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# insight

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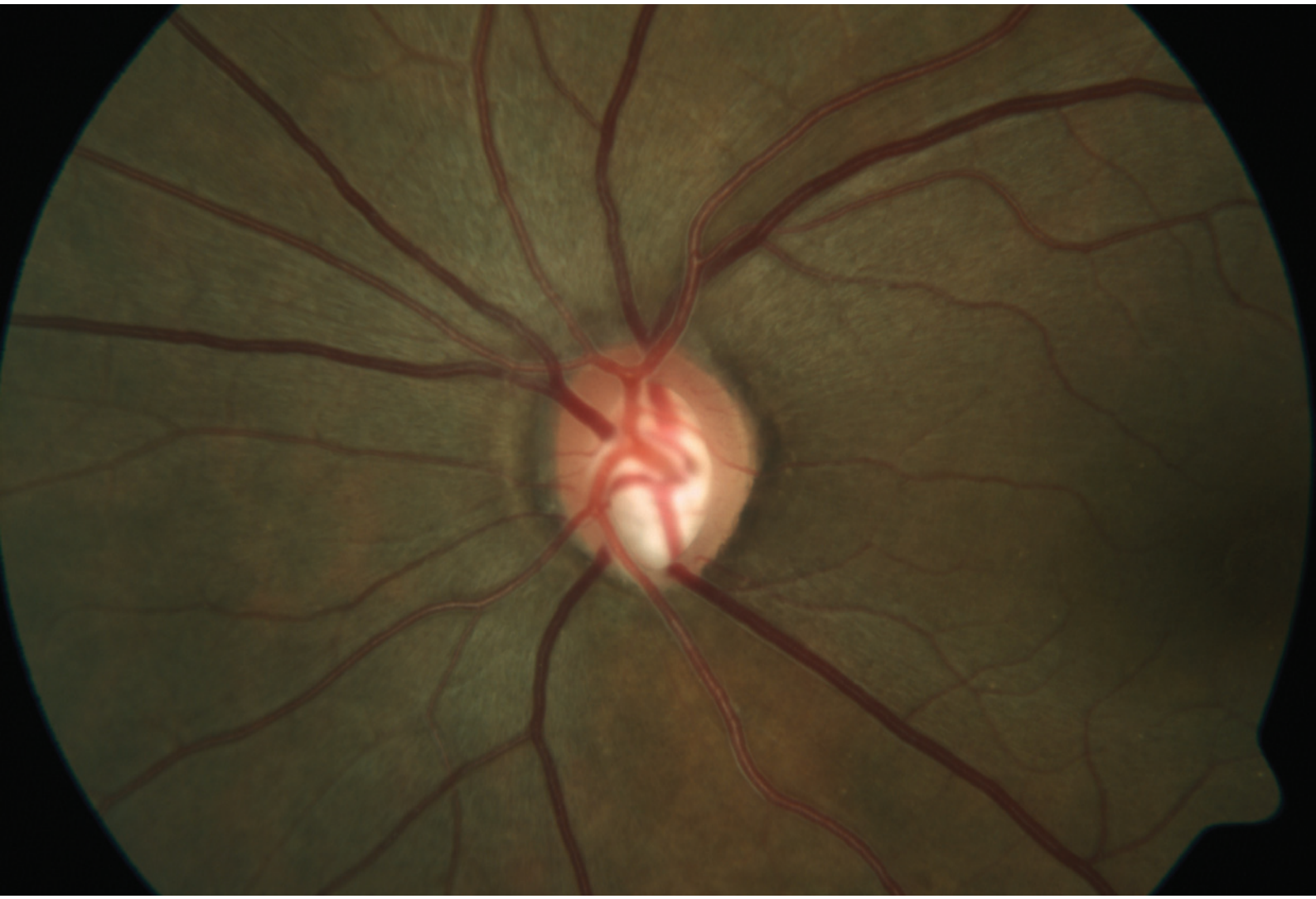

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**Sankara Nethralaya – The Temple of the Eye.**

It was in 1976 when addressing a group of doctors, His Holiness Sri Jayendra Saraswathi, the Sankaracharya of the Kanchi Kamakoti Peetam spoke of the need to create a hospital with a missionary spirit. His words marked the beginning of a long journey to do God's own work. On the command of His Holiness, **Dr. Sengamedu Srinivasa Badrinath**, along with a group of philanthropists founded a charitable not-for-profit eye hospital.

Sankara Nethralaya today has grown into a super specialty institution for ophthalmic care and receives patients from all over the country and abroad. It has gained international excellence and is acclaimed for its quality care and compassion. The Sankara Nethralaya family today has over 1400 individuals with one vision – to propagate the Nethralaya philosophy; the place of our work is an Alaya and Work will be our worship, which we shall do with sincerity, dedication and utmost love with a missionary spirit.

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# Neuroprotection in Glaucoma: Is it a Myth or Reality?

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Glaucoma, an optic neuropathy that results from gradual loss of retinal ganglion cells (RGC) over a period of time, is the second leading cause for blindness worldwide. In the management of glaucoma intraocular pressure (IOP) is the only modifiable risk factor and therapy is targeted towards the reduction of IOP. But there are certain limitations with IOP reduction approach, many patients show progression of disease in spite of IOP reduction, group of open-angle glaucoma patients will have IOP with in normal range and we call them as normal- or low-tension glaucoma and finally not all patients with ocular hypertension get converted to glaucoma. The concern here is mainly with first two groups, there seems to be a role for an IOP independent mechanism. This may be related to the poor perfusion of the optic nerve head because of any cardio vascular issues or death of RGC due to apoptosis. This knowledge has led researchers to look for non-IOP lowering therapy that is likely to cause better survival of RGC and it is called neuroprotection. Unfortunately, the initial study results from animal models never translated to clinical use. The assumed reasons for failure are—animal models use high IOP in normal young animals, study lasts only weeks, where as glaucoma is a chronic neurodegenerative disease and takes years for the progression of the disease. The major limiting factor for any kind of neuroprotection trial is long, chronic, slow progressive nature of glaucoma. The second cause is variable worsening rates among various patients.[1,2] In view of this neuroprotection in glaucoma is still remaining a myth for clinicians. The enthusiasm of researchers has not diminished. Search for a neuroprotection is continuing. Two clinical studies deserve mention when we talk about the neuroprotection and glaucoma. One is Memantine Glaucoma Clinical Trial and the other is the Low-pressure Glaucoma Treatment Study (LoGTS).[3]

Memantine Glaucoma Clinical Trial—Memantine an *N-methyl-D-aspartate* receptor (*NMDA* receptor or NMDAR) antagonist has shown to be a neuroprotective in numerous neurodegenerative diseases. In the memantine study, the drug group was compared with the placebo group in all forms of glaucoma in 1100 patients over a period of 9 years.[1,2] Unfortunately, the study results were never published because neither of the parallel arms met the primary outcome measure. Failure to obtain sufficient information from a long study involving millions of dollars has led people to slow down in neuroprotection research. Still researchers are trying to get the information out of the study mainly to know what went wrong in designing and execution of the study. This knowledge probably will help the researchers for better planning of the future programs. The LoGTS is a multicentric randomized study that compared timolol maleate 0.5% with brimonidine 0.2% on visual function in low-tension glaucoma. Brimonidine group has shown protective effect but had large number of dropouts mainly due to allergy.[3] At least this study suggests the need for further research in this direction.

The disappointments and the frustrations the researchers are facing in the field of neuroprotection are not unique to glaucoma. Similar kinds of problems are encountered in other chronic neurodegenerative diseases. It looks like there is a need to streamline the neuroprotection research to get better outcomes. Randomized trials should have well-defined homogenous glaucomas and outcome measures that involve functional and structural changes. Probably it is worthwhile to try prolonged drug delivery methods such as sub-Tenons or intraocular injections rather than the pills or drops. Hopefully with this the myth may become reality for neuroprotection for glaucoma. This new therapy may offer hope for millions of patients with glaucoma worldwide in combating the blindness.

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# Management of steroid induced ocular hypertension

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## Introduction

Steroids are used in ophthalmic and non-ophthalmic practice for a number of diverse clinical conditions. Like any therapeutic agent, these drugs too have adverse effects, including elevation of intraocular pressure (IOP) and iatrogenic glaucoma – a feature known as steroid responsiveness. Currently, there are no means of accurately predicting the steroid responsiveness in individuals put on steroid therapy. Steroid responsiveness is an inherited trait and complicates some of the steroid regimens with sight threatening consequences. Although predicting or avoiding the steroid responsiveness is not possible, the steroid ocular pressure response (OPR) can be tackled by judicious and careful clinical management.

## When starting steroid

Steroid induced IOP elevation usually occurs within few weeks of commencing the steroid therapy. Whenever starting the steroid therapy, it is prudent to record the baseline IOP and assess risk factors for OPR in all persons. Imaging optic nerve head (ONH) in those at higher risk (*vide infra*) is advisable. Equally important is to warn the patient about possibility of IOP elevation during the course of steroid therapy. This would help in complying with the follow-up regime for IOP monitoring. Monitoring for OPR after starting the steroid therapy by periodic checking of IOP is mandatory. This would help in early identification and prompt intervention for raised IOP.

## Who is at risk?

There are no known biomarkers to predict steroid responsiveness. However, nearly one-third of the population may respond, with an elevation of IOP of more than 6 mmHg. They are labelled as steroid responders. Out of these, 4–6% would respond with an IOP increase of more than 15 mmHg (1). They are called high risk steroid responders.

A subset of the population tends to be in high responder category; including patients of primary open angle glaucoma (POAG), disc suspects and first degree relative of POAG patients (2–4). There are certain other clinical conditions which are also reported to be associated with OPR. It includes but not limited to high (axial) myopia, connective tissue disorders, diabetes mellitus, traumatic angle recession, pigment dispersion syndrome and endogenous hypercortisolism (5–10).

Steroid responsiveness follows a bimodal age distribution. Younger patients (age <10 years) and elderly (>60 years) are more likely to have raised IOP following steroid use. This response tends to be more rapid and severe, then other age groups. In children, presser response tends to be greater and peak early (11).

Assessment of pre-existing risk factors for OPR would help in deciding mode of therapy, as some mode of therapy can be discontinued easily, where others are not easily reversed, if untoward rise in IOP occurs.

## Natural course of OPR

Corticosteroids have been shown to cause a rise in IOP through all modes of administration (12). However, presser response varies with pharmacodynamic factors viz. the type of steroid, the route of administration, dosage formulation and the duration of steroid use. In simple parlance, the closer the site of steroid administration is to the eye, the more likely the OPR. Generally, the ocular and periocular administration of steroid produces early and intense OPR than non-ophthalmic locally administered or systemic administration of steroids. Importantly, a patient's response to topical steroids does not predict the response to periocular steroids.

