EFFICACY AND SAFETY OF INTRAVITREAL TRIAMCINOLONE ACETONIDE IN THE MANAGEMENT OF RECALCITRANT DIABETIC MACULAR EDEMA

Dissertation submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI, INDIA

M.S. DEGREE EXAMINATION
BRANCH – III OPHTHALMOLOGY

APRIL – 2016

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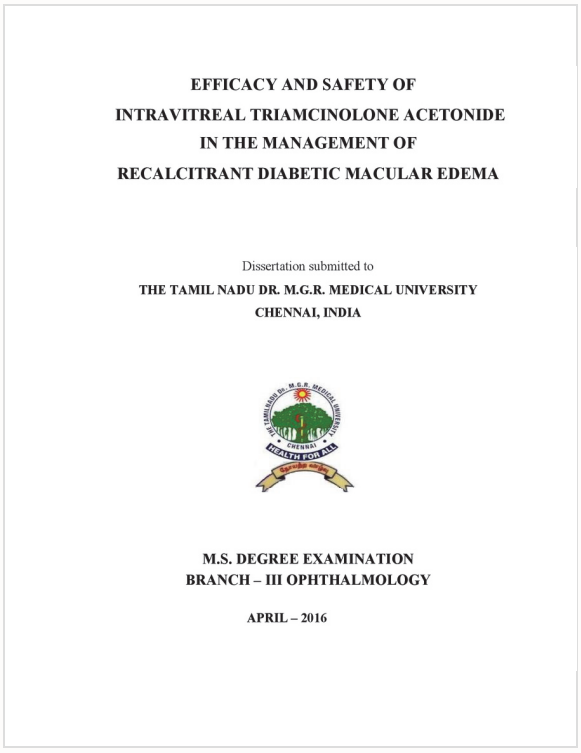

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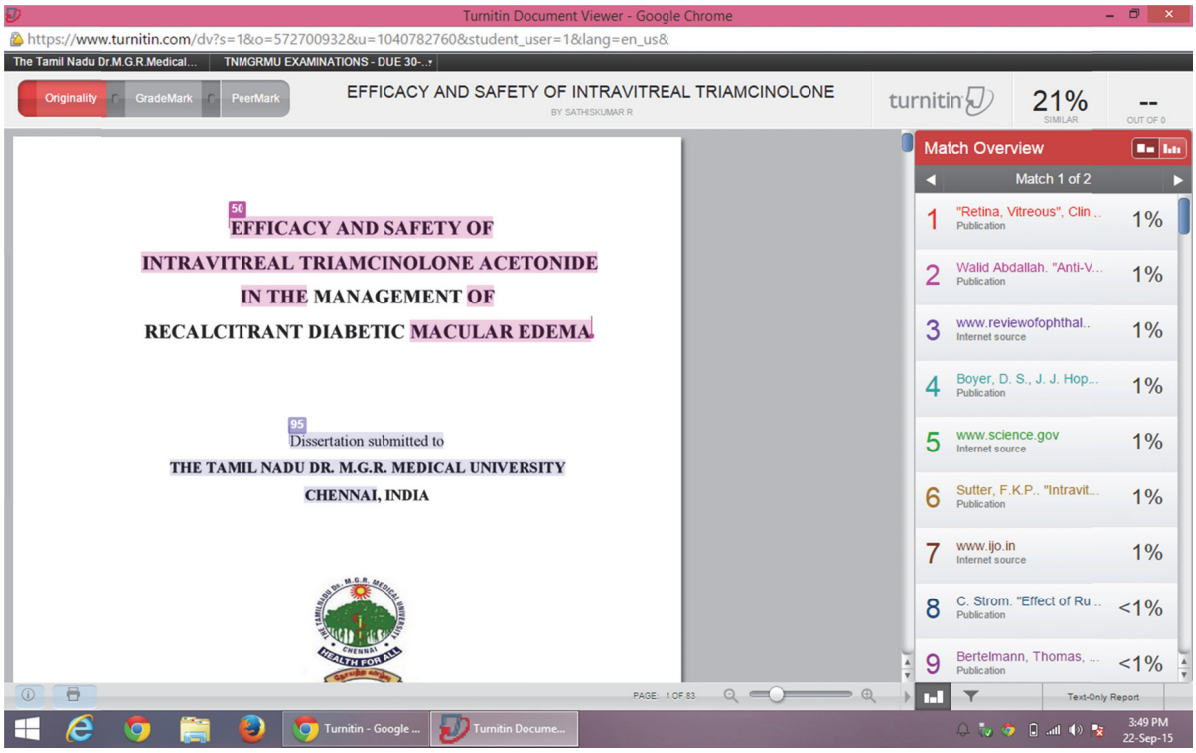
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(Guide)

Dr.AMJAD SALMAN, M.S,
Professor and Head of the Department,
Department of Vitreo-Retinal Services.

ENDORSEMENT BY THE HEAD OF THE INSTITUTION

This is to certify that the dissertation entitled "**EFFICACY AND SAFETY OF INTRAVITREAL TRIAMCINOLONE ACETONIDE IN THE MANAGEMENT OF RECALCITRANT DIABETIC MACULAR EDEMA"** is a bonafide work done by **Dr. SATHISKUMAR.R**, **postgraduate student in M.S (Ophthalmology) during JULY 2013 to MARCH 2016,** under the guidance of **Dr. C.G. VANILA, M.S., DNB.,** Professor of Ophthalmology, at our institute, in partial fulfillment for the award of M.S degree in Ophthalmology for the Tamil Nadu Dr. M.G.R. Medical University, Chennai.

Prof. Dr. C.A.NELSON JESUDASAN, M.S, D.O.M.S,
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Tiruchirapalli-620 001.

DECLARATION

I, **Dr. SATHISKUMAR.R**, solemnly declare that the dissertation entitled **"EFFICACY AND SAFETY OF INTRAVITREAL TRIAMCINOLONE ACETONIDE IN THE MANAGEMENT OF RECALCITRANT DIABETIC MACULAR EDEMA"** was done by me in the Department of Retina at Institute of Ophthalmology, Joseph Eye Hospital, Tiruchirapalli during the period from September 2013 to July 2015 under the direct guidance and supervision of **Dr.C.G.Vanila M.S,DNB.,** Professor and **Dr.V.Saravanan Selvaraj M.S,D.O,FRVS.,** Assistant Professor, Department of Vitreo-Retinal services, Institute of Ophthalmology, Joseph Eye Hospital, Tiruchirapalli. The dissertation is submitted to the **Tamil Nadu Dr.M.G.R Medical University, Chennai** in partial fulfillment for the award of **M.S. Degree in Ophthalmology.**

I have not submitted this dissertation on any previous occasion to any university for the award of any degree.

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Date:

Dr. SATHISKUMAR.R

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CONTENTS

Introduction

INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic disease which presents with high blood sugar usually due to inadequate secretion of insulin or resistance to insulin. The high blood sugar leads to symptoms such as polyphagia, polyuria and polydipsia.

The three main types of diabetes mellitus are :

- Type 1 DM or insulin-dependent DM is an idiopathic / immune-mediated destruction of pancreatic β cells, resulting in complete or near-total insulin deficiency.
- Type 2 DM or non- insulin-dependent DM (NIDDM) is characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production.
- Gestational diabetes, occurs in pregnant women without previous diagnosis of diabetes.

Diabetic retinopathy is a complication of diabetes mellitus and it is a major cause of preventable blindness in both developed and developing countries. It is becoming one of the leading causes of newly-diagnosed legal blindness amongst the working class people (National Diabetes Data group, 1995)[1]. Diabetic macular edema (DME) is one of the most common causes of visual impairment in DR.

The prevalence of DR in a diabetic population as reported by Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR)[1a] was 50.1%. The

incidence of DR in type1 DM (IDDM) patients, as reported by Diabetes Control and Complications Trial (DCCT)[2] is 54.2%. Similarly the United Kingdom Prospective Diabetes Study (UKPDS)[3] have reported the prevalence of DR in type 2 (NIDDM) patients was 35% to 39%.

In India, DR was detected in 52% of patients with NIDDM of over 25 years duration; non proliferative DR (NPDR) was seen in 41.7%, and proliferative DR (PDR) was seen in 10.3% (Mohan *et al*).[4]

In the Chennai Urban Rural Epidemiological Study (CURES),[5] which evaluated 26,000 patients, the prevalence of DR was 17.6% in an urban population. The Sankara Nethralaya Epidemiologic and Molecular Genetic Study (SN-DREAMS)[6] evaluated a sample of 5,999 patients in southern India. The prevalence rate of DR in an urban diabetic population was 18%, which correlated with the CURES report. A study of 4067 diabetic patients in Northern India noted the prevalence of DR to be 28.9%.[7]

The common cause of visual impairment in type 1 DM results from the complications due to proliferative diabetic retinopathy (PDR); commonly vitreous hemorrhage. In type 2 DM patients visual impairment is mainly due to diabetic macular edema. Since the majority of diabetics have type 2 disease, wherein macular edema is more common, macular edema accounts for more vision impairment than does proliferative retinopathy among all diabetes mellitus patients. (Klein *et al.).*[8] Hence, finding safe and effective treatment of DME becomes very important.

Diabetes Mellitus is essentially a microvascular disease. Mechanisms contributing to the microvascular damage in DR and DME include the direct toxic effects of hyperglycemia, altered cell signaling pathways, intracellular sorbitol accumulation, oxidative stress due to free radical excess, accumulation of advanced glycation end products, activation of protein kinase C, disruption of ion channels and chronic microvascular inflammation with leukocyte-mediated injury.[9] Chronic retinal microvascular damage results in death of pericytes, capillary basement membrane thickening, loss of vascular smooth muscle cells and proliferation of endothelial cells followed by capillary dysfunction manifesting with leakage and occlusion of the capillaries. This leads to capillary non-perfusion, retinal hypoxia and elevation of intraocular levels of vascular endothelial growth factor (VEGF) especially VEGF-A, a potent, diffusible, endothelial-specific mitogen that mediates many important physiologic processes, including the development and permeability of the vasculature. At present, there are several therapies available for the treatment of DME, including laser photocoagulation, intravitreal injection of anti-VEGF drugs, ocular corticosteroids and pars plana vitrectomy.

Laser photocoagulation has proven to be useful in limiting vision loss in the past three decades and is still considered a gold standard therapy for the treatment of DR.[10, 11] Intravitreal corticosteroids and anti-VEGF are being widely used as pharmacotherapy for DME. Ranibizumab and bevacizumab are the two main anti-VEGF agents for treatment of DME. However, the failure of laser photocoagulation and / or intravitreal anti-VEGF agents in a substantial subgroup of patients has prompted interest in other treatment methods.

The rationale for the use of corticosteroids and anti–VEGF agents in the treatment of DME based on the evidence, that the breakdown of the blood - retinal barrier leads to edema and is, in part, mediated by VEGF (Wilson *et al.*)[12]. Corticosteroids have been shown to regulate endothelial cell tight junctions, by inhibiting VEGF, inflammatory cytokines and growth factors. Triamcinolone acetonide, a corticosteroid, has anti-inflammatory and anti-angiogenic effects, based on experimental studies by Machemer *et al.*[13a] and clinical observations by Sutter *et al*.[13b,13c] Intravitreal triamcinolone acetonide has increasingly been reported in the management of neovascular, edematous and inflammatory diseases of the eye.

Studies by Martidis *et al*., Gillies, Sutter *et al*. and Jonas *et al*. have shown that intravitreal triamcinolone improves vision and reduces macular thickness in eyes with refractory DME that fails to respond to conventional laser photocoagulation.[13b,c,d]

The investigation on which this dissertation is based was a prospective, interventional study done at Retina Clinic of a tertiary eye care hospital in Tamil Nadu and aimed to evaluate the efficacy and safety of intravitreal triamcinolone acetonide in the management of recalcitrant diabetic macular edema.

Aim of the Study

AIM OF THE STUDY

To evaluate the safety and efficacy of intravitreal triamcinolone acetomide in the management of recalcitrant diabetic macular edema.

Primary Objective

The primary objective of the study was to evaluate the efficacy of intravitreal triamcinolone acetonide in the management of diabetic macular edema unresponsive to laser photocoagulation and the intravitreal anti-VEGF agent, bevacizumab. The response to treatment was monitored functionally by best corrected visual acuity and anatomically by optical coherence tomography (OCT) by measuring central macular thickness.

Secondary Objective

The secondary objective of the study was to evaluate the safety of intravitreal triamcinolone acetonide in the management of recalcitrant diabetic macular edema. The safety of the drug was monitored functionally by looking for decrease in visual acuity of one line by Snellen's chart, rise in intraocular pressure greater than 30 mm of Hg not responding to topical anti-glaucoma medications, and development of cataract as assessed by cataractous lenticular changes from the baseline.

Review of Literature

REVIEW OF LITERATURE

Diabetic retinopathy is a leading cause of severe visual loss in developed countries and emerging as the common cause of preventable blindness in India. Among diabetic patients with DR, 25 percent of patients have sight-threatening levels of retinopathy. When compared to the non-diabetic population, legal blindness (with best corrected visual acuity of 6/60 (20/200) or worse) is 25 times more common in the diabetic patients. (Kahn *et al*.)[14]

The exact cause of diabetic microvascular disease is unknown. Fundamentally, diabetes mellitus causes abnormal glucose metabolism which is due to decreased level of insulin or their activity. It is believed that exposure to hyperglycemia over an extended period results in a number of biochemical and physiologic changes that ultimately cause vascular endothelial damage.

Continuous increase in blood glucose levels in certain tissues sends the excess glucose into the aldose reductase pathway, where sugar is converted into their alcohols, ie; glucose to sorbitol and galactose to galactitol. Sorbitol and galactitol cannot easily diffuse out of cells, causing increased intracellular concentration. Increased levels of sorbitol affects the intramural pericytes of retinal capillaries, which eventually leads to the loss of their auto-regulatory function of retinal capillaries.[14a]. This results in weakness and localised out-pouchings of the retinal capillary walls and microaneurysm formation. These microaneurysms are the first ophthalmoscopically detectable changes in DR and are considered as the hallmark of non-proliferative diabetic retinopathy.

Microaneurysms, at moderate stages progress into intraretinal microvascular abnormalities (IRMA), which are shunts that run within the retina from arterioles to venules. When the wall of capillary or microaneurysm is weakened enough it may rupture giving rise to intraretinal hemorrhages and cotton-wool spots, which represent focal infarcts of the retinal nerve fiber layer. The increased permeability of the retinal vasculature can lead to retinal edema and the formation of protein and lipid-rich deposits, known as hard exudates.

Macular edema is the most common cause of visual impairment in diabetic patients, particularly those with type 2 diabetes. The four types of diabetic macular edema are focal exudative, diffuse exudative, ischemic and mixed; each type exhibits distinct signs and fundus fluorescein angiography (FFA) patterns:

a) In focal maculopathy, well-circumscribed retinal thickening, associated with complete or incomplete rings of exudates, is seen. FFA shows late focal hyperfluorescence due to leakage and good macular perfusion.
b) In diffuse maculopathy, diffuse retinal thickening may be associated with cystoid changes. FFA shows late diffuse hyperfluorescence, which may assume a central flower petal pattern in case of cystoid macular edema.
c) In ischemic maculopathy, signs are reduced visual acuity with a relatively normal appearance of the macula. FFA shows capillary non-perfusion at the fovea and enlargement of the foveal avascular zone.
d) Mixed maculopathy is characterized by features of both exudative and ischemic.

The **ETDRS (1985)**[10] defined **clinically significant macular edema (CSME)** as any one of the following.

(i) retinal thickening within 500 μm of the center of the macula;

(ii) Exudates within 500 μm of the center of the macula, if associated with retinal thickening; (which may be outside the 500 μm) or

(iii) retinal thickening one disc area (1500 μm) or larger, any part of which is within one disc diameter of the centre of the macula.

