UNIVERSITÄTSKLINIKUM HAMBURG-EPPENDORF

Klinik und Poliklinik für Augenheilkunde

Prof. Dr. med. Martin Spitzer

Long term safety and efficacy data of phakic patients with treatment naïve diabetic macular edema treated with the Dexamethasone implant: A five year follow-up

Dissertation

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vorgelegt von:

Alper Bilgic

aus Ankara/Türkei

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Prüfungsausschuss, der/die Vorsitzende: Prof. Dr. Thomas Renné

Prüfungsausschuss, zweite/r Gutachter/in: Prof. Dr. Martin Spitzer

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1. Introduction

1.1 Incidence of Diabetic Macular Edema

Diabetic macular edema (DME) is an important cause of vision loss worldwide. It affects nearly 100 million people worldwide that show some signs of macular edema secondary to diabetes. Some studies have shown that nearly 1 in 3 people with diabetes have some evidence of macular edema. The prevalence of DME is said by some to be higher in individuals with type 1 diabetes than those with type 2 diabetes. In a large prospective study enrolling 366 patients with type 1 diabetes (T1DM) and 15,030 with type 2 diabetes (T2DM), the annual incidence of DME was similar between the two groups (2.68% in T1DM and 2.22% in T2DM), while the sum incidence at 9 years was slightly higher in patients with T1DM (8.46% *versus* 6.36%, respectively). In patients that have been diagnosed with diabetes, the ten-year incidence of DME is approximately 20% in patients that were diagnosed before the age of 30, and approximately 40% in patients diagnosed over the age of 30. Another study found that approximately 27% of patients develop signs of macular edema within 9 years of diabetes onset, albeit subclinical. Several studies that address different demographics illustrate an increasing incidence of DME.[1-4]

1.2. Pathogenesis

The primary pathology lies in the disruption of the blood-retinal barrier (BRB). The BRB isolates the photoreceptors of the retina from the ophthalmic vasculature. The BRB functions in a complex manner that involves several factors that work in tandem; however, many of the specific physiologic processes are poorly understood. The BRB involves two major compartments: an outer and an inner barrier. Animal models have illustrated that the permeability of both compartments is disrupted after

the onset of diabetes. Disruption of this barrier results in the accumulation of macular edema; however, the process is more complicated than this and also involves various inflammatory markers upregulated by advanced glycation end-products (AGEs), hyperglycemia, and diabetes. Diabetes also results in vasoconstriction which upregulates vascular endothelial growth factor (VEGF) expression. VEGF also results in macular edema and results in vasculogenesis, which results in further retinal disease.[1,5,6]

1.2.1 Pathological Basis for Retinal Inflammation

The blood vessels supply nutrients and oxygen to neurons and eliminate metabolic wastes and carbon dioxide; the vascular endothelial cells make a semi-selective monolayer at the inner surface of the vessels, known as the inner BRB.[7,8] Reduced expression of the tight junction proteins that form the inner BRB has been observed in human retinal endothelial cells exposed to hyperglycemic conditions as well as diabetic animal models.[9]

Pericytes lining retinal capillaries maintain the integrity of the inner BRB, and an extracellular matrix known as endothelial basement membrane (EBM), which provides mechanical stability and interaction between endothelial cells and pericytes The pericytes regulate the blood flow and secrete inflammatory mediators promoting immune cells adhesion, extravasation, and migration into the extracellular matrix The pericytes express the major histocompatibility complex (MHC) class 1; they can express MHC class II in selected circumstances, supporting their role as antigen-presenting cells.[7,10,11]

The retinal macroglia contributes to metabolic support, electrolyte balance, and protection against oxidative stress. Müller cells produce interleukins (ILs), chemokines, and VEGF and contribute to local immune surveillance.

The cellular alterations seen in DME are the result of inflammatory cytokines secreted by glial cells, retinal pigment epithelium (RPE), macrophages, and activated leukocytes. The knowledge of the cytokines involved in DME is relevant from the therapeutic perspective, as periocular or intravitreal agents might be specifically designed for their inhibition.[7]

Eyes with DME have higher aqueous and vitreous levels of inflammatory and pro-angiogenic cytokines compared with healthy controls or diabetic patients with no diabetic retinopathy (DR).[7,12] The levels of these molecules correlate with DME severity, retinal thickness on optical coherence tomography (OCT), and the amount of leakage on fluorescein angiography (FA).[13] For instance, the placental growth factor (PGF) is a homolog of VEGF that binds to vascular endothelial growth factor receptor 1 (VEGFR-1) and promotes angiogenesis by inducing the growth and migration of endothelial cells.[14] PGF modulates inflammation and induces the chemotaxis of monocytes and macrophages.[7,14] Higher levels of PGF levels in aqueous humor correlate to DME severity.[15] Although intravitreal aflibercept inhibits PGF secretion and its effect, no approved antiangiogenic agent exclusively targets this pathway. Conversely, the use of steroids in the management of DME logically gains ground.

Angiopoietin subgroups have been shown to encourage VEGF secretion, promote vascular leakage and also neovascularization.[16] Agents blocking this pathway have the potential to act as antifibrotic, anti-neovascular and anti-inflammatory molecules.

We then understand that Faricimab has recently been shown to have great therapeutic potential because it acts upon this pathway.

1.3 Biochemical Pathways in Inflammation

1.3.1 Advanced glycation end products

Advanced glycation end products (AGEs) are biological macromolecules (proteins, lipids, or DNA) that become glycated after exposure to sugars. The formation of AGEs in diabetic patients increases in response to high glucose blood levels; AGEs are also induced by activation of the Renin-Angiotensin-Aldosterone-System (RAAS). Additional sources of AGEs are smoke and diet, with heated foods and high lipid and protein content.[17]

AGEs damage the endothelial junctional molecules (*occludins* and *cadherins*), directly activate leukocytes, increase the production of pro-inflammatory cytokines and chemokines (such as IL-6, IL-1β, TNF-α, and monocyte chemoattractant protein-1 (MCP-1), and promote the upregulation of the vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) on the endothelial cell surface[18]. Additionally, AGEs act on retinal cells either by a receptor-independent or a receptor-dependent pathway. Vascular endothelial cells, pericytes, microglia, Müller cells, and RPE cells constitutively express the receptor for advanced glycation end products (RAGEs); however, RAGEs are upregulated in diabetic patients.[19] The AGE-RAGE pathway induces ROS formation also through activation of the reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme and impairs antioxidant systems; AGEs production increases under oxidative conditions, amplifying this mechanism. Currently, there is no pharmacologic mechanism that targets this pathway.

1.3.2 Other pathogenetic mechanisms

The polyol pathway[20], the hexosamine pathway[21], the PKC (protein kinase C) pathway[22], the poly (ADP-ribose) polymerase pathway[23] and the renin angiotensin system[24] all induce inflammation through indirect mechanisms, principally through the formation of toxic alcohols, inducing vascular dysfunction, pericyte loss and promotion of apoptosis, thereby activating inflammatory pathways as also through transcription and overexpression of several genes that promote the formation of diabetic macular edema.

1.4 Clinical Application

The gist of this introduction is to infer that steroids have the potential to suppress inflammation that is the key to the pathogenesis of DME. Indeed, steroids are like a panacea when it comes to suppressing inflammation anywhere, their relatively weak effect on VEGF notwithstanding. Triamcinolone has long been used for DME management, especially prior to the advent of anti-VEGF agents.[20] Triamcinolone can be administered intravitreally[25] or through the sub-tenon route.[26] Triamcinolone fell out of favour because of potentially devastating side effects such as intractable glaucoma[27] as well as cataract progression and sterile endophthalmitis. Moreover, it never was approved for intraocular use apart from its approval in the US for intraoperative usage for visualisation of the vitreous scaffold.

1.4.1 The Dexamethasone implant

The use of the intravitreal dexamethasone implant (Ozurdex, Allergan, Irvine, CA) in diabetic macular edema (DME) has been established through several studies and analyses[28-33]. The debate of anti-VEGF first[31], versus steroid first[32], continues, with

continued preference for the former given the known adverse effects of cataract formation and ocular hypertension of the latter. The incidence of ocular hypertension with the use of the implant has been reported to be in the range of 10%-30% in various retrospective analyses[34,35]. Likewise, the incidence of cataract development and/or progression with steroid use is known[28-30]. It follows that its use in phakic patients is laced with reluctance. However, it is of note that should cataract formation occur, it does so 18-30 months of initiation of therapy and with multiple injections, as demonstrated in the MEAD trial[28]. The use of the implant comes to the fore when one considers special case-scenarios, such as pseudophakes[36-38] or patients unwilling for multiple injections[37] or possibly where finances are a concern. Indeed, the use of the implant has been shown to reduce the number of injections necessary to control DME over a period of 3 years[28,33,36,37,39,40,41], thereby reducing the number of patient-care visits and possibly the risk of endophthalmitis, given that it considerably lowers the number of procedures carried out.

1.5 DME Management

Current recommendations for DME management are outlined in the box (Box 1) below as per the publication by Cheung et al.[42]

Box 1: Recommendations for DME management.
Goal To achieve: ⌘ Best visual outcome ⌘ Edema improvement ⌘ Minimum treatment burden
Options First-line treatment with anti-VEGF in case of visual loss and CI-DME. Corticosteroids are important and are considered as second-line treatment
Baseline VA and CST should be considered while selecting anti-VEGF or corticosteroid.
Initial treatment Early monthly anti-VEGF (minimum 3 injections) Switch to steroids in case of poor response after 3–5 anti-VEGF injections
Follow-up schedule VA and OCT should be monitored based on which the follow up plan, whether fixed or individualized can be scheduled.

Box 1: Recommendations for DME management.

