcome
Compared to baseline entry into ANCHOR or MARINA
mean change in ETDRS letter score

Mean 1.6 injections/year

SEVEN-UP: Visual Outcome
Compared to baseline entry into ANCHOR or MARINA
mean change in ETDRS letter score

Mean 4.2 inj/year
Recent study on long-term outcomes: fixed interval dosing of anti-VEGF


89 patients, 109 eyes
Retrospective study
Average 10.5 inj/year
Follow-up 6.5 years

Macular atrophy is the key determinant of long term vision outcomes in treated AMD

Macular atrophy area correlates with final visual acuity

Change in macular atrophy area correlates with change in visual acuity

No correlation: fibrosis, intra- and subretinal fluid, macular thickening, total lesion size

Anti-VEGF therapy and geographic atrophy

In mouse studies, anti-VEGF drugs interferes with maintenance of the normal vasculature of the choriocapillaris

Anti-VEGF therapy and geographic atrophy

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In monkey eyes, bevacizumab reduces choriocapillaris endothelial cell fenestrations, with leukocytic occlusion of lumen

In AMD patients, number of anti-VEGF injections is associated with RPE and choroidal atrophy
- Young et al. Exacerbation of choroidal and retinal pigment epithelial atrophy after anti-VEGF treatment in neovascular age-related macular degeneration. Retina 2014 (n = 415, retrospective)
- Lois et al. Retinal pigment epithelial atrophy in patients with exudative age-related macular degeneration undergoing anti-VEGF therapy. Retina 2013 (n = 72, retrospective)

CATT geographic atrophy analysis

2-year trial, 1185 AMD eyes prospective, randomized
- ranibizumab vs. bevacizumab
- monthly vs. PRN

Geographic atrophy analysis
- 269 eyes with GA (20.4%)
- 194 eyes with follow-up

Incident GA
- No GA at baseline, onset GA at year 1 or 2
  - incidence outcome – any GA
  - 1,188 eyes at baseline - 82 with measurable GA (excluded)
  - by Year 2: 29% develop GA
- Ranibizumab: 43% increased risk compared to bevacizumab

Monthly vs PRN
- 27% vs 17%

GA growth
- GA present at baseline or year 1, 2
  - progression outcome
  - 269 eyes (20.4%), 194 with follow-up
  - Ranibizumab 0.49mm/year
  - Bevacizumab 0.36 mm/year
  - ranibizumab had significantly faster GA growth (p=0.02)

Monthly
- 0.45 mm/year
- PRN 0.43 mm/year
- no significant difference

CATT geographic atrophy

Ranibizumab
(vs bevacizumab)
Increased GA incidence
Increased GA growth rate

Frequent dosing
Increased GA incidence
• but not GA growth rate

“These results have raised a number of important safety questions among clinicians using anti-VEGF therapy in AMD patients...[and] suggest that chronic use may have some undesirable side effects.”

Macular Atrophy in treated AMD
proposed mechanisms

a) Natural progression of underlying dry AMD
- True geographic atrophy

b) Retinotoxic effect of anti-VEGF drugs
- Constitutive VEGF production for normal neuronal and vascular maintenance

c) Non-specific collateral damage
- Retinal/subretinal fluid & hemorrhage
- CNV extension, contraction/ischemia

Macular atrophy related to the cumulative history of exudative episodes over a patient’s entire course

SEVEN-UP Study: fellow eye comparisons

Methodology questions

1-2 year follow-up
• GA is a slow, chronic process

Define and measure GA
“sharply demarcated borders, visibility of underlying choroidal vessels, excavated or punched out appearance”
• excludes fibrosis, pigment, heme
• underestimation; skew toward treatment assoc. with exudation

Detect GA
Measurable eyes at baseline
• exclude any with subretinal heme or exudation obscuring GA
• misinterpret as new onset as heme clears
Bilateral exudative AMD at baseline
high frequency vs low frequency anti-VEGF treatments

Conclusions

Did intensive ranibizumab treatment for 24 months increase long-term development of macular atrophy?

NO: for patients with bilateral exudative AMD at baseline

MA in study eyes < MA in fellow eyes

- initial high frequency ranibizumab treatment did not appear to increase the risk of MA progression
- delayed, very low frequency treatment could give rise to more uncontrolled exudation, with nonspecific photoreceptor/RPE damage = macular atrophy
- MA is ubiquitous in treated AMD and its severity is correlated with vision outcome
- consistent suppression of exudation over many years may reduce macular atrophy progression and improve long-term outcomes