College guideline for diabetic retinopathy

Karen Wong

Hillingdon Hospital

Level of Evidence

- **Level 1**: evidence based on results of RCTs power calculations or other recognised means to determine statistical validity of the conclusion

- **Level 2**: evidence based on results of case studies, case series/ other randomise prospective or retrospective analysis of patient data

- **Level 3**: evidence based on expert opinion, consensus opinion or current recognized standard of care criteria. (no case series available

Level of Recommendations

- **Level A :** strength of evidence was universally agreed
- **Level B:** where the probability of benefit to the patient outweighed the risk
- **Level C:** Difference of opinion was recognised as to the likely benefit to the patient and decision to treat would be based after discussion with the patient

Management of Diabetic Retinopathy

- Vision loss from diabetic retinopathy mainly occurs by
  - Complications of PDR affecting macular
  - Loss of peripheral visual field resulting from ischaemia or as a result of laser treatment related damage

- Diabetic Retinopathy Study (DRS)
  - 60% reduction of severe visual loss in eyes treated with argon laser compared with control at 2 years

- Early treatment diabetic retinopathy study (ETDRS)
  - Recruited pts with non proliferative retinopathy or Proliferative retinopathy w/o high risk characteristics to determine optimal stage of PRP laser.
  - Early treatment group – 5 years risk of severe visual loss/vitty 2-6% compare with 4-10 % in deferred group.

Current recommendation

- Background retinopathy
  - No treatment
  - Monitored with annual digital photography in screening program
  - Opimise care of diabetic control

- Pre proliferative
  - Regular slit lamp biomicroscopy for feature of retinal ischaemia (Level A)
  - 4-6 months
  - Digital fundus colour photo as adjunct (Level B) +/- FFA
  - Consider Early PRP in very severe non proliferative retinopathy (48.5% risk of progression to high risk PDR in a year)
  - Early treatment Can reduce progression to high risk PDR by 50%

- PRP should be considered for pre proliferative DR:
  - In older patients with type 2 diabetics (Level 1)
  - Retinal view is difficult
  - Prior to cataract surgery: as inflammation can be associated with progression
  - In ONLY eye where 1st eye was lost to PDR
  - Regular clinic attendance is likely poor
  - Difficult to examine pt due to other reason

- Proliferative diabetic retinopathy
  - Full PRP for NVD, NVE
  - Delivered same day or within 2 weeks of diagnosis (Level A)
  - Baseline FFA to assess macular perfusion, retinal ischaemia; should not delay PRP (Level B)

  - **Technique:**
  - 1. Rx of all quadrants of pre and post equatorial retina outside macular vascular arcades
  - 2. emphasis on ischaemic retina near NVE but avoid direct NV application
  - 3. burn power enough to create grey white retinal response
  - 300-400microns burn size, 10-50ms duration, 1-1.5 spacing (532nm argon green laser)
  - Titrate energy when lasering periphery

  - Reduce SVL by 50-70%

Laser strategy

- Early PDR
  - Early NVE/NVD, NV complex flat and < 1/3 of disc diameter
  - PRP should be completed by 2/52 (1200-1800 burns)
  - If shorter duration used (20ms), consider increasing number of laser burns
  - Review 4/12

- Moderate PDR
  - NVD >1/3 disc diameter, forward NVD extending beyond disc margin of NVE: complexs in all quadrants, forward NVE in any quadrant
  - Primary PRP completed by 2/52 (2000-2500 burns), completed over 4 weeks
  - Review 3/12. sooner if poorly controlled

- Severe PDR
  - Large NVE complex in any quadrant, NVE with TRD, Large, forward NVD covering whole OD, NVD with TRD
  - Full PRP coverage of peripheral retina (3000 burns) over 2-3 sessions in 3-4 weeks
  - Complete over 4 weeks with more laser spots in initial sessions

  - **Young patients with type 1 diabetes with PDR**
  - Usually show macular ischaemia on pre laser FFA
  - Increase risk of macular oedema post PRP if too may burns applied
  - **Advise total laser burn to be delivered over 3-4 sessions within 4 weeks**

When to stop?