CSME requires laser photocoagulation, irrespective of the level of visual acuity, because treatment with laser photocoagulation reduces the risk of visual loss by 50%.[10]

The Early Treatment Diabetic Retinopathy Study (ETDRS), initiated in 1980 divided 3711 patients who presented with severe non-proliferative or early proliferative diabetic retinopathy in both eyes in to different groups. Patients were randomly divided into different groups of which 1 had aspirin 650 mg/day or placebo. One eye of the entire patients was subjected randomly to early photocoagulation and the other eye did not receive photocoagulation (deferral of photocoagulation). Patients were followed-up at every 4 months interval and photocoagulation initiated in eyes assigned to deferral as soon as high-risk proliferative retinopathy was detected. The study concluded that aspirin had no effect on progression of retinopathy or in vitreous hemorrhage. The risk of development of severe visual loss or eyes requiring vitrectomy, was low in eyes assigned to deferral (6% at 5 years) and the risk of progression was reduced by early photocoagulation (4% at 5 years). 208 patients underwent vitrectomy

during the study period of around 9 years. With regular follow-up and timely (panretinal) photocoagulation the 5-year collective rate of pars plana vitrectomy in ETDRS patients was 5.3%. Use of aspirin did not have any effect on the rate of vitrectomy.[10a]

Diana *et al*.[15] conducted a retrospective study in 92 patients (152 eyes) with persistent CSME and 32 patients (56 eyes) with resolved CSME. They found that persons with type 2 diabetes mellitus and persistent CSME had higher levels of glycosylated hemoglobin (HbA_1C) in the course of their disease than did patients with resolved CSME. Moreover, patients with bilateral disease had HbA_1C levels that were higher than those in patients with unilateral disease.

The Diabetes Control and Complications Trial (DCCT)[16] reported that intensive management of elevated blood glucose levels, as demonstrated by a reduction in the HbA_1C to 7.0%, was associated with decreased rates of development and progression of DR in patients with type 1 diabetes.

In addition, the United Kingdom Prospective Diabetes Study (UKPDS)[17] reported that intensive management of hyperglycemia, as demonstrated by a reduction in the HbA_1C to 7.0%, was associated with a 25% risk reduction in microvascular abnormalities and the need for retinal laser photocoagulation in type 2 diabetic patients, when compared with a control group receiving conventional management. After a six-year follow-up, a significantly smaller proportion of patients in the intensive treatment group than in the conventional group had a two-step progression (worsening) in DR. For every percentage point

decrease in HbA_1C (for eg., 8% -7%), there was a 35% reduction in the risk of microvascular complications.

Adamis *et al.*[18] reported that chronic inflammation, such as adhesion of leukocytes to the retinal vasculature and migration of leukocytes into the retina, may play a substantial role in the development of diabetic maculopathy and retinopathy.

Diagnostic modalities for diabetic microvascular disease include FFA and optical coherence tomography (OCT). OCT is a non-invasive, non-contact diagnostic tool that can perform tomography and provides high resolution cross-sectional imaging of the retina (optical histology), optic nerve head and vitreous with $\leq$ 10 μm axial resolution, using a near infrared light beam of 820 nm. (Puliafito *et al.*)[19] High definition spectral domain OCT provides resolution of retinal tissues of 5 μm.

OCT almost provides an in vivo histopathological visualization of retinal layers, and this helps in understanding the disease and its pathogenesis. OCT is a useful in monitoring the response to treatment in CSME (Otani *et al.*)[20]. There are 5 patterns of diabetic macular edema, namely, sponge-like thickening of the retinal layer, cystoid macular edema, subfoveal serous detachment, taut posterior hyaloid membrane, and tractional detachment at the fovea. Taut posterior hyaloid membrane and tractional detachment at the fovea can be easily diagnosed by OCT; more importantly, these two conditions are generally non-responsive to laser photocoagulation and require pars plana vitrectomy.

Lasers used in photocoagulation of retina include argon green (wavelength 514nm), neodymium yttrium aluminium garnet (Nd-YAG) laser (wavelength 532nm), krypton (wavelength 647nm), diode (wavelength 810nm) and dye (variable wavelength lasers). The average luminance from a continuous wave laser, set at 1 mW during photocoagulation, is 10,000Mw/cm^2. This light is absorbed in melanin in the retinal pigment epithelium (RPE) and increases the temperature to about 30º C. This leads to denaturation of proteins, clinically seen as whitening of the retina. Laser photocoagulation is one of the treatment modalities for diabetic macular edema. The photocoagulation may be focal, grid or panretinal in nature.

Focal Photocoagulation is indicated for focal leaks. The principle of focal laser photocoagulation is obliteration of leaking microaneurysm with laser. This modality of treatment is chosen for all leaking microaneurysms 500-3000μm from the fovea. The spot size is 100 to 200 μm and the duration is 0.1second. The endpoint is whitening or darkening of the microaneurysm. According to the ETDRS, focal laser photocoagulation for diabetic macular edema decreased the risk of moderate visual loss (doubling of initial visual angle), improved the possibility of moderate visual gain (halving of initial visual angle) and reduced retinal thickening[10].

Grid Photocoagulation is indicated for diffuse leaks. The principle of grid photocoagulation is that the RPE pump is stimulated. Grid photocoagulation is done 500 μm from the fovea, 500 μm from the temporal margin of the disc, sparing the papillo-macular bundle. The spot size is 100-200 μm and the duration is 0.05 seconds to 0.1 seconds. With regard to grid photocoagulation,

approximately 70% of eyes achieve stable visual acuity, 15% show improvement and 15% subsequently deteriorate; since it may take upto four months for the edema to resolve, retreatment should not be considered prematurely[10a]. Poor prognostic factors for grid photocoagulation include hard exudates involving the fovea, diffuse macular edema, cystoid macular edema, mixed (exudative and ischemic) edema and severe retinopathy at presentation and associated systemic factors like hypertension, renal disease and elevated HbA_1C levels[10b.]

Pan Retinal Photocoagulation (PRP) is indicated for high - risk PDR, which is defined by Diabetic Retinopathy Study (DRS, 1981)[21] as mild neovascularization of the disc (NVD) with vitreous hemorrhage or moderate to severe NVD (1/4 -1/3 area of disc) with or without vitreous hemorrhage or moderate (1/2 disc area) neovascularization elsewhere (NVE) with vitreous hemorrhage. PRP obliterates areas of infarction, decreases oxygen demand of the outer retina, makes choroidal oxygen available to the ischemic inner retinal layers and produces chorioretinal adhesions that resist vitreoretinal traction. Complications of PRP include loss of 1 or 2 lines of visual acuity, aggravation of macular edema, decrease in field of vision, formation of choroidal neovascular membrane, sub-retinal fibrosis, accidental foveal burns, vitreous hemorrhage, increase in intra-ocular pressure (IOP) and choroidal effusion.

The DRS (1981)[21]conducted a study on 1742 patients with either PDR or bilateral severe non-proliferative diabetic retinopathy (NPDR) with visual acuity 20/100 or better in each eye. One eye was randomly assigned to PRP and the other eye received no treatment. A 50% or greater reduction in the rates of severe visual loss < 5/200, on consecutive review visits 4 months apart, was

noted in eyes treated with PRP compared to no treatment, during a follow-up of over 5 years. Eyes with high risk PDR achieved the greatest therapeutic benefit.

The ETDRS (1985)[10] conducted a study in 3711 patients with mild NPDR through early PDR with visual acuity 20/200 or better in each eye. One eye was randomly assigned to photocoagulation (scatter and / or focal) and one eye to no photocoagulation. Early scatter photocoagulation resulted in a small reduction in risk of severe visual loss < 5/200 for at least 4 months; it was concluded that early scatter photocoagulation may be most effective in patients with type 2 diabetes, but is not indicated for eyes with mild to moderate DR.

In diabetic macular edema, the persistent traction over the macula leads to resistant macular edema; once the traction is relieved by **pars plana vitrectomy**, macular edema resolves. Pars plana vitrectomy is indicated in DME associated with macular traction from a thickened and taut posterior hyaloid membrane, and in diffuse macular edema without posterior vitreous detachment (Flynn et al.)[22] Complications of pars plana vitrectomy include intraoperative or post-operative retinal break / retinal detachment, intra-operative or post operative cataract, vitreous hemorrhage and glaucoma and band-shaped keratopathy due to use of silicone oil.

Pegaptanib is a nuclease-resistant RNA aptamer directed against VEGF-165 isoform, which is believed to be responsible for vascular permeability and ocular neovascularisation. Aptamers are oligonucleotide ligands that are selected for high affinity binding to molecular agents[29].

Bevacizumab is a full-length, recombinant humanized monoclonal antibody (I_gG) that blocks angiogenesis by inhibiting VEGF-A. Bevacizumab has been approved for the treatment of metastatic colorectal cancer[23] by Food and Drug Administration (FDA) of the USA. It has a molecular weight of approximately 149 kilo daltons. It has been suggested that the larger size of the bevacizumab molecule may offer an advantage in PDR over the smaller ranibizumab (a related anti-VEGF agent) molecule, because the location of neovascularization is pre-retinal. Another advantage of bevacizumab is that it has double the half-life of ranibizumab within the vitreous cavity.[24,25] This molecule is marketed as the anti-neoplastic agent Avastin® (Genentech Inc. California, USA), which is available for intravenous infusion as a clear to slightly opalescent, colorless to pale brown sterile aqueous solution. Avastin is available in a concentrate of bevacizumab 25mg/mL in a single dose vial, containing 100 mg and 400mg, in 4 mL and 16 mL respectively.

Bakri *et al*.[26] studied the ocular pharmacokinetics of bevacizumab in a rabbit eye after a single intra-vitreal injection of 1.25mg bevacizumab and observed that the half-life of the bevacizumab in the vitreous was 4.32 days and the maximum concentration of the drug in the serum, reached after 8 days. The serum concentration of the drug was about 0.8% of the maximum vitreous concentration. In another study, following a single intravitreal injection of 1.25mg of bevacizumab, concentrations of >10 µg/ml were maintained in the vitreous humour up to a period of 30 days. Bevacizumab at a concentration of 0.35 ng/ml at day one to 11.17 ng/ml at 4weeks were detected in the fellow uninjected eye. This suggests that bevacizumab enters the systemic circulation

through the anterior route, where it diffuses into the vitreous, rather than entering through the choroidal blood flow.[26]

Numerous studies have evaluated the use of intravitreal bevacizumab in the management of many other ocular pathologies, such as diabetic retinopathy,[24,27,28] branch retinal vein occlusion,[30,31] central retinal vein occlusion,[32,33]age-related macular degeneration[25,34-35] and neovascular glaucoma.[36,37] Systemic adverse effects have been reported, but these have followed administration of much higher systemic doses of bevacizumab to patients suffering from cancer. These adverse effects include perforation of the bowel, arterial thromboembolism, myocardial infarction, stroke and hypertension.[38,39] Patient mortality has also been reported.[39a.] However, none of the above complications has been reported following intravitreal injection of bevacizumab.

Visual hallucinations have been reported after intravitreal injection of bevacizumab, possibly due to the drug itself.[40] Other ocular adverse effects such as floaters, temporary rise of IOP, cataract formation or progression, retinal break and endophthalmitis have been attributed to the injection technique and not due to the drug itself [41]. The incidence of post injection endophthalmitis does not seem to differ from the 1/1000 incidence reported with other intravitreal injections.[42-45] Another important and specific concern is the development or progression of tractional retinal detachment after intravitreal bevacizumab in patients with advanced PDR[46].

Ranibizumab is a monoclonal antibody fragment (Fab portion) engineered using affinity – maturation (amino-acid modifications) to increase its binding affinity to all isoforms of VEGF and thereby preventing the binding of VEGF to its receptors in the eye. Ranibizumab inhibits angiogenesis in a dose-dependent manner,[47,48] morever, the systemic elimination half-life is reduced and systemic exposure and cytotoxicity and inflammation are minimized due to the absence of an Fc domain on the ranibizumab molecule.[49] Ranibizumab is the first anti-VEGF agent approved for intravitreal use in the management of DME and age-related macular degeneration.

Aflibercept (VEGF Trap-eye (VTE) Eylea,™ Regeneron, New York USA**)** is the newest anti-VEGF drug approved by the US-FDA for the treatment of DME. In contrast to antibody-based VEGF binding strategy used by bevacizumab and ranibizumab, aflibercept incorporates the second binding domain of the VEGFR-1 receptor and the third domain of the VEGFR-2 receptor. By fusing these extracellular protein sequences to the Fc segment of human IgG backbone, a chimeric protein with very high VEGF binding affinity is created, which binds all isomers of the VEGF-A family, VEGF-B and placental growth factor. Study of intravitreal administration of VEGF Trap-Eye in patients with DME (VISTA) and VEGF Trap-Eye in vision impairment due to DME (VIVID) are two global clinical trials which compared the efficacy and safety of aflibercept at variable dosing schedules compared to conventional photocoagulation for the treatment of centrally-involving DME.[49a,b] The efficacy of aflibercept is supported by the phase 3 trials VIVID and VISTA. In these parallel phase 3 studies, patients received aflibercept 2.0 mg every 4 weeks or

every 8 weeks. At 12 months patients in both trials gained 10.7 letters compared with 0.2 to 1.2 letter gains in the laser-treated group.

Anti-VEGF drugs are considered as first line therapy for patients with DME. The DRCR.net Protocol T study[64] affirmed the safety and efficacy of anti-VEGF agents in many patients. However, within the various clinical trials studying anti-VEGF therapy for DME, including the Protocol T study, study of ranibizumab injection in subjects with clinically significant macular edema with center involvement secondary to diabetes mellitus (RIDE) and study of ranibizumab injection in subjects with clinically significant macular edema with center involvement (RISE) clinical trials,[65] there are appreciable numbers of patients, (as much as one-third of total number) who do not respond to, or have an incomplete or inadequate response to, active therapy regardless of the anti-VEGF agent used.

Among patients for whom anti-VEGF therapy is incompletely effective, there may be a role for alternative therapeutic modalities and, in particular for corticosteroid therapy. Steroids have both anti-inflammatory and anti-angiogenic properties and, because of these properties, they are increasingly becoming a therapeutic option in retinal practice. Triamcinolone acetonide, dexamethasone and fluocinolone acetonide are the drugs used intravitreally for the treatment of DME and macular edema due to retinal vascular occlusive diseases, pseudophakic cystoid macular edema, exudative macular degeneration and posterior uveitis.The US-FDA has approved the intravitreal dexamethasone implant 0.7mg (**Ozurdex**, Allergan Inc,Irvine,CA) and fluocinolone acetonide

implant 0.19mg (**Illuvien,**Alimera sciences, Aldershot, UK) for the treatment of DME.

Dexamethasone is a potent anti-inflammatory steroid and its effect is six times stronger than that of triamcinolone aetonide. However, dexamethasone has a short half-life in the vitreous. An intravitreal implant of dexamethasone (0.7mg), in the form of a copolymer of lactic acid and glycolic acid, releases a comparable concentration by progressive biodegradation in the vitreous chamber for a period of up to six months after a single injection.

Zalewski *et al*.[66] reported on a five-month observation of patients with chronic DME who had previously been treated with photocoagulation and anti VEGF injections. Four weeks after dexamethasone injection, a significant decrease in the central retinal thickness and improvement in visual acuity was observed. This continued until 12 weeks of observation. The central retinal thickness gradually increased and the visual acuity after 5 months was similar to that of the pre-treatment status. Cataract was the observed adverse effect, but there was no long term increase in IOP following the implant. Intravitreal sustained release steroid implant offers a different DME therapeutic strategy, by providing localized delivery of the corticosteroid to maximize its anti-inflammatory, angiostatic and anti-permeability effects as well as minimize risks of systemic toxicity.

The **MEAD**[68] (Macular edema:Assessment of implantable dexamethasone in diabetes) study, a clinical trial involving 1,048 subjects with DME with BCVA of 20/200 (6/60 of Snellen's equivalent) to 20/50 (6/15 of

Snellen's equivalent), and central macular thickness more than 300 μm were randomly alloted in a 1:1:1 ratio to dexamethasone implant 0.7 mg, dexamethasone implant 0.35 mg or sham injection and followed up for a period of three years. Twenty-four subjects needed retreatment every six months based on OCT findings and retreatment criteria. The proportion (percentage) of patients with more than or equal to 15-letter improvement in BCVA from baseline to the end of the study was significantly greater in dexamethasone intravitreal implant treated groups, being 22.2% with dexamethasone intravitreal implant 0.7mg and 18.4% with dexamethasone implant 0.35mg and 12% in the sham treatment group. The mean average reduction in central retinal thickness from baseline was significantly greater with dexamethasone intravitreal implant treated group than the sham treatment group. The dexamethasone implant 0.7 mg group had mean reduction of CFT by 111.6μm, 107.9μm in the dexamethasone implant 0.35mg group and 41.9μm in the sham treatement group.