VA: Visual Acuity, CST : Central Subfield Thickness, CI-DME : Center Involving Diabetic Macular Edema, anti-VEGF: Anti-Vascular Endothelial Growth Factor

1.6 DME Classification

The following boxes (Box 2 and Box 3) classify respectively DME as per current recommendations:

Box 2: The ICO classification of DME.	
DME	**Findings on dilated ophthalmoscopy**
DME absent	No apparent retinal thickening or hard exudates at the posterior pole
DME present	Some retinal thickening or hard exudates at the posterior pole
Mild DME	Some retinal thickening or hard exudates at the posterior pole but outside the central subfield of the macula (1000 µm)
Moderate DME	Retinal thickening or hard exudates within the central subfield of the macula but not involving the center point
Severe DME	Retinal thickening or hard exudates involving the center of the macula

Box 2 : The ICO Classification of DME[43]

ICO: International Council of Ophthalmology; DME: Diabetic Macular Edema

Box 3: The DRCR.net Classification of DME.	
DRCR.net Classification	**Findings observable on dilated ophthalmoscopy**
No DME	No retinal thickening or hard exudates in the macula
Non-central-involved DME	Retinal thickening in the macula that does not involve the central subfield zone that is 1 mm in diameter
Central-involved DME	Retinal thickening in the macula that involves the central subfield zone that is 1 mm in diameter
Tractional	With vision loss (Macular tractional retinal detachment) Without vision loss (Extramacular membranes and tractional retinal detachment)
Non-Tractional	CI Non CI Combined

Box 3: The DRCR.net Classification of DME[44]

DRCR.net: Diabetic Retinopathy Clinical Research Network; DME: Diabetic Macular Edema; CI: Center-involved

1.6.1 OCT Based Classification of DME

Despite these classifications, a morphologic classification based on features visible on spectral domain optical coherence tomography (SD-OCT) is needed. SD-OCT

offers quantitative and qualitative information which is non-invasive, can be repeated and documented, and also measures central subfoveal thickness (CST) SD-OCT provides information regarding the following (Figure 1 demonstrates various layers of the retina and zones):

Figure 1

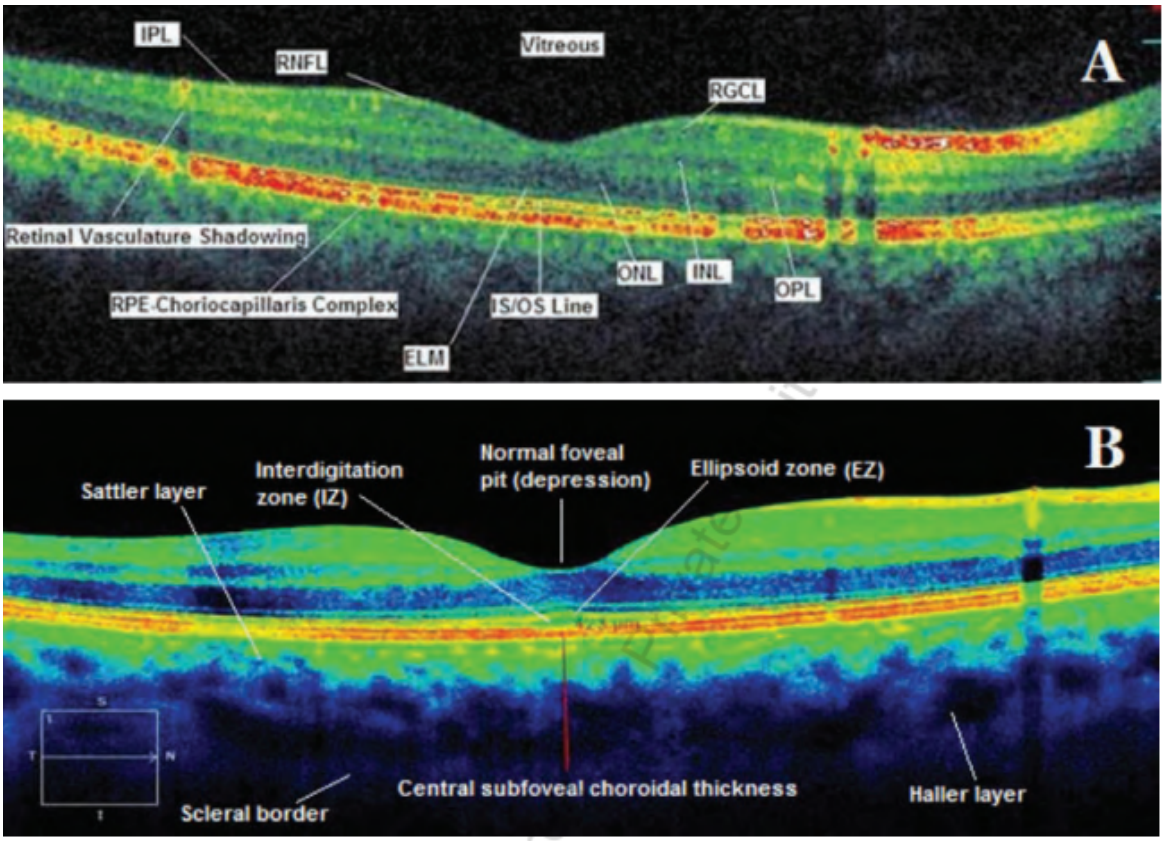


Figure 1: Normal spectral domain (A) and enhanced depth imaging (B) optical coherence tomography[45] (Image Courtesy Prof. Dr. Burak Turgut)

RGCL: Retinal Ganglion Cell Layer, RNFL: Retinal Nerve Fiber Layer, IPL: Inner Plexiform Layer, INL: Inner Nuclear Layer, OPL: Outer Plexiform Layer, ONL: Outer Nuclear Layer, ELM: External Limiting Membrane, IS/OS Line: Inner segment / Outer segment Line, IZ: Interdigitation zone, EZ: Ellipsoid zone

The following box (Box 4) elucidates certain classifications of DME based on various study groups:

Box 4: OCT based classifications of DME.

Author	OCT used	Parameters considered	DME classification
Otani *et al.* 1999[46]	OCT	Retinal thickness	Type 1= Sponge-like retinal swelling Type 2= Cystoid macular edema Type 3= Serous retinal detachment
Helmy *et al.* 2013[47]	SD-OCT	ELM and IS/OS layers' disruption with CME stage, Height of cyst and CMT	CME I=cysts <30% CME II=cysts 30–60% CME III=cysts 60–90% CME IV=cysts >90% Each grade subdivided into A–D if none, ELM, IS/OS, or both ELM and IS/OS
Reznicek *et al.* 2016[48]	SD-OCT and FA	"E"-factor (focal vs non-focal) BCVA before and during therapy	S=subretinal fluid A=area of retinal thickening V=vitreoretinal abnormalities E=etiology of leakage
Parodi *et al.* 2018[49]	SD-OCT	Tractional DME with CRT>400 µm Internal and external cysts Hard exudates found in vasogenic DME	Vasogenic=DME with vascular dilation Non-vasogenic=DME without vascular dilation Tractional Mixed
Arf *et al.* 2020[50]	SD-OCT	Morphological features	Type 1-Diffuse macular edema Type 2-Cystoid macular edema Type 3-Cystoid macular degeneration a. Serous macular detachment b. VMT or EM c. Hard exudates

Box 4: OCT based classification of DME[46,47,48,49,50]

SD-OCT: Spectral domain optical coherence tomography; CME: Cystoid macular edema; FA: Fluorescein angiography; VMT: Vitreomacular traction; EM: Epiretinal membrane; CRT: Central retinal thickness; BCVA: Best corrected visual acuity; ELM: External limiting membrane; IS/OS: Inner segment/Outer segment

1.7 Clinical Features of Inflammation in DME

Maurizio et al[51] identified vasogenic DME as an inflammatory[52] subtype of DME, which is also the most common type. Distinguishing features include:

1.) Central Retinal Thickness can be greater than 400 microns but can vary between 300-400 microns

2.) Internal and external cysts and hard exudates

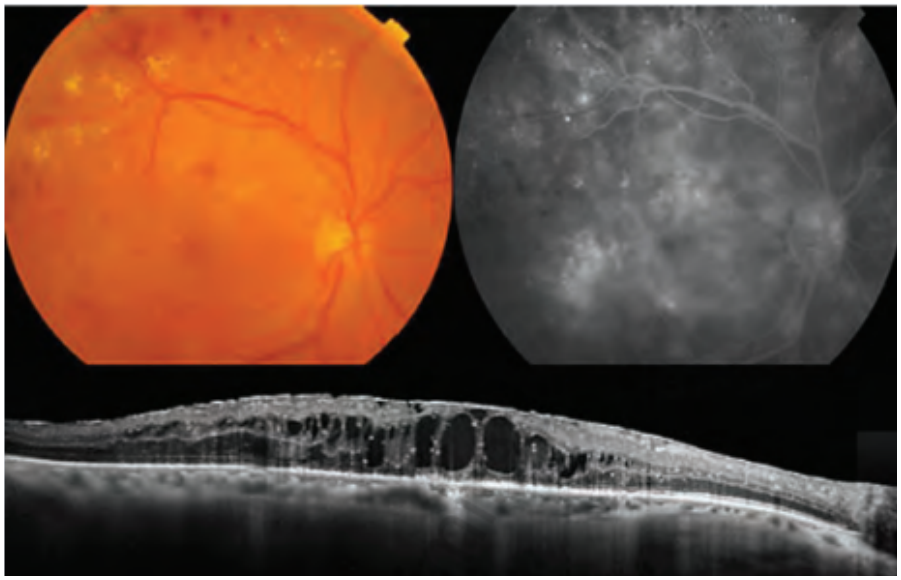
3.) Blood retinal barrier breakdown

4.) Retinal thickening

5.) Good response to laser and anti-VEGF and even steroids

The Figure 2 is an example thereof[53] (Image courtesy Dr. Rajav Raman)

Figure 2



Markers of Inflammation in DME:

Muni RH et al[51] demonstrated a significant association of high-sensitivity C-reactive protein (hsCRP) level and risk of clinically significant DME, suggesting that hard exudates have an inflammatory basis and are increased with an inflammatory pathology. While ICAM-1 is associated with the development of retinal hard exudates, higher baseline hsCRP level has a higher risk of clinically significant macular edema (CSME) and macular hard exudates in the Diabetes Control and Complications Trial (DCCT) cohort.[51]

1.7.1 Hyperreflective Dots

Retinal inflammation activates microglial cells, and they change in morphology, forming hyperreflective dots (HRD). As retinopathy progresses these HRD migrate towards outer retinal layers. They are distinct from hard exudates which cast a shadow and have the following characteristics:

1.) HRD are related to microglia activation
2.) They are smaller(<30 microns)
3.) They have similar reflectivity as nerve fiber layer
4.) There is absence of back-shadowing
5.) They are located in inner and outer retina
6.) They do not correspond to any specific lesion

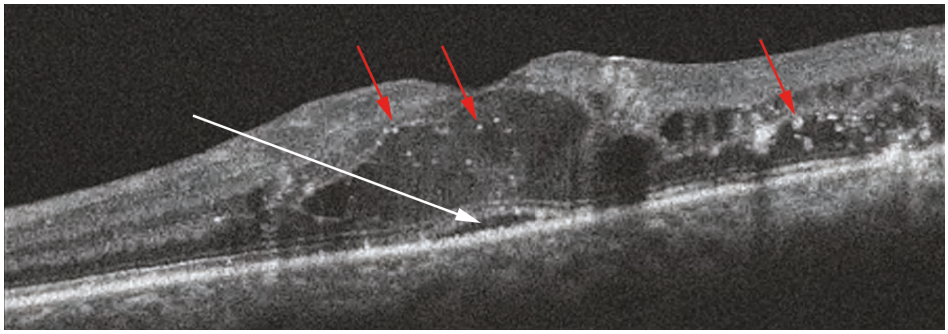
1.7.2 Serous Retinal Detachment

Giocanti-Auregan et al[54] assessed the consequence of serous retinal detachment (SRD) on functional and anatomical aftermaths in DME patients who received ranibizumab. They found that:

1.) SRD is associated with systemic factors
2.) SRD is a good marker for inflammation
3.) Patients who had better visual improvements could possibly have had a lower baseline best corrected visual acuity (BCVA)

The following figure (Figure 3) is an example of serous retinal detachment (white arrow) along with hyperreflective dots (red arrows).

