

Summary of Diabetic Retinopathy Studies

The Diabetes Control and Complications Trial (DCCT) (*NEJM* 1993;329:977-86)

Introduction: The DCCT was a multi center, randomized clinical trial designed to compare intensive with conventional diabetes therapy with regard to their effects on the development and progression of diabetic retinopathy.

Methods:

- ☞ 1441 patients, 29 centers, all IDDM
- ☞ Two cohorts: 1) Primary intervention → no DR, 2) Secondary Intervention → mild to moderate DR (used ETDRS criteria).

Treatment and Follow up:

- ☞ Conventional tx consisted of 1 to 2 injections of insulin. Intensive tx consisted of three or more injections or insulin pump.

Outcome:

- ☞ 25 steps graded, three step change sustained for 6 months.
- ☞ Severe NPDR
- ☞ PDR

Results:

- ☞ Primary intervention: Until 36 mths no difference.
>36 mths at least **50%** reduction.
Mean 6 yrs **76%** reduction of DR.
- ☞ Secondary intervention: >36 mths **54%** reduction.
- ☞ 47% reduction in severe DR.

Conclusion: ☞ Intensive tx of glucose in IDDM delays onset and slows progression of DR.

Diabetic Retinopathy Study (DRS)Arch Ophthalmol 97:654-55, 1979 &
Ophthalmology 88:583-600, 1981.**Report 1 of DRS (two years follow up)**

Introduction: The DRS is a randomized controlled clinical trial sponsored by the NEI to evaluate photocoagulation treatment for PDR. Begun in 1971. 1700 patients at 15 centers. Expedited results based on two year follow up.

Eligibility:

- ☞ VA \geq 20/100 in each eye
- ☞ PDR in at least one eye or severe NPDR in both
- ☞ Severe DR defined as 3 of 4:extensive hem/Ma, CWS, IRMA, VB
- ☞ Both eyes suitable for photocoagulation

Follow up & treatment:

- ☞ three month interval
- ☞ One eye of each patient randomly selected for treatment and the other observed.
- ☞ Randomized further to either xenon or argon laser.
- ☞ PRP and focal laser to NV on retinal surface.
- ☞ Standard photo 10a for NVD termed mild.

Study Design:

- ☞ One eye of each patient assigned randomly to PRP +/- focal tx +/- macular tx. The other eye assigned to follow up with no treatment.

Outcome:

- ☞ SVL defined as 5/200 at two consecutive visits 4 months apart.

Results:

| <u>SVL</u> | <u>TX</u> | <u>No Tx Reduction</u> | |
|------------|-----------|------------------------|-----|
| | 4.1% | 9.4% | 54% |

| <u>Recovery VA <5/200</u> | <u>TX</u> | <u>No TX</u> |
|------------------------------|-----------|--------------|
| | 12.2% | 28.6% |

| <u>Cumulative SVL(2yrs)</u> | <u>Tx</u> | <u>No TX Reduction</u> |
|-----------------------------|-----------|------------------------|
| | 6.4% | 16.3% 61% |

Small loss of VA 2 to 4 lines

Argon laser tx > then no tx but same after 2 years.

Xenon laser tx (17.8%) > no tx (8.1%)

VF scores

Same in all groups except xenon.

Cumulative event rate (SVL)

| | | |
|------------------|-----------|--------------|
| <u>No new NV</u> | <u>Tx</u> | <u>no Tx</u> |
| | 2.7% | 2.4% |

| | | |
|------------|-----------|--------------|
| <u>NVE</u> | <u>Tx</u> | <u>no Tx</u> |
| | 4.5% | 9.6% |

| | | | |
|------------|-----------|--------------|------------------|
| <u>NVD</u> | <u>Tx</u> | <u>no TX</u> | <u>Reduction</u> |
| | 8.4% | 24.5% | 66% |

Report 3 further defined as did this article the “high risk” PDR by studying these cumulative risks.

Conclusions:

☞ PRP + focal tx has benefit in reducing event over a two year period. Some evidence that small VA loss & VF loss occurred in xenon group.

☞ High risk PDR was clearly defined. So NVE with VH & all NVD were associated with high occurrence of SVL in untreated compared to treated groups. Follow report 3!

Report 3 of DRS

Identified four retinopathy factors that increase the 2 year risk of developing SVL (<5/200 at 2 visits, 4 mths apart). The risk grows as the number of risk factors grows.