The dexamethasone intravitreal implant appeared to be well-suitable for the treatment of DME in vitrectomized eyes; as in these eyes the intravitreally administered drug clears more rapidly when compared to non-vitrectomized eyes. The **CHAMPLAIN** study[69] evaluated 55 patients of DME resistant to treatment and a history of previous pars plana vitrectomy. The study eyes that were resistant to conventional treatment received a single injection of 0.7-mg dexamethasone intravitreal implant and were followed up for a period of 26 weeks. At the end of 26 weeks, these eyes showed clinically significant improvements in both visual acuity and vascular leakage from DME and this

difference being statistically significant. At the eight week, 30.4% of patients had gained more than or equal to 10 letters improvement in BCVA.

The **fluocinolone acetonide (**FA) implant is a non-biodegradable intravitreal corticosteroid implant that is delivered using a 25-gauge injector into the vitreous cavity. The implant is designed to release a sustained concentration (0.2μg/day) of FA continuously for 36 months. Fluocinolone implant is a second-line therapy for the treatment of vision impairment associated with chronic DME, considered insufficiently responsive to laser photocoagulation and anti-VEGF therapy. Bertelmann et al. reported on the long-term follow-up of a patient with DME receiving a FA intravitreal implant. The central retinal thickness decreased sharply at one month following start of treatment and gradually rose again after three months of treatment; cataract and increased IOP where the adverse effects reported. The fluocinolone acetonide for DME (FAME) studied 953 eyes of patients with refractory DME after one or more laser therapy treatments and randomized them in a ratio of 1:2:2 for sham injection, low-dose fluocinolone acetonide insert releasing 0.2 μg/day, or high-dose fluocinolone acetonide insert releasing 0.5 μg/day.[27,28] At 36 months, 28.7% of low dose and 27.8% of high dose of implant-treated eyes versus 18.9% of sham eyes demonstrated an improvement of 15 or more letters and this difference was statistically significant. An additional subgroup analysis showed benefit among patients with diabetic macular edema for three or more years. Drug-related (corticosteroid) side effects were noted; cataracts progressed in nearly all phakic eyes and up to 8.1% of eyes required incisional glaucoma surgery.

Intra-vitreal corticosteroids represent another option for the management of diabetic macular edema; one such corticosteroid is **triamcinolone acetonide** (TA), a potent, synthetic, highly-selective glucocorticoid with marked anti-inflammatory action. Triamcinolone is a 9α derivative of prednisolone -9α fluoro, 11β, 21dihydroxy-16α,17α,21-tetrahydroxy-1,4-pregnadiene-3,20-dione 16,17-acetonide ($C_{24}H_{31}FO_6$). TA is a long-acting depot preparation of triamcinolone. After intravitreal injection, measurable concentrations of the drug are expected to last for 3 months (93 ± 28 days) in the absence of vitrectomy [50], the mean half-life of triamcinolone being 18.7 ± 5.7 days.

Protein kinase C is an enzyme that plays an important role in ocular vascular permeability; inhibition of protein kinase C decreases vascular permeability, therein reducing macular edema. TA acts by inhibiting protein kinase C and thereby inhibits the production and stability of VEGF.

In addition to VEGF-mediated breakdown of the blood-retinal barrier, inflammation is now believed to play an important role in DR and DME.[50b,c] Inflammation is a nonspecific response to injury that includes a variety of functional and molecular mediators, including recruitment and activation of leukocytes. Molecular and functional changes that are characteristic of inflammation such as leukostasis, adhesion molecules, increased prostaglandins and aggregation of macrophages have been detected in the retinas of diabetic patients. Leukocytes possess large cell volume, high cytoplasmic rigidity and a natural tendency to adhere to the vascular endothelium and the ability to generate toxic superoxide radicals and proteolytic enzymes[50d]. It appears that retinal leukostasis may play a key role in the pathogenesis of DR.

DME increases expression of intercellular adhesion molecule-1 (ICAM-1) in the retina, and produces an interaction between this adhesion molecule on the retinal endothelium with the CD 18 adhesion molecule on monocytes and neutrophils, contributing to the diabetes-induced increase in leukostasis within retinal vessels. This attraction and adhesion of leukocytes to the vascular wall contribute greatly to the inflammatory process. Moreover, leukostasis contributes to the development of capillary non-perfusion in retinal vessels, which may ultimately cause death of retinal endothelial cells.[50a]

TA produces a broad suppression of the immune system and achieves an anti-inflammatory effect by a number of mechanisms, including inhibition of cyclooxygenase and lipooxygenase pathways. Synthesis of prostaglandins and leukotrienes is inhibited, resulting in a local reduction of inflammatory mediators and decreasing complement levels, migration of lymphocytes, production of vasoamines and interleukins, circulating monocytes, and macrophage activity. The resultant anti-inflammatory effect contributes to the reduction of edema.

McCuen *et al*.[51] proved that triamcinolone was safe in rabbit eyes, while Young *et al*.[52] reported that intravitreal triamcinolone was safe and effective for cystoid macular edema in uveitis. Martidis *et al.*[53]. described a prospective, non-comparative, interventional case series involving 16 eyes with CSME that had failed to respond to at least two previous sessions of laser photocoagulation. Following intravitreal injection of TA (4 mg/0.1 ml), mean improvements in visual acuity of 2.4, 2.4 and 1.3 Snellen lines were noted at follow-up visits of 1,3 and 6 months, respectively; the central macular thickness decreased by 55%,

57.5% and 38%, respectively, over the same intervals. These researchers attributed the more significant reduction in edema, as compared to the improvement in visual acuity, to the injection being given after the chronic edema had already caused severe dysfunction; they, hence, suggested early injection in severe cases.

Larsson *et al*.[54] demonstrated that a single intravitreal injection of TA (4mg/0.1 ml) effectively reduced the foveal thickness in diabetic macular edema and improved the visual acuity; although there did not appear to be a strong correlation between reduction of foveal thickness and improvement in visual acuity, there was a correlation between reduction in foveal thickness and the age of the patients, namely, there was a significant reduction of macular edema in younger patients.

Massin *et al*.[55] also reported improvement in macular thickness proportionate to improvement in visual acuity, but the effect was only transient, necessitating repeat injections.

In a prospective, double-masked, placebo-controlled, randomized clinical trial, macular edema was noted to decrease (by 115 μm) in 25 of 33 (75%) triamcinolone-treated eyes versus five of 32 (16%) placebo-treated eyes, while edema increased in 0 versus 6 eyes, respectively, which were significant findings (Sutter *et al*.)[13a]; the gain in visual acuity was 5.6 ± 1.2 Snellen letters in triamcinolone-treated eyes, which was significantly better than the gain of -0.1 ± 1.5 letters seen in placebo-controlled eyes. However, the study period was short (3 months) emphasising the need to study longer-term outcomes. In this context,

the study of Jonas *et al*.[56] yielded important results: following the use of 25mg triamcinolone for treatment, maximum improvement in visual acuity was seen usually two to five months after injection, following which the visual acuity deteriorated and the macular edema recurred after 6 months, necessitating repeat injection.

The DRCR protocol I,[56a] an important clinical trial assessed three different treatment schemes for the treatment of DME: intravitreal 0.5 mg ranibizumab with prompt or deferred laser (focal/grid), or intravitreal 4mg triamcinolone acetonide combined with laser (focal/grid) compared with laser alone (focal/grid).[56a] At the end of two-years, compared with the focal/grid laser alone group, the mean change from baseline in the BCVA letter score was 3.7 letters gain in the ranibizumab with prompt laser treatment group, 5.8 letters gain in the ranibizumab with deferred laser group, and 1.5 letters lesser (worsened) in the triamcinolone acetonide with prompt laser group. When analysing the pseudophakic group of patients only, triamcinolone acetonide showed BCVA results comparable to that of ranibizumab, indicating that decreased acuity in the phakic eyes treated with triamcinolone acetonide plus laser could be, at least in part, attributed to the formation of cataract; the drug-related side effect of triamcinolone acetonide. At the end of two-years, the percentages of eyes with central macular thickness $\geq$ 250 μm were 59% in the laser alone group, 43% in the ranibizumab with prompt laser treatment group, 42% in the ranibizumab with deferred laser treatment group, and 52% in the triamcinolone acetonide with prompt laser treatment group. These results show the potential of intravitreal triamcinolone acetonide to serve as a less expensive, but comparable, therapy to

intravitreal anti-VEGF agent ranibizumab. However, anti-VEGF therapy has become first-line therapy especially in phakic DME patients, but intravitreal triamcinolone acetonide can be utilized in phakic patients who do not have access to ranibizumab.

Complications following the intra-vitreal use of TA can be attributed to the injection procedure or to the corticosteroid suspension. Major ocular-side effects include transient elevation of IOP (Jonas *et al*.)[57], cataract (Urban *et al*.)[58] and endophthalmitis and pseudo-endophthalmitis (Sutter *et al*.)[59]; rarer complications include conjunctival ulceration, lenticular damage, retinal detachment and vitreous hemorrhage.

Following a single intra-vitreal injection of 4 mg of triamcinolone, Beer *et al.*[50] noted that the IOP was elevated by 10 mmHg or greater in 27.9% of eyes; an increase in lOP of 5 mm Hg or greater occured in 4.1±4.8 weeks, while the maximum lOP was reached in 6.6 ± 5.1 weeks. In addition, there was a significant difference between mean pre-injection IOP (15.12 mmHg) and the maximum post-injection IOP (20.74 mmHg) (Beer *et al*.).[50] In a related study (Sutter *et al*.),[13a] IOP was found to be elevated by 5mm Hg or more in 10 (30%) of 33 eyes that had received 4 mg of triamcinolone, compared to one of 32 eyes (3%) in placebo-treated groups. A significant difference in elevation of IOP to more than 25mmHg was found in 18% of triamcinolone - treated eyes and in 3% of placebo-treated groups; fortunately, the IOP was brought to satisfactory levels in all cases with topical anti-glaucoma drugs and significant progression of cataract was noted in only one eye in each group.

Jonas *et al*.[56] studied 272 patients (305 eyes) who received 20mg of TA. The mean IOP increased significantly after the first intra-vitreal injection, from 15.3±2.9 mmHg at baseline to a maximum of 22.3±7.0 mmHg. IOP readings were >21 mmHg in 41.2%,30 mmHg in 11.4%, >35 mmHg in 5.5% and >40 mmHg in 1.8%. Mean IOP started to rise one week after injection and returned to baseline values approximately 8 to 9 months after injection. Interestingly, 302of 305 (99%) eyes responded to anti-glaucoma medication while in the remaining three eyes (1 %), filtering surgery was performed. Younger age was significantly associated with triamcinolone-induced ocular hypertension.

Cekic *et al*.[60] assessed cataract progression following one, two or three intravitreal triamcinolone injections for various indications. Visual acuity did not change after a single injection nor did it change in the control group, but decreased after multiple injections. A single intravitreal injection was found to induce posterior subcapsular cataract development whereas multiple injections resulted in cataract progression in all layers. This study did not reveal any difference in terms of cataract progression between triamcinolone - injected eyes in diabetic and non-diabetic patients.

Sutter *et al*.[59] reported one patient with infectious endophthalmitis (coagulase negative Staphylococcus species) who sought treatment eight days after injection; the infection was successfully treated with intravitreal antibiotics. In a related study (Moshfighi *et al*.[42,61]), eight eyes of eight patients who received intravitreal triamcinolone (0.87%) developed acute endophthalmitis (median time to presentation was 7.5 days [range 1 - 15 days]). One eye

demonstrated gram positive cocci in chains and three patients ended with no perception of light.

Roth *et al.*[62] observed the occurrence of an extensive inflammatory response a few days after intravitreal injection of triamcinolone in seven eyes, five eyes of which had previously undergone vitrectomy; vitreous tap was done and culture was negative in all eyes. This non- infectious (pseudo) endophthalmitis was believed to have occurred due to an acute reaction to the vehicle of the drug (6.9 mg sodium chloride for isotonicity, 15 mg benzyl alcohol as a preservative, 7.5 mg carmellose sodium and 0.4 mg polysorbate 80). However the vehicle caused no such reaction in rabbit eyes (McCuen *et al.*[51]). These findings suggest that the reaction is common in vitrectomized and pseudophakic eyes, wherein the relatively unicameral nature of the eye allows an easy access of triamcinolone to the ocular structures, leading to a brisk immune response.

Although anti-VEGF agents bevacizumab, ranibizumab and aflibercept, is becoming the treatment of choice for centrally involving DME, the sustained-release low-dose dexamethasone implant and fluocinolone acetonide implants will limit the frequency of intravitreal injections required with intravitreal anti-VEGF therapy. Corticosteroid implants limit the cost of repeated treatment with expensive anti-VEGF therapies and minimize the risk of endophthalmitis, because of the lesser number of injections. While the fluocinolone acetonide implant lasts much longer than the dexamethasone implant, it appears to have a increased risk in IOP elevation and cataract formation.

In a sense, anti-VEGF agents are both therapeutic and diagnostic in patients with DME, as the underlying pathophysiology of DME, is in large part VEGF-mediated. However, there is a growing appreciation that inflammatory mediators are active in the underlying disease process and they contribute significantly to vascular permeability and edema suggesting that the late phase of DME is caused by inflammatory mediators rather than angiogenic mediators. This second disease pathway explains the inadequate response in some patients to anti-VEGF therapy. Data suggest that continued anti-VEGF therapy may eventually engender a response. However, this strategy may expose patients to an excessive number of injections with slow results; continued anti-VEGF therapy without resolution of the anatomy may itself create a chronic type of DME that responds poorly to a second delayed treatment strategy, wherein patients never achieve the visual outcomes they would have derived with earlier intervention.

Cumulatively, all these data suggest that there are three categories of patients with DME:

(1) those with disease that is predominantly VEGF-mediated, and who therefore will derive great benefit from anti-VEGF therapy;

(2) those in whom the disease is not predominantly VEGF-mediated, and who therefore will not benefit from anti-VEGF injections; and

(3) those in whom there are both VEGF-mediated and inflammatory processes involved.

These latter two categories would likely benefit from corticosteroid therapy, whereas the last group may require a combination approach that takes

advantage of the beneficial properties of both anti-VEGF injections and corticosteroids.

There are two corticosteroid implants, dexamethasone and fluocinolone acetonide approved for treatment of DME. Although TA is not a US-FDA approved drug for treating DME, the high cost of the implantable corticosteroids, when compared with the TA, and reported side effects related to cataract development and potential for IOP elevation with implantable corticosteroids, there may be a role to use TA.TA could still be a cost effective treatment of recalcitrant DME for those patients who do not respond or show an inadequate response to laser photocoagulation and intravitreal anti-VEGF agents.

Hence, in the present investigation an attempt was made to evaluate the efficacy of intravitreal triamcinolone acetonide in the management of diabetic macular edema that had failed to respond to laser photocoagulation and intravitreal bevacizumab. In addition, the safety of intravitreal administration of triamcinolone acetonide in managing this condition was monitored.

Patients & Methods

PATIENTS AND METHODS

A prospective interventional study was performed on patients presenting at the Retina Clinic of a tertiary eye care hospital in Tamilnadu between July 2013 and July 2015. The aim was to study the efficacy and safety of intravitreal triamcinolone acetonide in management of recalcitrant diabetic macular edema. This study was approved by the Institutional Ethics Committee.

1. Calculation of a relevant sample size:

About 10-30% of DME patients do not respond to conventional laser photocoagulation and intravitreal anti-VEGF agents and are recalcitrant. For calculation of a relevant sample size for the current study, the following elements were used and the recommended sample size calculated using www.raosoft.com/samplesize.html online sample size calculator. (URL accessed on:19-09-2013)

Margin of error	–	5%
Level of confidence	–	95%
Population size	–	500
Response distribution	–	85%

The sample size "n" and margin of error "E" given by

$$\mathbf{X} = Z\,(^{c}/_{100})^{2} r\,(100-r)$$

$$\mathbf{N} = {}^{Nx}/_{((N-1)E^{2}+x)}$$

$$\mathbf{E} = \mathbf{Sqrt}\left[{}^{(N-n)x}/_{n\,(N-1)}\right]$$

where N is the population size, r is the fraction of responses being studied and Z (c/100) the critical value for the confidence level c. The estimated sample size was 141 patients.