Figure 3



1.7.3 Pearl Necklace Sign

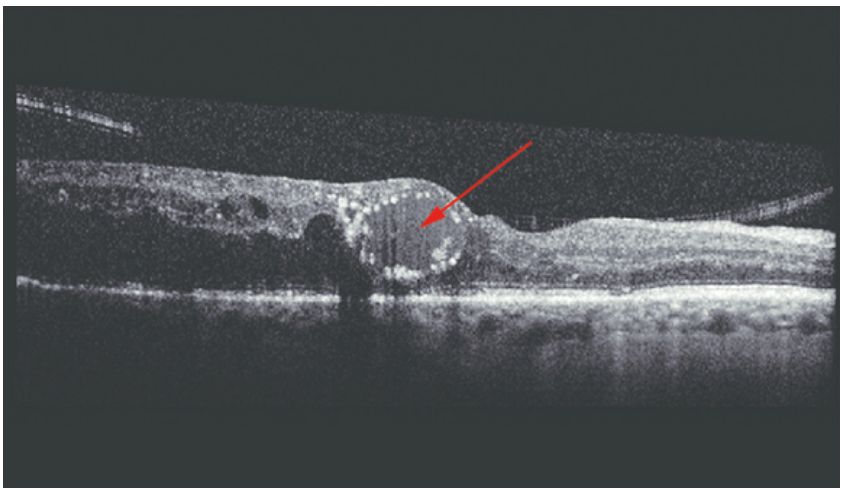
The pearl necklace sign[55] is a novel SD-OCT finding in the outer plexiform retinal layer in exudative macular disease. The hyperreflective foci are comprised of lipoproteins, and are seen as a ring around the inner wall of cystoid spaces.

1.) Pearl necklace sign (Figure 4) is suggestive of inflammatory changes.

2.) Such patients usually have VA ranging from 20/30 to hand movement.

3.) Though they resolve after anti-VEGF therapy and/or focal macular laser, they tend to recur.

Figure 4



Ajay K, Mason F, Gonglore B, Bhatnagar A. Pearl necklace sign in diabetic macular edema: Evaluation and significance. Indian J Ophthalmol. 2016 Nov;64(11):829-834[56]. (Permission is obtained)

Overall, DME shows disruptions at or comprises of the following:

1.) Ellipsoid zone

2.) External limiting membrane

3.) Hyperreflective intraretinal foci

4.) Vitreoretinal interface

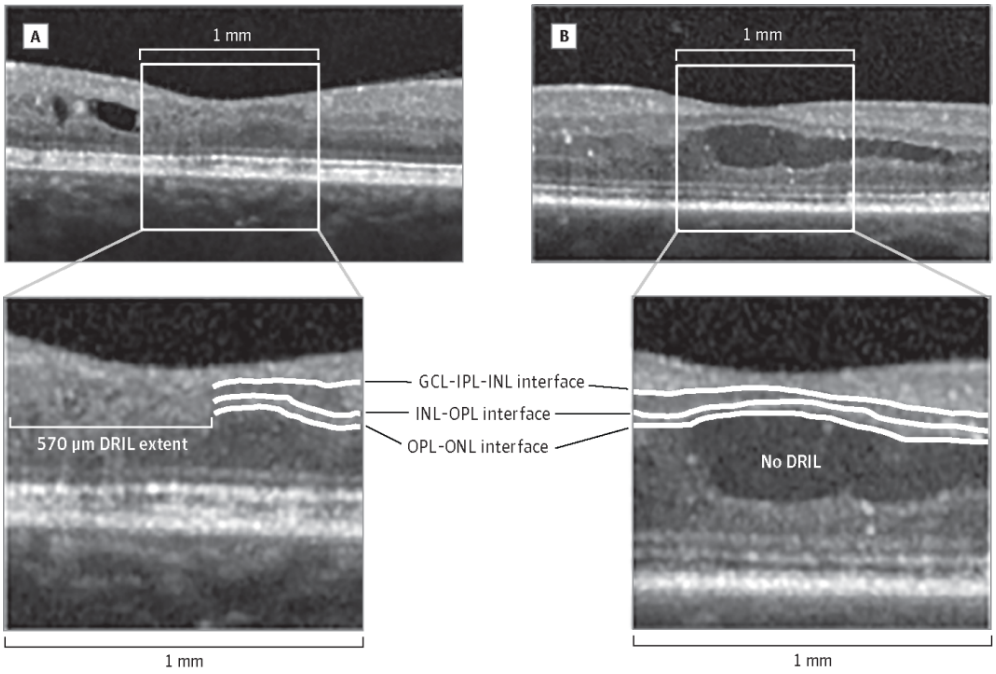
5.) Subfoveal fluid

6.) Intraretinal cysts

7.) Disorganization of the retinal inner layers (DRIL)

The Figure 5 is an example of DRIL:

Figure 5



A, DRIL is present, and retinal layer boundaries can only be partially identified at the right-hand edge of the 1-mm box. B, DRIL is absent, and all retinal layer boundaries can be identified throughout the 1-mm box. The presence or absence of DRIL is

independent of other pathology, such as intraretinal cystic changes. Insets are magnifications of the central 1-mm-wide area to show segmentation of the inner retinal layers, with white lines demarcating interfaces between ganglion cell–inner plexiform complex (GCL-IPL), inner nuclear layer (INL), outer plexiform layer (OPL), and outer nuclear layer (ONL).[57] (Permission is obtained)

1.7.4 Autofluorescence

Another sign suggestive of inflammatory basis is autofluorescence[58] in the macular area. It could either be a pseudo-autofluorescence, or lipofuscin deposits in microglia. There is also suggestion of hyperreflective dots in the vitreous and choroidal thickness as other biomarkers. Hyper autofluorescence in diabetic macular edema, causes oxidative damage, and release of peroxidation products in lipofuscin, which gets deposited in the microglia. When the luteal pigments get displaced by cystic fluid, it can lead to pseudo autofluorescence. Disorganization of Inner Retinal Layers (DRIL)[56] are suggestive of a poor visual outcome and possibly inflammatory DME.

These clinical markers of inflammation are important in that they suggest which patients are more likely to benefit from the use of intravitreal steroids for management of DME.

2. Materials and Methods

2.1 Background of the Study

Although phakic patients have been a part of earlier studies on the role of the dexamethasone implant (DEX-I) in DME, a thorough literature search (on Scopus, Google Scholar, Science Direct, the Cochrane Library and PubMed on 20th May

2022 using the key words: diabetic macular edema, phakic patients, DEX-I, Ozurdex®, primary therapy, steroids and ocular hypertension, steroids and cataract, diabetic eye disease management, proliferative diabetic retinopathy, clinically significant macular edema, and *pro re nata* (PRN) dosing revealed a paucity of literature (long term prospective studies in particular) on the role of the DEX-I (*pro re nata)* as primary therapy in phakic patients with early treatment naive DME. We had earlier conducted a two-year prospective study[58] to look at the long-term consequences of using the DEX-I as primary therapy for treatment naïve phakic patients with diabetic macular edema. The purpose of this analysis is to look at the five-year results (as an extension study) of the same set of patients and what the efficacy and safety of the DEX-I looks like.

2.1.1 Purpose of the Study

We undertook this retrospective study to determine the long-term consequences of the intravitreal DEX-I (used *pro re nata* or PRN) in phakic patients with early treatment naïve DME, to determine whether the DEX-I is a valid alternative to anti-VEGF therapy over and to determine its bearing on retreatment over a five-year period. The study includes data from all 153 patients who were recruited for the primary two year follow up[58] (as many as could be followed up for 60 months).

2.1.2 Procedure

This retrospective analysis incorporated all phakic patients with treatment naïve DME who had been recruited for the primary two-year analysis[59] (the results of which have already been published). For the sake of completion, we have reiterated the procedure for recruitment for the primary analysis for ease of interpretation.

2.1.3 Primary Analysis

This was a prospective, case series on consecutive phakic patients with treatment naïve DME conducted between April 2012 and May 2016. The ethics committee approved the study and it adhered to the tenets of Helsinki. The approval number at the Sudhalkar Eye Hospital was 2022/02/01 for the long-term analysis. Since this was a retrospective study, the ethics committee approval was not a must as per Indian code for research. Informed consent was obtained from the patients at inclusion after complete discussion of the disease process, the alternatives to dexamethasone therapy and potential side effects and complications versus the suggested benefits of steroid therapy for DME. All patients were to receive the intravitreal DEX-I PRN. I, Alper Bilgic, was registered as a research fellow with the Sudhalkar Eye Hospital and Retina Center also the MS Sudhalkar Medical Research Foundation during the study period. The hospital and the medical research foundation are in the western Indian state of Gujarat. All the study patients were from India. I had complete access to all physical and electronic records and was responsible for data collection, analysis and giving final shape to the study protocol and its conduct.

2.1.4 Inclusion Criteria

Study patients were required to be >18 years old, be phakic and have 1) Treatment naïve CSME secondary to diabetes mellitus (central macular subfield thickness greater than 300 microns) with or without neurosensory detachment 2) Corrected distance visual acuity (CDVA) between 0.3 logMAR-1.0 logMAR (20/40-20/200) as noted on the Early Treatment for Diabetic Retinopathy Study (ETDRS) chart and 3) presentation within 6 months of onset of symptoms. One eye of each patient was

included in the study. If both eyes were eligible, one eye was randomly selected using a random number table.

2.1.5 Exclusion Criteria

Patients with ocular comorbidities that could affect or confound the study outcome, those with an incomplete follow up and patients who were known steroid responders or had a history of pars plana vitrectomy (ppV) were excluded. Patients with cataract of sufficient grade to preclude imaging and warrant surgery at presentation itself were also excluded. Also excluded were patients with uncontrolled diabetes mellitus (HbA1c >10%) or any uncontrolled systemic disease and any contraindication to steroid use.

2.1.6 Examination

All patients underwent a complete anterior and posterior segment evaluation clinically (including intraocular pressure – IOP documentation with the Goldmann Applanation Tonometer), received Fundus Fluorescein Angiography (FFA) (Zeiss, Jena, Germany) and SD-OCT (Opko Oti, USA, Florida) macular analysis including central subfield thickness measurements. Clinical examination, IOP measurements and OCT scans were repeated at each visit. FFA was repeated if macular ischemia was suspected and, in the event, that the treating ophthalmologist suspected proliferative disease or that the patient required focal laser therapy. Diabetes mellitus (and all systemic comorbidities) were managed in strict consult with a physician. Compliance with physician visits was monitored.

2.1.7 Procedure

Intravitreal DEX-I was carried out under asepsis using a standardized technique. When required, patients underwent phacoemulsification and intraocular lens (IOL) implantation using a standardized technique. A single surgeon performed all surgeries. Injections were performed on a PRN basis. Patients who required cataract surgery were injected with the DEX-I 2 weeks prior to the scheduled date of surgery, similar to the Reldex Study.[36]

2.1.8 Follow up Schedule

Patients were seen on days 1 and 7 postoperatively and weekly thereafter until complete resolution of edema (defined subsequently) on OCT and then followed monthly thereafter for 24 months. In the event that a second injection was necessary (retreatment: defined subsequently), the patients were followed up weekly post-injection until the edema resolved again and then again followed up monthly thereafter till the end of 24 months. Repeat intravitreal dexamethasone injections could be given every 3 months, if necessary, but not before 3 months. Standard 7-field Fundus Photography was performed at baseline and then postoperatively at months 1,6,12,18,24. Fundus photographs were evaluated for change in hard exudates using the algorithm described by Marupally et al.[60]

2.1.9 Rescue Therapy

Patients were eligible for rescue therapy with anti-VEGF agents or focal laser as per the ophthalmologist's discretion. If there was incomplete resolution of edema after the first injection at the end of 3 months, a second intravitreal dexamethasone injection was given. If there was incomplete resolution of macular edema one month

after the second injection, further treatment was possible with intravitreal ranibizumab/aflibercept or laser or a combination of anti-VEGF injection and laser and even surgery, where applicable. Patients with worsening DR could be managed in accordance with standard protocols, medically or surgically[13]. For example, patients who developed proliferative disease could receive pan-retinal photocoagulation and the follow-up regime was correspondingly individualized for each patient. Patients who demonstrated worsening of DME and/or DR were received therapy appropriate to the stage and severity of their disease and continued to be followed up as mandated till the end of the said follow-up period.

