**DIABETIC RETINOPATHY UPDATE**

Understanding pathogenesis, new trials and advances in our management.

Professor Ian McAllister
Lions Eye Institute
Perth

November 2018

---

**1 out of 3 diabetic patients worldwide currently have DR**

This represents 93 million people worldwide

Number of patients (aged 20-79 years) with diabetic retinopathy worldwide, 2010 (estimation)

<table>
<thead>
<tr>
<th>No. of patients with DR (millions)</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic Retinopathy</td>
<td>93</td>
</tr>
<tr>
<td>Proliferative DR</td>
<td>17</td>
</tr>
<tr>
<td>Sight-threatening DMO</td>
<td>21</td>
</tr>
<tr>
<td>Sight-threatening DMO</td>
<td>20</td>
</tr>
</tbody>
</table>

---

**Screening for diabetic retinopathy**

- **Adults with type 1 diabetes** should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist within 5 years after the onset of diabetes.
- **Patients with type 2 diabetes** should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist shortly after the diagnosis of diabetes.

If there is no evidence of retinopathy, for one or more eye exams, then exams every 2 years may be considered.

If diabetes retinopathy is present, subsequent examinations for type 1 and type 2 diabetic patients should be repeated annually by an ophthalmologist or optometrist. If retinopathy is progressing or sight-threatening, then examinations will be required more frequently.

Women with preexisting diabetes who are planning pregnancy or who have become pregnant should have a comprehensive eye examination and be counselled on the risk of development and/or progression of diabetic retinopathy. Eye examination should occur in the first trimester with close follow-up throughout pregnancy and no 1 year postpartum.

---

**Pathogenesis of Diabetic Retinopathy**

Diabetic retinopathy results from a complex interplay between neurological and vascular damage that results from hyperglycaemia-induced metabolic stress. From the microvascular perspective, hypoperfusion early in the disease due to the loss of cells making up the endothelium ultimately leads to compensatory growth of new fragile and leaky blood vessels. Compromise of the blood retinal barrier integrity leads to the extravasation of fluid and inflammatory mediators, creating sight threatening oedema and exacerbating inflammatory conditions. Concurrent or preceding neurological dysfunction perpetuates damage.

---

**Diabetic Retinopathy**

Schematic overview of the pathogenesis of diabetic retinopathy

---

**Understanding pathogenesis, new trials and advances in our management.**

- Professor Ian McAllister
- Lions Eye Institute
- Perth

**November 2018**

- Diseases and Health Care: Diabetes Care. 2012;35:556-64.
- VTDR: Vision-threatening diabetic retinopathy
Risk factors for diabetic retinopathy

1. duration of diabetes
2. glycaemic control (DCCT)
3. microalbuminuria
4. serum lipids: elevated plasma cholesterol is associated with increased risk of hard exudates and is an independent risk factor for visual impairment
5. hypertension
6. pregnancy

Treatments for diabetic retinopathy

- Risk factor correction
- Laser
  - Panretinal for PDR
  - Focal for macular oedema
- Intravitreal corticosteroids
  - Triamcinolone
  - Dexamethasone implant eg Osuredes
- Intravitreal anti-VEGF agents
  - Avastin
  - Lucentis
  - Eylea
- Vitrectomy surgery for vitreous haemorrhage, tractional retinal detachment
- Systemic treatments
  - Fenofibrates

Regression of new vessels after pan retinal laser (PRP)
Minimal signs of retinopathy seen in this well controlled type 1 diabetic of 30 years however the FA shows extensive mid-peripheral ischaemia and early neovascularization requiring peripheral pan retinal photocoagulation.

Super wide angle (180-degree) colour photos and fluorescein angiogram

Diabetic macular oedema (DMO) is the major cause of legal blindness in the working population in western world.