2. Assesing eligibility of patients for the study

2.1 Inclusion Criteria

Patients were included in the study if the following criteria were satisfied:

a) Eyes with recalcitrant diabetic macular edema (defined as those cases of macular edema refractory to treatment following adequate focal / grid laser photocoagulation and 2 doses of intravitreal bevacizumab, in which resolution of macular edema had not occurred within one month of treatment, as assessed by clinical examination and measured by OCT)

b) Eyes exhibited best corrected visual acuity 6/18 or worse;

c) Eyes exhibited central macular thickness >300μm in OCT;

d) Provided written informed consent to participate in the study.

2.2 Exclusion Criteria

Patients were not considered for enrolment in the study if any one of the following criteria were present:

a) Suffered from glaucoma;
b) Suffered from ocular hypertension
c) Had retinal and optic nerve head pathology affecting visual acuity; or
d) Did not provide written informed consent to participate in the study.

3. Examination of eligible individuals

Complete medical and ocular history were taken at the baseline visit. All patients were subjected to complete ophthalmic examination which included:

a) Measurement of best corrected visual acuity for distance and near (Snellen's charts)

b) Measurement of intraocular pressure (IOP) (Goldman applanation tonometer);

c) Slit lamp biomicroscopy;

d) Fundus examination by slit lamp biomicroscopy using +90D lens and indirect ophthalmoscopy using +20D lens;

e) Fundus photography. (*Zeiss FF450 plus IR*);

f) Fundus fluorescein angiography (FFA);

g) Measurement of macular thickness by Spectral Domain OCT (*Carl Zeiss Inc.Dublin USA*);

All patients were informed of the procedure and its possible complications and written informed consent was obtained; the Institutional Ethics Committee approved the study.

4. Therapy

4.1 Procedure for intravitreal administration of triamcinolone acetonide

A pre-injection single drop of povidone-iodine (5%) solution was applied to the eye followed by thorough cleaning of the eyelashes and application of a lid speculum. 0.5% proparacaine hydrochloride drops were applied topically. 0.05 ml (2 mg) of triamcinolone acetonide (Tricort^{TM} -Cadila Pharma, Ahmedabad, India, or Stancort^{TM}, Ranbaxy Pvt.Limited, Gurgaon, Haryana

India) was drawn into a 1 cc syringe fitted with a 30 gauge needle. The site of injection was 3.5 mm and 4 mm from the limbus in pseudophakic and phakic eyes, respectively. The injection site was usually in the inferotemporal quadrant. The needle was introduced downward and posteriorly with the bevel of the needle facing anteriorly; this was done to avoid contact of the drug with the macula. After injection, the needle was removed simultaneously with the application of a cotton-tipped applicator over the site of entry to prevent regurgitation of the injected material and vitreous. Indirect ophthalmoscopy was performed to check for central retinal artery pulsation; paracentesis was performed if central retinal artery pulsation was present or the globe felt tense. One drop of topical antibiotic solution (ofloxacin 0.3% eye drops) was administered and the eye was patched.

The patient was made to sit up immediately after injection and to continue maintaining an erect posture for at least 6 hours; this was to ensure that the drug assumed a dependent position and did not collect over the macula. For the next few days, the patient was instructed to sleep on his or her back, to prevent anterior migration of the drug in pseudophakic and aphakic eyes; such migration would otherwise clog the trabecular meshwork and lead to early increase in IOP, as noted by Vedantham et al[63].

4.2 Additional therapeutic measures

All patients were started on antibiotic eye drops 6 times a day for one week, and acetazolamide 250 mg three times daily for two days.

5. Follow-up of patients

Follow - up examination was done at one week, one month, three months and six months.

At each follow up visit,the following tests were done:

a) Measurement of best corrected distant and near vision;

b) Measurement of IOP (Goldman applanation tonometers);

c) Slit lamp examination;

d) Fundus examination (+90D lens and indirect ophthalmoscopy);

e) Fundus photography;

f) Measurement of central macular thickness by OCT.

6. Criteria for significant elevation in intraocular pressure

A significant elevation of IOP was deemed to have occurred if there was an increase of more than 5mm Hg from baseline at any post-injection visit or if the IOP exceeded 21mm Hg.

7. Outcome measures sought

The main outcome measures noted were:

a) The best corrected visual acuity

b) The central foveal thickness (CFT) (as measured by OCT).

8. Statistical analysis

Statistical Analysis was done using one-way analysis of variance (ANOVA) and post hoc testing by Tukey's HSD test to compare the differences in BCVA and CFT at different time points of examination.

Results

RESULTS

Over a period of 23 months (September 2013 to July 2015), 36 patients underwent intravitreal administration of triamcinolone acetonide for recalcitrant diabetic macular edema (DME) at Joseph Eye Hospital, Tiruchirapalli and were considered for inclusion in the study. Of these, 19 patients were excluded due to one or more exclusion criteria, hence 17 patients were included in the study. In four patients, both eyes were administered the drug. Hence, 21 eyes of 17 patients were included in the study.

About 10-30% of DME patients do not respond to conventional laser photocoagulation and intravitreal anti-VEGF agents and are recalcitrant. For calculation of a relevant sample size for the current study, the following elements were used and the recommended sample size calculated using www.raosoft.com/samplesize.html online sample size calculator. (URL accessed on 19.09.2013)

Margin of error	–	5%
Level of confidence	–	95%
Population size	–	500
Response distribution	–	85%

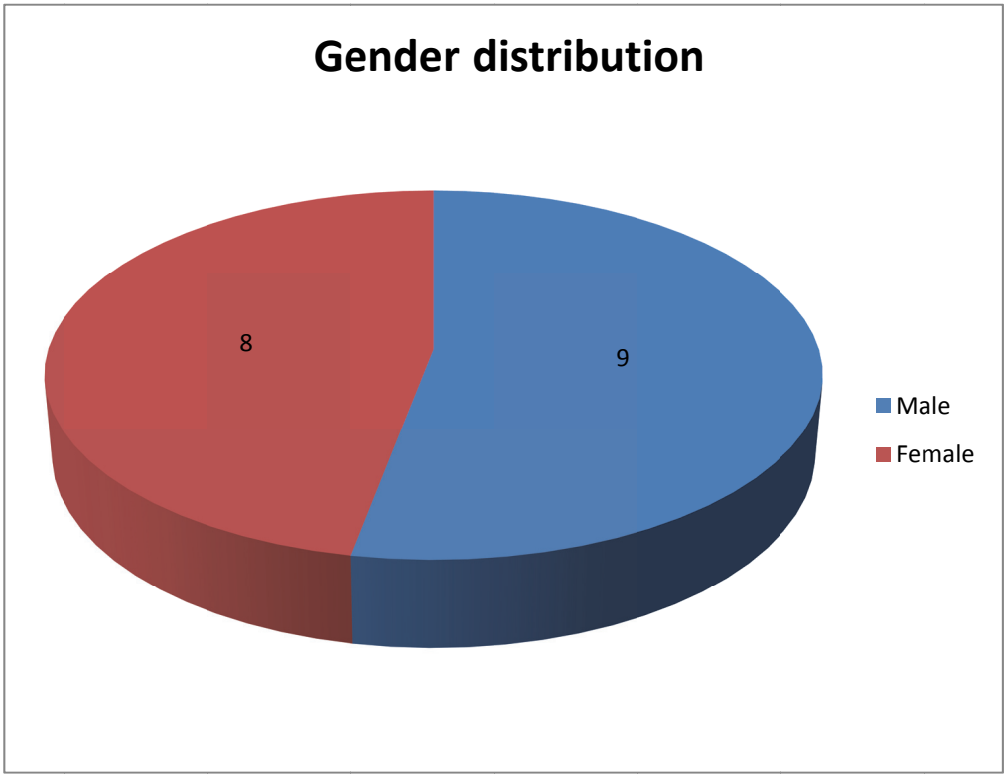
The estimated sample size was 141 patients. Due to various constraints and the limited duration of the study period, only 21 eyes of 17 patients could be enrolled in the current study.

1. DEMOGRAPHY OF PATIENTS

1.1 Gender distribution of the enrolled patients

Of the 17 patients enrolled in the study, nine (53%) patients were male and eight (47%) were females. (Fig.1)

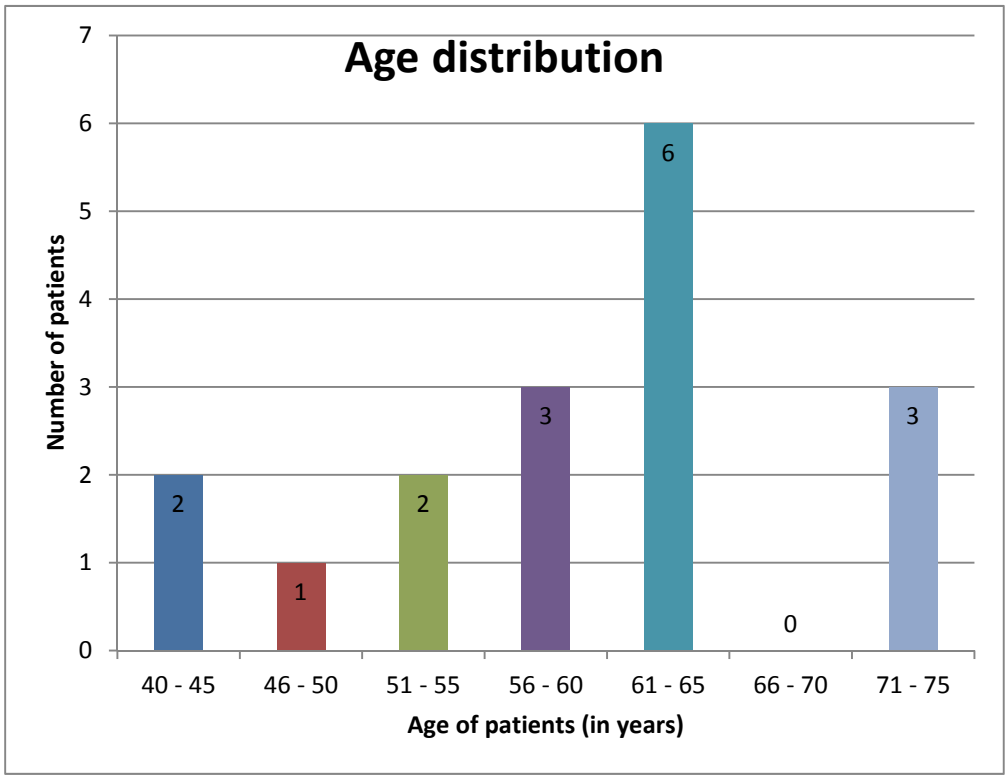
Figure 1. Gender of patients with recalcitrant diabetic macular edema enrolled in the study.



1.2 Age characteristics of the enrolled patients

In this study, the mean age of the 17 patients was 59.47 ± 9.6 years (range 40 to 75 years), with two patients (11.8%) in the 40 to 45 year age group, one patient (5.9%) in the 46 to 50 year age group, two patients (11.8%) in the 51-55 year age group, three patients (17.6%) in the 56-60 year age group, six patients (35.3%) in the 61-65 year age group and three patients (17.6%) in the71-75year age group. (Fig.2)

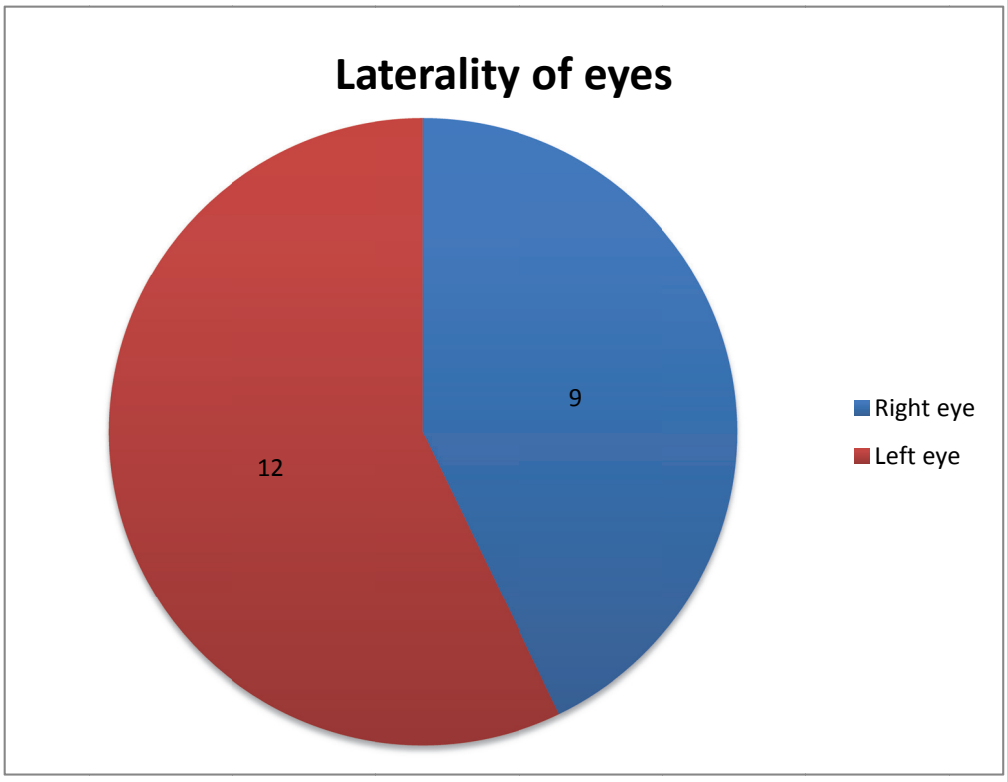
Figure 2. Age distribution of patients with recalcitrant diabetic macular edema enrolled in the study.



1.3 Laterality of eyes with recalcitrant macular edema in diabetic individuals enrolled in the current study

Twenty-one eyes presented with recalcitrant diabetic macular edema and intravitreal triamcinolone acetonide was given for the right eye in nine instances (43%) and for the left eye in twelve instances (57%). (Fig.3)

Figure 3. Laterality of eyes with recalcitrant macular edema in diabetic individuals enrolled in the current study.



1.4 Duration of diabetes in the patients enrolled in the current study

In this study, 12 (70.6%) of patients had suffered from diabetes mellitus for between 1 to 10 years duration, three (17.65%) had a duration of diabetes ranging between 11 to 20 years and two (11.75%) patients had suffered from diabetes for 21 to 30 years (Table 1). The mean duration of diabetes in patients with recalcitrant diabetic macular edema who were administered intravitreal triamcinolone acetonide was 8.94 ± 6.60 years.

Table 1. Duration of diabetes mellitus in patients with recalcitrant diabetic macular edema enrolled in the current study

Duration of diabetes (years)	No.of patients	Percentage of total (%)
1-10	12	70.6
11-20	3	17.65
21-30	2	11.75
Total	17	100%

1.5 Mean HbA_1C values at different time points in patients with recalcitrant diabetic macular edema enrolled in the study

In this study, the mean HbA_1C (glycosylated haemoglobin) values of patients with recalcitrant diabetic macular edema enrolled in the study were 8.2 ± 0.96 % at baseline, 7.7 ± 0.73 % at 3 months after the injection of intravitreal triamcinolone acetonide and 7.7 ± 0.57 % at 6 months after the intravitreal injection of triamcinolone acetonide. (Table 2); this difference was not statistically significant. (one way analysis of variance [ANOVA], Fisher 'f' value [d.f.=2] = 2.95; P=0.06).

Table 2. Mean HbA_1C values at different time points in patients with recalcitrant diabetic macular edema enrolled in the study.