The presser response after topical steroids varies with type of steroid formulation (Table 1). However, in general, with topical steroid therapy,

**Table 1.** Incidence, time course and risk factors for OPR with different routes of steroid administration.

| Route of administration | IOP response | | | Risk factors for IOP elevation |
|---|---|---|---|---|
| | Timing of elevation* (in weeks) | Response level** (%) | Timing of reversal*** (in weeks) | |
| Topical | 3–6 | 20 | 1–4 | POAG, OHT, PDS, DM, RA |
| IVTA | 4–8 | 30–50 | 16–24 | Young age, high myopia, non-vitrectomized eyes, multiple injections (1) |
| Periocular | 2–20 | 50–80 | 20–40 | Depot preparation, POAG |
| Oral systemic | 8 | 20–40 | 12–18 | Prolonged and high dose continuous therapy |

**Table 2.** Incidence and mean rise in IOP with different topical steroids.

| Steroid | Incidence of significant IOP elevation (%) | Mean rise in IOP (mmHg) |
|---|---|---|
| Dexamethasone alcohol 0.1% | 7–14 | 5–10 |
| Prednisolone acetate 1% | 7 | 10 ± 1.7 |
| Difluprednate 0.05% | 3–5 | 3.0 ± 1.3 |
| Flurometholone acetate 0.1% | 3 | 3.9 ± 4.1 |
| Loteprednol etabonate 0.5% | 2 | 9.2 ± 5.8 |
| Rimexolone 1% | 2 | 5.9 ± 4.4 |

the rise in IOP occurs a few days (usually only after 5 days) or weeks (typically 2–6 weeks) of commencement (13). Hence, the patient should be monitored within 2 weeks of starting therapy or earlier if the risk is higher. However, though rare, reports of rise in IOP within hours of starting the intensive steroid therapy have published (14). Periodic IOP check is indicated initially after every 4 weeks for 2–3 months, then every 6 months if therapy is continued (12). Needless to say, the frequency can be titrated depending on the presence of risk factors and clinical course.

After sub-tenon injection of triamcinolone (STT), IOP elevation occurs in nearly 50–80% of patients (15). Rise in IOP may be bilateral in a subset of them. The effect is more with multiple injections than with a single injection, and more with depot preparation than non-depot preparation. The IOP elevation can occur from 2 weeks to 5 months, and returns to the baseline in most cases by 10 months (16). In one study, 20% of patients developed glaucoma following STT injections (17).

IOP is likely to rise sometime in 50–75% of the eyes receiving intravitreal steroid implants (16). IOP elevation usually occurs between 2 and 4 weeks of injection, and peaks at 2 months before returning to normal in 4–6 months (16). Dexamethasone challenge prior to IVTA has a low sensitivity, high specificity and positive predictive value. IOP elevation in dexamethasone challenge tends to correlate with IOP elevation after IVTA (18). This may have clinical meaning in weighing the risk and benefits of IVTA, but the dexamethasone challenge requires a time lag of 4 weeks to decide.

The monitoring of IOP in eyes with intravitreal implant is recommended. The suggested protocol is to check IOP 30 min after injection and then at 1 week. Further follow-up is fortnightly for the first month and then monthly for up to 6 months (after IVTA and dexamethasone implantation) and 9 months (after flucinolone implantation) (19).

Systemic steroids produce IOP elevation at higher doses or after prolonged administration for weeks to months (20). The IOP usually increases by 30–50% from the baseline. In steroid responders, IOP elevation with systemic steroid use is usually 60% of that produced by topical steroids (21). The presser response may not click with pulse steroid therapy. The presser response was not seen after 8 week of pulse therapy with oral methylprednisolone when compared with continuous therapy with prednisolone (22). IOP monitoring is recommended in all patients receiving 10 mg or more prednisolone daily for long duration. After baseline IOP, periodic IOP should be checked at 1, 3 and 6 months and then 6 monthly (12).

With inhaled corticosteroids (ICS), presser response is most likely to occur in persons with family history of glaucoma (23). The risk is dose dependent and increases nearly three times for persons who use more than four puffs a day (24). Persons without family history of glaucoma or low IOP at the time of initiation of ICS therapy are not associated with increased odds of OPR (24).

Presser response secondary to steroid use is usually reversible, when steroid therapy is limited to a period of <12 months (20). Although, most elevated IOPs spontaneously descend to basal level after cessation of the steroid therapy, progressive glaucomatous changes may occur. The steroid response lasting more than 6 weeks after topical steroid therapy, usually takes 1–4 weeks after cessation of topical therapy (14).

IOP elevation after intravitreal steroids (read IVTA) may take about 6–8 months to normalize after the last injection and usually require medical therapy for control of IOP during this period (25). In case of repository steroids, the implant may have to be surgically removed (25).

Nearly 70% of steroid responders require IOP lowering medical therapy at some time (26). Duration of IOP lowering therapy depends on the presser response and pre-existing disc condition, in addition to response to therapy. Medical therapy may be required for weeks to years to keep the IOP under control (27). In a subset (nearly 2%) of patients, elevated IOP does not return to base level (28) it includes those who received prolonged duration of steroids (usually more than a year), those with higher baseline IOP or with pre-existing glaucomatous nerve damage (29).

Normal individuals who are steroid responders run a higher risk of developing POAG subsequently (30). In one study, 13% of high corticosteroid responders developed glaucomatous visual field loss during the follow-up period of 5 years (31).

## Treating steroid induced IOP elevation

The OPR is a reversible phenomenon and IOP tends to normalize after variable duration of cessation of steroid therapy. However, IOP elevation can produce or accelerate glaucomatous changes in eyes depending on factors like pressure sensitivity of optic nerve fibres, the presence of pre-existing disc damage or POAG or duration of therapy. The risk of optic nerve damage (iatrogenic glaucoma or steroid induced glaucoma), in individuals with elevation of IOP following steroid therapy warrants lowering of IOP (16,31). Discontinuation of steroid therapy is best way to manage steroid related elevation of IOP. However, some modes of steroid administration, such as sub-tenon injections or IVTA, cannot be reversed easily, if IOP rises. In general, when considering treatment of steroid induced IOP elevation four clinical scenarios arise:

1 Is the cause of elevated IOP steroid therapy?

2 Is it feasible to discontinue the steroid?

3 What to do, if steroids cannot be discontinued?

4 What if the IOP remain elevated despite discontinuation of steroids?

It is essential to ascertain clinically, the cause of the raised IOP in patients on steroid therapy. Under certain clinical situations, like those associated with ocular inflammation or trauma, the primary cause itself may be, at least partially, responsible for IOP elevation which may paradoxically require increase in dose of steroids.

If the underlying ocular or medical condition can be treated with steroid sparing drugs, discontinuation of steroids is the most prudent approach. This can normalize the IOP in one to 4 weeks (14). However, in all such cases, a close follow-up is required as in nearly 3% of them discontinuation of steroid therapy does not reverse the OPR, even after the wash off period (32). This is again seen in patients of glaucoma or their close family members and after chronic steroid use. In such cases, IOP lowering medications should be started.

In cases of intravitreal implants, IOP need to be managed with topical IOP lowering drugs till the crystals resolve. This usually takes 6 months. In 2% of cases with IVTA, the IOP is not controlled medically and require surgical removal of depot by pars plana vitrectomy (33). Additional trabeculectomy may be required. Need for surgical intervention is usually more in younger patients, higher baseline IOPs and pre-existing glaucomatous disc changes. Similarly, in cases with subtenons depot, the depot preparation should be excised with or without trabeculectomy if IOP is medically uncontrolled

In cases where discontinuation of steroid is not feasible, or IOP remains elevated after discontinuation of steroids, medical therapy for elevated IOP should be instituted and IOP and optic disc monitored regularly.

### Choosing glaucoma therapy

Another clinical quandary is the choice of topical ocular pressure lowering drug. Prostaglandin analogues (PGAs) are otherwise the first line drugs but controversy exists (34,35) concerning their use in inflamed eyes due to the theoretically higher risk of anterior uveitis, development of cystoid macular oedema and reactivation of herpes simplex keratitis (36). There is little evidence that PGA disrupt the blood-aqueous barrier (37,38) and only anecdotal evidence suggesting an increased risk of these rare finding (39). In some studies on uveitic cases with raised IOP attributable to corticosteroid response, use of PGA was not associated with increase in inflammation (37,40). However, still the prudent approach would be to use PGA in such cases when other topical anti-glaucoma medicines have not lowered IOP to the patient's target range (38), especially avoiding them as front line therapy in pseudophakic and aphakic patient (41).

In 1–5% of patients IOP may not control with medical management alone, necessitating the need of laser or surgical intervention (42,43). Younger patient with glaucomatous changes are more likely to require surgical intervention (26). Laser trabeculoplasty can be attempted to lower the IOP, however, there are un-equivocal results reported in literature (44,45). Laser trabeculoplasty perhaps can be used as trabeculotomy sparing procedure in eligible patients. Filtration surgery offers an effective means of controlling IOP in uncomplicated cases refractory to medical therapy (39,46,47).

Glaucoma shunts may be considered in eyes with active inflammation or conjunctival scarring. Another consideration for implant selection is plate size. In eyes with fluocinolone acetonide implants, larger plate size may result in a higher risk of hypotony. An implant with a smaller plate size is probably less likely to cause chronic hypotony in patients with uveitis and steroid implants (39). In patients with IVTA and high IOP, Ahmed valve implantation has proved to be effective (44,47).

The management of steroid induced pressure response is summarized in Figure 1.

