New Developments in the treatment of Diabetic Retinopathy

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• Management of diabetic retinopathy
  — Interventions
    a. primary (prevention)
    b. secondary (treatment options for DRP)
  — What does it mean for everyday practice?
Management of diabetic retinopathy

Primary intervention

• Glycemic control
  Intensive control (HbA1c = 7.2%) vs conventional control (HbA1c = 9.1%)*
  – Reduction of incidence of DRP by 76%
  – Reduction of progression of DRP by 54%

• Blood pressure control
  Tight blood pressure (<150/<85 mm Hg) control vs conventional control (<180/<105 mm Hg) **
  – 34% reduction in DRP progression
  – 47% reduction in visual acuity deterioration
  – 35% reduction in laser photocoagulation

• Lipid-lowering therapy
  Dyslipidemia increases the risk of DRP, especially diabetic macular edema

* The Diabetes Control and Complications Trial (DCCT) - 6.5 years of follow-up
** United Kingdom Prospective Diabetes Study (UKPD) – 9 years of follow-up
Management of diabetic retinopathy

Secondary intervention

- Laser intervention
  - Severe nonproliferative and proliferative DRP
  - Diabetic macular edema

- Interventions with intravitreal agents
  - Corticosteroids
  - Anti-angiogenesis agents

- Surgical intervention
  - Vitrectomy for vitreous hemorrhage and proliferative DRP
  - Vitrectomy for other reasons such as diabetic macular edema
Management of diabetic retinopathy

**Secondary intervention**

- **Medical intervention**
  - Anti-platelet agents
  - Protein Kinase C inhibitors (Ruboxystaurin)

- **Laser intervention**
  - Severe nonproliferative and proliferative DRP
  - Diabetic macular edema

- **Interventions with intravitreal agents**
  - Corticosteroids
  - Anti-angiogenesis agents

- **Surgical intervention**
  - Vitrectomy for diabetic macular edema
  - Vitrectomy for vitreous hemorrhage and proliferative DRP
Medical intervention

- Antiplatelet agents
  - 650 mg aspirin has no effect on DRP (positive or negative) – ETDRS
  - Circumstantial evidence that aspirin may delay the incidence of DRP
Medical intervention

- Protein kinase C (PKC) inhibitors

Non-selective PKC inhibitors: side-effects

Ruboxistaurin (PKC-β inhibitor)
- Phase II and III
- Therapeutically effective:
  - Preventing visual loss
  - Resolution of macular edema
  - No effect on progression from NPDR to PDR
- Limited side-effects

Hyperglycemia → Diacylglycerol (DAG) → Protein kinase C activation

- Decreased retinal bloodflow
- Thickening of basement membrane
- Enhancement of capillary permeability
Medical intervention

- Octreotride (synthetic analogue of somatostatin)

- Aldose reductase inhibitors
  - RCTs: sordinil and tolrestat
  - No effect on DRP incidence or progression 3-5 years
Laser intervention

Nonproliferative and proliferative DRP

Mild and moderate nonproliferative DRP
• No photocoagulation (unless for macular edema)

Severe and very severe nonproliferative DRP (4-2-1 rule)
• Consider panretinal photocoagulation, especially for:
  – Type II diabetes
  – Impending cataract surgery
  – Pregnancy

Proliferative DRP
• Panretinal photocoagulation generally indicated.

High risk proliferative DRP
• Panretinal photocoagulation
• Vitrectomy
Diabetic macular edema

- Clinical significant macular edema (CSME)
  - Focal laser treatment
  - Grid laser treatment
Retinal thickening ≤ 500 µm of center
Hard exsudates at or within 500 of center (if adjacent retina is thickened)
Thickening 1 disc area or larger if within 1 disc diameter of center.
Not clinically significant
1 disc diameter
Not clinically significant
**Triamcinolone (IVTA)**

- Several small RCTs show improvement in macular edema and visual acuity

- RCT (n=69, follow-up 2 years)
  - Twice the chance of improved visual acuity
  - Half the chance of visual loss

- Significant disadvantages
  - Significant side-effects
    - Cataract (50%)
    - Elevated intraocular pressure (40%)
    - Medically uncontrollable glaucoma (1-2%)
    - Endophthalmitis (1:1000)
  - Repeat injections may be necessary (duration of effect is approximately 6-9 months for 20 mg – 2-4 months for 4 mg)
Intravitreal agents

Triamcinolon (IVTA)

- Suggestions for use:
  - In diabetic macula edema
  - An option in refractory cases
  - An option in very pronounced, diffuse edema
  - Consider a combination with focal / grid laser after 4-6 weeks
**Anti-angiogenic agents**

- Three trials
  - Finished (phase II) Pegaptanib (Macugen®)
    - 172 patients with DME
    - 34% versus 10% improvement of ≥ 10 letters
    - decrease in macular thickness
  - Ongoing
    - Ranibizumab (Lucentis®) - RESOLVE study
    - Bevacizumab (Avastin®) - US National Eye Institute
Anti-angiogenic agents

• Suggestions for use:
  – Perhaps in diabetic macular edema (glaucoma patients / steroid responders)
  – In case of very severe proliferations
    a. Neovascular glaucoma
    b. Very severe retinal proliferies
    c. Always additional treatment necessary!
Vitrectomy

- Guideline indications
  - Dense nonclearing vitreous hemorrhage
  - Tractional retinal detachment involving or threatening the macula
Surgical intervention

Vitrectomy

- The role of vitrectomy has expanded:
  - Recurrent vitreous hemorrhage despite maximal PRP
  - Diabetic macular edema in combination with vitreous traction
  - Diabetic macular edema evidence of traction
  - Progressive PDR despite laser (especially type I)
Surgical intervention
Surgical intervention

Vitrectomy

• Important:
  – Create a posterior vitreous detachment
  – In case of traction, consider removing the ILM to ensure complete removal of tractional membranes
  – Consider very peripheral laser
Ischemia and proliferations
Ischemia and proliferations

Laser treatment

Cryo therapy
Ischemia and proliferations

- Laser treatment
- Cryo therapy
- Vitrectomy + endolaser
Ischemia and proliferations

- Laser treatment
- Cryo therapy
- Vitrectomy + endolaser

Laser treatment

Very severe proliferations

Anti-angiogenic agents
Diabetic macular edema?
Diabetic macular edema

Vitreomacular traction

Vitrectomy
Diabetic macular edema

- Focal
- Diffuse
  - Vitreomacular traction
  - Laser treatment
  - Vitrectomy
  - Angiogram
Diabetic macular edema

- Focal
- Diffuse

Vitreomacular traction

Laser treatment

Vitrectomy

IVTA
Diabetic macular edema

- Focal
- Diffuse

Laser treatment

Vitreomacular traction

Unresponsive
- OCT
- Angiogram

Vitrectomy
Diabetic macular edema

- **Vitreomacular traction**
- **Focal**
- **Diffuse**
  - **Laser treatment**
  - **Unresponsive**
    - **OCT Angiogram**
      - Diffuse edema no traction
- **Vitrectomy**
Diabetic macular edema

Vitreomacular traction

Focal

Laser treatment

Diffuse

Unresponsive

OCT

Angiogram

Diffuse edema no traction

Vitrectomy

IVTA (α-VEGF)
The End