Month	**HbA_1C % (Mean ± Standard deviation)**
Baseline	8.2 ± 0.96
3 months	7.7 ± 0.73
6 months	7.7 ± 0.57

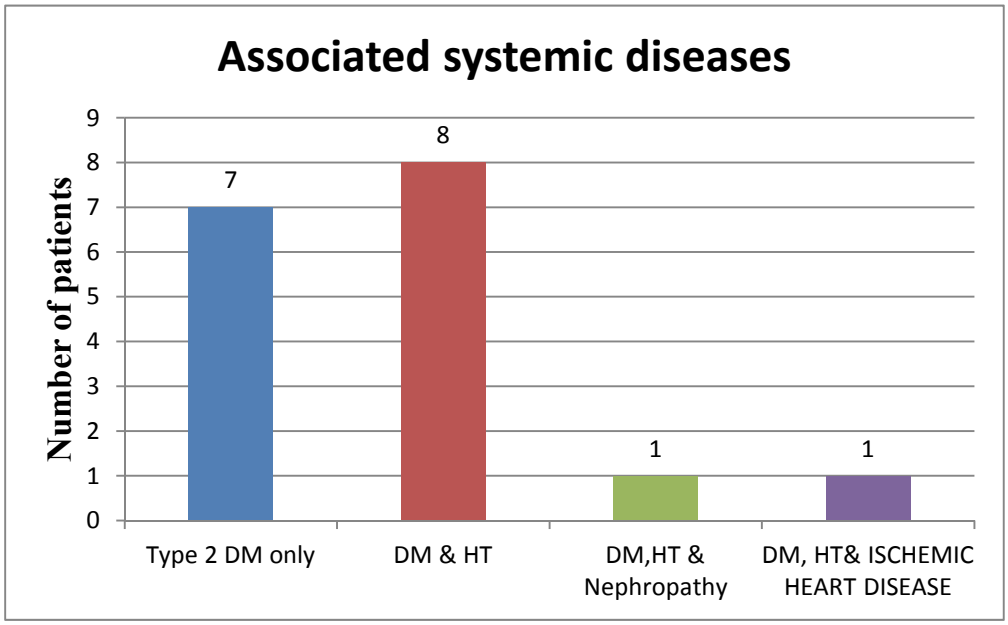
Abbreviation: HbA_1C = glycosylated haemoglobin

Statistical Analysis: One way analysis of variance [ANOVA], Fisher 'f' value [d.f.=2] = 2.95; P=0.06).

1.6 Associated systemic diseases in patients with recalcitrant diabetic macular edema enrolled in the study

In this study, all 17 patients presented with recalcitrant diabetic macular edema, and suffered from type 2 diabetes mellitus; however,10 (59%) patients had other associated systemic diseases (Fig.4). Eight (47%) patients presented with hypertension and diabetes, one (5.9%) patients had diabetic nephropathy along with hypertension and diabetes and one patient (5.9%) had ischemic heart disease along with hypertension and diabetes. Seven (41%) patients presented with type 2 diabetes mellitus only.

Figure 4. Associated systemic diseases in patients with recalcitrant diabetic macular edema enrolled in the study



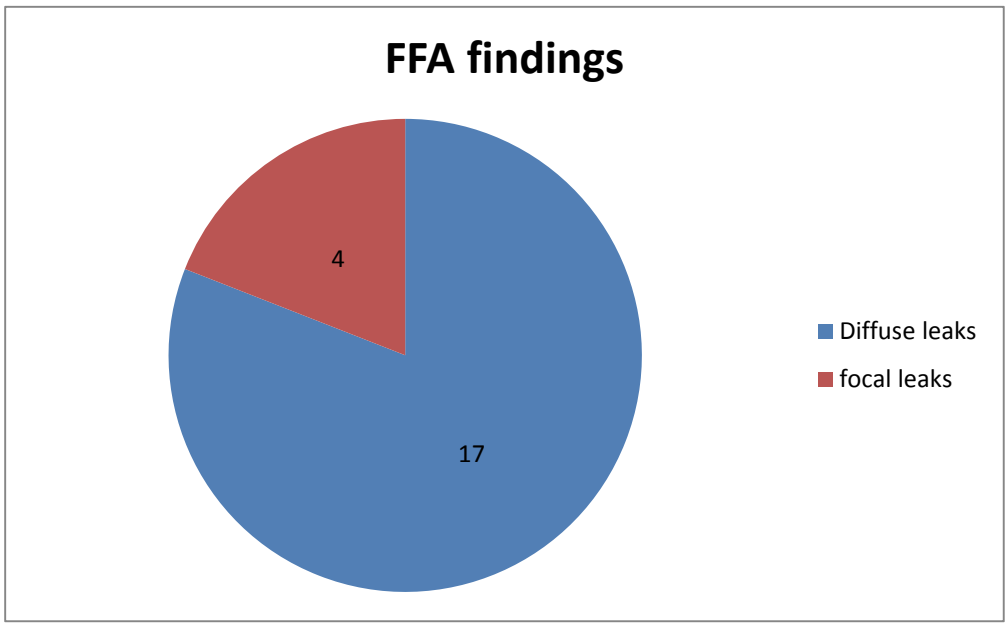
Abbreviations: DM = diabetes mellitus; HT = hypertension

2. OCULAR FINDINGS IN DIABETIC PATIENTS WITH RECALCITRANT MACULAR EDEMA

2.1 Fundus fluorescein angiography findings in eyes with recalcitrant diabetic macular edema enrolled in the study.

In this study, of the 21 eyes enrolled with recalcitrant diabetic macular edema, 17 (81%) eyes exhibited diffuse leaks and four (19%) eyes exhibited focal leaks in fundus fluorescein angiography. (Fig.5)

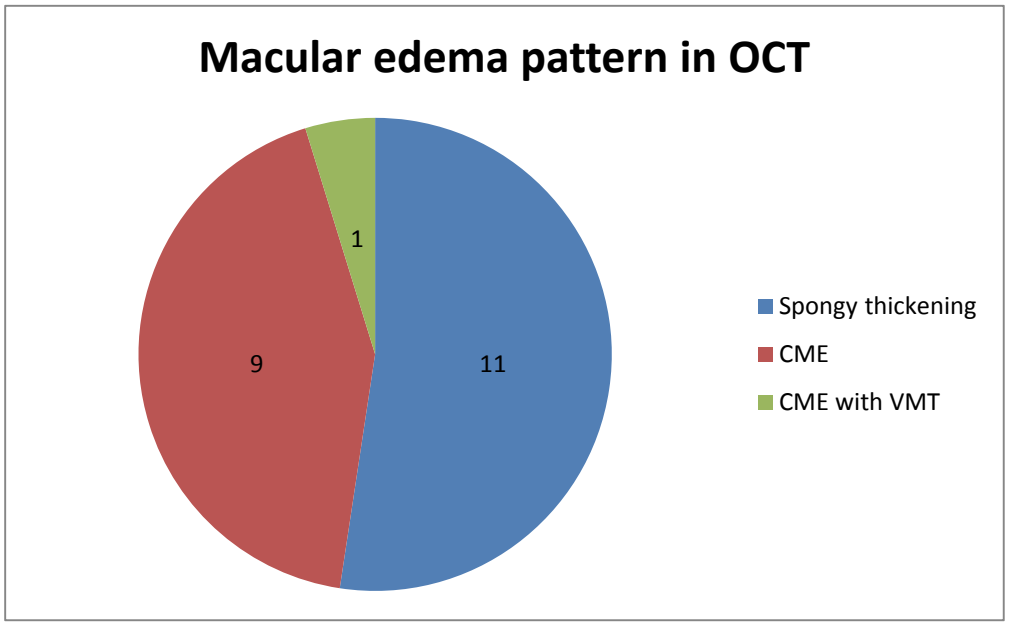
Figure 5. Fundus fluorescein angiography findings in eyes with recalcitrant diabetic macular edema enrolled in the study



2.2 Pre-treatment optical coherence tomographic findings in eyes with recalcitrant diabetic macular edema enrolled in the study.

In this study, of the 21 eyes enrolled with recalcitrant diabetic macular edema, optical coherence tomography (OCT) was able to detect spongy thickening in 11 (52%) eyes and cystoid macular edema in nine (43%) eyes and one eye (4.8%) exhibited cystoid macular edema associated with vitreo-macular traction. (Fig.6)

Figure 6. Pre-treatment optical coherence tomographic (OCT) findings in eyes with recalcitrant diabetic macular edema enrolled in the study.

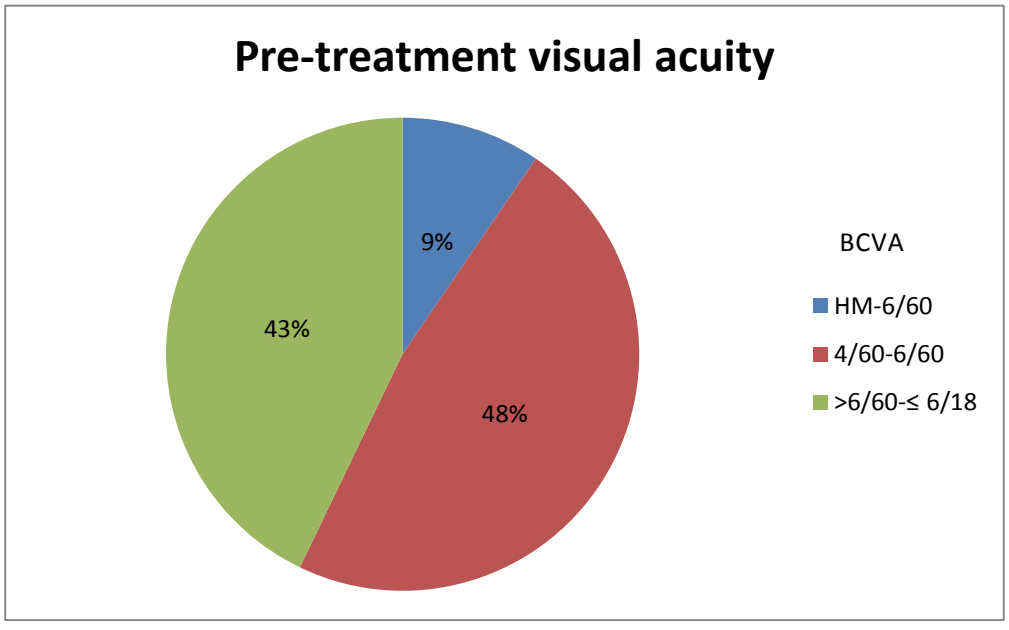


Abbreviation : CME = cystoid macular edema,VMT= vitreo-macular traction

2.3 Pre-treatment best corrected visual acuity in eyes with recalcitrant diabetic macular edema enrolled in the study.

In this study, of the 21 eyes enrolled with recalcitrant diabetic macular edema, two (9%) eyes had a best corrected visual acuity in the range of HM to ≤ 3/60 of Snellen's visual acuity chart, ten (48%) eyes had a best corrected visual acuity in the range of > 4/60 to ≤ 6/60 of Snellen's visual acuity chart and nine (43%) eyes had best corrected visual acuity in the range of > 6/60 to ≤6/18 of Snellen's visual acuity chart. (Fig.7)

Figure 7. Pre-treatment best corrected visual acuity in eyes with recalcitrant diabetic macular edema enrolled in the study.



Abbreviation: BCVA= best corrected visual acuity (Snellen's chart); HM=hand movements.

3. POST-TREATMENT PARAMETERS

3.1 Mean best corrected visual acuity (BCVA) at different time points in eyes with recalcitrant diabetic macular edema following intravitreal administration of triamcinolone acetonide in the current study.

All patients had recalcitrant diabetic macular edema, which had not responded to laser photocoagulation and at least two doses of intravitreal injections of bevacizumab. All patients received an intravitreal injection of triamcinolone acetonide (2 mg/0.05 ml).

The mean best corrected visual acuity (BCVA) in the eyes that received triamcinolone acetonide (TA) was (in decimals) 0.14 ± 0.07 (pre injection), 0.26 ± 0.12 (one week after injection of TA), 0.39 ± 0.20 (one month after injection of TA), 0.32 ± 0.15 (3 months after injection of TA) and 0.18 ± 0.10 (6months after injection of TA (Table 3); these differences were statistically significant (one-way analysis of variance [ANOVA]; Fisher 'f' value = 11.804; P< 0.001).

Since these differences were significant, post-hoc testing by Tukey's HSD test (highest square difference [HSD, expressed as `q']) was performed to assess the significance of intragroup (2 mean values) differences at different time points of examination. Here, significant differences emerged between the mean pre injection (0.14 ± 0.07) and mean one week after TA injection BCVA values (q= 4.1; P < 0.05), the mean pre injection (0.14 ± 0.07) and mean one month after TA injection BCVA values (q= 8.5; P < 0.01) and the mean pre injection (0.14 ± 0.07) and mean three months after TA injection BCVA values (q=6.1;P < 0.01) (Table 4a,b,c); however, the difference between the mean pre injection (0.14 ± 0.07) and mean six months after TA injection BCVA values

(q=1.4; P > 0.05) was not statistically significant (Table 4d). Similarly, significant differences emerged between the mean 1 week (0.26 ± 0.12) post-TA injection and 1 month post-TA injection mean BCVA values (q=4.4; P < 0.05) (Table 4e), but there was no significant difference between the 1 week and 3 month post TA injection mean BCVA values (q=2.04; P > 0.05) (Table 4f) and between the 1 week and 6 month post-TA injection mean BCVA values (q=2.73; P>0.05) (Table 4g). There were no significant differences between the 1 month and 3 month post-TA injection mean BCVA values (q=2.4; P > 0.05) (Table 4h). However, significant differences were observed between the 1 month and 6 month post-TA injection mean BCVA values (q=7.2; P <0.01) and between the 3 month and 6 month post- TA values (q=4.8; P < 0.01). (Table 4i,j) (Fig-8).

Figure 8. Change in mean best-corrected visual acuity at various time points in eyes treated with triamcinolone acetonide for recalcitrant diabetic macular edema.

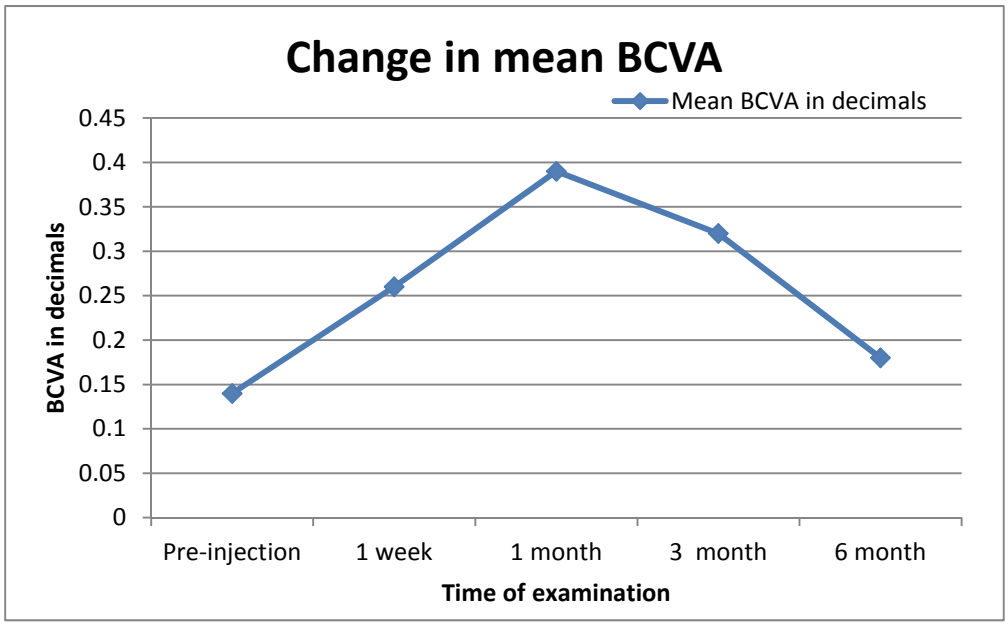


Table 3. Mean best corrected visual acuity (BCVA) at different time points in eyes with recalcitrant diabetic macular edema following intravitreal administration of triamcinolone acetonide in the current study.