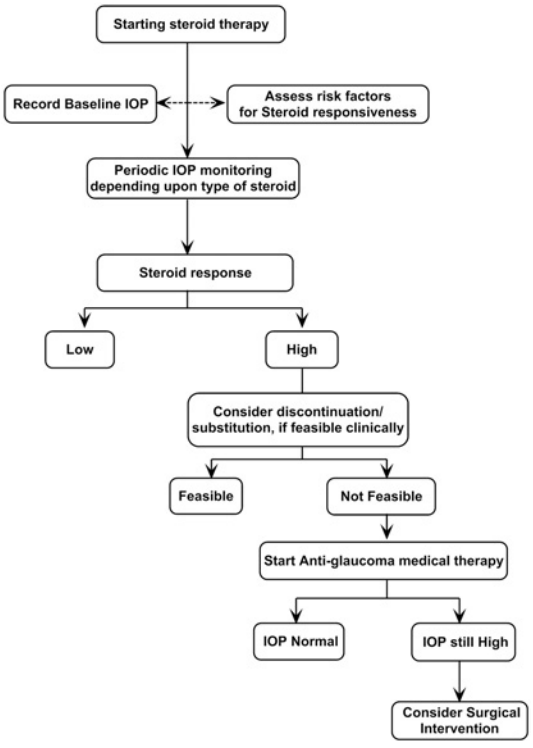


**Figure 1.** Schematic flow diagram of management of steroid induced pressure response.

## Conclusion

Management of steroid induced OPR require a comprehensive plan and stepwise approach. It would be a prudent approach to document baseline IOP and ONH prior to commencement of the steroid therapy. Measures to control IOP needs to be individualized depending upon cause and degree of presser response. Regular monitoring of IOP in patients on chronic steroid therapy depending upon duration and type of steroid therapy should be undertaken; and patients with risk factors for OPR must be under close follow-up even after cessation of steroid therapy until IOP returns to normal level.

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# Pharmacotherapy of Diabetic Macular Oedema: Making Sense of Clinical Trials

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## Introduction

Diabetic macular oedema (DME) is a frequent, and sight-threatening, complication of Diabetic Retinopathy, and an important cause of moderate vision loss in individuals with Diabetes Mellitus. The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) estimated that after 20 years of known diabetes, the prevalence of DME was ~28% in both type 1 and type 2 diabetes mellitus.[1]

The treatment of DME still remains a difficult challenge for ophthalmologists. The Early Treatment of Diabetic Retinopathy Study (ETDRS) helped to both define the natural history of DME and showed the benefit of focal/grid laser treatment, which has been the main stay of therapy for DME for several decades.[2] The detrimental effects of laser therapy, including scar expansion and its failure to achieve significant visual improvement, created the impetus to further investigate disease pathophysiology and treatment alternatives. A number of prospective clinical trials have demonstrated the efficacy of medical therapies targeting vascular endothelial growth factor (VEGF) and inflammatory mediators, both in conjunction with laser treatment and as monotherapy. Here in we summarize the major clinical trials and what implications they hold for the clinicians in treating DME.

## Overview

The various treatment modalities currently available for treatment of DME include:

I. Laser Photocoagulation
II. Anti-VEGF
  a. Ranibizumab (Lucentis)
  b. Bevacizumab (Avastin)
  c. Pegaptanib (Macugen)
III. VEGF Trap
  a. Aflibercept (Eylea)
IV. Steroid
  a. Short acting:
    i. Intravitreal Triamcinolone Acetonide
  b. Long acting:
    i. Dexamethasone implant (Ozurdex)
    ii. Fluocinolone Acetonide (FA) (Retisert, Iluvien)

I. Laser Photocoagulation:

1. ETDRS[2]
- Randomized Clinical Trial.
- Seven hundred and fifty-four eyes that had clinically significant macular oedema and mild to moderate diabetic retinopathy were randomly assigned to focal argon laser photocoagulation while 1490 such eyes were randomly assigned to deferral of photocoagulation.
- After 1 year of follow-up, retinal thickening in the centre of the macula was present in only 35% of eyes assigned to immediate photocoagulation compared with 63% of eyes assigned to deferred photocoagulation. There was a statistically significant benefit of laser photocoagulation in this group of eyes.
- Translation into practice: Laser photocoagulation is the benchmark against which all therapies are evaluated.

II. Anti-VEGF

a. Ranibizumab: (RBZ) (Lucentis; Genentech Inc.) is a humanized monoclonal antibody fragment that binds all active forms of VEGF-A.[3]

The following are the major trials on it:

- RESOLVE.[4]
- Safety and efficacy of ranibizumab in DME with centre involvement.
- Twelve-month, multicentre, sham controlled double-masked study.
- $N = 151$.
- Patients were randomly assigned 1:1:1 to RBZ (0.3 or 0.5 mg) or sham. The treatment schedule comprised three monthly injections, after which treatment could be stopped/reinitiated with an opportunity for rescue laser photocoagulation.

Results:

| Group | Mean gain in letters (ETDRS) | Central retinal thickness (CRT) reduction | Mean Inj |
|---|---|---|---|
| Group 1 (RBZ 0.3) | +11.8 | −200.7 μm | 10.2 |
| Group 2 (RBZ 0.5) | +8.8 | −187.6 μm | 10.2 |
| Group 3 (Sham Inj) | −1.4 | −48.4 μm | 8.9 |

- Translation into practice: RESOLVE was one of the first studies which established the effective role of RBZ in DME management.

1. READ-2[5–7]

- Ranibizumab for oedema of the macula in diabetes study.
- Prospective, randomized, interventional, multicentre clinical trial.
- *N* = 126.
- Subjects were randomized 1:1:1 to receive 0.5 mg RBZ at baseline and months 1, 3 and 5 (group1), focal or grid laser photocoagulation at baseline and month 3 if needed (group 2) or a combination of 0.5 mg RBZ and focal or grid laser at baseline and month 3 (group 3).
- After 6 months through 24 months patients received *bimonthly* injection if they met treatment criteria. In spite of good visual outcomes at month 24,there was persistence of oedema in three groups (340, 286 and 258 microns, respectively).

  Looking at persistence of CME at third year groups were reviewed and treated with intensive RBZ *monthly* if they met treatment criteria.
- Results: 6 months

| Group | Mean gain in letters | Mean CRT reductions |
|---|---|---|
| Group 1 (RBZ) | +7.4 | −106.3 µm |
| Group 2 (L) | −0.43 | −82.8 µm |
| Group 3 (RBZ + L) | +3.8 | −117.2 µm |

At month 24 the mean letter gain in RBZ, L and RBZ + L group was 7.7, 3 and 6.8, respectively. Letters gains of the same groups after intensive monthly RBZ injection at third year from baseline was 10.3, −1.6 and 8.9, respectively.

- Translation into practice: Visual outcomes of RBZ group are consistently better than the laser groups. No difference bet RBZ/RBZ + laser in visual outcomes. Patients unable to come for strict monthly follow up can still be maintained on bi monthly injections with good visual outcomes.

2. RESTORE[8,9]

- Efficacy and safety of ranibizumab in patients with visual impairment due to diabetic macular oedema.
- To demonstrate superiority of RBZ 0.5 mg monotherapy or combined with laser over laser alone in DME.
- A randomized, double-masked, multicentre, laser-controlled phase III study.
- *N* = 345.
- Patients were randomized to RBZ + sham laser (SL), RBZ + L or sham injections + L. RBZ/sham was given for 3 months then pro re nata (PRN); laser/SL was given at baseline then PRN (patients had scheduled monthly visits).
- The study was continued for 2 years with patients getting RBZ on PRN basis and the laser group became eligible for RBZ.
- Results: 1 year

| Group | Mean gain in letters | Mean reductions in CRT | No. of Inj |
|---|---|---|---|
| Group 1 (RBZ + Sham L) | +6.1 | −118.7 µm | 7.0 |
| Group 2 (RBZ + L) | +5.9 | −128.3 µm | 6.8 |
| Group 3 (Sham Inj + L) | +0.8 | −61.3 µm | 7.3 |

- BCVA gain, CRT decrease observed at month 12 were maintained at month 24 (RBZ: 7.9 letters, 140.6, prior RBZ + L: 6.7 letters, 133.0), with an average of 3.9 (prior RBZ) and 3.5 injections (prior RBZ + L). In patients treated with laser alone in the core study, the mean BCVA, CRT improved from month 12 to month 24 (5.4 letters, 126.6) with an average of 4.1 RBZ injections.
- Translation into practice: RBZ/RBZ + L is effective in PRN dosage in maintaining vision in DME patients. Late start of RBZ in patients previously treated with laser only can also regain significant vision with intensive therapy. This was the first study to show significant quality of life gain following RBZ treatment (NEI VFQ-25).

3. RISE/RIDE[10,11]

- Ranibizumab injection in subjects with clinically significant macular oedema with centre involvement secondary to diabetes mellitus.
- Two parallel, methodologically identical, phase III, multicentre, double-masked, sham injection controlled, randomized studies.
- *N* = 377 patients in RISE, 382 patients in RIDE.

- Monthly intravitreal RBZ (0.5 or 0.3 mg) or sham injections.
- Results:

| Group | Mean gain in letters | | Mean CRT reduction | | No. of Inj | |
|---|---|---|---|---|---|---|
| | RISE | RIDE | RISE | RIDE | RISE | RIDE |
| Group 1 (RBZ 0.5 mg) | +11 | +11.4 | 269.1 | 266.7 | 36 | |
| Group 2 (RBZ 0.3 mg) | +14.2 | +10.6 | 261.2 | 261.8 | | |
| Group 3 (Sham Inj) | +4.3 | +4.7 | 200.1 | 213.7 | | |

- Translation into practice: Long-term monthly RBZ use is safe and effective. No difference between 0.3 and 0.5 mg group. Based on this data, FDA has approved 0.3 mg RBZ for DME treatment.

4. DRCR.Net Protocol I[12,13]

- Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for DME.
- Randomized, multicentre clinical trial.
- $N = 854$.
- Randomization to one of the following four groups:
  Group A: Sham injection + focal laser,
  Group B: 0.5 mg injection of intravitreal RBZ + prompt laser,
  Group C: 0.5 mg injection of intravitreal RBZ + deferred focal laser,
  Group D: 4 mg injection of intravitreal Triamcinolone + prompt laser.
- Results: 1 year

| Group | Mean gain in letters | Mean reductions in CRT | No. of Inj |
|---|---|---|---|
| Group A (Sham Inj + L) | +3 | −133 µm | — |
| Group B (0.5 RBZ + L) | +9 | −144 µm | 11 |
| Group C (0.5 RBZ + def L) | +9 | −170 µm | 13 |
| Group D (IVTA + L) | +4 | −95 µm | 4 |

- The patients in the RBZ group only were treated through 3 years.
- The estimated mean change in visual acuity letter score from baseline through the 3-year visit was 2.9 letters more (9.7 vs. 6.8 letters) in the deferral group compared with the prompt laser treatment group.
- Translation into practice: RBZ with deferred laser has better outcomes when compared with prompt laser. In pseudophakes RBZ group and Triamcinolone groups have similar outcomes.