- Regression of new vessel: blunting of NV growing tips or replacement with fibrosis
- In advance cases new vessels may persist despite full PRP. (Level A) Such stable NVs require monitoring but probably do not require further PRP
- FFA may be repeated if in doubt
- Consider vitrectomy with endolaser of active neovascularisation despite comprehensive laser treatment

- Advanced PDR
  - When PRP appear to have little effect on new vessel progression, development of TRD, hagm, consider EARLY VITRECTOMY to preserve sight in type 1 diabetics
  - EARLY vitrectomy if delay in applying PRP 2y to vitreous haemorrhage or poor retinal view.
  - Consider Intravitreal anti VEFG injection prior to vitty to reduce risk of intraoperative complication and surgical time (Level 1)

Diabetic maculopathy treatment

- ETDRS:
  - For eyes with CSMO, moderate visual loss (15 or more letter loss in ETDRS charts) was reduced from 24% to 12 % at 3 years with prompt treatment

  - CSMO:
  - Retinal thickening at or within 500 microns of fovea
  - Hard exudates at or within 500 microns of the fovea if associated with adj. retinal thickening
  - Area of retinal thickening one disc area in size, at least part of which is within one disc diameter of fovea

- Photocoagulation using modified ETDRS protocol (Level 1)
  - All leaking MA 500-3000 microns from fovea reacted directly with 50 microns spot, 0.05-0.1s
  - Greyish reaction beneath MA needed. Grid Rx was performed to areas of retinal thickening
  - Grid was performed from 500-3000 microns superiorly and inferiorly and to 3500 microns temporary. 2 burn width apart, NO BURN within 500 microns of disc

- Emerging evidence to suggest similar outcome can be achieved with subthreshold micropulse diode laser (Level 2)

- Intravitreal antiVEGF with prompt or delayed focal laser is most effective in preserving vision when centre involved macular oedema is present and VA reduced to 20/32 or less (Level 1)

Intravitreal steroid treatment

- Preservative free intravitreal triamcinolone monotherapy is INFERIOR to laser treatment at 3 years f/u (level 1) DRCRnet study
- Intravitreal PF triamcnolone combined with laser is also INFERIOR to ranibizumab with immediate or deferred laser, except with patients who are pseudophakic (Level 1)- DRCRnet group study
- Fluocinolone slow release implant (Iluvien) is effective in treatment of DMO (Level 1) – FAME study (licensed for use in UK esp in unresponsive case)
  - High rate of increased IOP and cataract need to be considered
- Other steroid drug deliver systems in development awaiting result (I-vation) – Triamcinolone acetonide trans-scleral helical implant

Intravitreal VEGF inhibitors

- Pegaptanib (Macugen)
- 172 patients
  - At wk 36, median VA was better with 0.3mg group compared with sham (34% improved VA vs 10%)
  - Mean CRT decreased by 68 microns in 0.3 gp vs increase of 4 microns in sham (p=0.02)
  - No difference in difference dose of pegaptanib (0.3, 1mg, 3mg)

- Ranibizumab

- RESOLVE
  - Safety and efficacy of ranibizumab in treatment of DMO at 12 mths (0.3mg ranibizumab/ 0.5mg ranibizumab/sham)
  - 3 initial monthly injection
  - Thereafter can receive laser Rx if required
  - At 12 months, treatment arms has mean gain of 10.3 letters vs decline of 1.4 letters in sham ($p<0.0001$)

- RESTORE
  - Ranibizumab 0.5mg + sham laser/ranibizumab + active laser/ sham inj + active laser
  - Gain of 6.1 letters for ranibizumab monotherapy vs 0.8 letters who received laser alone ($p<0.0001$)
  - Combined gp; gain of 5.9 letters

- DRCRnet study

  - 0.5mg ranibizumab + prompt laser Rx
  - 0.5mg inj + deferred laser (at least 24 wks later)
  - 4mg IVTA with prompt laser
  - Sham inj with prompt laser

  - Pt with VA 6/9-6/90 + Central subfield thickness of >250 microns recruited
  - 4 monthly loading dose
  - Retreat if VA <84 letters with evidence of improvement (10% reduction of Central thickness or VA improved by 5 letters or more)

  - At 1 yr, 0.5mg inj group combined with prompt or deferred laser Rx showed SUPERIOR improvement in BCVA compare with Laser alone
  - Subgroup analysis: in pseudophakic pt at baseline, improvement in BCVA is similar in IVTA gp vs inj gp. Hence initial finding of no significant BCVA improvement could be due to cataract formation in phakic pt.

