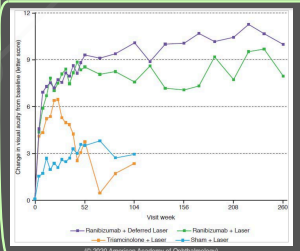
Diabetic Macular Edema (II): Treatment

Introduction
- treatment is indicated for center-involved DME
- factors to consider before treatment of non-center-involved DME (asymptomatic with normal visual acuity)
  - proximity of exudates or thickening to fovea
  - status and course of fellow eye
  - treatment risks
  - systemic conditions or medications (such as thiazolidinediones) that might exacerbate or cause DME
  - presence of high-risk PDR
  - any anticipated cataract surgery
    - initiate DME treatment before PRP and prior to cataract surgery to reduce the risk of worsening DME

Anti-VEGF drugs
- drugs
  - pegaptanib
  - bevacizumab
  - ranibizumab
  - aflibercept
  - brolucizumab
- adverse events
  - endophthalmitis ≈ 1 in 1000
  - systemic thromboembolic events
    - no demonstrated consistent differences in intraocular or systemic safety between anti-VEGF agents
    - not shown to be more common after intraocular anti-VEGF treatment
- DRCR.net Protocol I
  - intravitreal anti-VEGF superior to laser for center-involved DME
  - intravitreal ranibizumab with prompt or deferred (≥24 weeks) focal or grid-pattern laser more effective at both 1- and 2-year in increasing visual acuity than focal/grid laser alone or in combination with triamcinolone acetonide injections
  - in ranibizumab groups, vision gains accrued in first year of therapy were maintained through 5 total years of follow-up, despite number of injections progressively decreasing
  - adding focal/grid-pattern laser at initiation of intravitreal ranibizumab is no better, and is possibly worse, than deferring laser treatment for ≥24 weeks



- RISE and RIDE
  - ranibizumab rapidly and sustainably improved vision, reduced risk of further vision loss, and improved macular edema in patients with DME, with low rates of complications
- VIVID / VISTA
  - after 5 monthly injections, groups receiving aflibercept, both monthly and every 2 months, had substantial visual acuity gains compared with laser photocoagulation
- DRCR.net Protocol T study
  - aflibercept superior to bevacizumab at 1 and 2 year(s)
  - aflibercept superior to ranibizumab at 1 year but statistically similar at 2 years
  - in eyes with mild visual impairment (20/32 to 20/40) visual results were equivalent at both 1 and 2 years for all 3 treatment groups

Intravitreal Steroid
- intravitreal triamcinolone acetonide
  - DRCR.net Protocol B
    - at 2 years, focal/grid laser more effective, with fewer adverse effects, than 1-mg or 4-mg preservative-free intravitreal triamcinolone
  - DRCR.net Protocol I
    - at 2 years, intravitreal triamcinolone acetonide in combination with laser was inferior to ranibizumab with or without laser therapy, as well as to laser treatment alone
    - results from steroid-treated eyes that were pseudophakic at baseline were similar to those from anti-VEGF treated eyes and superior to laser-treated eyes
      - steroid may be a reasonable alternative to anti-VEGF in pseudophakic eyes with DME
- sustained-release steroid implants (dexamethasone and fluocinolone acetonide)
  - improved rates of ≥ 3 lines visual acuity gain
  - DRCR.net Protocol U
    - eyes with persistent center-involved DME after ≥ 6 prior injections of anti-VEGF agents
    - combination therapy with continued anti-VEGF treatment and a dexamethasone implant
      - showed greater improvement in retinal thickening over 6-month study period
      - did not show superior vision gains when compared to continued anti-VEGF treatment alone
- because of higher rates of cataract and glaucoma, corticosteroids are usually considered second-line agents for DME
- useful alternative for eyes that are not candidates for or have been refractory to anti-VEGF therapy

Macular laser photocoagulation
- indications
  - DME from clearly focal leakage that can be easily targeted by laser
  - resistance to anti-VEGF therapy
  - poor candidate for anti-VEGF therapy
    - medically unstable
    - unable to adhere to near monthly treatment
- ETDRS
  - macular focal- or grid-pattern laser photocoagulation of CSME versus observation
    - reduced the risk of moderate vision loss
    - increased the chance of vision improvement
    - associated with only minor visual field loss
- adverse effects
  - paracentral scotomas
  - decreased vision
  - transient increased edema
  - inadvertent foveal burns
  - choroidal neovascularization
  - laser scar expansion
  - subretinal fibrosis
- risk factors for poor visual outcome
  - macular ischemia (extensive perifoveal capillary nonperfusion)
  - hard exudates in the fovea
- technique
  - guided by fluorescein angiography & OCT thickness map
  - laser parameters
    - spot sizes of 50–100 µm
    - burn durations ≤ 0.1 second
  - focal (direct) pattern
    - for focal leackage
    - directly treat all leaking microaneurysms between 500 µm - 3000 µm from center of macula
    - green or yellow wavelengths
  - grid pattern
    - for diffuse leakage or zones of capillary non-perfusion
    - areas of diffuse leakage ≥ 500 µm from center of macula and temporal margin of optic disc
    - light-intensity
    - 1 burn width separation between burns
    - green- or yellow-wavelength
  - repeated every ≥16 weeks until retinal thickening resolves or all of leaking microaneurysms adequately treated
  - micropulse, or sub–threshold intensity burns, may be as effective as standard macular laser treatment while reducing damage to RPE and outer retinal layers
- in current clinical practice, treatment of eyes with DME can usually be delayed until progression of edema threatens or involves center of macula
- treatment of peripheral nonperfusion as visualized on ultra-wide-field FA with scatter photocoagulation does not improve visual acuity or retinal thickening in eyes with DME

Pars plana vitrectomy
- indications
  - macular traction from
    - epiretinal membrane
    - posterior hyaloid
    - creation of PVD or epiretinal membrane peeling can be effective in reducing retinal thickening
  - first-line therapy without macular traction
    - more widely used outside US
- outcome
  - generally improves retinal thickening
  - inconsistent effects on visual acuity
    - substantial vision gain or loss after vitrectomy
- DRCR.net Protocol D
  - vitrectomy reduced retinal thickening in most eyes with DME and vitreomacular traction
  - median visual acuity remained unchanged over 6-month
    - 38% gained ≥ 10 letters
    - 22% lost ≥ 10 letters