5. READ-3 [14]

- To compare two different dosage of RBZ in DME treatment.
- Phase 2, 2-arm randomized controlled trial.
- $N = 152$.
- Group 1 (IV RBZ 2.0) monthly injections, group 2 (IVR0.5): monthly injections. After month 6, eyes evaluated and additional RBZ injections given on an as needed basis if DME still present on OCT.
- Results:

| Group | Mean gain in letters | Mean reductions in CRT |
|---|---|---|
| Group 1 (RBZ 2.0) | +7.46 | −163.86 µm |
| Group 2 (RBZ 0.5) | +8.69 | −169.27 µm |

- Translation into practice: Higher dosage of RBZ did not provide any additional benefit.

b. Bevacizumab: Bevacizumab (IVB) (Avastin; Genentech Inc., San Francisco, CA, USA) is a full-length humanized antibody that binds to all types of VEGF. It is used in and licensed for tumour therapy.[3]

1. BOLT[15]

- Bevacizumab or laser therapy in the management of DME.
- Prospective randomized controlled trial.
- $N = 80$.
- Patients were randomized to receive either bevacizumab, i.e. group A or laser, group B (1:1).
- Results:

| Group | Mean gain in letters | Mean reductions in CRT | No. of Inj |
|---|---|---|---|
| Group A (Inj) | +8.6 | −146 µm | 13 |
| Group B (L) | −0.5 | −118 µm | 4 |

- Translation into practice: Bevacizumab is effective in treating DME but diabetes being a chronic condition further long-term studies are required to validate its efficacy.

c. Pegaptanib: Pegaptanib (PG) (Macugen; Eyetech Pharmaceuticals Inc., New York, NY, USA) is a pegylated aptamer that targets only the VEGF 165 isoform and is currently

approved for the treatment of neovascular age-related macular degeneration.[3]

- Sultan et al.[16]
- Multicentre international 2-arm placebo-controlled RCT.
- $N = 260$.
- Group 1 (IVP, $n = 133$ eyes): 0.3 mg IV PG sodium, group 2 (C, $n = 127$ eyes): sham injection.
- Injections every 6 weeks up to week 48 (nine injections); at investigator determination (ETDRS criteria), laser photocoagulation could be performed at week 18.
- At 2 years, the PG group showed a statistically significantly greater improvement in mean BCVA compared with sham. However, there was no statistically significant difference in the proportion of patients with an improvement of 10 letters or more.
- Translation into practice: Evidence as of now does not show significant visual gains with PG.

III. VEGF Trap: (Aflibercept) VEGF Trap-Eye is a 115-kDA recombinant fusion protein comprising the key VEGF binding domains of human VEGF receptors 1 and 2 fused to the Fc domain of human immunoglobulin G1.23 VEGF Trap-Eye is a pan isoform VEGF-A inhibitor whose binding affinity to VEGF is substantially greater than that of either bevacizumab or ranibizumab.[17]

1. DA VINCI

- DME and VEGF Trap-Eye: investigation of clinical impact.
- Randomized, double-masked, multicentre, phase 2 clinical trial.
- $N = 221$.
- Participants were assigned randomly to one of five treatment regimens: VEGF Trap-Eye 0.5 mg every 4 weeks (0.5q4); 2 mg every 4 weeks (2q4); 2 mg every 8 weeks after three initial monthly doses (2q8); or 2 mg dosing as needed after three initial monthly doses (2PRN), or macular laser photocoagulation (L).
- Results:

| Group | Mean gain in letters | Mean reductions in CRT | No. of Inj |
|---|---|---|---|
| Group 1 (0.5q4) | +11.0 | −165.4 µm | 11.7 |
| Group 2 (2q4) | +13.1 | −227.4 µm | 10.8 |
| Group 3 (2q8) | +9.7 | −187.8 µm | 7.2 |
| Group 4 (2PRN) | +12 | −180.3 µm | 7.4 |
| Group 5 (L) | −1.3 | −58.4 µm | — |

- Significant gains in BCVA from baseline achieved at week 24 were maintained or improved at week 52 in all VEGF Trap-Eye groups.
- Translation into practice: VEGF trap holds promise because of longer duration of action. But further studies are required to find out the optimum dosage and long-term efficacy.

IV. Steroids

Triamcinolone Acetonide: Various trials have evaluated Triamcinolone in DME. All trials evaluated intravitreal administration and at three different dosages (1, 4 and 8 mg).

DRCR conducted a major prospective trial evaluating Triamcinolone.

1. DRCR IVTA study[18]

- Evaluated the efficacy and safety of IVTA (4 and 1 mg) against laser in DME.
- Prospective multicentre study.
- $N = 840$.
- For the 2-year primary outcome, the mean change in the visual acuity letter score from baseline was $+1 \pm 17$ in the laser group, $-2 \pm 18$ in the 1 mg triamcinolone group and $-3 \pm 22$ in the 4 mg triamcinolone group.
- Translation into practice: Macular laser procedures have much better visual acuity outcomes in long term when compared with intravitreal triamcinolone.

2. DRCR.Net Protocol I (please see previous section for details)

- Translation into practice: In pseudophakic eyes, intravitreal triamcinolone with prompt focal/grid laser may be equally effective as ranibizumab at improving visual acuity and reducing retinal thickening, but is associated with an increased risk of intraocular pressure elevation.

3. FA: Illuvien is an injectable 25 g intravitreal insert, which releases Fluocinolone at two doses 0.2 and 0.5 µg/day for 3 years.[19]

FAME

- FA for DME.
- To assess long-term efficacy and safety of intravitreal inserts releasing 0.2 µg/day (low dose) or 0.5 µg/day (high dose) FA in patients with DME.

- Three-arm placebo-controlled randomized controlled trial.
- $N = 956$.
- Dosage 0.2 µg/day FA intravitreal insert vs. 0.5 µg/day FA intravitreal insert vs. sham injection in the ratio (2:2:1).
- Results:

| Group | Mean gain in letters | Mean reductions in CRT |
|---|---|---|
| Group A (0.2 µg/day FA) | +4.4 | −167.8 µm |
| Group B (0.5 µg/day FA) | +5.4 | −177.1 µm |
| Group C (Sham) | +1.7 | −111.3 µm |

- Significantly improved visual acuity in patients with DME in group A and B over 2 years and significantly fewer incisional glaucoma procedures were needed in the low-dose insert group.
- Almost 90 % of the phakic patients required cataract surgery.
- Translation into practice: Lower dose steroid implants still have a role in refractory DME, after properly explaining the patients about the potential risk of intraocular pressure hike and cataract progression.

4. Retisert: Retisert is a sterile, non-biodegradable intravitreal implant implanted surgically through a pars plana scleral opening. It contains 0.59 mg FA. It releases 0.5 µg/day for 1000 days.[20]
   - Retisert trial evaluated the 3-year efficacy and safety results of FA intravitreal implants in eyes with persistent or recurrent DME.
   - Prospective, evaluator-masked, controlled, multicentre clinical trial.
   - $N = 196$.
   - Patients were randomized 2:1 to receive 0.59-mg FA implant or standard of care (SOC additional laser or observation).
   - Three years after implantation, the difference in the rates of three-line VA improvements was no longer significant between two groups.
   - Translation into practice: Looking at minimal visual gains and higher rate of complications this dosage of steroid is out of vogue.

5. Dexamethasone: Ozurdex is a dexamethasone drug delivery system which releases 700 µg of dexamethasone intravitreally via a 22 G injection system.[21]
   - Haller et al. (2010)[21] evaluated two doses of Dexamethasone in DME.
   - Patients were randomized into three groups (700 µg/ 350 µg/Laser).
   - $N = 171$.
   - At 90 days the 700 µg group showed significantly higher visual gains compared with laser group (33 vs. 12%). However, at 180 days there was no statistically significant difference across the groups.
   - Translation into practice: Larger trials are needed to assess the long-term safety and efficacy of dexamethasone implants.

## Conclusion

Current body of evidence suggests RBZ as the most effective pharmacotherapy for DME. Multiple injections of RBZ are needed to maintain vision in patients with DME. RBZ is well tolerated without significant ocular or systemic side effects. In patients who are unable to come for monthly follow up, can still get benefit from RBZ on a PRN basis. Cost of therapy remains a concern specially in developing nations. Reports have suggested annual cost of maintaining one line of vision with RBZ is as high as 23000 US dollars compared with 6000 US dollars with Triamcinolone.[22] Bevacizumab is effective in DME though needs validation by larger well-designed long-term multicentre trials. Macular laser is indicated as a primary therapy in patients with significant focal leakage or as a rescue measure. Steroids have a definite role in pseudophakes and in refractory DME.

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# Choroidal Detachment as a Complication of Trans-scleral Cyclophotocoagulation with Diode Laser: A Case Report

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## Introduction

Trans-scleral cyclophotocoagulation (TSCPC) with diode laser is a popular modality in the management of refractory glaucoma (1,2). A few vision-threatening complications such as phthisis (3), deterioration of visual acuity (3) and sympathetic ophthalmitis (4) have been reported with this mode of treatment. We report the case of a 50-year-old man with refractory glaucoma who developed massive choroidal detachments following diode TSCPC. Choroidal detachment is a very rare complication of diode TSCPC with limited literature available.

## Case history

A 50-year-old gentleman presented to us in April 2004 with complaints of intermittent pain in the right eye for the past 6 months. He had been using topical steroids along with a combination of latanoprost 0.005% and timolol maleate 0.5% eye drops once daily in the right eye. His left eye had no perception of light due to neovascular glaucoma secondary to a vein occlusion. The best corrected visual acuity (BCVA) in his right eye was 20/20, N6. Anterior segment evaluation of the right eye revealed peripheral anterior synechiae (PAS) extending from 7'o clock to 2'o clock. Examination of the left eye revealed corneal opacity with no view of the anterior chamber and other structures beyond. Intraocular pressure (IOP), as measured by applanation tonometry, was 24 mmHg in the right eye. Gonioscopy of the right eye revealed angle closure with three quadrants of goniosynechiae. Optic nerve head evaluation showed a cup disc ratio of 0.6:1 with an inferior notch and a normal periphery in the right eye. Central corneal thickness measured with ultrasonic pachymetry was 518 µm in the right eye. He subsequently underwent an Nd:YAG laser iridotomy for management of presumed primary angle closure glaucoma in the right eye.

He reported to us again in March 2006 with uncontrolled IOP in his right eye on maximum medical treatment. He underwent trabeculectomy with Mitomycin-C (0.04% × 1 min) [Oncocin 2 mg (Chandra Bhagat Pharma)] in the right eye in June 2006 following which the IOP stabilized to 16 mmHg with a good diffuse avascular bleb.

The patient reported to us again in June 2011, when his vision had decreased to 20/50, N10 in the right eye. He was now using a combination of timolol maleate 0.5% and dorzolamide 2% twice daily along with brimonidine tartrate 0.15% twice daily.