Risk Factors and Associated Risk

| Risk | Risk factor | Risk of SVL |
|------|---|--|
| 1. | Preretinal hemorrhage | Risk of SVL is approx 3 to 6% for any factor alone. Risk of SVL is 6% for two factors. Risk soars to 25 to 35% for 3 risk factors. |
| 2. | NV | |
| 3. | NVD (within 1 dd) | |
| 4. | NVD: 1/4 to 1/3 DA (10a) NVE: 1/2 DA | |

Report 8 of DRS

Introduction: The DRS is a randomized controlled clinical trial sponsored by the NEI to evaluate photocoagulation treatment for PDR.

Eligibility:

- ☞ VA \geq 20/100 in each eye
- ☞ PDR in at least one eye or severe NPDR in both
- ☞ Both eyes suitable for photocoagulation

Follow up & treatment:

- ☞ four month interval
- ☞ Eyes randomized between argon and xenon arc photocoagulation.

DRS Photocoagulation Techniques

| Scatter | Argon | Xenon |
|--------------|------------------------|---------------------------|
| No. Of burns | 800-1600 (500 μ) | 400-800 (3 $^{\circ}$) |
| Size | 500-1000 (1000 μ) | 200-400 (4.5 $^{\circ}$) |
| Exposure | 0.1 sec | not specified |
| Focal | NVE, NVD, CSME | same |

Early Treatment Diabetic Retinopathy Study (ETDRS)

Report #1: Photocoagulation for Diabetic Macular Edema

Introduction: The ETDRS is a NEI supported multi center, randomized clinical trial designed to answer the following three major questions:

- 1) When in the course of DR is it most effective to initiate PRP?
- 2) Is photocoagulation effective in the TX of macular edema?
- 3) Is ASA TX effective in altering the course of DR?

Report 1 only deals with question 2. 29 centers involved.

Patients/Methods: April 1980 to August 1985 3,928 patients were enrolled. Patients had early PDR, mild to severe NPDR and/or macular edema in each eye.

Eligibility: For this study only patient with mild to mod NPDR and macular edema were studied.
VA \leq 20/200 & no other ocular disease.

Study Design: For this part of the study the following eyes were considered. They underwent two randomizations.

- 1) Patients with CSME + mild to mod NPDR → Immediate Photo vs Deferral (until HR/PDR)
- 2) Immediate Photo → Panretinal + f/u focal vs Immediate Focal

Immediate focal vs deferral was compared.

Treatment: Used FA. "Macular edema": retinal thickening 1 DD or HE. CSME.

Focal: Ma and focal leakage sites → 50 to 100 μ argon blue green or green only, 0.1sec to obtain whitening with no Bruch's rupture.

TX >500 μ to 2DD initially. If VA >20/40 + CSME persists than up to 300 μ treated unless perifoveal capillary dropout.

Diffuse: Diffuse leakage or non perfusion within 2 DD of

center tx'd with grid.
 Light to mod intensity burns $\leq 200\mu$ in size. Use 50 to 200 μ . One burn between.
 In papillomacular bundle but not closer than 500 μ from center.

Treatable Lesions

| |
|---|
| Discrete points of retinal hyperfluorescence or leakage (most Ma) |
| Areas of diffuse leakage |
| Ma |
| IRMA |
| Diffuse leaking cap bed |
| Retinal avascular zone |

Outcome: Doubling of visual angle (ie 20/20 to 20/40) called moderate visual loss (corresponds to 15 letters).
 FM 100 hue test. Goldman perimetry.

Without regard to ASA as it didn't really make a difference.

Follow up: 6 weeks than every 4 months.

Results: **VA**
Risk of MVL(same for %eyes VA>20/100)

| Time | Treatment | Control | Reduction |
|---------|-----------|---------|-----------|
| 1 year | 5% | 8% | 50% |
| 2 years | 7% | 16% | 50% |
| 3 years | 12% | 24% | 50% |

Key points:

- ☞ Visual prognosis worse in eyes with low VA at baseline. But if Va was >20/40 then improvement of 6 letters on avg. Not much improvement with good initial improvement.
- ☞ Beneficial effect demonstrated in eyes with CSME and **not** in **NON-CSME** eyes. Non CSME eyes developed CSME at the same rate with or without treatment.
- ☞ Pretreatment 75% had RT. At one year 35% in tx group had RT whereas 63% in deferral group did.
- ☞ Small statistically insignificant differences observed in tx vs no tx with VF. No difference with FM-100 observed.

- Conclusions:
- 1) Most people use argon green laser to avoid xanthophyll uptake with blue wavelength.
 - 2) Diffuse leakage carries worse prognosis
 - 3) Focal and grid treatment is indicated for CSME. Need CLE to detect RT & do as soon as CSME. Even good acuity benefits.

Report #2 of the ETDRS

Purpose: To define CSME & define “treatable lesions”.