Time of examination	Mean BCVA (in decimals) (n=21)
Pre-injection (baseline)	0.14 ± 0.07
1 week after injection of TA	0.26 ± 0.12
1 month after injection of TA	0.39 ± 0.20
3 months after injection of TA	0.32 ± 0.15
6 months after injection of TA	0.18 ± 0.10

Abbreviation: TA- triamcinolone acetonide

Statistical Analysis: One-way analysis of variance (ANOVA); Fisher 'f' value = 11.804; P<0.001 (simultaneous comparison of all mean values)

Table 4. Post hoc testing (Tukey's HSD test) to compare the differences in mean best-corrected visual acuity at different time points following injection of triamcinolone acetonide

Sl.No	Comparison between different time points of examination	q value	P value
a	Baseline vs 1 week value	4.1	< 0.05
b	Baseline vs 1 month value	8.5	< 0.01
c	Baseline vs 3 month value	6.1	< 0.01
d	Baseline vs 6 month value	1.4	>0.05 (not significant)
e	1 week vs 1 month value	4.4	<0.05
f	1 week vs 3 month value	2.04	>0.05 (not significant)
g	1 week vs 6 month value	2.73	>0.05 (not significant)
h	1 month vs 3 month value	2.4	>0.05 (not significant)
i	1 month vs 6 month value	7.2	<0.01
j	3 month vs 6 month value	4.8	<0.01

3.2 Mean central foveal thickness (CFT) at different time points in eyes with recalcitrant diabetic macular edema following intravitreal administration of triamcinolone acetonide in the current study

The mean central foveal thickness (CFT) in eyes with recalcitrant diabetic macular edema that received triamcinolone acetonide was (in μm) 536.5 ± 115.3 (pre injection), 380.7 ± 95.6 (1 week post injection), 280.9 ± 71.6 (one month post-injection), 283.6 ± 76.8 (three months post-injection) and 370.2 ± 114.3 (six months post-injection) (Table 5); these differences were statistically significant [one-way ANOVA; Fisher 'f' value = 24.4; P<0.001]. Since these differences were significant, post-hoc testing by Tukey's method was done. Here, significant differences emerged between the pre-injection and one week post-TA injection mean CFT values (q=7.4; P<0.01), pre-injection and one month post-TA injection mean CFT values (q= 12.1; P < 0.01), between the pre-injection and three-month post-TA injection mean CFT values (q= 12.01; P < 0.01) and between the pre-injection and six month post-TA injection mean CFT values (q= 7.9; P < 0.01). Similarly, significant differences emerged between the 1 week post-TA injection and 1 month post-TA injection mean CFT values (q=4.7; P =0.01), 1 week post-TA injection and 3 month post-TA injection mean CFT values (q=4.6; P =0.01) and 1 week post-TA injection and 6 month post-TA injection mean CFT values (q=0.5;P <0.05).

The difference between the 1 month post-TA injection and 3 month post-TA injection mean CFT values was not statistically significant (q=0.12; P >0.05). However, the differences between the 1 month post-TA injection and 6 month post-TA injection mean CFT values (q=4.0; P =0.05) and between the 3

month post-TA injection and 6 months post-TA injection mean CFT values (q=4.11; P < 0.05) were statistically significant. (Table 6) (Fig.9).

Figure 9. Change in mean central foveal thickness at various time points in eyes treated with triamcinolone acetonide for recalcitrant diabetic macular edema.

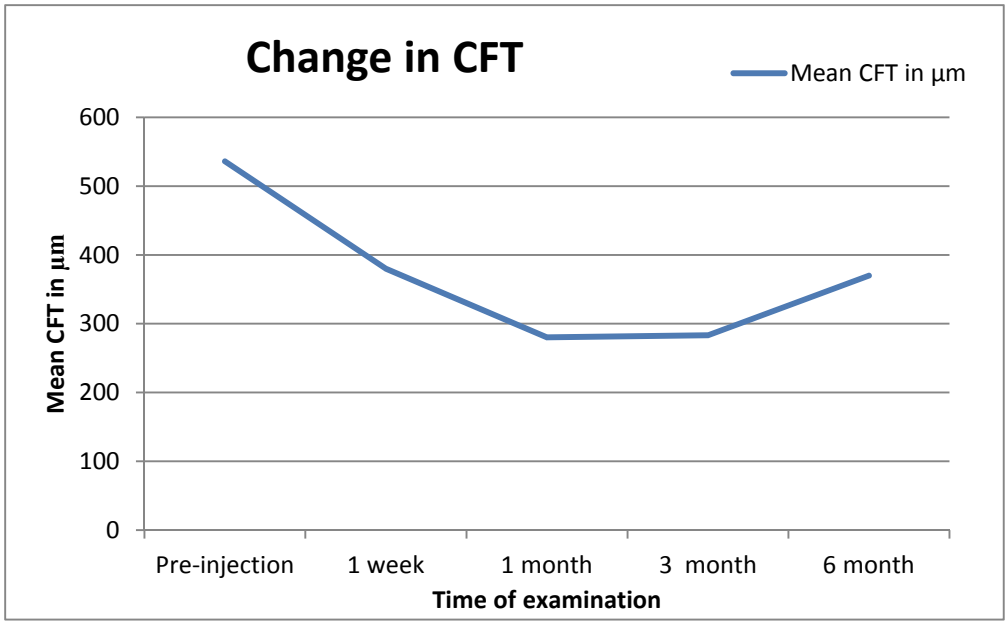


Table 5. Mean central foveal thickness (CFT) at different time points in eyes with recalcitrant diabetic macular edema following intravitreal administration of triamcinolone acetonide in the current study

Time of examination	Mean central foveal thickness (in µm) (n=21)
Pre-injection (baseline)	536.5 ± 115.3
1 week after injection of TA	380.7 ± 95.6
1 month after injection of TA	280.9 ± 71.6
3 months after injection of TA	283.6 ± 76.8
6 months after injection of TA	370.2 ± 114.3

Abbreviation: TA= triamcinolone acetonide

Statistical Analysis: One-way analysis of variance (ANOVA); Fisher 'f' value = 24.4; P<0.001 (simultaneous comparison of all mean values)

Table 6. Post hoc testing (Tukey's HSD test) to compare the differences in mean central foveal thickness at different time points following injection of triamcinolone acetonide.

Sl.No	Comparison between different time points of examination	q value	P value
a	Baseline vs 1 week value	7.4	< 0.01
b	Baseline vs 1 month value	12.1	< 0.01
c	Baseline vs 3 month value	12.01	< 0.01
d	Baseline vs 6 month value	7.9	< 0.01
e	1 week vs 1 month value	4.7	= 0.01
f	1 week vs 3 month value	4.6	≈0.01
g	1 week vs 6 month value	0.5	< 0.05
h	1 month vs 3 month value	1.2	>0.05 (not significant)
i	1 month vs 6 month value	4.0	= 0.05
j	3 month vs 6 month value	4.11	<0.05

4. SAFETY OF INTRAVITREAL ADMINISTRATION OF TRIAMCINOLONE ACETONIDE

4.1. Mean intraocular pressure (IOP) at different time points in eyes with recalcitrant diabetic macular edema following intravitreal administration of triamcinolone acetonide in the current study

The mean intraocular pressure (IOP) in the eyes with recalcitrant diabetic macular edema that received triamcinolone acetonide was (in mm Hg) 17.4 ± 2.2 (pre injection), 18.0 ± 2.1 (1 week post injection), 18.4 ± 2.2 (one month post-injection), 18.6 ± 5.12 (three months post-injection) and 20.3 ± 11.8 (six months post-injection) (Table 7); these differences were not statistically significant (ANOVA; Fisher 'f' value = 0.689; P = 0.6). Since these differences were not significant, post-hoc testing by Tukey's method was not performed for the IOP readings. Patients who had increased IOP in the injected eye responded well to topical anti-glaucoma medications; however, one eye developed intractable glaucoma, which necessitated anti-glaucoma surgery on the affected eye.

Table 7. Mean intraocular pressure (IOP) at different time points in eyes with recalcitrant diabetic macular edema following intravitreal administration of triamcinolone acetonide in the current study

Time of examination	Mean IOP (in mm hg) (n = 21)
Pre injection (baseline)	17.4 ± 2.2
1 week after injection of TA	18.0 ± 2.1
1 month after injection of TA	18.4 ± 2.2
3 months after injection of TA	18.6 ± 5.12
6 months after injection of TA	20.3 ± 11.8

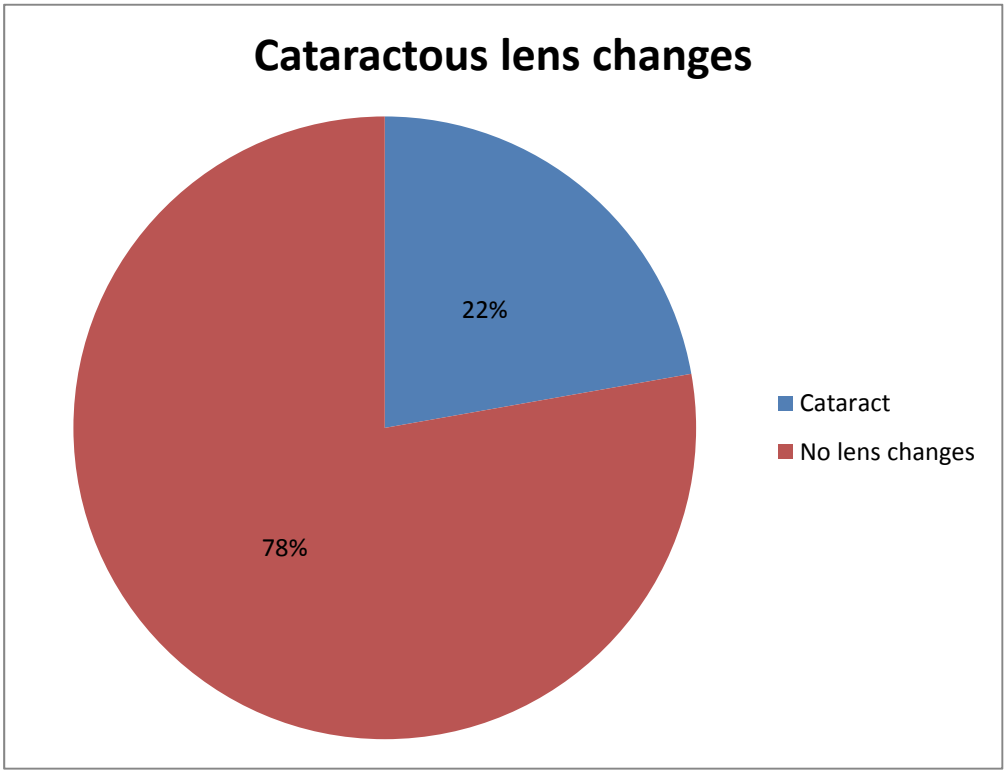
Abbreviation: TA-triamcinolone acetonide

Statistical Analysis-One-way analysis of variance (ANOVA); Fisher 'f' value = 0.689; P = 0.6 (all mean values compared simultaneously) (not significant)

4.2 Crystalline lenticular changes following intravitreal injection of triamcinolone acetonide in eyes with recalcitrant diabetic macular edema enrolled in the study.

Out of 21 eyes enrolled in the study, three eyes were pseudophakic and 18 eyes were phakic. Of the 18 phakic eyes, four eyes (22.2%) developed cataract following intravitreal injection of triamcinolone acetonide for which cataract surgery and intraocular lens implantation were done. (Fig 10)

Figure 10. Proportion (percentage) of total eyes with recalcitrant diabetic macular edema which exhibited crystalline lenticular changes following intravitreal injection of triamcinolone acetonide



4.3 Other complications / side-effects following intravitreal administration of triamcinolone acetonide

There was no episode of infectious or non-infectious endophthalmitis, retinal detachment, vitreous hemorrhage or lenticular damage in the eyes with recalcitrant diabetic macular edema following intravitreal administration of triamcinolone acetonide.

Discussion

DISCUSSION

Macular edema is one of the most common causes of decreased visual acuity in diabetic retinopathy.[8] Approximately 10% of all diabetic patients manifest macular edema, with 40% of the patients showing involvement of the centre of the macula. [71]

Anti-VEGF drugs are considered as first-line therapy for patients with DME. The DRCR.net Protocol T study[64] affirmed the safety and efficacy of anti-VEGF agents in many patients. However, within the various clinical trials studying anti-VEGF therapy for DME, including the Protocol T study, study of ranibizumab injection in subjects with clinically significant macular edema with center involvement secondary to diabetes mellitus (RIDE) and study of ranibizumab injection in subjects with clinically significant macular edema with center involvement (RISE) clinical trials,[65] there are appreciable numbers of patients (as much as one-third of total number) who do not respond to, or have an incomplete or inadequate response to, active therapy regardless of the anti-VEGF agent used. There is a growing appreciation of the fact that inflammatory mediators are active in the underlying disease process and that they contribute significantly to vascular permeability and edema; in fact the late phase of DME appears to be caused by inflammatory mediators rather than angiogenic mediators. This second disease pathway explains the inadequate response in some patients to anti-VEGF therapy. Among patients for whom anti-VEGF therapy is incompletely effective, there may be a role for alternative therapeutic modalities and, in particular, for corticosteroid therapy.

Steroids have both anti-inflammatory and anti-angiogenic properties and, because of these properties, they are increasingly becoming a therapeutic option in retinal practice. They have been shown to reduce macular thickness and improve visual acuity in eyes with refractory DME that fails to respond to conventional treatment.[13a,b,c,d,53,55,56] Triamcinolone acetonide, dexamethasone and fluocinolone acetonide are the steroid drugs used intravitreally for the treatment of DME.

The United States Food and Drug Administration (US-FDA) has approved the intravitreal dexamethasone implant 0.7mg (**Ozurdex™**, Allergan Inc,Irvine,CA) and fluocinolone acetonide implant 0.19mg (**Illuvien™**, Alimera sciences, Aldershot, UK) for the treatment of DME. Triamcinolone acetonide is not a US-FDA approved drug for treating DME. However, due to the high cost of the implantable corticosteroids, when compared with that of triamcinolone acetonide, and reported side effects related to cataract development and potential for IOP elevation with implantable corticosteroids, there may be a role for triamcinolone acetonide use. Triamcinolone acetonide could be considered a cost-effective treatment of recalcitrant diabetic macular edema for those patients who do not respond, or show an inadequate response, to laser photocoagulation and intravitreal anti-VEGF agents.

This prospective, interventional study spanning a period of 23 months, encompasses the results of 21 eyes of 17 patients with recalcitrant diabetic macular edema (DME) who had received an intravitreal injection of 2 mg of triamcinolone acetonide. The results have been evaluated and the safety and efficacy of the procedure was analysed.

With reference to demographic characteristics in this study, the patients who underwent intravitreal triamcinolone acetonide for the treatment of recalcitrant diabetic macular edema were almost equally matched for gender and laterality of the eye (Figs. 1&3). The mean age of the study patients who received intravitreal triamcinolone acetonide was 59.47 ± 9.6 years (Fig.2). All the patients enrolled in the study had type 2 diabetes mellitus, with 70.6% of the patients having suffered from diabetes for around 10 years. (Table 1) In this study, 59% of the patients had other associated (co-morbid) systemic diseases along with diabetes (Fig.4).

Larson *et al*.[54] treated 24 eyes with diabetic macular edema with intravitreal injection of 4mg of triamcinolone acetonide and followed up the patients for 3 months. Martidis *et al*.[53] treated 16 eyes with diabetic macular edema with intravitreal triamcinolone acetonide (4mg) and performed follow up for 6 months. Sutter et al.[13b] treated 34 eyes with 4mg of intravitreal triamcinolone acetonide and 35 eyes with placebo injection and followed up the patients for 3 months. In the present study, 21 eyes were treated with **2mg of triamcinolone acetonide** and followed up for 6 months at intervals of 1 week, 1month and 3 months.

The DRCR protocol I,[56a] an important clinical trial assessed three different treatment schemes for the treatment of DME: intravitreal 0.5 mg ranibizumab with prompt or deferred laser (focal/grid), or intravitreal 4mg triamcinolone acetonide combined with laser (focal/grid) compared with laser alone (focal/grid).[56a] At the end of two-years, compared with the focal/grid laser alone group, the mean change from baseline in the BCVA letter score was 3.7

letters gain in the ranibizumab with prompt laser treatment group, 5.8 letters gain in the ranibizumab with deferred laser group, and 1.5 letters lesser (worsened) in the triamcinolone acetonide with prompt laser group. When analysing the pseudophakic group of patients only, triamcinolone acetonide showed BCVA results comparable to that of ranibizumab, indicating that decreased acuity in the phakic eyes treated with triamcinolone acetonide plus laser could be, at least in part, attributed to the formation of cataract; the drug-related side effect of triamcinolone acetonide. At the end of two-years, the percentages of eyes with central macular thickness ≥250 μm were 59% in the laser alone group, 43% in the ranibizumab with prompt laser treatment group, 42% in the ranibizumab with deferred laser treatment group, and 52% in the triamcinolone acetonide with prompt laser treatment group. These results show the potential of intravitreal triamcinolone acetonide to serve as a less expensive, but comparable, therapy to intravitreal anti-VEGF agent ranibizumab. However, anti-VEGF therapy has become first-line therapy especially in phakic DME patients, but intravitreal triamcinolone acetonide can be utilized in phakic patients who do not have access to ranibizumab.