Examination revealed increase in the extent of peripheral synechial angle closure, visible along the peripheral corneal surface [(Fig. 1) AS-OCT] along with corneal decompensation and signs of early pseudo exfoliation on the anterior lens capsule. A diagnosis of irido-corneal endothelial syndrome was entertained at this point in time. IOP was 18 mmHg on three anti-glaucoma medications (AGM). Central corneal thickness in the right eye had increased to 646 µm.

He underwent a re-trabeculectomy with Mitomycin-C (0.04% × 3 min) in July 2011 following which IOP reduced to 10 mmHg. Subsequently, a penetrating keratoplasty with cataract extraction was performed in September 2011 due to a decompensated cornea and a shallow anterior chamber.

After a stable period of 3 months, IOP started rising to 34 mmHg with maximum medical treatment. Since the superior conjunctiva showed extensive scarring, he was advised to undergo TSCPC with diode laser.

The patient was treated with TSCPC with diode laser (2100 mW/2000 ms/21 shots) in the inferior 180° in April 2012. The IOP dropped to 18 mmHg during the first post laser week.

The patient reported 20 days later with complaints of sudden diminution of vision in the right eye. The best corrected visual acuity in the right eye was 20/200, N36. Examination of the right eye showed a clear compact corneal graft with a diffuse bleb and 360° PAS. IOP measured 6 mmHg. There was no significant inflammation. Dilated evaluation of the right eye revealed 360° massive choroidal detachment. The left eye was status quo.

Treatment with topical and oral steroids and cycloplegics was started. Gradually, over a period of ~5 months, the choroidal detachment resolved and IOP rose to 26 mmHg.

On his next follow-up in September 2012, BCVA had improved to 20/40, N6 in the right eye. IOP was controlled at 18 mmHg on timolol maleate 0.5% eye drops twice daily in the right eye.

On his last visit, 7 months post-laser BCVA was 20/40, N6 with an IOP of 20 mmHg on a single AGM. Visual field evaluation did not reveal any progression of disease. He has been advised to continue his AGM and review every 2 months for IOP check up.

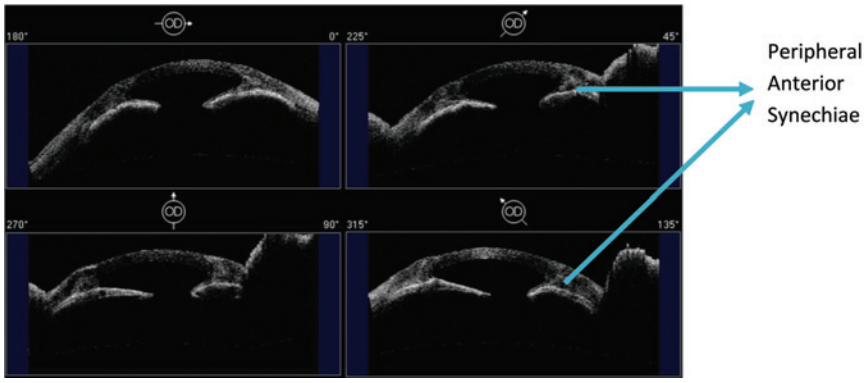


**Figure 1.** Anterior segment OCT showing extensive synechial closure of the angle.

## Discussion

TSCPC with diode laser is an accepted modality of management in refractory cases of glaucoma (1,2,5) as in patients who have had previously failed glaucoma filtering or tube surgeries, poor vision potential and in cases of painful blind eyes secondary to raised IOP.

Although most complications following diode CPC are transient, a few severe, sight threatening complications such as phthisis bulbi (3), severe intraocular inflammation (4), sympathetic ophthalmitis (4) and hypotony (6,7) have been reported.

Choroidal detachment is a rare complication of TSCPC and, in our patient, may have been precipitated by hypotony that causes transudation of fluid from the choroidal capillaries to the suprachoroidal space. The detachment itself may have reduced aqueous production and initiated a vicious cycle of hypotony.

Excessive laser energy, noted by the appearance of "pop" sounds during laser application, has been noted to increase the risk of post laser inflammation and hypotony (8). The parameters of the laser used in our case were well within the acceptable range.

Mistlberger et al. (9) have reported the development of choroidal effusions in one case of aphakic glaucoma and two pseudophakic glaucoma in their series of 204 patients. The laser parameters were similar to our case.

Quagliano et al. (10) have reported a case of a 9-year-old girl with bilateral Sturge–Weber syndrome who developed massive choroidal detachment in the immediate post-operative period after TSCPC with diode laser which completely resolved with conservative management. She had undergone filtering surgeries with development of massive choroidal detachment post-operatively. However, choroidal effusion and expulsive choroidal hemorrhage are known complications of Sturge–Weber syndrome. To conclude, choroidal detachment is a rare complication of TSCPC. Early recognition of this problem and appropriate management can assist in preservation of vision.

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# OZURDEX® for Treatment of Recalcitrant Macular Edema Secondary to Retinal Vein Occlusion: Short-term Results

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## Introduction

Macular edema (ME) is a common cause of vision loss in both branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO) (1–5). Several therapies are being studied for the treatment of ME associated with RVO. These include anti-vascular endothelial growth factor (VEGF) agents (6), laser photocoagulation (7) and corticosteroids (6,7). Intravitreal injections of the lipophilic corticosteroid triamcinolone acetonide have been shown to have beneficial effects in eyes with RVO. The common complications associated with this drug are cataract and raised intraocular pressure (IOP) (8).

Dexamethasone is a potent, water-soluble corticosteroid that can be delivered into the vitreous cavity by the dexamethasone intravitreal implant (DEX implant; OZURDEX, Allergan, Inc., Irvine, CA, USA). We undertook a study to evaluate the short-term effect of dexamethasone implant (Ozurdex) in subjects who had non-resolving ME secondary to retinal vein occlusion despite prior treatment with various other modalities.

## Materials and methods

In this retrospective, interventional case series, five eyes of five patients with ME secondary to vein occlusion were reviewed. Patients with symptoms for at least 6 months were included. All patients had refractory ME, having received prior treatment at least 3 months prior to undergoing Ozurdex™ injection. Exclusion criteria included macular ischemia, history of IOP elevation in response to steroid treatment in either eye and history of glaucoma. All patients underwent comprehensive ocular examination. After obtaining an informed consent, patients underwent intravitreal dexamethasone implant in the operating room under topical anesthesia. Complete ocular examination and optical coherence tomography (OCT) was performed at periodic intervals, at months 1, 2, 3 and 4. The primary outcome measures were best corrected visual acuity and change in central macular thickness on OCT monthly. The secondary outcome measure was any rise in IOP.

## Results

The mean age of the patients was 58.2 years (range 54–64 years). There were two females and three male patients. The mean duration of retinal vein occlusion at the time of diagnosis was 8.5 months (range 6–12 months). Three patients had diabetes mellitus with no retinopathy changes. All patients had received either laser or intravitreal injection of steroid/anti-VEGF 3 months prior to Ozurdex™ injection with no significant improvement (Table 1). The mean follow-up was 2 months (range 1–4 months). The mean baseline visual acuity was 0.58 log MAR units (range 0.1–1.0) and mean central macular thickness was 482.2 µm (range 271–865). The mean visual acuity improved to 0.33 log MAR units and mean central macular thickness decreased to 183.65 µm ($p = 0.005$) at 1 month. The mean visual acuity was 0.48 log MAR and mean central macular thickness was 222 µm ($p = 0.007$) at the second month follow-up. The mean visual acuity was 0.12 log MAR and mean central macular thickness was 132 µm ($p = 0.004$) at the third month follow-up. The mean visual acuity was 0.57 log MAR and mean central macular thickness increased to 381.4 µm ($p = 0.06$) at the fourth month follow-up (Figures 1 and 2). Out of five patients, two patients needed anti-glaucoma treatment for control of increased IOP. On gonioscopy, all patients had open iridocorneal angles.

**Table 1.** Clinical features of five patients with recalcitrant macular edema due to RVO undergoing Ozurdex injection.

| Case | Age (years) | Sex | Eye | Prior treatment | Diagnosis | BCVA before injection | CMT before injection |
|---|---|---|---|---|---|---|---|
| 1 | 64 | F | OD | Bevacizumab × 3, IVTA × 2, Laser × 1 | CRVO | 6/60, N36 | 669 |
| 2 | 55 | M | OD | IVTA × 1, Laser × 1 | CRVO | 6/18, N8 | 553 |
| 3 | 57 | M | OD | Bevacizumab × 3 | BRVO | 6/18, N8 | 480 |
| 4 | 61 | F | OD | Bevacizumab × 3 | BRVO | 6/118, N8 | 291 |
| 5 | 54 | M | OS | Laser × 2 | BRVO | 6/18, N8 | 418 |

F, female; M, male; OD, right eye; OS, left eye; CMT, central macular thickness in µm; IVTA, intravitreal triamcinolone; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; OCT, optical coherence tomography; BCVA, best corrected visual acuity.

**Table 2.** Central macular thickness (CMT) and best corrected visual acuity (BCVA) after intravitreal Ozurdex injection in five eyes with retinal vascular occlusion (RVO).

| Case | Postoperative 1 month | | Postoperative 2 months | | Postoperative 3 months | | Postoperative 4 months | | Maximum IOP (mmHg) |
|---|---|---|---|---|---|---|---|---|---|
| | BCVA | CMT (µm) | BCVA | CMT (µm) | BCVA | CMT (µm) | BCVA | CMT (µm) | |
| 1 | 6/36, N10 | 202 | 6/18, N6 | 260 | NA | NA | 6/36, N8 | 729 | 22, controlled by Timolol maleate 0.5% twice daily |
| 2 | NA | NA | 6/18, N6 | 184 | 6/12, N6 | 164 | 6/36, N8 | 440 | 14 |
| 3 | 6/9, N6 | 170 | NA | NA | 6/9, N6 | 137 | 6/18, N8 | 200 | 24, controlled by Travoprost 0.004% once daily |
| 4 | 6/9, N8 | 137 | NA | NA | 6/9, N6 | 127 | 6/18, N8 | 338 | 19 |
| 5 | 6/7.5, N8 | 104 | NA | NA | 6/6, N6 | 100 | 6/12, N8 | 200 | 16 |

BCVA, best corrected visual acuity; CMT, central macular thickness in µm; IOP, intra ocular pressure; NA, not available.