2.1.10 Definitions

Complete resolution of macular edema was defined as a reduction in CSMT to 250 microns or less with complete disappearance of intraretinal fluid/cysts and subretinal fluid, if any.

An incomplete response was defined as a CSMT>250 microns and/or persistence of intraretinal cysts or regions of retinal thickening fluid 3 months after the last dexamethasone implant injection. This made the patient eligible for retreatment either with a second implant injection or anti-VEGF/laser therapy.

Ocular hypertension was defined as absolute IOP>25mm Hg and/or a rise in 10mm Hg from baseline over the follow-up period. Cataract grading was done as per the lens opacity classification system III. (LOCS III)

All patients were managed on an intent-to-treat basis.

2.1.11 Outcome Measures

The primary outcome measure was the change in CDVA as assessed at 24 months. Secondary outcome measures included determining the proportion of patients who gained >15 letters from baseline to the final visit (month 24), change in CST at months 1,6,12, 18 and 24 and time to resolution of edema after the first injection, the median number of injections and complications if any (specifically the incidence of ocular hypertension, cataract formation, and cataract surgery and other complications).

2.1.12 Statistical Analysis

Descriptive statistics was used to analyze categorical variables in terms of size (absolute frequencies) and proportions (relative frequencies). The significance of the change in CDVA over time was determined using the repeated measures ANOVA test. The repeated measures ANOVA test was also used to determine change in CST, the hard exudate area, and IOP changes over time. Statistical significance was set at $p<0.05$.

2.2 Five-Year Analysis

The current study was conducted in a retrospective manner and chose to analyze all patients who have completed a 5-year follow-up after recruitment. The parameters for the assessment and the statistical analyses carried out remained unchanged from the primary study. We have chosen to report data semi-annually in the current data, not unlike (in part at least) the primary 2-year follow-up. The following parameters were noted and have been reported and we reiterate the same for ease of interpretation.

2.2.1 Inclusion Criteria

As already stated, all recruited study patients were required to be >18 years old, be phakic and to have 1) treatment naïve CSME (clinically significant macular edema) secondary to diabetes mellitus (central macular subfield thickness greater than 300 microns) with or without neurosensory detachment 2) CDVA between 0.3 logMAR-1.0 logMAR (20/40-20/200) as noted on the ETDRS chart and 3) presentation within 6 months of the onset of symptoms. One eye of each patient was included in the study. If both eyes were eligible, one eye was randomly selected using a random number table.

2.2.2 Exclusion Criteria

Patients with ocular comorbidities that could affect or confound the study outcome, those with an incomplete follow up and patients who were known steroid responders or had a history of PPV were excluded. Patients with a cataract of sufficient grade to preclude imaging and warrant surgery at the presentation itself were also excluded. Also excluded were patients with uncontrolled diabetes mellitus (HbA1c >10%) or any uncontrolled systemic disease and any contraindication to steroid use.

2.2.3 Examination

All patients underwent a complete anterior and posterior segment evaluation clinically (including IOP documentation with the Goldmann Applanation Tonometer) ,received FFA (Zeiss, Jena, Germany) and SD-OCT (Opko Oti, USA, Florida) macular analysis including central subfield thickness measurements. Clinical examination, IOP measurements, and OCT scans were repeated at each visit. FFA was repeated if macular ischemia was suspected and, in the event, that the treating

ophthalmologist suspected proliferative disease or that the patient required focal laser therapy. Diabetes mellitus (and all systemic comorbidities) were managed in strict consult with a physician. Compliance with physician visits was monitored.

2.2.4 Procedure

Intravitreal dexamethasone implant injection was carried out under asepsis using a standardized technique. When required, patients underwent phacoemulsification and intraocular lens (IOL) implantation using a standardized technique. A single surgeon performed all surgeries. Injections were performed on a PRN basis. Patients who required cataract surgery were injected with the DEX-I 2 weeks prior to the scheduled date of surgery, similar to the Reldex Study[36].

2.2.5 Follow-up Schedule

Patients were followed up every 3 months if they had not received an intravitreal DEX-I injection. If a patient required an additional implant, the schedule was the same as mentioned for the 2 years follow up study: days 1, 7, and 30 and then monthly for 6 months, at which point in time the follow-up schedule would be extended to 3 months provided there was no residual edema and no recurrence of edema. Repeat intravitreal dexamethasone injections could be given every 3 months if necessary, but not before 3 months. Standard 7-field Fundus Photography was performed at baseline and then postoperatively at months 1,6,12,18,24, 30, 36, 42, 48,54, 60. Fundus photographs were evaluated for change in hard exudates using the algorithm described by Marupally et al[59].

2.2.6 Rescue Therapy

Patients were eligible for rescue therapy with anti-VEGF agents or focal laser as per the ophthalmologist's discretion. If there was an incomplete resolution of edema after the first injection at the end of 3 months, a second intravitreal dexamethasone injection was given. If there was an incomplete resolution of macular edema one month after the second injection, further treatment was possible with intravitreal ranibizumab/aflibercept or laser or a combination of anti-VEGF injection and laser and even surgery, where applicable. Patients with worsening DR could be managed by standard protocols, medically or surgically[13]. For example, patients who developed proliferative disease could receive pan-retinal photocoagulation and the follow-up regime was correspondingly individualized for each patient. Patients who demonstrated worsening of DME and/or DR received therapy appropriate to the stage and severity of their disease and continued to be followed up as mandated till the end of the said follow-up period. This is similar to our protocol for 24 months and our primary publication[56].

2.2.7 Definitions

Complete resolution of macular edema was defined as a reduction in CSMT to 250 microns or less with complete disappearance of intraretinal fluid/cysts and subretinal fluid if any.

An incomplete response was defined as a CSMT>250 microns and/or persistence of intraretinal cysts or regions of retinal thickening fluid 3 months after the last DEX-I injection. This made the patient eligible for retreatment either with a second implant injection or anti-VEGF/laser therapy.

Ocular hypertension was defined as absolute IOP>25 mmHg and/or a rise in 10 mm Hg from baseline over the follow-up period. Cataract grading was done as per the LOCS III classification.

All patients were managed on an intent-to-treat basis.

2.2.8 Outcome Measures

The primary outcome measure was the change in CDVA as assessed at 60 months. Secondary outcome measures included determining the proportion of patients who gained >15 letters from baseline to the final visit (month 60), change in CST at months 30, 36, 42, 48, 54, 60 and time to resolution of edema after the first injection, the median number of injections and complications if any (specifically the incidence of ocular hypertension, cataract formation and cataract surgery and other complications).

2.2.9 Statistical Analysis

Descriptive statistics were used to analyze categorical variables in terms of size (absolute frequencies) and proportions (relative frequencies). The significance of the change in CDVA over time was determined using the repeated measures ANOVA test. The repeated measures ANOVA test was also used to determine change in CST, the hard exudate area and IOP changes over time with Bonferroni adjustments for post-hoc analysis, wherever applicable. The Fisher's exact test was used for pairwise comparisons with the Benjamini Hochberg adjustments, wherever applicable. Statistical significance was set at $p<0.05$.

Data collection was in accordance with rules set out for the retrieval of information for retrospective studies. The data collected included and was qualified by the aforementioned modifications.

3. Results

A total of 153 patients were found to be eligible for the primary study. These 153 patients constituted 15.78% of a total of 972 patients with DME at our institute in the said period from 2012-2016. Data were retrieved for all patients to determine patients who managed to complete the five year-follow with at least 3 visits per year over 5 years. A total of 122 patients were noted to have been available for analyses in terms of five-year follow ups and these form the basis for our study.

Upon analysis, the following grounds for attrition were noted in decreasing order of frequency: relocation (14), non-compliance (12), second opinion (3), and death (2).

The overall patient profile is mentioned in table 1. The distribution of type and grade of cataract (per LOCS III classification) is mentioned in table 1. The median duration from onset of symptoms to presentation was 52.4 days (SD 5.14 days; range 4-48 days). The median duration of diabetes mellitus was 18.42 years (SD-5.24 years; range 9-29 years). Fifty-nine patients had associated arterial hypertension (well-controlled) while 43 patients had associated dyslipidemia. Table 1 also lists the associated disease profile of the patients. The mean HbA1c at baseline was 7.8± 0.26. The mean HbA1c level at the final follow-up was 6.6± 0.37. The change in HbA1c was significant (p=0.017). The mean weight of patients at baseline was 66.1and 4kg±7.56 kg. The mean weight at final follow-up (2 years) was 63.35±8.22 kg. The weight change was insignificant (p=0.27). Figures 6 and 7 describe an illustrative case.

Table 1: Preoperative Demographics and Distribution of Systemic Comorbidities in the Study Population(Year 2-Year 5)

Age (Median±SD) years(range)	61.39±3.39(43-67 years)
Male: Female Ratio	75:47
Distribution of Cataract Grade and Type (LOCS III)	**number of eyes (n)**
Clear Lens	37
Nuclear Sclerosis Grade I	29
Posterior Subcapsular + Nuclear Sclerosis Grade II	17
Nuclear Sclerosis Grade II	19
Cortical Cataract + Nuclear Sclerosis + Posterior Subcapsular	14
Cortical Cataract + Nuclear Sclerosis	7
Associated Comorbidities, number(n)*	
Hypertension	59
Dyslipidemia	43
Osteoarthritis	11
Congestive Cardiac Failure	08
Hypertension+ Dyslipidemia	25

* All patients had type II diabetes mellitus

3.1 Visual acuity

The change in CDVA was significant as is seen in Table 2a (p=0.012). The improvement was sustained over the 24 months. The median CDVA improved from 0.62±0.10 at baseline to 0.45±0.26 logMAR at 60 months as is seen in Table 2b (p=0,016).72/122(59.01%) patients demonstrated a 15 letter gain at month 60. The number of patients with CDVA of >=20/40 at each study visit has been documented in Figure 9. As seen, 51/122 (41.08%) of the patients demonstrated visual gain

>=20/40 at the end of the five-year follow up. The mean change in CDVA from baseline at each study visit is documented in figure 6. As evident, the maximal gain in vision occurred in the first few weeks of therapy and then stabilized over the five years of follow-up. The median time to 15-letter improvement in BCVA from baseline was noted to be 25.4 days(SD-3.25; range 15-60 days). Overall, improvement was sustained in the overwhelming majority of patients.

3.2 Central Subfield Macular Thickness

Tables 2a and 2b also depict the reduction in CST over time. The CST improved significantly at one month and the improvement was maintained over the follow-up period of 60 months (p=0.013). OCT analysis and fundus photography also documented a reduction in hard exudates post-therapy and systemic control. The mean time to complete the resolution of macular edema was 15.42 days (SD-3.5 days range 7-28 days). All patients demonstrated complete resolution of macular edema within the first post-injection month.