Bevacizumab

- BOLT study (80)
  - DMO patients receiving either 1.25mg IVB or laser
  - 3 injections at 6 wks interval, then prn 6 weekly thereafter
  - 1 yr follow up, inj gp gain 8 ETDRS letter vs loss of 0.5 ETDRS letters in laser gp (p-0.0002)
- Ahmadieh et al. (115)
  - Sham/ 1.25mg IVB x3/ combined IVB 1.25mg + 2mg IVTA follow by 2 inj of IVB at 6 weeks interval
  - Both Rx groups has better VA compare with sham group. No different btw Rx gps
- PACORES study (139)/ Lam et al. (52)
  - no significant difference in outcome between those given 1.25mg dose of inj vs 2.5mg dose

Aflibercept (VEGF- Trap-Eye)

- Soluble VEGF receptor fusion protein binds to all isoforms of VEGF-A
- Higher binding affinity compared to ranibizumab and bevacizumab hence longer duration of action
- DAVINCI study:
  - Mean gain in VA at 1 year = 9.7 letters in 2mg 8 weekly gp
  - 12 letters in 2mg Prn group
  - 13.1 letters in 2mg 4 weekly group
  - -1.3 letters in laser treated group (level 1)

CSMO	Centre involved?	VA	Phakic?	OCT	Rx
YES	NO		Either		Laser
YES	YES	Normal /min. reduced (>78 letters)	Either		Laser or observe if leak v close to fovea /not safe to laser
YES	YES	78-24 letters	Either	>250 microns central subfield thickness	VEGF inj +/- laser. If non responder, consider IVTA implant
YES	YES	78-24 letters	Pseudophakic	>250 microns central subfield thickness	VEGF inj OR IVTA +/- laser OR fluocinolone (Iluvien) implant if unresponsive to other Rx

Pt with maculopathy in presence of retinal vascularisation

- Rx Depends on age of pt and relative severity of retinopathy

- In young patients with active V, treat the new vessels first with PRP (or concurrently with macular laser)
  - As NV in these pts may run an aggressive course
  - To fractionate PRP into multiple sessions to avoid exacerbation of macular odedma

- In those with lower risk of PDR, to treat macular first or concurrently with PRP

Diabetic retinopathy in Pregnancy

Type 1 Diabetics:

- 63% have retinopathy in at least 1 eye in early pregnancy
- Progression occurs in 27%
- Not associated with post partum worsening of retinopathy followed for 5 years after delivery

Type 2 Diabetics:

- Known duration often short
- 14% was noted to have retinopathy in early pregnancy
- Progression only in minority (Level 2)

Pre conception care

- Should be informed about the need for assessment of diabetic retinopathy before and during pregnancy (Level A)

- Statins and renin angiotensin system blocking drugs should be **DISCONTINUED** before conception (and at 1st antenatal booking if not done prior) (Level A)

- Rapid optimisation of poor glycaemic control should be **DEFERRED** at least **till after retinal assessment** (Level B)

Retinal assessment during pregnancy

- Those with pre existing diabetics should be offered retinal assessment by DIGITAL IMAGING following
  - 1st antenatal clinic appt
  - At 28 weeks (if 1st appt result is normal)
  - Addition screening at 16-20 weeks if 1st screen show retinopathy (Level A)

- Those with pre-proliferative diabetic retinopathy diagnosed during pregnancy should have ophthalmic follow up for **AT LEAST 6 MONTHS** following birth of baby (Level A)

- **TROPICAMIDE ALONE** should be use if mydriasis is required during pregnancy (Level A)

- Diabetic retinopathy **SHOULD NOT** be considered as a contraindication to rapid optimisation of glycaemic control in women who present with a high HbA1C in early pregnancy however **RETINAL ASSESSMENT IS ESSENTIAL** (Level A)

- Diabetic retinopathy should not be considered a contraindication to vaginal birth (Level A)

- PDR in pregnancy can deteriorate rapidly and requires closer monitoring. Prompt laser treatment is required.

- Review should be at **2 WEEKS following primary PRP Treatment**

- Adequately treated PDR during pregnancy is not a contraindication to normal vaginal delivery

- MDTs approach is essential in planning management in such cases involving obstetrician, diabetologist and ophthalmologists (Level A)

DR in children & adolescents

- Prevalece of DR during adolescence (T1DM)

AGE AT FUNDUS PHOTO	PREVALANCE
10-13 YRS	1`%
14-15 YEARS	5.8%
16-18 YEARS	17.7%

Prevalence of DR 6 years after diagnosis T1DM)

Under age 11	8%
Pre pubertal children	12%
Adolescents	25%
Pubertal adolescent	19%

- In young ppl, T2DM develops at around 13.5 years during peak of physiological puberty

- More common in non Caucasians
- Higher rate of obesity and hypertension

- WESDR identified adolescent age 15-19 have the HIGHEST rate of progression to sight threatening disease within 10 yrs compared with paediatric or adult patients

Management

- Early counselling for both young person and family
- MDT approach
- TIDM: dilated fundus photography annually from age 12 ? 10 in future (Level 2)
- Children and adolescents with T2DM should undergo dilated fundus photography ANNUALLY from diagnosis (Level B)

THANK YOU