## Discussion

We report the short-term results of five patients with refractory ME secondary to retinal vein occlusion treated with intravitreal dexamethasone implant (Ozurdex™). Significant decrease in central retinal thickness was seen on OCT in all five patients within 3 months of injection with improvement in visual acuity. However, all patients developed rebound thickness at 4 months of follow-up. The periodicity of OCT scan monitoring of such eyes in GENEVA study was at baseline, months 3 and 6 (9). This pattern of evaluation did not reveal two aspects of treatment response. The first being a sustained drug release device, did the ME resolve as early as 1-month post-injection and secondly how early was post-injection 'rebound' ME encountered. The first aspect constitutes important information since it effectively rules out having to consider addition of an anti-VEGF agent (in combination with ozurdex) for achieving 'quick therapeutic' response. The second aspect is important in determining the 'optimal' interval for re-treatment which in our study was about 4 months as in most cases rebound was seen during the fourth month. Of the five patients, two showed increase in IOP, which was successfully controlled with anti-glaucoma medication. Our preliminary study in Indian eyes is limited by small sample size and short duration of follow-up of up to 4 months. Although our study has small numbers and a short-term follow-up, it provides important information for the clinician while considering Ozurdex™ as a treatment option for eyes with recalcitrant ME. Larger studies with longer duration follow-up are required to validate our findings.

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# Persistent Accommodative Spasm

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## Introduction

Accommodative spasm (AS) is a rare and involuntary condition where there is greater accommodative response than the accommodative stimulus (1). In the literature, AS is also termed as accommodative excess, hyper-accommodation and ciliary spasm (1,2). The most probable aetiology reported is attributed to psychogenic factors (2). AS has been attributed either to excessive action of ciliary muscle or to excessive flexibility of the lens. Other causes are use of either systemic or topical cholinergic drugs, head trauma, meningeal inflammation, migraine, brain tumours and myasthenia gravis. It is also reported that AS could be due to prolonged near work, uncorrected hyperopia and emotional disturbances (3). Rutstein and Marsh-Tootle (1) has reported that AS can also be triggered by occlusion of contralateral eye.

AS can occur suddenly, may be unilateral or bilateral and constant or intermittent. Symptoms of AS include variable blurring of distance and/or near vision, fluctuating vision, headache, photophobia/glare, eyestrain associated with near work, double vision and eye pain (4). Clinically AS is confirmed by difference in subjective and objective refraction $\geq -0.50$DS (accepting more minus in dry refraction and plano or lesser plus in

**Table 1**

| Visit | Complaints | Retinoscopy | BCVA | Management |
|---|---|---|---|---|
| 1st visit | Blurred vision<br>Bitemporal headache (symptomatic since 4 months) | OD: −2.00DS/−1.25DCx 60<br>OS: −2.00DS/−0.75DCx160 | OD: −1.50DS/−0.75DCx70 (6/9)<br>OS: −1.00DS (6/9); N6 with effort | CTC (+1.25DS −OU)<br>PMT [OD: −2.00DS/−0.50DCx45 (6/6p),<br>OS: −1.25DS/−0.50DCX105 (6/6p)]<br>Atropine (1%) eye drop for 3 weeks (thrice/week) |
| 2nd visit (after 3 weeks) | Blurred vision (same as 1st visit) | OU: +1.75DS Highly varying | OD: +1.50DS (6/9)<br>OS: +1.25DS (6/9)<br>OU: +2.50DS (N6) | New glasses given<br>Atropine (1%) eye drop for 3 months (once/week) |
| 3rd visit (after 3 months) | No complaints | OD: +1.00DS<br>OS: +1.25DS | OU: plano (6/6eff), (+0.00) N6 | Nil glasses<br>Stop atropine eye drop after 1 month |
| 4th visit (after 6 months) | Blurred vision<br>Bitemporal headache (symptomatic since 3 months) | OU: −0.25DS (varying) | OD: −1.00DS (6/9)<br>OS: −1.25DS (6/9) | Atropine (1%) eye drop for 4 months (twice/week)<br>Continue old glasses |
| 5th visit (after 5 months) | Review as advised<br>Antipsychotic drugs stopped | OU: −0.75DS Highly varying | OD: +1.50DS (6/9)<br>OS: +1.25DS (6/9)<br>OU: +2.50DS (N6) | Continue old glasses<br>Atropine (1%) eye drop for 2 months (twice/week) |
| 6th visit (after 2 months) | Review as advised<br>Glare<br>Eye pain | OD: +0.50DS/−0.75DCx 20<br>OS: + 0.75DS/−0.75DCx160 | OD: +1.50DS (6/9)<br>OS: +1.25DS (6/9)<br>OU: +2.50DS (N6) | Stop atropine eye drop<br>Start homide (2%) eye drop on alternate days for 4 months<br>Accommodative flipper (±2.00DS) |
| 7th visit (after 4 months) | Blurred vision<br>Glare | Highly varying from +0.50DS to −3.00DS | OD: +1.00DS (6/6)<br>OS: +1.00DS (6/6)<br>OU: +2.50DS (N6) | Continue homide (2%) eye drop on alternate days<br>Accommodative flipper (±2.00DS) |

BCVA: best corrected visual acuity, CTC: cyclopentolate tropicamide cyclopentolate, PMT: post mydriatic test, OD: oculus dexter, OS:oculus sinister, OU: oculus uterque

cycloplegic refraction), lead in dynamic retinoscopy, may or may not be associated with esodeviation and pupillary miosis (2). AS when associated with pupillary miosis and excessive convergence is called spasm of near reflex (5). The treatment option for AS includes added plus lenses, vision therapy and strong cycloplegic drugs like atropine is prescribed. We report a unique case where the AS was not relieved even upon instillation of atropine eye drops for 1 year.

## Case report

A 14-year-old female accompanied by her father with the main complaints of fluctuating vision and bitemporal headache since 4 months. She gave a positive history of psychological problem and she was under antipsychotic drugs. The dry retinoscopy was found to be −2.00DS/−1.25DCX60 in right eye and −2.00DS/−0.75DCX160 in left eye. She accepted −1.50DS/−0.75DCx70 (6/9, N6) in right eye and −1.00DS (6/9, N6) in left eye. The cover test for distance was orthophoria, the near cover test was noted to be four prisms of exophoria. Cycloplegic refraction (cyclopentolate 0.5%, tropicamide 1%) revealed hyperopia of +1.25DS in both eyes. The anterior and posterior findings of patient were within normal limit. Under post mydriatic test, her acceptance was found to be myopic correction (Table 1). The accommodative response at 40 cm revealed the lead of accommodation with −0.75DS. The amplitude of accommodation was noted to be 16D monocularly and binocularly (which is expected for the age: Hofstetter's average). The stereo acuity was found to be 40 arc-second with random dot stereograms.

Hence she was diagnosed to have AS. To break the spasm atropine (1%), eye drops for 3 weeks was advised and she was followed up after 1 month. Still the AS was found to be persistent, so she was advised to continue atropine eye drops. After 4 months, the symptoms were completely relieved, refraction was stable and her acceptance was plano. The atropine eye drops was stopped. The subject reported the same symptoms after 3 months. The AS was found to be re-occurred, so she was advised to continue atropine eye drops. She was switched over to homide eye drops as patient was suffering from eye pain since 2 months, due to long-term use of atropine drops. She was also advised to use accommodative flippers to control the spasm. The findings and follow-up plan is shown in Table 1.

The AS in the above case is still persistent and the subject is under regular follow-up for relief of symptoms.

## Discussion

AS is a rare clinical condition accounting for the prevalence of 6.4% among all accommodative disorders in hospital-based population (6). The probable aetiology for AS in our case may be psychogenic in nature, which was confirmed by the report from psychiatrist. The report revealed that she was in her ninth grade in ICSE (Indian Certificate of Secondary Education) syllabus, which was the cause for her stress. She was also advised to shift to an easier board of education if the stress continues. AS resulting from psychogenic factors have been reported by Rustein et al. (2), Daum (3). Hence a referral to psychiatric consultants and counselling should be considered for psychologically induced AS. Faucher and De Guise (7) reported the AS may also be associated with spasm of convergence and miosis. In our case, there was only AS associated with mild latent hyperopia, exophoria, and normal pupil size. Rustein et al. (2) noted that in AS, hyperopes will accept lesser plus or plano, emmetropes and myopes will accept more minus which disappears with cycloplegia, which was also seen in our case. The AS in our case was clinically confirmed by the difference in dry and cycloplegic refraction findings, varying dry retinoscopy reflex and lead in dynamic retinoscopy. A short acting drug like cyclopentolate or homide may or may not break the spasm. Hence a strong cycloplegic agent such as atropine is mandatory to rule out AS. There was a recurrent attack of AS in our case may be because of abruptly stopping the atropine eye drop once the symptoms were vanished. Hence atropine should be continued and gradually weaned off once the symptoms subside. Added plus lenses, Hart chart and accommodative facility exercises should also be supplemented during the weaning off period. Rustein et al. (2,4) also reported that AS can be orthoptically intervened during the weaning phase of atropine. For the same reason, an accommodative flipper was implemented for above case as a part of vision therapy. It is evident from the study done by Shah et al. (8) that homide eye drop is less effective in relaxing accommodation in comparison with atropine eye drops. Since our subject complained of eye pain with atropine eye drop, she was switched over to homide eye drops. Diamond et al. (9), Chia (10), and Luu et al. (11) have reported the side effects associated with the use of atropine eye drops. The common side effects of atropine eye drops reported in literature are allergic conjunctivitis, dermatitis, neural retina toxicity and eye irritation. So, the side effects of atropine eye drops should be ruled out prior instillation or during the treatment of AS if atropine eye drops is advised.

## Conclusion

Psychogenic factors are the most probable aetiology behind AS. So, if the patient is found to be under antipsychotic drugs, then AS can be

suspected. AS arising from psychogenic factors must be referred to a psychiatric for a comprehensive evaluation. Atropine eye drops has been showing good results in the diagnosis and therapeutic management of AS. Gradual weaning off atropine eye drop is advised rather than abrupt stopping. In cases of persistent and recurrent AS, atropine can be continued and gradually weaned off based on the refraction stability. The subject should be educated for the side effects of atropine eye drops prior to treatment and during the treatment phase to avoid all possible systemic and ocular side effects due to atropine instillation. Vision therapy such as accommodative flippers, added lenses and Hart chart must be advised for patient with AS. Periodic orthoptics evaluation once the spasm is relieved will help us to know the status of accommodation.