- CSME:
- 1) RT $\leq 500 \mu\text{m}$ from center.
 - 2) HE $\leq 500 \mu\text{m}$ from center with assoc RT.
 - 3) 1 DA of RT. within 1 DD from center.

Treatable lesions:

Directed at all lesions 2DD from center defined as “treatable” if associated with RT.

- 1) Discrete points of retinal hyper fluorescence or leakage (most Ma) that were $500\mu\text{m}$ from center.
- 2) Focal leaks 300 to $500 \mu\text{m}$ from center.
- 3) Areas of diffuse leakage

Ma
IRMA

- 4) Diffuse leaking cap bed
- 5) Retinal avascular zone outside 500μ only (other than FAZ)

Treatment techniques:

- Focal:
- 1) Ma and focal leakage sites \rightarrow 50 to 100μ argon blue green or green only, 0.1sec to obtain whitening with no Bruch’s rupture. Avoid flame hem & D/B heme ($>125\mu$). If within $500 \mu\text{m}$ 50μ and 0.05 sec.
 - 2) TX $>500\mu$ to 2DD initially. If VA $>20/40$ + CSME persists than up to 300μ treated unless perifoveal capillary dropout.

- Diffuse:
- 1) Diffuse leakage or non perfusion within 2 DD of center tx’d with grid.
 - 2) Light to mod intensity burns 50 to 200μ in size. Use 50 to 200μ . One burn between.
 - 3) In papillomacular bundle but not closer than 500μ from center.

Follow up treatment:

4 months after initial treatment and 4 month intervals thereafter if CSME then additional treatment.

Clinical guidelines:

- 1) ETDRS did not address the timing of macular laser. But since tx only preserves vision then seems stupid to wait for worsening. PRP and cataract surgery worsen the edema.
- 2) Treatment for RT in center requires judgement as to timing.
HE with RT 500 μ less urgent.
RT 1DA within 1 DD less urgent still.

ETDRS (taken from Jakobiec)

- Eligibility:
1. VA \geq 20/40
 2. Mild NPDR to non high risk PDR +/-mac edema
 3. Both eyes suitable for photocoagulation

- Major Design Features:
- 1) One eye of each pt assigned randomly to early PRP and the other to deferral (careful f/u and PRP if high risk PRP develops)
 - 2) Pts assigned to ASA vs placebo

- Conclusions:
- 1) Both early and deferral were followed by low rates of SVL.
After 5 years SVL deferral 2-10%
After 5 years SVL early 2-6%
 - 2) PRP is not indicated for mild to moderate NPDR but should be considered as retinopathy approaches the high risk stage and usually should not be delayed when high risk stage is present.

The Diabetic Retinopathy Vitrectomy Study Research Group Report #5

Arch Ophthalmol 1990: 108:958-964

Introduction: DRVS is a multi center clinical trial sponsored by the NEI includes a randomized trial of early Vitrectomy for eye with severe vitreous hemorrhage due to DR.

Eligibility:

- ☞ VA \leq 5/200 at two visits for 1 month
- ☞ VH for no more than 6 months (1-6 months)
- ☞ Macula on by U/S
- ☞ Type 1 DM if Dx <20 years and on insulin. Type II if age >40 years or not on insulin.

Major Study Design:

- ☞ One eye eligible.
- ☞ Eligible eyes randomized to either immediate tx or deferral. Deferral group underwent Vitrectomy if VH still present, VA <5/200 after 12 months or if center of macula came off.

Results:

- ☞ Early Vitrectomy group had better chance of VA 20/50 or better at F/U to 4 years if the following: Type I DM, Type I DM less than 20 years. Type I DM >20 years still had benefit but not as great.
- ☞ In most severe PDR >10/20 at 4 years in 50% of early vit group vs. 12% in conventional management
- ☞ No sustained effect in Mixed or Type II DM.
- ☞ Early Vitrectomy group had greater chance of NLP.

Conclusions: ☞ Early Vitrectomy indicated in VH of Type I DM patients.

NB. Also an arm of this study which looked at extensive, active, NV, or fibrovascular proliferations.

Major design same as previous except waiting time was only 6 months.

Chance of VA > 10/20 increased by early Vitrectomy at least in eyes with sever vessels.

Group NR Very severe PDR with useful vision

Eligibility Criteria:

1. VA \geq 20/200
2. Center macula on
3. Extensive, active, neovascular, or fibrovascular proliferations

Major study design: Same as above except conventional tx included Vitrectomy after 6 months

Conclusions: Chance of VA \geq 10/20 increased by early Vitrectomy, at least for eyes with very severe new vessels