Complications following the intra-vitreal use of triamcinolone acetonide can be attributed to the injection procedure or to the corticosteroid suspension. Major ocular-side effects include transient elevation of IOP, (Jonas *et al.*)[57] cataract (Urban *et al.*)[58] and endophthalmitis and pseudo-endophthalmitis (Sutter *et al.*);[59] rarer complications include conjunctival ulceration, lenticular damage, retinal detachment and vitreous hemorrhage.

Following a single intra-vitreal injection of 4 mg of triamcinolone acetonide, Beer *et al.* [50] noted that the IOP was elevated by 10 mmHg or greater in 27.9% of eyes; an increase in IOP of 5 mm Hg or greater occured in 4.1± 4.8 weeks, while the maximum IOP was reached in 6.6 ± 5.1 weeks. In addition, there was a significant difference between mean pre-injection IOP (15.12 mmHg) and the maximum post-injection IOP (20.74 mmHg) (Beer *et al.*)[50]. In a related study (Sutter *et al.*)[13a], IOP was found to be elevated by 5mm Hg or more in 10 (30%) of 33 eyes that had received 4 mg of triamcinolone acetonide, compared to one of 32 eyes (3%) in placebo-treated groups. A significant difference in elevation of IOP to more than 25mmHg was found in 18% of triamcinolone -treated eyes and in 3% of placebo-treated groups; fortunately, the IOP was brought to satisfactory levels in all cases with topical anti-glaucoma drugs and significant progression of cataract was noted in only one eye in each group.

Cekic *et al.*[60] assessed cataract progression following one, two or three intravitreal triamcinolone injections for various indications. Visual acuity did not change after a single injection nor did it change in the control group, but decreased after multiple injections. A single intravitreal injection was found to induce posterior sub-capsular cataract development whereas multiple injections resulted in cataract progression in all layers.

Although triamcinolone acetonide, is efficacious in treating diabetic macular edema, various studies[50,566a,57,58,59,60.] have reported that cataract formation and rise of intraocular pressure were the most common drug-related side-effects following intravitreal injection. Hence, in the present study, 2mg of

triamcinolone acetonide was used to assess the efficacy of the drug in recalcitrant diabetic macular edema and safety of the drug.

At the end of the Diabetes Control and Complications Trial (DCCT)[16a], the patients in the conventional-therapy group were offered intensive therapy, and the care of all patients was transferred to their own physicians. Retinopathy was evaluated on the basis of centrally-graded fundus photographs in 1208 patients during the fourth year after the DCCT ended, and nephropathy was evaluated on the basis of urine specimens obtained from 1302 patients during the third or fourth year, approximately half of whom were from each treatment group. The difference in the median glycosylated hemoglobin (HbA_1C) values between the conventional-therapy and intensive-therapy groups during the 6.5 years of the DCCT (average, 9.1 percent and 7.2 percent, respectively) significantly narrowed during follow-up (median during 4 years, 8.2 percent and 7.9 percent, respectively). Nevertheless, the proportion of patients who had worsening retinopathy, including proliferative retinopathy, macular edema, and the need for laser therapy, was lower in the intensive-therapy group than in the conventional-therapy group (odds reduction, 72 percent to 87 percent). The proportion of patients with an increase in urinary albumin excretion was significantly lower in the intensive-therapy group at 6 months.

Diana *et al*.[15] conducted a retrospective study in 92 patients (152 eyes) with persistent clinically significant macular edema (CSME) and 32 patients (56 eyes) with resolved CSME. They found that persons with type 2 diabetes and persistent CSME had higher levels of HbA_1C in the course of their disease than

did patients with resolved CSME; moreover, patients with bilateral disease had HbA_1C levels that were higher than those in patients with unilateral disease.

In the present study, the mean HbA_1C value was 8.2% at baseline,7.7% at 3 months and 7.7% at 6 months follow-up; this reduction in mean HbA_1C values was not statistically significant (P=0.06) (Table 2). Consistent with the values reported by Diana *et al*., in the current study,the mean HbA_1C of the patients with recalcitrant DME was high throughout the study period and four patients had bilateral involvement and persistently higher levels of HbA_1C throughout the study period.

In the current investigation, nephropathy was observed in one patient who had bilateral DME whose mean HbA_1C was above 7.9% and whose visual acuity was poor; the chronic diabetic macular edema was refractory to treatment necessitating repeated intravitreal injections. This observation was similar to that made in the DCCT / Epidemiology of Diabetes Interventions and Complications Research Group report.[16a.]

With reference to improvement in **visual acuity,** in the current study, a significant improvement (increase) in mean BCVA of 0.12 decimals was noted in the first week following injection of triamcinolone acetonide, with a maximum of 0.25 decimals (Table 3). This improvement in BCVA was sustained for up to 3months post-injection; after 3 months, the mean BCVA showed a decline to approach, at the end of 6 months, almost pre-treatment mean BCVA values (Table 3).On comparing the pre-injection mean BCVA value with the mean values post-injection at different time points, a statistically significant

increase in mean BCVA values at 1week, 1 month and 3 months was observed (Table 3); however there was no significant difference noted between the pre-injection mean BCVA value and the mean BCVA value at the end of 6 months. When post-injection mean BCVA values at different time points were compared, a significant improvement was noted when the one week mean BCVA and 3 month mean BCVA values were compared (Table 3, Fig.8). However, the best mean BCVA value was noted at 1 month post-injection, and the mean BCVA value was essentially similar at 3 months post-injection and lower (decreased/worsened) at 6 months post-injection (Tables 3,4; Fig.8).These results possibly reflect intravitreal concentrations and pharmaco kinetics of triamcinolone acetonide.

Beer *et al.*[50] studied the serial intraocular concentrations and pharmacokinetics of triamcinolone acetonide after a single intravitreal injection of 4mg and reported that measurable concentrations of the drug are expected to last for 3 months (93 ± 28 days) in the absence of vitrectomy,[50] the mean half-life of triamcinolone being 18.7 ± 5.7 days. These observations possibly explain the findings of the current study that the positive effect of triamcinolone acetonide on BCVA was noted up to 3 months, after which the effect of the drug appear to wane.

Martidis *et al.*[53] described a prospective, non-comparative, interventional case series involving 16 eyes with CSME that had failed to respond to at least two previous sessions of laser photocoagulation. Following intravitreal injection of triamcinolone acetonide (4 mg/0.1 ml), mean improvements in visual acuity of 2.4, 2.4 and 1.3 Snellen lines were noted at follow-up visits of 1, 3 and 6

months, respectively; the central macular thickness decreased by 55%, 57.5% and 38%, respectively, over the same intervals. These researchers attributed the more significant reduction in edema, as compared to the improvement in visual acuity, to the injection being given after the chronic edema had already caused severe dysfunction; they, hence, suggested early injection in severe cases.

Larsson *et al.*[54] demonstrated that a single intravitreal injection of triamcinolone acetonide (4mg/0.1 ml) effectively reduced the foveal thickness in diabetic macular edema and improved the visual acuity; although there did not appear to be a strong correlation between reduction of foveal thickness and improvement in visual acuity, there was a correlation between reduction in foveal thickness and the age of the patients, namely, there was a significant reduction of macular edema in younger patients.

With reference to reduction in **central foveal thickness**, the current study appears to demonstrate the efficacy of one intravitreal injection of triamcinolone acetonide in reducing the macular edema that is refractory to laser photocoagulation and anti-VEGF agents, at least in the short term. In all the eyes that received intravitreal triamcinolone acetonide, a dramatic anatomic improvement in DME that had been resistant to all previous treatments was noted. This improvement occurred as soon as one week, with maximum effect at one month, post-injection; the resolution appeared to be sustained up to 3 months post-injection, after which the effect appeared to decline (Tables 5,6; Fig.9). These results are consistent with the results of Martidis *et al*.[53] who reported 55%, 58% and 38% reduction in thickness by 1, 3 and 6 months respectively.

Comparable with the results of Martidis *et al*.[53] and Larsson *et al*.,[54] in the current study, there appeared to be a significant reduction in mean central foveal thickness when pre-injection values and post-injection triamcinolone acetonide values were compared. On analyzing the post-injection mean CFT values at various time points, there was significant reduction in mean CFT values between pre-injection and post-injection; there was significant reduction in CFT even at 6 months (Tables 5,6; Fig.9). However, there was no significant difference between the mean CFT values at 1 month and 3 months, suggesting there was no further reduction in central foveal thickness after 1 month post-injection. Triamcinolone acetonide effectively reduced the foveal thickness in diabetic macular edema and improved visual acuity; there did not appear to be a strong association between reduction of foveal thickness and visual acuity, which can be attributed to the injection being given after the chronic edema had already caused severe dysfunction.

In this study only 2 mg of intravitreal triamcinolone was administered to treat recalcitrant diabetic macular edema and the results are comparable with the results of other workers[13c,53,54,55] who administered 4 mg of intravitreal triamcinolone acetonide to treat diabetic macular edema.

Zalewski *et al*.[66] reported on a five –month observation of patients with chronic DME who had previously been treated with photocoagulation and anti VEGF injections. Four weeks after the treatment with intravitreal dexamethasone implant (Ozurdex™), a significant decrease in the central retinal thickness and improvement in visual acuity was observed at 4 weeks. This continued until 12 weeks of observation had elapsed. The central retinal

thickness gradually increased and the visual acuity after 5 months was similar to that of the pre-treatment status.[66] These investigators attributed the decline in response to decrease in concentration of dexamethasone released.[66]

Rishi *et al*.[74] reported the short-term results of intravitreal dexamethasone implant in eyes which had previously been treated with photocoagulation and anti VEGF injections and were recalcitrant to treatment. These investigators observed a significant reduction in central retinal thickness, compared to baseline levels, at 1 month and maximum reduction in macular thickness was seen at 1 month. However, reappearance of clinically significant macular edema was noted at 4 months. These workers concluded that the beneficial effect on visual acuity and reduction in macular thickness seen initially persists until 3 months and tends to wane off by the 4th month.[74]

Similar to the results obtained by Zalewski *et al*.[66] and Rishi *et al*.,[74] the present study which used 2 mg of intravitreal triamcinolone acetonide for recalcitrant DME, showed improvement in mean BCVA and reduction in central retinal thickness. Maximum improvement in mean BCVA was noted at 1 month; the effect tended to wane after 3 months and completely disappeared at 6 months (Tables 3,4,5,6; Fig 8,9).

Complications of intravitreal triamcinolone acetonide are reported to include IOP elevation, cataract formation or progression, retinal detachment, and endophthalmitis. Among the complications, IOP elevation is the most commonly reported one.[51,57,59] Oh et al.[75] reported that five of 40 eyes developed temporary IOP elevation and required temporary treatment. Martidis *et al.*[53] also reported

cataract progression and increased incidence of glaucoma after intravitreal triamcinolone acetonide. In the current study, although there was no significant difference between pre-injection and post-injection mean IOP values, two eyes showed an increase in IOP, requiring treatment, which normalized after temporary treatment; one eye developed intractable glaucoma for which the patient underwent anti-glaucoma surgery. Jonas *et al*.[56] noted the peak elevation in IOP at 3 to 5 months after injection; a similar observation was made in the current study. Jonas et al.[56] and Sutter *et al*.[13b,c] reported IOP elevation in 26.9% and 30% of their patients, whereas in the current study it was observed only in two eyes (9%) (Table 7).This lower percentage in the current study was possibly due to the lower dosage, 2mg of intravitreal triamcinolone acetonide, used to treat recalcitrant diabetic macular edema. However, a large sample size needs to be studied before arriving at a definitive conclusion.

Sutter *et al*.[59] reported that cataract surgery was performed in 44% of their patients treated with intravitreal triamcinolone acetonide, whereas in the present study cataract developed in four (22%) (Fig.10) eyes; cataract extraction with IOL surgery was done in these patients. Here also, the lower dose of triamcinolone acetonide used in the current study possibly explains these differing results. However, a larger sample size and dose-dependent comparison needs to be studied to arrive at a definitive conclusion.

Audren *et al*.[76] reported that although no remarkable complication due to intravitreal injection was observed during the follow-up period, intravitreal triamcinolone acetonide has potential side- effects, including an increase in IOP and cataract development.

Chan *et al*.[77] were of the opinion that, even if the ocular hypertensive effects were similar between the injection types, the cumulative effects of the intraocular steroids would lead to increased cataractogenesis, and each injection would expose the eye to the small but serious risk of infective endophthalmitis. Retrospective reports of intravitreal triamcinolone acetonide injection indicate a pre-injection endophthalmitis risk between 0% and 0.87%.[78-80] Severe complications, such as infectious endophthalmitis or retinal detachment, were not observed within the follow-up period in the present study.

A limitation of the present study was that the calculated patient sample size could not be achieved due to several reasons, the most important being the relatively short duration of investigation. Due to this, unequivocal interpretations could not be made, although definite trends were evident. A study on a large sample-size of patients would help to clarify these aspects.

Summary

SUMMARY

This study entitled “Efficacy and safety of intravitreal triamcinolone acetonide in the management of recalcitrant diabetic macular edema”, was performed at the Retina clinic, Joseph Eye Hospital, Tiruchirapalli, during the period from September 2013 to July 2015.

The aim of the study described in this dissertation was to evaluate the safety and efficacy of intravitreal triamcinolone (2mg/0.05ml) in the management of diabetic macular edema unresponsive to laser photocoagulation and the intravitreal anti-vascular endothelial growth factor (VEGF) agent, bevacizumab, over a six-month treatment period.

Primary outcome measures evaluated during the study period were:

a) an improvement in mean best corrected visual acuity (BCVA)

b) a reduction in mean central foveal thickness (CFT), as assessed by optical coherence tomography (OCT) and

c) complications related to the intravitreal injection or drug.

This investigation was a prospective interventional study which was performed over a period of 23 months. Seventeen patients (21 eyes), comprising nine males and eight females (age range 40 to 75 years), who presented with recalcitrant diabetic macular edema (DME), unresponsive to conventional laser photocoagulation and the intravitreal anti-VEGF agent bevacizumab, who satisfied the inclusion criteria and who provided consent for participation, were enrolled in the study. The patients who underwent intravitreal triamcinolone

acetonide for the treatment of recalcitrant diabetic macular edema were almost equally matched for gender and laterality of the eye. The mean age of the study patients who received intravitreal triamcinolone acetonide was 59.47 ± 9.6 years.

All the patients enrolled in the study had type 2 diabetes mellitus, with 70.6% of the patients having suffered from diabetes for around 10 years. All 17 patients presented with recalcitrant diabetic macular edema, and suffered from type 2 diabetes mellitus; however,10 (59%) patients had other associated (co-morbid) systemic diseases. Eight (47%) patients presented with hypertension and diabetes, one (5.9%) patient had diabetic nephropathy along with hypertension and diabetes and one patient (5.9%) had ischemic heart disease along with hypertension and diabetes. Seven (41%) patients presented with type 2 diabetes mellitus only.

In this study, of the 21 eyes enrolled with recalcitrant diabetic macular edema, 17 (81%) eyes exhibited diffuse leaks and four (19%) eyes exhibited focal leaks in fundus fluorescein angiography.

In this study, of the 21 eyes enrolled with recalcitrant diabetic macular edema, optical coherence tomography (OCT) was able to detect spongy thickening in 11 (52%) eyes and cystoid macular edema in nine (43%) eyes; one eye (4.8%) exhibited cystoid macular edema associated with vitreo-macular traction.

The mean glycosylated haemoglobin (HbA_1C) value was 8.2% at baseline, 7.7% at 3 months and 7.7% at 6 months follow-up; this reduction in mean HbA_1C values was not statistically significant. (P =0.06).The mean HbA_1C

of the patients with recalcitrant DME was high throughout the study period. Four patients had bilateral involvement and persistently higher levels of HbA_1C throughout the study period.