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# Molecular Genetic Testing in Ophthalmology

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Inherited ophthalmic diseases affect almost all parts of the eye from the lid, anterior segment, posterior segment and optic nerves. The inherited eye diseases include Mendelian or single-gene disorders and complex diseases. More than 500 genes have been identified that contribute to inherited eye diseases (1). More number of genes are identified and added to the list every day with advancement in genomic technology. Molecular genetics research has revealed the vast genetic heterogeneity in certain diseases like Leber's congenital amarousis (LCA), retinitis pigmentosa (RP), Bardet Biedle syndrome (BBS), congenital stationary night blindness (CSNB), where defects in different genes cause similar phenotype. Allelic heterogeneity is also reported, where phenotypically different diseases like certain corneal dystrophies (congenital hereditary corneal dystrophy (CHED), Fuch's endothelial corneal dystrophy (FCD)) are caused by different mutations in the same gene (2). Though research has unraveled the genetic basis of both Mendelian and complex ophthalmic diseases, currently genetic testing or molecular diagnosis has immediate application for single gene disorders.

## What is the need for genetic testing?

Genetic testing is recommended by well-informed physician/ophthalmologist when a patient is diagnosed with an inherited eye disease, and the purpose for such a testing can be broadly classified as (i) diagnosis/confirmation, (ii) prognosis (based on the genotype phenotype data available), (iii) treatment/management, (iv) counseling and (v) research (3). The critical steps of genetic testing include (i) complete and accurate clinical diagnosis of the genetic eye disease, (ii) pre-test counseling explaining the possible implications of the test as well as its limitation, (iii) investigation of the genomic DNA of the affected index patient and/or the family members, (iv) analyses of the data obtained from DNA testing along with reference to recent published literature and updated public DNA/mutation database, (v) correlating the DNA data obtained with the clinical findings, (vi) counseling the patients about the interpreted genetic test results, their implications and (vii) social or rehabilitation counseling wherever deemed necessary. The best clinical value of genetic testing is achieved when the results and their implications are discussed thoroughly with the patients by a knowledgeable physician or trained counselor.

Monogenic genetically heterogenous inherited eye diseases like RP, CSNB and many others also exhibit different pattern of inheritance like autosomal or X-linked, either dominant or recessive disease. The pattern of inheritance is primarily identified based on the family pedigree drawn, when the patient reports to the genetic clinic or counselor. The accuracy of identifying the mode of inheritance depends on complete information provided by the patient and his/her family members. Pattern of inheritance is easy to identify in a pedigree with more than one affected person either across or along a generation. However, identifying the pattern of inheritance becomes difficult when the patient presents as an isolated case without a family history. Molecular genetic testing identifies and/or confirms the pattern of inheritance and aids in accurate risk prediction for the other family members and kin. For example an isolated case of RP presenting in first or second decade of life could either be an autosomal-recessive or X-linked recessive disease. In an autosomal-recessive inheritance, the recurrence risk of the disease in the sib(s) is 25%, whereas in an X-linked recessive pattern, the disease is not manifested in female sibs, while the male sibs have 50% chance of having the disease. Also in an individual with autosomal-recessive disease the probability of the disease to re-occur in the next generation in a non-consanguineous mating is that of the general population (<5%), whereas in an X-linked recessive disease, it is not passed on to the son, but the daughter is an obligate carrier.

Although inherited eye diseases, especially the retinal degenerative diseases, do not currently have any treatment options, vision scientists have been working on gene replacement therapy, where the functional copy of the defective gene is delivered through viral vectors. Following the success of *Rpe65*-LCA gene augmentation therapy using recombinant adeno-associated virus 2 (rAAV2) in canine models, clinical trials of *RPE65*-LCA gene augmentation therapy was initiated in humans. The safety and efficacy results of the 3-year follow-up after using rAAV-*RPE65*–LCA gene therapy trials have shown that there is no systemic toxicity but an improvement in visual functions in varying degree localized to the area of treatment in all patients administered with the gene therapy and ocular adverse event if any were related to surgery only. The data published from trials on 15 adults and children also reveal that extrafoveal treatment was sufficiently safe,

whereas treating the fovea had no benefit but some risk (4).

The promising results of gene therapy trials give hope to patients, treating physicians and vision scientists. With the encouraging results of human gene therapy trials, genetic testing to identify the causative gene becomes mandatory as knowledge of this will be necessary to offer such therapy in future after they have been approved as a treatment modality.

## Carrier or pre-symptomatic testing

Once the causative gene and the mutation is identified in an affected individual in the family, carrier testing in case of autosomal-recessive or X-linked recessive disease can be offered to the unaffected sibs or the prospective spouse to make an informed reproductive choice. Pre-symptomatic testing can be offered in case of autosomal-dominant diseases that help the physician (i) administer preventive therapy if possible before clinical damage to the tissue, (ii) increase surveillance for treatable manifestations of the diseases and it also helps the individual make informed reproductive or carrier choices (5).

The identification of causative gene and mutations also opens up the possibility of pre-natal genetic testing. For instance, pre-natal genetic testing for retinoblastoma offers stringent surveillance from birth for early detection and treatment in mutation-positive infant. However, the diseases for which this can be offered depends on treatment, management, surveillance or prevention strategies available for the disease and are primarily governed by the rules and regulations of pre-natal genetic testing of the countries.

## Genetic testing in complex diseases

Genome-wide association studies (GWAS) have identified many risk variants for complex diseases like age-related macular degeneration (AMD), primary angle closure glaucoma (PACG) (6,7). Interaction of multiple genetic variants or loci with each other and with environment contributes to the disease expression in complex diseases. The presence of one or few of the variants is not highly predictive of the disease development. Hence, genetic testing in complex disease or pre-symptomatic testing in unaffected individual with a family history of such diseases is not recommended till specific therapeutic or surveillance options are available for individuals with specific genotype (5).

## Syndromic ocular inherited diseases

Most of the inherited ocular disease, like retinal degenerative diseases or corneal dystrophies, affects only the eye; however, there are also syndromic forms. Usher syndrome is an autosomal-recessive disease characterized by RP, hearing loss and some time vestibular dysfunction. Bardet–Biedl syndrome (BBS) is characterized by rod-cone dystrophy, truncal obesity, postaxial polydactyly, cognitive impairment, male hypogonadotrophic hypogonadism, complex female genitourinary malformations and renal abnormalities (8). Both these diseases are genetically heterogenous. Molecular genetic testing and identification of the mutation not only aids in molecular conformation of the disease but also helps the physician to plan for treatment if any or effective management of systemic manifestations like cochlear implant for hearing impairment (depends on the subtype of Usher syndrome and if detected at an early age), hormone therapy for hypogonadism, management of obesity, screening for renal cysts etc. Senior Loken syndrome is characterized by nephronophthisis and retinal degeneration and the gene involved is *IQCB1*. Recently, *IQCB1* was also identified to cause Leber congenital amarousis (LCA) in 4% of the cohort studied and 60% of the affected were found to have renal abnormalities upon re-inspection (9). Thus, screening and identification of mutations in *IQCB1* in LCA indicates the need to follow up for kidney disease in these patients. von Hipple-Lindau (VHL) is an autosomal-dominant inherited neoplastic disorder, with most common tumors being retinal and central nervous system haemangioblastomas, clear renal cell carcinoma (RCC), phaeochromocytoma, pancreatic islet tumors and endolymphatic sac tumors. Published mutation data reveal that patients with truncating mutations in the *VHL* tumor suppressor gene do not usually develop pheochromocytoma, while patients with missense mutation are at the risk of developing pheochromocytoma (10). Thus, a molecular genetic testing here not only identifies the type of mutation, but allows the patient and family to know the risk for other tumors as well.

## Methodologies for gene screening

Gene screening using Sanger sequencing has been the gold standard for mutation detection. Rapid detection techniques, like PCR-based restriction fragment length polymorphism (PCR-RFLP) or allele-specific PCR (AS-PCR) to identify specific mutation, have also been used. In genetically heterogenous diseases like RP, LCA or BBS, all the known candidate genes need to be screened. This becomes very labor intensive, expensive and time consuming. If there is prior knowledge of the mutation or gene prevalence in a given population, then gene testing strategies can be designed so as to screen the most frequently occurring mutation or gene first, followed by rest of the

genes, thereby reducing the cost and time taken for testing. Advancement in sequencing technologies has ushered in an era of next-generation sequencing (NGS) where parallel sequencing of multiple loci is possible. NGS-based targeted re-sequencing of candidate genes is cost-effective especially in a genetically heterogenous diseases and is becoming the method of choice for genetic testing or screening (11–13).

## Study of chromosomes

Genetic testing involving DNA sequencing using various strategies has grown rapidly over the last decade. However, peripheral blood lymphocyte culture to analyze the karyotype for structural and numerical abnormalities of the chromosomes is still pertinent in molecular diagnosis of certain diseases. Down, Edward and Patau syndromes are due to trisomies of chromosomes 21, 18 and 13, respectively, and have characteristic clinical features including ophthalmic manifestations. Structural chromosomal defects like deletion of 13q14 or 11p13 are reported in retinoblastoma or aniridia, respectively. Ocular developmental anomalies like microphthalmos, anaophthalmos, nanophthalmos and coloboma also show chromosomal abnormalities. The risk for such recurrences in further offspring is higher if the parents are carriers of structural rearrangements like Robertsonian translocations. Chromosome study of the affected and parents becomes very essential here for risk prediction and counseling (14). The traditional karyotyping using GTG banding has a very low resolution of several megabases. Techniques like fluorescent in situ hybridization (FISH), spectral karyotyping (SKY), comparative genome hybridization (CGH) and whole-chromosome painting were developed, which use fluorescent probes that increased the sensitivity of detection, but still detected rearrangements/deletions/duplications of several megabases only and requires a metaphase spread of the chromosomes. Now, we have oligonucleotide arrays for array-based CGH and single-nucleotide polymorphism (SNP)-based arrays from commercial vendors for molecular cytogenetics that detect copy number variations (CNVs), facilitate precise determination of structural variation boundaries and have high sensitivity and resolution of >5–10 kb (15).

## Cost of genetic testing and turnaround time

The cost incurred for testing and turnaround time for the results are two important aspects of genetic testing. Direct Sanger sequencing of large number of genes as in RP or LCA would be very expensive (approximately Rs. 80,000–1,00,000/- per sample) and also require considerable time (say 6–8 months to screen about 15 genes). With the advent of parallel sequencing using the NGS platforms, the cost of screening all the candidate genes per sample is considerably reduced (approximately Rs. 25,000 per sample). Multiplexing of samples with specific indexing is possible while using NGS-based parallel sequencing where the samples are processed in batches of 48 or 96 in numbers, which contributes greatly to the cost reduction. In inherited eye diseases, the process of degeneration is slow and usually the ophthalmologist suggests a yearly review or follow-up. In such conditions, it makes sense to take advantage of longer turnaround time for the benefit of cost reduction. In clinical conditions where genetic test results offers access to therapeutic options or if the information is needed urgently for reproductive or career decisions, a short turnaround time (2–3 weeks) with higher cost of testing is justified. Thus, a clinically relevant turnaround time based on the clinical situation can be defined by the testing laboratory and the referring physician (5).