3.3 Injections

The average number of injections over 5 years was 3.1(SD 1.2; range 3-8). The injection procedure per se was uneventful in all patients. The median treatment-free interval was 11.14 months (SD-4.15 months; range 3-25 months). Seven patients required rescue therapy at some point of time till the end of the follow up period. 89/122 patients had experienced subconjunctival hemorrhage at the time of injection at least once. 52 patients experienced subconjunctival hemorrhage 2 or more times over 5 years.

3.4 Cataract

Twenty-nine patients (18.95%) required cataract surgery during the course of follow-up in the first two years. An additional thirty-seven (24.18%) patients underwent cataract surgery from year 3 to year 5 (in the entire 5-year follow up 43.13%). The median time to cataract surgery was 16.24 months (SD-3.5 months; range 8-20 months) after recruitment in the first two years. For the continued follow up, patients were operated a median of 34.4 months (SD4.5 months, range 8-45 months) after recruitment. Of these 29 patients in the first two years, 3 patients with a clear lens at baseline developed cataracts (posterior subcapsular) during the course of follow-up at a median of 14.2 months after initiation of therapy. All three had received at least 2 injections, with one receiving 3 in the said to follow up period. Two patients received a second injection after 6 months; one patient required a second injection 3 months after the first and then a third injection 6 months after the second. Seven patients of these 29 required a second injection a median of 4.4 weeks after cataract surgery for recurrent macular edema. At the end of 2 years, 23/153 patients had a clear lens. The median number of injections in these 23 patients was 1.2, close to the overall median of 1.6. Of these 23, 20 completed the five years follow-up period. 8/20 out of these patients developed a new cataract during year 3 to 5. The median number of injections from years 3 to 5 in these patients was 1.8. The remaining 102 patients had some degree of pre-existing cataract. Subset analysis revealed that the CDVA gain at the end of follow-up was no different from those who did not receive cataract surgery during the follow-up period (p=0.23).

3.5 Ocular Hypertension

The IOP at different points in time is depicted in table 2. 24/122 patients (20.26%) were documented to have developed Ocular hypertension at some point in time during the 5-year follow-up period. The median time to onset of ocular hypertension was 48.24 days (SD-12.14 days; range 15-90 days). From year 3 to year 5, the median time to onset of ocular hypertension in hitherto normotensive patients was 34.56 days with a mean of 7 days. 20/31 patients were managed well with monotherapy in the first two years. From year 3 to year 5, 24/122 patients were managed with monotherapy. 8/31 patients required 2 anti-glaucoma medications for IOP control in the first two years of follow-up while 3 patients required 3 medications. From year 3 to year 5, those numbers were 7 and 3 respectively. None of the patients required trabeculectomy. A total of 37 patients had an IOP>20 mm Hg at some point in time during the follow-up period. It is important to note that during the entire 5-year follow-up period, the median duration of IOP rise was 2.45 months (SD-1.2 months, range 1.5-7 months). Not one patient demonstrated persistent IOP rise beyond 8 months.

3.6 Hard Exudates

The mean area of hard exudates was determined to be 2.37 mm (SD 1,32 mm; range 0.89 mm-2.33 mm) at baseline. The change in area over time is portrayed in table 2. Only 7 patients demonstrated an insignificant change in hard exudates over the follow-up period.

Table 2a: Change in median CDVA, CST, hard exudates, and IOP over 2 years.

Parameter	Baseline	1 month	6 months	12 months	18 months	24 months
CDVA*(logMAR)	0.62±0.10	0.34±0.08	0.36±0.12	0.35±0.09	0.38±0.11	0.40±0.08
CST(microns)*	397±47.24	212.12±28.20	228.5±34.62	210.14±29.32	224.45±28.14	236.33±19.43
IOP(mm Hg)*	13.42±4.20	16.24±3.24	17.13±2.86	14.12±4.12	12.16±4.22	15.12±4.57
Hard Exudates*	2.37±1.32	2.12±1.16	1.82±0.970	0.87±0.14	0.72±0.34	0.69±0.13

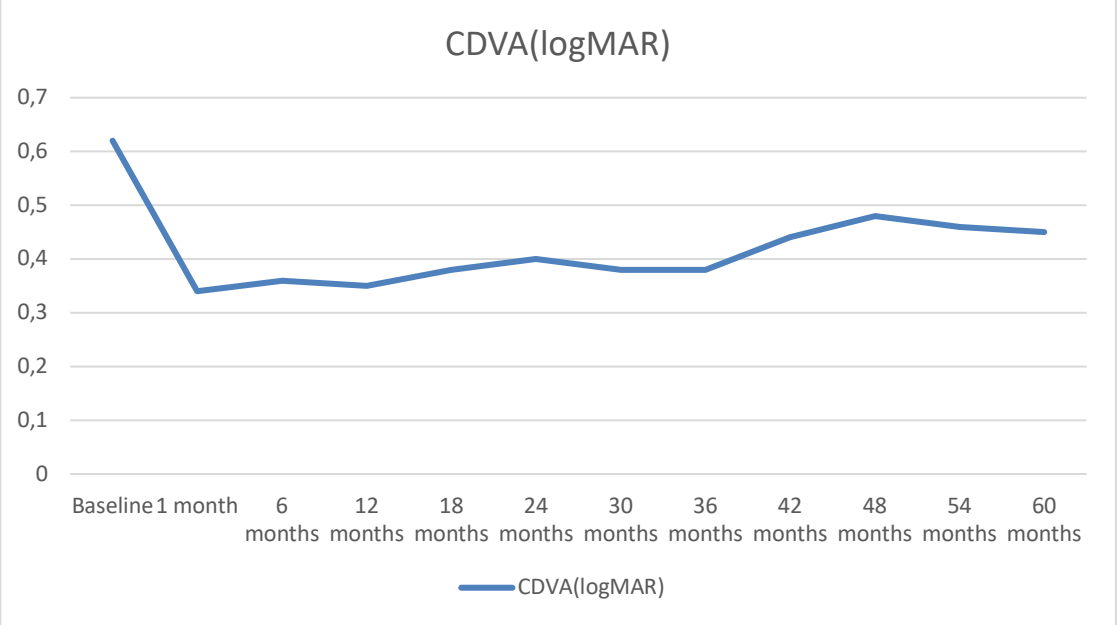
*All four parameters were assessed monthly but the change at certain definite time points has been mentioned here for the sake of uniformity. IOP in particular was carefully assessed at months 2 and 3 post injection to ensure the detection of the development of ocular hypertension.

Table 2b: Change in median Corrected Distance Visual Acuity(CDVA), Central Subfield Thickness(CST) and Intraocular Pressure(IOP) and hard exudates over time (year 2-year 5)

Parameter	Baseline	30 months	36 months	42 months	48 months	54 months	60 months
CDVA*(logMAR)	0.62±0.10	0.38±0.12	0.38±0.14	0.44±0.21	0.48±0.20	0.46±0.22	0.45±0.26
CST*(microns)	397±47.24	272.42±28.20	288.5±44.62	240.14±26.52	272.45±27.24	267±28.44	264.33±29.43
IOP*(mm Hg)	13.42±4.20	14.44±3.44	16.23±2.44	15.22±4.22	13.26±5.12	13.7±4.2	16.22±4.50
Hard Exudates*	2.37±1.32	0.72±0.45	0.74±0.17	0.63±0.48	0.54±0.50	0.53±0.44	0.48±0.30

Figure 6 shows the CDVA change over 5 years.

Figure 6



3.7 Illustrative Case

Figure 7

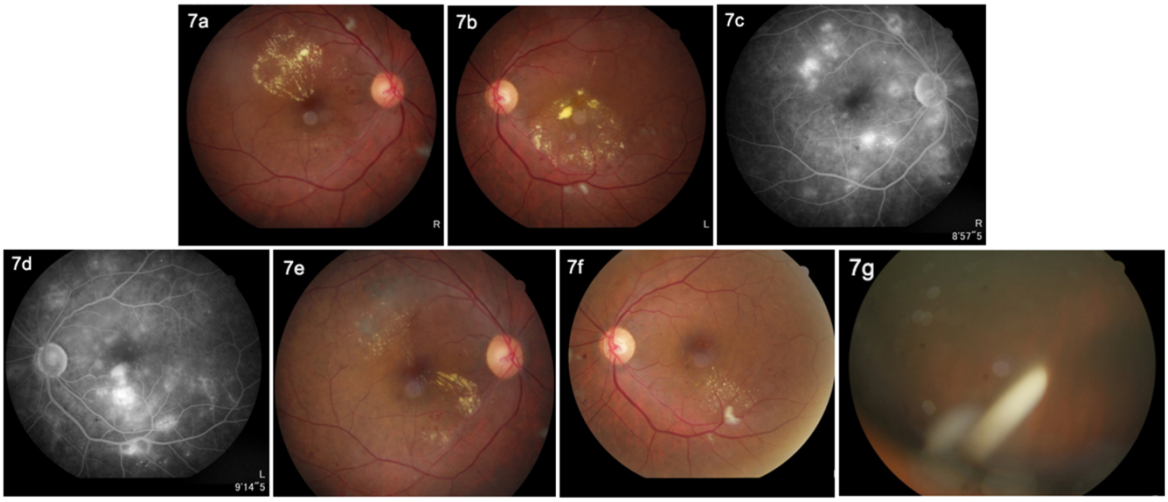


Figure 7a and 7b show the fundus photograph of the right eye and left eye respectively of a 58-year-old lady with type II DME since 11 years at baseline. There is obvious DME with retinal thickening, hard exudate clumps and scattered dot and blot hemorrhages.

The diagnosis of DME is confirmed on FFA (Figure 7c and 7d). There is evident multipoint leakage. The patient received focal laser photocoagulation (7e) in the right eye and intravitreal dexamethasone implant (DEX-I) injection in the left eye (7f). The implant can be seen in Figure 7g.