In the current investigation, nephropathy was observed in one patient who had bilateral DME, whose mean HbA_1C was above 7.9% and whose visual acuity was poor; the chronic diabetic macular edema was refractory to treatment, necessitating repeated intravitreal injections.

In the current study, a significant improvement (increase) in mean BCVA of 0.12 decimals was noted in the first week following injection of triamcinolone acetonide, with a maximum of 0.25 decimals. This improvement in BCVA was sustained for up to 3months post-injection; after 3 months, the mean BCVA showed a decline and at the end of 6 months, approached pre-treatment mean BCVA values. On comparing the pre-injection mean BCVA value with the mean values post-injection at different time points, a statistically significant increase in mean BCVA values at 1week, 1 month and 3 months was observed; however, there was no significant difference noted between the pre-injection mean BCVA value and the mean BCVA value at the end of 6 months. When post-injection mean BCVA values at different time points were compared, a significant improvement was noted when the one week mean BCVA and 3 month mean BCVA values were compared. However, the best mean BCVA value was noted at 1 month post-injection, and the mean BCVA value was essentially similar at 3 months post-injection and lower (decreased/worsened) at 6 months post-injection. These results possibly reflect intravitreal concentrations and pharmacokinetics of triamcinolone acetonide.

The current study demonstrated the efficacy of one intravitreal injection of triamcinolone acetonide in reducing macular edema that was refractory to laser photocoagulation and anti-VEGF agents, at least in the short-term. In all the eyes that received triamcinolone acetonide, a dramatic anatomic improvement in DME that had been resistant to all previous treatments was noted. This improvement occurred as soon as one week, with maximum effect at one month, post-injection; the resolution appeared to be sustained up to 3 months post-injection, after which the effect appeared to decline.

On analyzing the post-injection mean CFT values at various time points, there was a significant reduction in mean CFT values between pre-injection and post-injection; there was significant reduction in CFT even at 6 months post-injection. However, there was no significant difference between the mean CFT values at 1 month and 3 months post-injection, suggesting there was no further reduction in CFT one month after injection. Triamcinolone acetonide effectively reduced the foveal thickness in diabetic macular edema and improved visual acuity; there did not appear to be a strong association between reduction of foveal thickness and visual acuity, which can be attributed to the injection being given after the chronic edema had already caused severe dysfunction.

In this study, only 2 mg of intravitreal triamcinolone was administered to treat recalcitrant diabetic macular edema; the results obtained were comparable to those achieved by other workers who administered 4 mg of intravitreal triamcinolone acetonide to treat diabetic macular edema. Intravitreal triamcinolone acetonide in a dose of 2mg/0.05ml, yielded similar results and trends in improvement in mean BCVA and reduction in central retinal thickness.

Maximum improvement in mean BCVA was noted at 1 month, but the effect tended to wane after 3 months and to completely disappear at 6 months.

The mean intraocular pressure (IOP) in the eyes with recalcitrant diabetic macular edema that received triamcinolone acetonide was (in mm Hg) 17.4 ± 2.2 (pre injection), 18.0 ± 2.1 (1 week post injection), 18.4 ± 2.2 (one month post-injection), 18.6 ± 5.12 (three months post-injection) and 20.3 ± 11.8 (six months post-injection); these differences were not statistically significant (ANOVA; Fisher 'f' value = 0.689; P = 0.6). Patients who had increased IOP in the injected eye responded well to topical anti-glaucoma medications; however, one eye developed intractable glaucoma, which necessitated anti-glaucoma surgery on the affected eye. In the current study rise in IOP was observed only in two eyes (9%). This lower percentage in the current study was possibly due to the lower dosage, 2mg of intravitreal triamcinolone acetonide, used to treat recalcitrant diabetic macular edema. However, a large sample size needs to be studied before arriving at a definitive conclusion.

In the present study, cataract developed in four (22%) eyes; cataract extraction with IOL surgery was done in these patients. Here also the lower dose of triamcinolone acetonide used in the current study possibly explains the lower frequency of cataract occurrence, compared to the results of other workers. However, a larger sample size and dose-dependent comparison needs to be studied to arrive at a definitive conclusion. Severe complications, such as infectious endophthalmitis or retinal detachment, were not observed within the follow-up period in the present study.

Overall, intravitreal triamcinolone acetonide appeared to be efficacious in the treatment of recalcitrant diabetic macular edema with improvement in BCVA and reduction in CFT atleast in the short term (1 and 3 months). It is evident that, in addition to VEGF-mediated vascular permeability and macular edema, the inflammatory mediators are also active in the underlying disease process and that they contribute significantly to vascular permeability and edema. Intravitreal triamcinolone acetonide in a low dose (2mg/0.05ml) appeared to be as efficacious as 4mg/0.1ml in treating diabetic macular edema with the lower frequency of drug related side-effects. Thus, there may be a role for alternative therapeutic modalities and, in particular, triamcinolone acetonide for patients for whom anti-VEGF therapy is incompletely effective.

A limitation of the present study was that the calculated patient sample size could not be achieved due to several reasons, the most important being the relatively short duration of investigation. Due to this, unequivocal interpretations could not be made, although definite trends were evident. A study on a large sample-size of patients would help to clarify these aspects.

Conclusion

CONCLUSION

- Intravitreal triamcinolone acetonide appears to be effective in the management of recalcitrant diabetic macular edema.
- Reduction of macular edema and improvement in best corrected visual acuity was statistically significant in the short term (1 month and 3 months).
- Adequate control of glycemic status ($HbA_1C < 7.0\%$) is important for the resolution of recalcitrant macular edema.
- The effect of intravitreal triamcinolone acetonide appears to be transient, necessitating repeat injections 6 months after the first dose.
- Rise of intraocular pressure and cataract fomation due to intravitreal triamcinolone acetonide appears to be less with a dose of 2mg/0.05ml.
- Complications due to the procedure, such as vitreous hemorrhage and endophthalmitis are very rare.
- Intravitreal triamcinolone acetonide can still be a safe therapeutic option in patients who are resistant to conventional laser photo coagulation and intravitreal anti-VEGF agents.

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Proforma

PROFORMA

Name: Age/Sex: M.R.No:

Address:

Phone no: Date:

Complaints:

Medical history:

Diabetes (duration):

Hypertension:

Nephropathy:

Treatment history:

Personal history: Smoking / Alcohol

Investigations: (Date:)

BP: Pulse Rate: RBS:

HbA1c: Urine Albumin:

Base Line

Three Months

Six Months

General Examination:

Ocular Examination		RE	LE
Vision	Distant vision without correction		
	Best corrected Vn		
	Near vision without correction		
	Best corrected Vn		
IOP (Baseline)			

Anterior segment	Lids &Adnexa		
	Conjunctiva		
	Cornea		
	AC		
	Iris		
	Pupil		
	Lens		
Posterior segment-Fundus			
Media			
Disc	Colour		
	Margins		
	CD ratio		
	NRR		
	Vessels		
Macula			

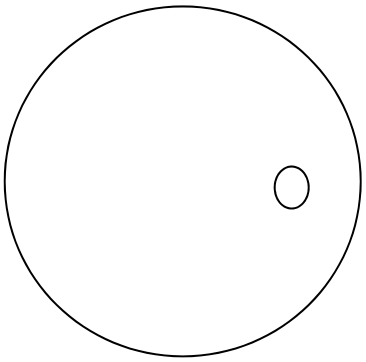
Provisional Diagnosis:

RE:

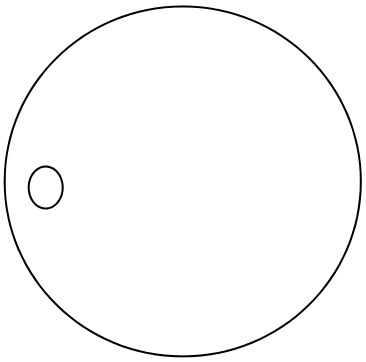
LE:

Fundus :

RE



LE



FFA:

OCT:

Details of LASER treatment:

Details of Intravitreal Bevacizumab (Avastin) :

Details of Intravitreal Triamcinolone Acetonide:

Follow up:

Date	Duration	BCVA	IOP	OCT (CFT)	Lens status
	1week				
	1 month				
	2nd month				
	3rd month				
	4th month				
	5th month				
	6th month				

Response to treatment:

Master Chart

KEY TO MASTERCHART

BCVA	-	Best Corrected Visual Acuity in decimals
IOP	-	Intraocular Pressure in mmHg
HbA_1C	-	Glycosylated haemoglobin in percentage
CFT	-	Central Foveal Thickness
FFA	-	Fundus Fluorescein Angiography
CME	-	Cystoid Macular edema
OCT	-	Optical Coherence Tomography

S.No	M.R.NO	AGE	SEX	DM	Other Sys. Illness	EYE	PRE INJECTION								POST INJECTION- 1 week						POST INJECTION -1 month				POST INJECTION-3 months					POST INJECTION-6 months					Name	
							HbA_1C (%)	BCVA	BCVA in decimals	Lens status	IOP	CFT (in µ)	OCT pattern	FFA	BCVA	BCVA in decimals	Change in BCVA	IOP	CFT (in µm)	change in CFT	BCVA	BCVA in decimals	IOP	CFT (in µm)	HbA_1C (%)	BCVA	BCVA in decimals	IOP	CFT (in µm)	HbA_1C (%)	BCVA	BCVA in decimals	IOP	CFT (in µm)		Complications
1	1053851	65	M	Type 2, 10 years	HT	RE	8.0	6\36	0.16	NS gr2	18	318	Spongy thick	Diffuse leak	6\18	0.33	0.17	20.6	265	53	6\9	0.66	20	210	6.9	6\12	0.5	18	216	8.2	6\24	0.25	18	385	Arumugam	nil
2	1053851	65	M	Type 2, 10 years	HT	LE	8.0	6\18p	0.3	NS gr2	20	355	Spongy thick	Diffuse leak	6\12p	0.5	0.2	20	316	39	6\9p	0.66	20	219	6.9	6\12	0.5	20	320	8.2	6\24	0.25	20	429	Arumugam	nil
3	1058946	54	M	Type 2, 15 years	Nephropathy, HT	RE	8.5	5\60	0.08	NS gr2, PSC	16	676	CME	Diffuse leak	6\36	0.16	0.08	20	482	194	6\36	0.16	22	209	8.0	6\24	0.25	20	248	7.4	6\60	0.1	25	453	Veeramani	Cataract
4	1058946	54	M	Type 2, 15 years	Nephropathy, HT	LE	8.5	5\60	0.08	PCIOL	20	617	CME	Diffuse leak, NVE	6\24	0.25	0.17	22	426	191	6\24	0.25	22	181	8	6\36	0.16	24	196	7.4	6\60	0.1	70	444	Veeramani	increased IOP
5	1023269	65	F	Type 2, 10 years	nil	RE	9.2	6\60	0.1	NS gr1, ACC	20	510	Spongy thick	diffuse leak	6\36	0.16	0.06	17	326	230	6\18	0.33	14	228	9	6\24	0.25	14	300	8.4	6\60	0.1	14	436	chinnammal	nil
6	1023269	65	F	Type 2, 10 years	nil	LE	9.2	6\60	0.1	NS gr1, ACC	20	579	centrally inv.CME	diffuse leak	6\36P	0.16	0.06	14	324	255	6\24P	0.25	14	303	9	6\24	0.25	14	282	8.4	6\36	0.16	14	310	chinnammal	Cataract
7	1074003	44	M	Type 2, 1year	HT	LE	7.4	6\36	0.16	CLEAR	18	479	Spongy thick	IRMA, NVE, Focal leaks, CNP areas	6\12	0.5	0.34	21	346	133	6\9p	0.66	19	229	7	6\12	0.5	20	202	7	5\60	0.08	20	200	muthukumar	Cataract
8	1093740	64	M	Type 2, 17 years	nil	RE	8	5\60	0.08	NS gr1, ACC	14	582	CME, VMT	NVE, Diffuse leaks	6\36P	0.16	0.08	14	417	165	6\36	0.16	16	376	7.9	6\24	0.25	14	320	7.8	5\60	0.08	14	696	Ramasamy	nil
9	1082625	63	M	Type2, 2 years	HT, CAHD	RE	11	6\36	0.16	PCIOL	17	509	Spongy thick	Diffuse leaks	6\18	0.33	0.17	20	276	233	6\12	0.5	20	261	8.6	6\60	0.1	20	507	7.2	6\18	0.33	20	211	sakthivel	nil
10	1084901	73	F	Type2, 2 years	HT	RE	9	6\60	0.1	NS gr3	18	530	CME	Diffuse leaks	6\24	0.25	0.15	18	350	180	6\12	0.5	18	242	9	6\18p	0.33	18	231	8.4	6\60	0.1	20	527	Rajeswari	nil
11	1104572	57	M	Type 2, 25 years	nil	LE	7	6\60	0.1	CLEAR	18	644	CME	Diffuse leaks	6\36p	0.25	0.15	18	461	183	6\24	0.25	18	229	7.2	6\24	0.25	18	191	7.2	6\24	0.25	20	220	solomon	nil
12	1128425	59	M	Type 2, 3 years	nil	LE	7.4	6\60	0.1	PCIOL	18	487	Spongy thick	Diffuse leaks, CNP areas	6\36	0.16	0.06	18	265	222	6\18	0.33	20	214	7.4	6\18	0.33	18	265	7.6	6\18	0.33	18	265	Marudhai	nil
13	1139231	55	F	Type 2, 10 years	HT	LE	8	6\24	0.25	CLEAR	17	367	Spongy thick	IRMA, Focal leaks, CNP areas	6\12	0.5	0.25	18	228	139	6\9P	0.66	17	276	7.2	6\12	0.5	17	324	7.7	6\18P	0.33	18	375	Sagayamary	nil
14	1092218	40	F	Type 2, 8 years	HT	RE	7	6\24	0.25	CLEAR	22	588	Spongy thick	Focal leaks, NVE	6\18p	0.33	0.08	16	495	106	6\18	0.33	20	408	7.4	6\18	0.33	14	385	7	6\18p	0.33	18	352	Suryakala	nil
15	1092218	40	F	Type 2, 8 years	HT	LE	7	6\60	0.1	CLEAR	18	733	Spongy thick	Focal leaks, NVD	6\24P	0.25	0.15	18	522	211	6\60	0.1	19	412	7.4	6\36	0.16	20	340	7	6\60	0.1	14	367	Suryakala	nil
16	1155427	46	F	Type 2, 17 years	nil	LE	8.4	6\24P	0.25	NS gr1	14	462	CME	NVE, Diffuse leaks	6\24	0.25	0	16	355	107	6\18	0.33	16	355	8.4	6\18	0.33	38	169	8.4	6\36	0.16	22	344	Usha	IOP rise
17	1133011	71	M	Type 2, 10 years	nil	LE	9.2	3\60	0.05	NS gr1 PSC gr3	14	740	Spongy thick	CNP areas, diffuse leaks	6\60	0.1	0.05	18	583	157	6\36	0.16	18	367	8	6\60	0.1	18	341	8.4	5\60	0.08	16	243	Duraisamy	Cataract
18	1131714	72	F	Type 2, 4 years	nil	LE	7.8	6\36	0.16	NS gr2 ACC	14	489	Spongy thick	IRMA, diffuse leaks	6\18	0.33	0.17	18	378	111	6\18p	0.33	18	326	7.4	6\24	0.25	16	302	7	6\36	0.16	16	386	Rozario	nil
19	1166711	64	F	Type 2, 8 years	HT	LE	8.4	2\60	0.03	NS gr 2	16	628	CME	Diffuse leaks	6\60	0.1	0.07	16	483	145	6\36	0.16	18	344	7.8	6\24	0.25	16	282	8.2	5\60	0.08	16	388	Mani	nil
20	1142594	63	M	Type 2, 2 years	HT	RE	7.4	6\36	0.16	NSgr1	16	534	CME	Diffuse leaks	6\24	0.25	0.09	18	380	154	6\9P	0.66	18	274	7.4	6\12	0.5	16	288	7.6	6\24	0.25	16	396	Subramani	nil
21	1169966	56	F	Type 2, 8 years	HT	RE	8	5\60	0.08	CLEAR	18	440	CME	Diffuse leaks	6\36	0.16	0.08	18	317	123	6\9	0.66	20	235	7	6\9	0.66	18	246	7.2	6\24	0.25	18	348	Madhavi	nil