## Molecular genetic testing under research

In genetically heterogenous monogenic inherited eye diseases, the candidate genes identified till date contribute to 50–70% of the disease (16, 17). Research studies are undertaken to identify rest of the contributing genes that would help in further understanding the pathogenesis of the disease and in designing gene-based therapy studies/trials or drug-based therapies. Whole-exome or whole-genome sequencing by NGS gives enormous amount of data at a very reasonable cost. However, usefulness of such a massive amount of data under routine diagnostic is still limited since (i) vast amount of sequence variation in the genome is incompletely characterized, (2) the cost of meaningful analysis of such variations in individual patients is high, i.e. the cost involved in carrying out experiments to understand the implication of the identified, uncharacterized variation will be very high, (3) the inability to determine the parental origin of potentially recessive alleles without also testing family members and (4) the responsibility and financial and psychological cost of counseling a patient on discovery of other disease-related variations observed in the genome. Thus, at present whole-exome or -genome sequencing can be restricted to research studies till the clinical relevance of such tests is completely established. Research studies on complex diseases continue to explore the functional significance or contribution of the identified risk variants, to design effective targeted drug therapies and to identify highly predictive specific variant(s) (5).

We at the SNONGC Department of Genetics and Molecular Biology offer peripheral blood lymphocyte culture and karyotyping and

DNA-based gene testing for few genes and diseases. The list of the tests is given below.

| S. no. | Test |
|---|---|
| 1 | Chromosomal study (PBLC method) |
| 2 | Cytogenetic analysis for retinoblastoma |
| 3 | RPE65 gene screening for retinitis pigmentosa/leber congenital amarousis |
| 4 | Rhodopsin (RHO) gene screening for autosomal-dominant retinitis pigmentosa |
| 5 | RS1 gene screening for retinoschisis |
| 6 | PAX6 gene screening for aniridia |
| 7 | CYP1B1 gene screening for congenital glaucoma |
| 8 | MYOC gene screening for open angle glaucoma |
| 9 | BBS genes screening for BBS |
| 10 | Screening the three primary mitochondrial mutations for leber hereditary optic neuropathy (LHON) |

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# Chromovitrectomy

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Chromovitrectomy indicates the use of vital dyes in staining the transparent vitreous jelly and the preretinal tissue and membrane's (internal limiting membrane and epiretinal membrane).

USES: 1. Improved visualization of preretinal structures. 2. Ensures complete removal of the tissue. 3. Decreases associated complications.

| Ideal dye |
|---|
| • Should selectively stain the tissue of interest<br>• Should provide enough contrast<br>• Easy elimination from vitreous cavity and physiologically degradable<br>• Should be biocompatible and photochemically stable |

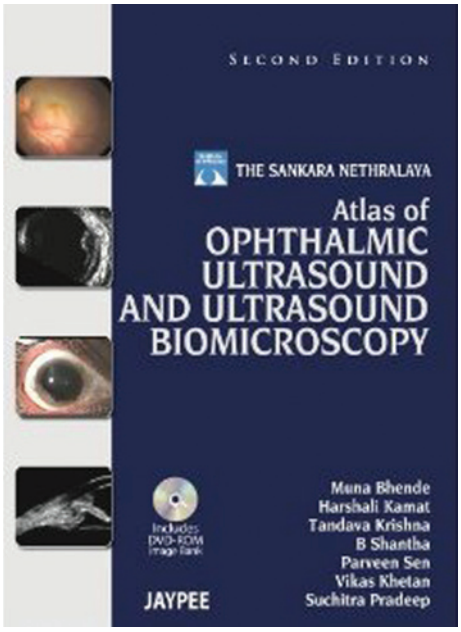
TYPES:

| Generation I | Generation II | Generation III |
|---|---|---|
| Indocyanine green (ICG) | Infracyanine green<br>Trypan blue<br>Triamcinolone acetonide | Brilliant blue<br>Chicago blue<br>Patent blue<br>Bromophenol blue |

| Dyes | Properties |
|---|---|
| ICG (0.5 mg/ml) | • Has high affinity for extracellular component of ILM. Stains and makes the ILM taut<br>• Anterior capsular staining and negative staining of ERM<br>• Hypo-osmotic ICG can cause osmotic damage to retina<br>• Phototoxicity, RPE alteration and visual field defect |
| Infracyanine green (0.5 mg/ml) | • Modified iodine-free version of ICG<br>• Dissolved in 5% glucose giving an iso-osmotic solution<br>• Staining similar to ICG but less safer profile |
| Brilliant blue (0.25 mg/ml) | • Ideal for ILM staining<br>• Subretinal migration causes RPE atrophy<br>• Neuroprotective |
| Trypan blue (0.15–0.3%) | • High affinity to glial tissue<br>• Stains anterior capsule and ERM<br>• Stains edge of a retinal break |
| Patent blue (0.24%) | • Stains anterior capsule<br>• Moderate affinity to ERM and vitreous<br>• Mild reversible retinal toxicity |
| Bromophenol blue (0.2–1.2%) | • Stains anterior capsule and ERM |
| Triamcinolone acetonide | • Stains vitreous gel and posterior vitreous cortex for ensuring PVD induction<br>• Gets deposited on ERM, ILM and makes it easy to identify them<br>• Reduce breakdown of blood aqueous barrier and preretinal fibrosis |
| Sodium fluorescein (0.6%) | • Stains vitreous<br>• 1–2% solution can stain ILM |
| Heavy brilliant blue (0.05%) | • Mixed with 10% DNS 2:1 ratio<br>• Better staining with less quantity |

Techniques of staining:

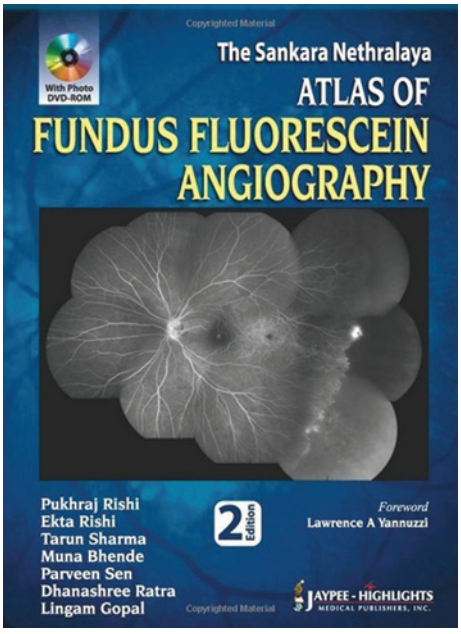
| | |
|---|---|
| **Air-filled or dry technique**<br>• Done after fluid gas exchange<br>• Higher concentration of dye at posterior pole<br>• Higher incidence of retinal toxicity | **Fluid-filled technique**<br>• Direct injection in BSS/RL-filled eye<br>• Immediate washout, less staining and less toxic |
| **Vitreo retinal ILM colour enhance**<br>• Brush-like device. Silicon tube with metal cover and tip made of silk filament<br>• Preloaded with dye which is directly painted on the retinal surface | **To reduce toxicity**<br>• Use lowest concentration for shortest possible time<br>• PFCL can be injected directly over macular hole to prevent subretinal dye migration<br>• Light pipe kept as far away as possible from retinal surface to avoid phototoxicity |




## The Sankara Nethralaya Atlas of Ophthalmic Ultrasound and Ultrasound Biomicroscopy, 2nd edition, Hardcover: 440 pages, Jaypee Brothers Medical Pub.

The second edition of *The Sankara Nethralaya Atlas of Ophthalmic Ultrasound and Ultrasound Biomicroscopy*, while retaining its original layout and flavour, has considerably widened its scope to include anterior segment imaging using ultrasound biomicroscopy. The original chapters, which involved imaging of the posterior segment and orbit, have been updated with addition of many new images, though the techniques of evaluation have remained unchanged over the years. The new section ultrasound biomicroscopy includes common and rare conditions, which involve the anterior segment with corresponding photographs where possible. Practical issues, such as when to perform the test in a given condition, what to look for, and the implications on treatment have been dealt with in a brief fashion. The atlas aims to educate the novice and, at the same time, refresh the knowledge of the qualified ophthalmologists in one of the segments in the always fascinating field of ophthalmic imaging – ultrasonography.

## The Sankara Nethralaya Atlas of Fundus Fluorescein Angiography, Hardcover: 606 pages, Jaypee Brothers Medical Pub.




A lot has changed in the field of vitreous retina since the first edition of *The Sankara Nethralaya Atlas of Fundus Fluorescein Angiography* came out in 2004. Not only has our ability to investigate and diagnose clinical conditions improved but the rapidly evolving treatment options have had a major impact on disease modulation due to significant advances in multimodal retinal imaging, the advent of anti VEGF era and path breaking changes in drug delivery systems. A good knowledge of the changes occurring in the fluoroscein angiogram is not only important for correct diagnoses and management of eye disorders, but also in determining end points. Even though optical coherence tomography, OCT, is a fast emerging as a noninvasive retinal imaging tool, the role of FFA in diagnosis and treatment and follow up remains integral to the management of retinal conditions. In this edition, we have added twenty new chapters and revised most of the previous ones. In doing so, we have preserved the original format of the chapters while the layout of the sections remains intact. A "self test" chapter has been included at the end. Each section has been colour coded to improve user friendliness while adding to the aesthetic appeal of the book. Nearly 400 new images have been added in this edition. References have been revised and updated. Also in this edition, we have included a photo DVD ROM so that the tech savvy user can browse the book on the go. The aim of bringing out this book is to have a comprehensive reference guide on the fluoroscein angiographic findings in different disorders, so as to help the readers in understanding and managing these types of cases. This book is not intended to be a textbook on fluoroscein angiography, but the text has been kept to a minimum. On the other hand, a colour fundus photograph, a red free photograph and pictures of different phases of the angiogram are included for almost all cases. A detailed legend is given for all photographs.

The book intends to be a ready reckoner for the practicing vitreo-retinal surgeon/medical retinal specialist as much as a reference guide for vitreo-retinal fellows. The same holds true for uvea specialists and fellows Comprehensive ophthalmologists will find this book very useful in arriving at the correct diagnosis and appropriate management of their patients. This book has a unique format and includes over 1500 images and photographs to provide a visual representation of the disease process. Every attempt has been made to include as many representative cases as possible in each section.