Figure 8

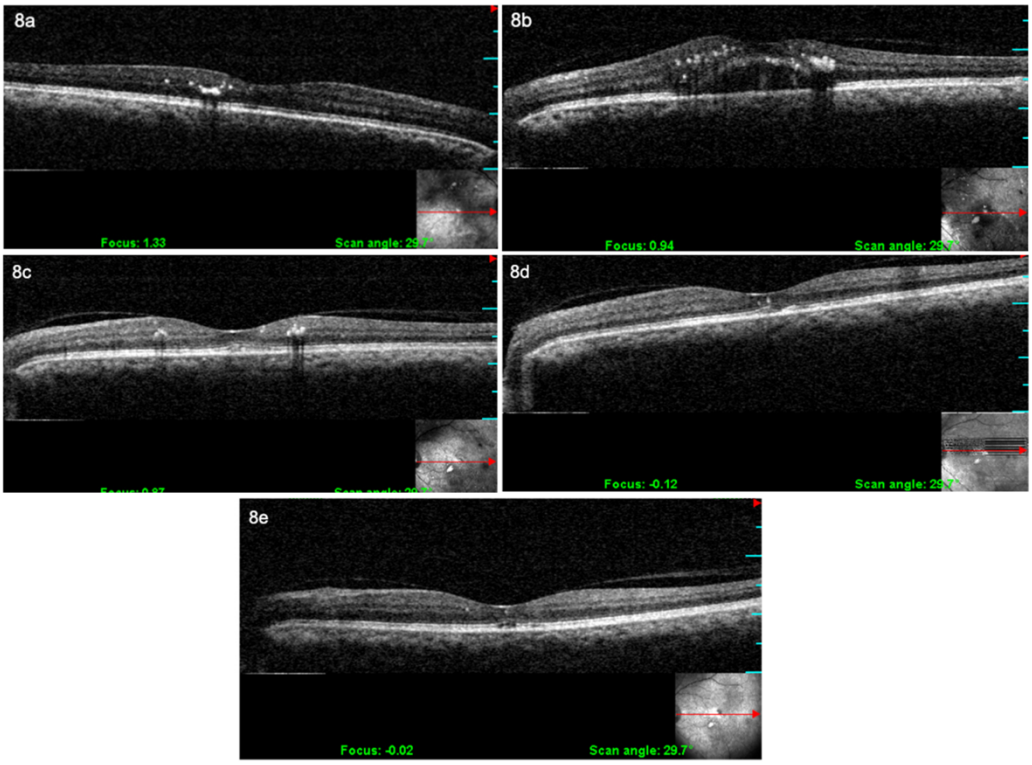
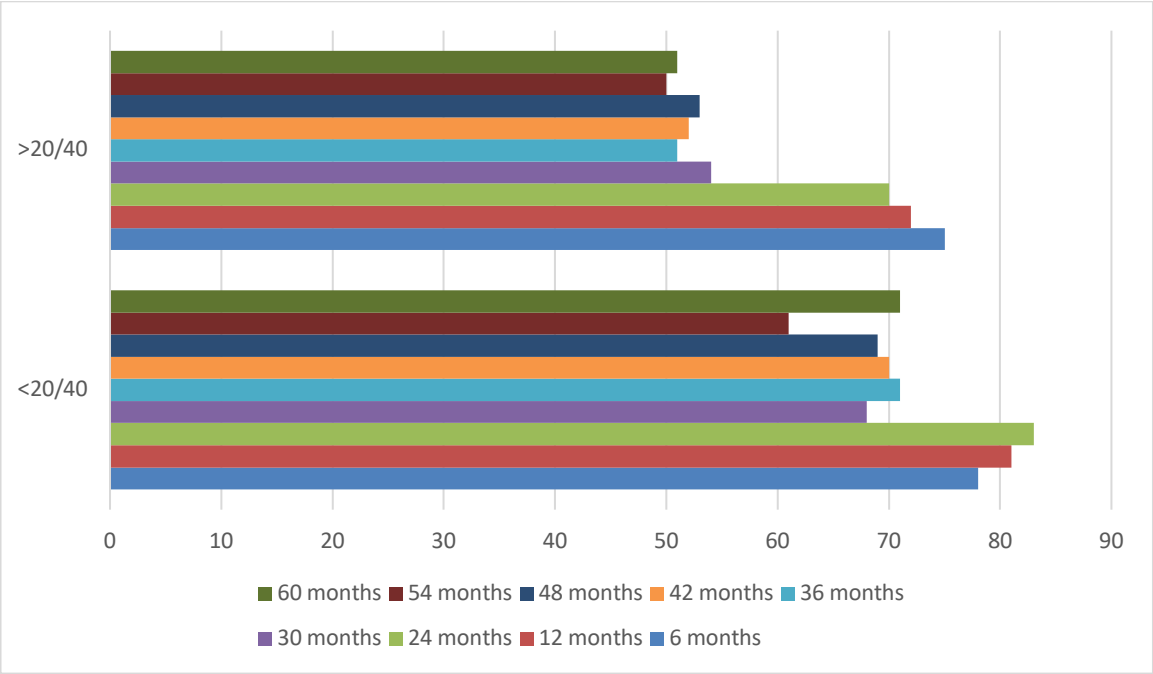


Figure 8a shows evident exudates in the right eye near the foveal center but no DME, 8b demonstrates evident exudation, hyperreflective dots and subretinal fluid in the left eye confirming the severity and diagnosis of DME, Figure 8c shows the OCT scan of the left eye of the same patient one month after the intravitreal DEX-I injection. There is complete resolution of DME, however some intraretinal exudates are still seen. 8d shows continued absence of DME and exudates at one year in the left eye. Figure 8e demonstrates continued absence of DME in the left eye at 5 years. This patient has received only one injection over 5 years in the left eye.

Figure 9 is a graph that demonstrates the number of patients with a CDVA of 20/40 or better at every semi-annual follow up.

Figure 9



3.8 Other complications and events

Four patients had developed proliferative disease during the course of the primary study. They received appropriate panretinal photocoagulation and the proliferation subsided. They developed no further complications till the end of the follow-up period. These four patients did not have significantly worse outcomes in terms of visual gain at month 24 as compared to the rest of the study population; 0.40±0.12 logMAR in the rest of the patients versus 0.43± 0.16 logMAR in the subset of 6 patients; p=0.27. An additional 2 patients developed proliferative disease over the next 3 years. They were managed by panretinal photocoagulation. 7/122 patients required a switch of therapy. All seven patients were initiated on intravitreal ranibizumab therapy. The need for switch happened a median of 33.24 months (SD-

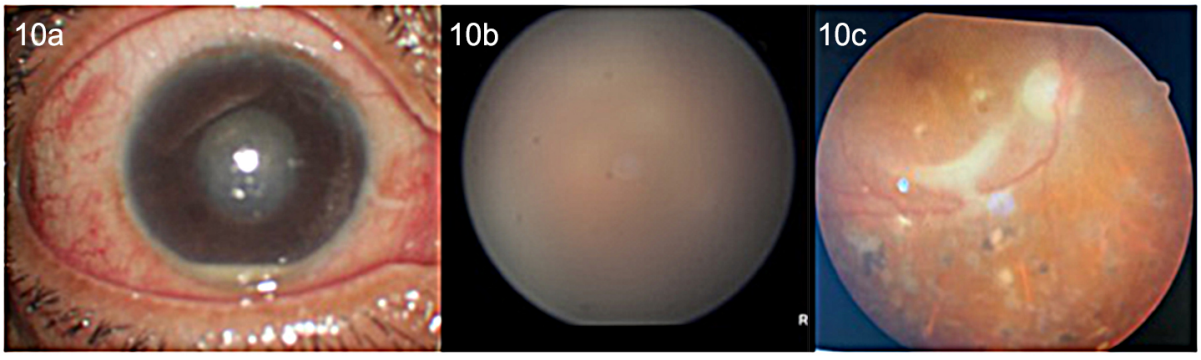
2.2 months; range 30-45 months) after enrollment in the study. The median number of intravitreal ranibizumab injections required after switch was 6.25 injections (SD-2.2; range 3-11). No complications were noted during the said period. None of these patients required further change in therapy until the end of the follow up period.

A 59-year-old lady developed post-injection endophthalmitis after the 4th intravitreal dexamethasone implant injection and 34 months after recruitment for the primary study. The patient received pars plana vitrectomy and empirical intraocular vancomycin and ceftazidime along with a vitreous biopsy. Silicone oil was injected at the end of a complete vitrectomy The aspirate showed presence of Methicillin Resistant Staphylococcus Aureus (MRSA) sensitive to Vancomycin. A further 2 intravitreal injections were administered 72 hours apart. The infection cleared completely and the BCVA eventually improved to 6/9(in decimal: 0.9). The silicone oil was removed 6 months after the primary vitrectomy.

Figure 10demonstrates the initial presentation:

Figure 10a demonstrates evident hypopyon and retrolenticular exudates. The patient was pseudophakic. Figure 10b demonstrates evident exudation in the fundus image. Figure 10c demonstrates the complete resolution of infection with silicone oil in situ. There are laser photocoagulation scars seen.

Figure 10



The patient recovered well as this photograph was taken 2 weeks after the primary vitrectomy.

Apart from this patient, none of the patients had any vision-threatening complications/sequelae until the end of the follow-up period.

4. Discussion

This study demonstrates excellent outcomes without significant risks with the use of the intravitreal dexamethasone implant as primary therapy in phakic patients with early treatment naïve DME. All patients showed at least a ten letter gain with nearly 60% of patients showing a gain of 15 letters or more at the end of the five-year follow up. 75/153 (45.5%) of the patients demonstrated a CDVA of 20/40 or better at the end of the two-year follow-up. This percentage dropped marginally to 41.8% at the end of 5 years. The maximal gain in vision was seen after the first injection; further injections served more to stabilize vision. All patients who required cataract surgery demonstrated visual gain after cataract surgery. The area of hard exudates demonstrated significant reduction over the two-year follow-up period. Fewer than 2 injections were required on an average in the said follow-up period. Only 3 patients with a clear lens developed cataracts and required cataract surgery till the end of the2-year follow-up period, although that number increased during the five year follow-up. Not a single patient required rescue therapy and none of the patients had any permanent vision threatening consequences over 2 years but eventually 7 patients were switched to anti-VEGF therapy in the following 3 years. Seven eyes showed progression of diabetic retinopathy with four eyes requiring laser therapy for proliferative disease over the 2 years follow-up period, and that number went up as expected over the 5 years follow up period. Compliance was high and ensured by

the necessity of strict compliance with guidelines set by insurance companies (nationalized companies in India) protocol about follow-ups and reinjections, as well as the probable danger of withdrawal of treatment reimbursement in the event of non-compliance by the patient. Compliance was also ensured by strict implementation of the outreach program by a dedicated team.

The use of the dexamethasone implant in DME has been validated through several studies[1-3,14-26]. The general trend as noted in literature as well as real life scenarios is to use it as a second line drug for DME (in chronic or treatment resistant cases that no longer respond to anti-VEGF agents and/or focal laser therapy). Reluctance to use it as primary therapy (vis-à-vis anti-VEGF agents) is essentially a fallout of potential complications of dexamethasone use, such as cataract or ocular hypertension. Indeed, the FDA currently lists DME in patients scheduled for cataract surgery as an indication for primary therapy with the dexamethasone implant in phakic patients[7]. Anti-VEGFs are generally considered safe drugs with no major adverse events reported when used with a little care. The flipside of anti-VEGF use is multiple injections, with the added treatment and cost burden that would logically follow (unless bevacizumab was being used exclusively). It is noteworthy that most universal insurance schemes (of which all patients included in the study were clients) do not permit the use of bevacizumab, including bevacizumab from a compounding pharmacy as first line therapy for DME. The probable reason for that is that the manufacturing agency does not have intravitreal use on its label. In a court of law, that would render this drug off-label. Consequently, the use of this drug would become a criminal act especially if it leads to complications. Secondly, even if the courts do permit the use of off-label drugs (for example, the use of silicone-oil in retinal detachment surgery is still off-label), it has to be single-use and cannot be

through a multi-dosing vial. In other words, one vial of bevacizumab will strictly be valid, at least in the eyes of the law, for one patient only. Multiple patients cannot be injected through one vial.