A bilateral case of severe DMO documented by colour photos, fluorescein angiography and OCT

Risk of focal grid photocoagulation for diabetic macular oedema

- Laser scar expansion
- Paracentral scotomata
- Elevation of central visual field thresholds
- Secondary choroidal neovascularisation
- Subretinal fibrosis
- Alteration in colour perception

(Peripheral pan-retinal laser for proliferative diabetic retinopathy can cause – constriction of the peripheral visual field, reduction in night vision and contrast sensitivity)

Consequences of DMO:
Intra- and extra-retinal lesions

Colour photographs, FA and corresponding OCT in severe DMO
Consequences of DMO:
Intra- and extra-retinal lesions

Colour photographs and corresponding OCT in severe DMO

Intravitreal Injections for DMO

- Avastin
- Lucentis
- Eylea
- Triamcinolone
- Osurdex (Dexamethasone implant)

Osurdex dexamethasone implant

Injection volume 0.05cc

Mean change in BCVA from baseline over time (RESTORE study)

Patients receiving DEX PS DDS* generally showed greater improvements in mean BCVA from baseline during the study compared with sham

166 year old type 2 diabetic, DMO 8 months, laser grid X 2 with minimal effect, VA 6/18
2 years later, 9 injections of Avastin (treat and extend), VA now 6/7.5, last injection 4 months ago
Anti-VEGF for management of DME – Key points

Efficacy
- Effective and fast acting
- Targets one mediator: VEGF
- Real-life data differs from study data – Outcome depends on # of injections and baseline VA
- Not all patients respond the same – Approx. 20–40% of patients are insufficient responders
- Some patients become resistant or develop rebound oedema

Safety
- Generally low risk of serious systemic adverse events
- However, caution should be exercised when treating patients with a recent (3–6 months) CV event
- Possible increased risk of arterial thromboembolic events following intravitreal use of anti-VEGFs, but evidence is inconsistent
- Risk for compliance/capacity issues

Dexamethasone implant – Key points

Efficacy
- Targets multiple inflammatory mediators, not only VEGF
- Good efficacy, in both short and long duration DME patients
- Fast acting and long duration
- Patient suitability (in accordance with licence)
- Low injection regimes, which means less burden for healthcare system and patients
- Patients may respond after unresponsiveness to anti-VEGF therapies
- Patients previously treated with laser therapy or anti-VEGF therapies can be treated with DEX

Safety
- Increase of IOP (normally transient) and cataract
- Minimal or no systemic side effects (limited systemic circulation)

Pars plana vitrectomy

Vitrectomy with removal of cortical vitreous & epiretinal membranes

Fenofibrate: Key Point Summary

- Fenofibrate, classically used as a lipid-modifying agent, is a systemic treatment option that delays DR progression at any stage of the disease
- In ACCORD Eye, fenofibrate reduced the progression of diabetic retinopathy by 40% (p=0.036). This benefit was independent of glycaemic control or other risk factors
- In the FIELD Study, fenofibrate significantly reduced the need for a first laser treatment for DR by 31% (p=0.0002)
- The mechanism of action of fenofibrate in DR is not fully understood, but appears to be independent of its lipid-modifying effects

Fenofibrate provides a systemic treatment option to reduce DR progression at early stages

- Fenofibrate is approved in Australia for use at any stage of DR.
- It can be given to any patient with existing DR regardless of baseline lipid levels or HbA1c.
- Unlike current standard therapy, laser treatment, fenofibrate is non-invasive and there is no risk of ocular side effects

Lipidil is indicated for the reduction in the progression of diabetic retinopathy in patients with type 2 diabetes and existing diabetic retinopathy. Lipidil does not replace the appropriate control of blood pressure, blood glucose and blood lipids in reducing the progression of diabetic retinopathy
**Two Ph III studies in ~36 Countries, ~200 sites**

- UK, US, Canada, Latin America

**Three arms:**
- Brolucizumab 3 mg, Brolucizumab 6 mg or aflibercept 2 mg via 1:1:1
- Total enrollment of 534 patients (178 per arm)

**Two arms:**
- Brolucizumab 6 mg and aflibercept 2 mg via 1:1
- Total enrollment of 356 patients (178 per arm)

**Brolucizumab:** Longer acting VEGF antibody fragment