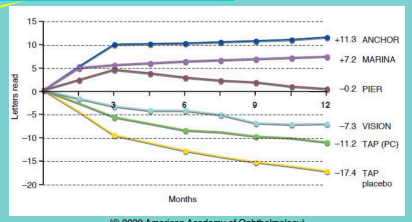
Neovascular AMD (III): Management (I): Antiangiogentic Therapies

Antiangiogenic Therapies

Anti-VEGF dosing intervals

fixed interval

- ranibizumab
  - MARINA & ANCHOR studies — monthly
    - at 12 months
      - 95% of ranibizumab-treated patients
      - 62% of sham-treated patients and
      - 64% of PDT-treated patients
      - loss of fewer than 15 ETDRS letters
    - 30%–40% of ranibizumab-treated patients
      - improvement of ≥15 letters
      - ≤ 5% in the control participants
    - at 24 months
      - 90% of ranibizumab-treated eyes lost < 15 ETDRS letters
  - EXCITE & PIER studies — q 3 month
    - improvements (similar to MARINA and ANCHOR studies) over the first 3 months
    - treatment effects declined in participants undergoing quarterly (every 3 months) dosing as opposed to monthly dosing
- quarterly treatment is suboptimal ⚠



(© 2020 American Academy of Ophthalmology)

"as-needed"

- dosing
  - regular monthly treatment until macula is dry
  - resume injections only when signs of recurrent exudation appear
- ranibizumab
  - 3 monthly injections, followed by various as-needed regimens
    - PrONTO
    - SAILOR
    - SUSTAIN
    - HORIZON
    - studies
  - all of these studies had vision and OCT outcomes comparable to or reduced compared to MARINA and ANCHOR
  - in HORIZON study patients lost ≈ 8 letters once regimen was switched from monthly injections to as-needed

"treat and extend"

- regular monthly treatment until macula is dry
- treatment continues at progressively increasing intervals

Treatment effect modifiers

- facilitates drug penetration
- vitreoretinal interface status
  - fewer injections needed — hyaloidal separation
  - VA is not affected
  - more injections needed — epiretinal membrane

Complications

- minor ocular complications
  - common
    - local irritation
    - subconjunctival hemorrhage
- serious ocular complications — rare
  - vitreous hemorrhage
  - retinal detachment
  - persistent ocular hypertension
  - inflammation
  - ≤ 1/2000 — endophthalmitis
  - especially for PEDs > 600 µm in height — anti-VEGF therapy in eyes with fibrovascular PED
  - RPE tear
  - contraction of underlying type 1 CNV
- systemic complications
  - systemic administration of bevacizumab increases risk of
    - hypertension
    - MI & CVA — thromboembolic events
    - GI perforations and bleeding
  - conflicting evidence whether intravitreal injections increase the rate of these complications

Angiogenesis

- Angiogenesis cascade
  - vasodilation of existing vessels
  - increased vascular permeability of existing vessels
  - degradation of surrounding extracellular matrix
  - migration and proliferation of endothelial cells
  - endothelial cells join to create lumen
  - new capillaries develop and mature
- Activators of angiogenesis
  - vascular endothelial growth factor(VEGF)
    - homodimeric glycoprotein
    - has a heparin-binding growth factor specificity for vascular endothelial cells
    - functions
      - lymphangiogenesis
      - angiogenesis
      - increased vascular permeability
      - prevents endothelial cell apoptosis
    - role in AMD
      - increases in RPE cells in early stages of AMD
      - high concentrations in excised CNV
      - high concentration in vitreous of eyes with AMD
    - 4 major VEGF isoforms — VEGF165 is the most dominant in AMD
  - fibroblast growth factor (FGF)
  - transforming growth factor α (TGF-α)
  - TGF-β
  - angiopoietin-1
  - angiopoietin-2
- Inhibitors of angiogenesis
  - thrombospondin
  - angiostatin
  - endostatin
  - pigment epithelium–derived factor (PEDF)

Antiangiogenic Agents

- Pegaptanib
  - RNA oligonucleotide ligand (or aptamer)
  - binds human VEGF165
- Ranibizumab
  - recombinant humanized antibody fragment (Fab)
  - binds to and inhibits all active isoforms of VEGF-A as well as their active degradation products
  - HARBOR
    - compared higher-dose (2.0 mg) with standard-dose (0.5 mg)
    - found no difference in visual acuity or anatomical outcomes between higher-dose and standard-dose
- Bevacizumab
  - full-length monoclonal antibody against VEGF
  - used "off-label" for the treatment of AMD
  - clusters of severe vision loss due to endophthalmitis — secondary to substandard and erroneous compounding practices
  - comparison
    - bevacizumab
      - larger
      - 2 antigen-binding domains
      - longer systemic half-life after intravitreal injections — ~21 days
      - costs substantially less — 40x lower
    - ranibizumab
      - smaller
      - single doma
      - shorter systemic half-life after intravitreal injections — 2.2 hours
  - CATT
    - bevacizumab was noninferior to ranibizumab therapy in monthly or as-needed delivery schedules over 2 years
    - systemic adverse events were significantly greater in bevacizumab (39.9%) than in ranibizumab (31.7%) group
    - death and arteriothrombotic events were not statistically different
    - geographic atrophy development or increase appeared to be stimulated by anti-VEGF therapy
- Aflibercept
  - ligand-binding elements of extracellular domains of VEGFR1 and VEGFR2 fused to constant region (Fc) of IgG
  - binds both VEGF and placental-like growth factor
  - fully penetrates all retinal layers
  - VIEW 1 and VIEW 2 studies
    - all aflibercept regimens demonstrated noninferiority to ranibizumab monthly regimen
    - after 3 monthly doses, aflibercept administered every 2 months showed similar efficacy to ranibizumab administered monthly
    - patients receiving monthly aflibercept (2 mg) gained 10.9 letters of visual acuity, whereas those receiving monthly ranibizumab (0.5 mg) gained 8.1 letters (P< .01)
    - safety profiles were similar for both aflibercept and ranibizumab

Ophthalmology Mind Maps/Arman Mashayekhi, MD