This study refrains from a direct comparison of efficacy and safety to anti-VEGF agents as there was no comparative arm in our study. However, it is easy to note that far fewer injections were required for treatment of early naïve DME as compared to patients who were treated by anti-VEGF agents, per past studies[11,14,16]. Also, historical comparisons (to past literature[11]) reveals that our study noted fewer injections for early treatment naïve DME when compared to anti-VEGF agents. The latest head-to-head multicentric study demonstrated non-inferiority of the dexamethasone implant to ranibizumab with fewer injections required over a 12 months period[10]. Anatomic outcomes are generally considered to be better with the dexamethasone implant as compared to anti-VEGF agents[9,14]. However, there is only modest correlation between anatomic outcomes and visual acuity gain[17]. That said, reduction in macular edema would probably reduce long term damage to retinal structure and function. It is important to note that diabetic macular edema is a chronic disease and correspondingly, therapy has to be sustained and in the long-term.

I refrain from a detailed cost analysis as well, considering that this was not part of the study. However, it seems logical to note that fewer injections would translate into lower costs and eventually fewer visits in the real world (unless bevacizumab was being used exclusively). Also, we mandated additional follow-ups for documentation of resolution of edema as part of the study, a requirement that has little practical importance; generally speaking, use of the dexamethasone implant would normally reduce follow up except the mandatory 2 months follow-up for IOP monitoring).

Thus, the higher number of follow-up visits is a fallout of the study and not required in daily practice. Finally, we document that there is no cumulative risk of IOP spikes in patients[5]. Thus, patients who do not demonstrate an IOP spike after the first injection may be spared additional IOP monitoring visits. Additionally, fewer injections would also mean a lower risk of endophthalmitis as it reduces the number of intraocular procedures that an eye has to undergo.

Similar studies on phakic patients (as a subgroup) have revealed the following:

The IRGREL-DEX Study[18] in 2018 looked at the use of the implant in naïve and refractory eyes over 24 months. 22/38 phakic eyes (57.9%) underwent cataract surgery(15 in the naïve group and 7 in the refractory group). This rate was similar to the MEAD trial of 59% over a 3 year period. Five eyes in the naïve group and 13 eyes in the refractory group required therapy for high IOP (14% in all), with none requiring surgery. This rate was lower than the MEAD trial of 41.5% but the average number of implants was higher than the MEAD trial (5 vs 3.5). Panozzo G[19] et al in 2015 followed 20 phakic eyes (12 naïve and 8 with persistent edema previously treated) to define 'recurrence' of DME in a PRN regimen. They also looked at key safety variables including ocular hypertension and lens opacities. They had no increase in lens opacities at last follow up in all eyes, and they had transient increase in IOP between 2-4 months. The median recurrence of DME occurred at 5 months. This study showed the safety and utility of the use of DEX-I in phakic eyes.
The BEVORDEX study[14] compared intravitreal Avastin (IVA) with the DEX-I for DME. Both groups received PRN therapy. The primary outcome was a 10 letter or more visual gain. However, secondary outcomes included adverse events. There were 42 eyes in the IVA group and 46 eyes in the DEX group. Subgroup analysis showed progression of cataract in 13% of the patients in the DEX group and 4.8% in IVA

group. One patient in the IVA group and 3 patients in the DEX group required cataract surgery. IOP spikes were higher in the DEX group compared to the IVA group (46% of DEX vs 19% of IVA had an increase of 5 mmHg or more from baseline), but all were managed successfully either simply with observation or with topical therapy. Escobar-Barranco JJ[20] et al in 2015 compared the response to treatment of refractory and naïve DME with the use of DEX implants. They included phakic patients as a sub-group. They showed that visual improvement and CMT reduction was better in the naïve group. 5/36 naïve and 16/40 in refractory group were pseudophakic at baseline. At final follow up only 2 eyes in the refractory group and none in the naïve group developed cataract.

Real life analyses[18,19,22-26] of the use of the dexamethasone implant in DME have revealed comparative results insofar as naïve eyes are concerned and even previously treated eyes did better with the implant compared to sham therapy[1]. In general, treatment naïve eyes show superior visual gain with fewer injections[18]. The actual visual gain varies based probably on the duration of DME and associated ocular comorbidities and perfusion status of the retina. However, in most studies, treatment naïve eyes are generally a part of an overall population with DME that includes pseudophakic and previously treated eyes. Our study results seem superlative at first sight; this has obviously a lot to do with the fact that we only included patients with early treatment naïve DME who were well controlled and had minimal systemic derangement. There was little or no structural damage at baseline as all included patients had onset of symptoms within 3 months of presentation. Retrospective studies[25, 26] on the Indian populace have reported a similar number of injections; these are obviously not directly comparable to our study given that the current study was prospective. However, a median of 1 to 1.2 injections is generally

reported in Indian studies. Whether this has anything to do with Indian ethnicity or simply with a lack of compliance needs further analysis.

The AUSSIEDEX[32] study reported a mean of 2.5 injections over a 52 week follow up in 200 eyes with treatment naïve patients numbering 57. It was a prospective study but only about 25% of patients were treatment naïve, implying that refractory/recalcitrant DME was an important factor in the study, thereby indirectly implying the need for more injections. Overall, 20% patients needed some measure of IOP control, and one patient was discontinued because of high IOP. None of the patients required incisional glaucoma surgery.

A meta-analysis[61] published recently demonstrates that over 6 months, there is no significant difference between phakic and pseudophakic eyes and that naïve patients tend to always do better than previously treated eyes. Likewise, early switch patients tend to do better as well.

Hard exudate quantification[27,59] and monitoring is an important aspect of management of diabetic macular edema, as sub-foveal hard exudate sedimentation can compromise visual recovery. Semi-automated quantification has been proposed recently and has been shown to be reliable and accurate[12]. The authors discuss why semi-automated quantification is probably better than Image J processing. A recent publication proposes OCT based estimation of hard exudates[28]. All patients demonstrated significant reduction in hard exudates over the said follow up period. This was probably a combined effect of therapy for macular edema and systemic control.

Twenty-nine patients underwent cataract surgery over the two year follow up period. Overall, 66 patients received cataract surgery. Twenty-six of these had pre-existing

cataract. Three patients with a clear lens developed cataract in the present follow up period and all three had received at least 2 injections, with one receiving 3. All patients had received at least 2 injections within the year. Our rate of cataract formation is far lower than what has been noted thus far[1,3]; we attribute this to the lower injection rate and possibly shorter follow up, at least at the beginning of the study. But our rates of cataract surgery increase over the five year follow up period. This is not unexpected, and we attribute this to age, diabetic status as well as the use of the dexamethasone implant. Also of note is the fact that most trials conducted thus far have not generally included treatment naïve patients; indeed, in many instances a subset of patients included in these trials had been treated earlier with steroids. Also, for example in the MEAD study, the duration of DME prior to inclusion was far greater, indicating systemic derangements which themselves may have influenced cataract formation.

Overall, a few patients developed proliferative disease during the course of follow-up; they received timely pan-retinal photocoagulation in accordance with established protocols for treatment of pan-retinal photocoagulation[13,31] and in accordance with IRB approval for patients who worsen during the course of the study. Rescue therapy was not necessitated by this development; their future course was uneventful. The visual gain noted in these patients did not differ significantly from the rest of the study population.

The incidence of ocular hypertension is comparable to past literature[5,6]. Not a single patient required trabeculectomy and the IOP returned to baseline by month 6 in all patients. The incidence of filtration surgery for patients receiving the dexamethasone implant is quite low; i have noted it to be 0.2%[35]and the only patient who did receive filtration surgery in this study on dexamethasone implant position and IOP

fluctuations.[35] was one with chronic uveitis. My present analysis here was obviously not powered to detect this and i did not have a single case of uncontrolled IOP. However, the other obvious implication of this fact is that the risk of uncontrolled IOP rise (despite maximal topical therapy) is minimal and that DME or phakic status *per se* are not independent risk factors for the development of ocular hypertension[5,6]. Also, the solitary patient in our analysis of over 432 eyes[5] who required filtering surgery for control of ocular hypertension had chronic uveitis.

One patient developed post injection endophthalmitis and was attended to timely with pars plana vitrectomy, intraocular antibiotics, silicone oil injection and appropriate culture analysis. The visual recovery was good and the patient eventually underwent oil removal.

The study was limited by the lack of masking and of a comparative arm. All patients presented early; they would have probably required fewer injections had anti-VEGF agents been used exclusively too. Notwithstanding, there are several points of interest in this study. The primary aim of this study was a stand-alone analysis of the utility and safety of the DEX-I as primary therapy in phakic eyes with early treatment naïve DME and not a head-to-head trial with anti-VEGF therapy. This study is, to the best of our knowledge, the first and one of the largest that deals exclusively with phakic patients with early (< 3 months onset) treatment naïve DME treated PRN with the dexamethasone implant as primary therapy. The study shows excellent visual outcomes that were sustained over the follow period. We document time to complete resolution of edema from the time of injection in these patients. The study demonstrates that fewer than 2 injections are required in the said population over two years with a very acceptable safety profile. One can perhaps recommend that patients with a clear lens receive not more than one implant injection per year.

Patients with clear lenses who received one injection per year or less did not develop cataract. This study does not attempt to suggest a replacement of anti-VEGF therapy as primary therapy for DME; it simply strives to analyze the possible use of the implant as primary therapy and whether it can be done with reasonable safety and efficacy. We also discuss below case scenarios of phakic patients wherein the implant might be more useful as primary therapy. The mandatory follow ups as advised by insurance companies with universal health care policies and our outreach program ensured strict compliance with follow-up; we also treated relatively healthy patients with relatively acute symptoms, meaning frequent hospital visits due to other diabetes complications or loss of follow up due to death was not a major problem unlike other studies

Our studies reiterates and buttresses recent recommendations by experts in the European region. In a recently conducted consensus board by Kodjikian et al[62].The panelists recommended the preferential use of DEX-I for patients with limited availability for multiple injections, those who needed to undergo cataract surgery or who had a recent cardiovascular history, and as a therapeutic alternative to anti-VEGF in patients with a history of vitrectomy, retinal serous detachment, hyper-reflective points, or dry exudates in OCT. Not all suggestions put forth to the advisory board were validated but as is evident from the write up above, most of the recommendations are logical. The same holds true for recommendations for the fluocinolone implant[63]; while safety is of paramount importance, the efficacy of the implant and comfort of the patient cannot be sidelined. Indeed, with newer classifications coming in, it is important that these classifications be used to appropriately guide therapy, therapeutic choice and prognostication. One such clasification[64] is highlighted here for the sake of completion:

In a recently based consensus meeting for the tomographic classification of DME, seven tomographic qualitative and quantitative features are taken into account and scored according to a grading protocol termed TCED-HFV, which includes foveal thickness (T), corresponding to either central subfoveal thickness or macular volume, intraretinal cysts (C), the ellipsoid zone (EZ) and/or external limiting membrane (ELM) status (E), presence of disorganization of the inner retinal layers (D), number of hyperreflective foci (H), subfoveal fluid (F), and vitreoretinal relationship (V). Four different stages of the disease, that is, early diabetic maculopathy, advanced diabetic maculopathy, severe diabetic maculopathy, and atrophic maculopathy, are based on the first four variables, namely the T, C, E, and D. The different stages reflect progressive severity of the disease. A novel grading system of diabetic maculopathy is hereby proposed. The classification is aimed at providing a simple, direct, objective tool to classify diabetic maculopathy (irrespective to the treatment status) even for non-retinal experts and can be used for therapeutic and prognostic purposes, as well as for correct evaluation and reproducibility of clinical investigations.

Whereas anti-VEGF agents continue to be the first choice in DME patients with clear crystalline lens (in most young patients with DME), the dexamethasone implant can be a useful alternative in older phakic patients with logistic issues who cannot come for follow up on a regular basis (be it multiple appointments, long distance travel or other factors). It also appears useful in phakic DME patients with pre-existing cataract in the perioperative period in whom cataract surgery is being contemplated in the near future as it can cover the perioperative period, aid resolution of postoperative inflammation and possibly reduce the incidence of postoperative CME or CSME. Reliable compounding pharmacies are not a frequent occurrence in most

developing countries while bevacizumab as first line therapy for DME is not approved in several European countries[28] and in nationalized insurance schemes in South Asia which follow the universal health care model. These patients (especially in India and the South Asian region) tend to benefit from the curtailing of the number of injections as it tends to reduce treatment costs and the use of bevacizumab is discouraged because complications arising from its use amounts to negligence[30]. Finally, it is a useful alternative in phakic patients with a history of cardiovascular or cerebrovascular accidents in whom one may hesitate to have multiple anti-VEGF injections. The same is true for pregnant patients in whom intravitreal anti-VEGF injections may be contraindicated in most instances. All of the aforementioned conditions hold water in terms of approval in European lands with universal condition as far as primary therapy with the DEX-I is concerned. Patients with clear lenses can be given the option of a switch to anti-VEGF and/or laser therapy in the event that they experience a recurrence within a year of the first injection. This can probably reduce the treatment burden not only on patients but also for doctors, society and payors to some extent insofar as DME is concerned. Finally, the higher rate of endophthalmitis with steroid use is offset by fewer injections[31].

To conclude, the dexamethasone implant appears useful for early treatment naïve DME in phakic patients and can improve vision significantly and sustainably, over 5 years with less than 2 injections on an average per year with an acceptable rate of side-effects, none of which threatened sight permanently till the end of the follow up period. The only exception was the patient who developed post injection endophthalmitis which was a consequence of probable sterility violation and had little to do with the implant itself. Overall, the implant is safe and efficacious and plays a definite role in reducing the treatment burden insofar as DME is concerned.

5. Summary

Introduction: This retrospective study looks at the long term follow-up of treatment naïve phakic patients with diabetic macular edema who received the intravitreal dexamethasone implant as primary therapy. The current study is a continuation of a prospective study that published the two-year follow up of the same set of patients.

Methods: The current analysis managed to obtain data from 122/153 patients who were a part of the original study comprising adult patients with type II diabetes mellitus after accounting for attrition, exclusion or death. Patients were to receive the intravitreal dexamethasone implant as primary Therapy.

Results: The study results show that the results obtained at year 2 were maintained through to year 5 in the vast majority of patients, with only a few patients requiring switch therapy and/or laser photocoagulation. Additional patients required cataract surgery and all surgeries were performed uneventfully. One patient developed postoperative endophthalmitis after the injection procedure. The incriminated organism was Methicillin Resistant Staphylococcus Aureus and the patient's eye recovered completely after pars plana vitrectomy, intraocular antibiotics and silicone oil injection. Nearly a fifth of the patients demonstrated ocular hypertension, with all patients being managed with topical IOP lowering therapy alone. None of the patients required systemic IOP lowering medication or incisional surgery for uncontrolled ocular hypertension. All patients who demonstrated ocular hypertension showed normalization of intraocular pressure by the end of the follow up period. The mean number of injections in 5 year follow-up was 3,1 comparable to the two-year follow up results.(1,6 Injections)

Conclusions: Notwithstanding the lack of a comparative arm, the study thus reaffirms the safety and efficacy of the intravitreal dexamethasone implant as primary therapy for management of treatment naïve DME in phakic patients with diabetes mellitus.

5. Zusammenfassung

Einführung: Die intravitreale Steroidtherapie bei phaken Patienten wird aufgrund der Befürchtung, dass dadurch eine Linsentrübung induziert werden könnte, bislang nur in Ausnahmefällen durchgeführt. Diese retrospektive Studie befasst sich mit langfristigen Verlaufskontrollen behandlungsnaiver phaker Patienten mit diabetischem Makulaödem, die ein intravitreales Dexamethason-Implantat als Primärtherapie erhielten. Die aktuelle Studie ist eine Fortsetzung einer prospektiven Studie, die das zweijährige Follow-Up derselben Patientengruppe veröffentlichte.
Methoden: Im Rahmen der aktuellen Analyse, konnten bei 122 der ursprünglich 153 Patienten der 2-Jahresstudie die 5-Jahres-Daten erhoben werden,
Ergebnisse: Die Studienergebnisse zeigten, dass die im Jahr 2 erzielten Ergebnisse bei der überwiegenden Mehrheit der Patienten bis zum Jahr 5 beibehalten wurden, wobei nur wenige Patienten auf eine Therapie mit anti-VEGF Injektionen umgesetzt werden und bzw. oder eine Laserphotokoagulation erhalten mussten. Weniger als 10% der Patienten benötigten im Laufe der 5 Jahre eine Kataraktoperationen. Eine Patientin entwickelte nach der Injektion eine postoperative Endophthalmitis. Der dafür verantwortliche Organismus war Methicillin-resistenter Staphylococcus aureus. Das Auge der Patientin erholte sich vollständig nach einer Pars Plana Vitrektomie, mit intraokularer Antibiotikagabe und Silikonölimplantation. Fast ein Fünftel der Patienten entwickelte eine transiente okuläre Hypertonie, wobei alle Patienten erfolgreich mit nur einer einzigen topischen IOD-senkenden Therapie behandelt werden konnten. Kein Patient benötigte eine systemische IOD-senkende Medikamente oder eine fistulierende Chirurgie aufgrund einer unkontrollierten okulären Hypertonie. Die durchschnittliche Zahl der Injektionen im 5 jährigen Follow-up betrug 3,1, wobei 1,6 Injektionen innerhalb der ersten 2 Jahre erfolgt waren.
Schlussfolgerungen: Trotz des Fehlens einer Vergleichsgruppe bestätigt die Studie die Sicherheit und Wirksamkeit des intravitrealen Dexamethason-Implantats als Primärtherapie des therapienaiven diabetischen Makulaödems bei phaken Patienten mit Diabetes mellitus Typ II.

6. Abbreviations

DME – Diabetic Macular Edema

T1DM – Typ 1 Diabetes Mellitus

T2DM – Typ 2 Diabetes Mellitus

BRB – Blood Brain Barrier

AGEs – Advanced glycation End-products

VEGF – Vascular Endothelial Growth Factor

EBM –Endothelial basement membrane

MHC – Major Histocompatibility Complex

IL – Interleukin

RPE – Retinal Pigment Epithelium

DR – Diabetic Retinopathy

OCT – Optical Coherence Tomography

FA – Fluorescein Angiography

PGF – Placental Growth Factor

VEGFR-1 – Vascular Endothelial Growth Factor Receptor 1

RASS – Renin-Angiotensin-Aldosterone System

MCP-1– Monocyte Chemoattractant Protein-1

VCAM-1 – Vascular Cell Adhesion Molecule 1

ICAM-1 – Intercellular Adhesion Molecule 1

RAGEs – Receptor for Advanced Glycation End-products

NADPH – Nicotinamide Adenine Dinucleotide Phosphate

PKC – Protein Kinase C

VA – Visual Acuity

CST – Central Subfield Thickness

CI-DME – Center Involving Diabetic Macular Edema

DRCR.net – Diabetic Retinopathy Clinical Research Network

SD-OCT – Spectral Domain Optical Coherence Tomopgraphy

RGCL– Retinal Ganglion Cell Layer

RNFL – Retinal Nerve Fiber Layer

IPL – Inner Plexiform Layer

INL – Inner Nuclear Layer

OPL – Outer Plexiform Layer

ONL – Outer Nuclear Layer

ELM – External Limiting Membrane

IS/OS Line – Inner segment / Outer segment Line

CMT – Central Macular Thickness

BCVA – Best Corrected Visual Acuity

hsCRP – high-sensitivity C-Reactive Protein

CSME – Clinically Significant Macular Edema

DCCT – Diabetes Control and Complications Trial

HRD – Hyperreflective Dots

SRD – Serous Retinal Detachment

DRIL – Disorganization of the Retinal Inner Layers

GCL-IPL – Ganglion Cell Layer – Inner Plexiform Layer

PRN – Pro Re Nata

CDVA – Corrected Distance Visual Acuity

ETDRS – Early Treatment for Diabetic Retinopathy Study

ppV – pars plana Vitrectomy

IOP – Intraocular Pressure

CME – Cystoid Macular Edema

FFA – Fundus Fluorescein Angiography

DEX-I – Dexamethasone Implant

IOL – Intraocular Lens

LOCS III – Lens Opacity Classification System III

MRSA – Methicillin Resistant Staphylococcus Aureus

IVA – Intravitreal Avastin

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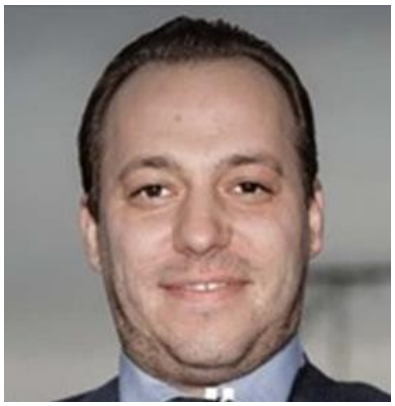
9. Curriculum Vitae



Personal Information

Name	Alper Bilgic
Date of Birth	01.09.1979
Date of Place	Ankara/Turkey
Nationality	German
Adress	Mittelstr. 35
	27568 Bremerhaven, Germany
Tel	+49 471 40016
Mobil	+49 173 1505937
Email	drbilgicalper@yahoo.com
Website	www.alphavision.care

Education and Work Experience

2022 Fellow of European Board of Ophthalmology (FEBO)
2009-2022 Owner und Consultant of Ophthalmology in the private Alpha Vision Ophthalmology Practices in Bremerhaven and Dorum
2014-2022 Observer and research Fellow in Sudhalkar Eye Hospital and Retina Center also in Sudhalkar Medical Research Foundation, Baroda, Gujarat, India
2009 Ophthalmologist
2008-2009 Residency in the Augenpraxisklinik in Lübeck, Dr.Machemer et al.
2007-2008 Residency in der University Clinic of Kiel, Department of Ophthalmology, Chairman: Prof. Dr. Johann Roider
2007-2008 Residency in the StiftungsklinikumMittelrhein and Eye Center of Koblenz, Department of Ophthalmology, Chairmen: Dr. Schmitz-Valckenberg, Dr. Papoulis, Dr. Derse
2007 Medical Equivalence Exam and Approbation
2004- 2007 Residency in the University Clinic of Tübingen, Department of Ophthalmology, Chairman: Prof. Dr. K.U. Bartz-Schmidt
1997-2003 Medical School of 9 September of University of Izmir/Turkey (M.D.)
1991-1997 Junior High and High School in Izmir Turkish College in Izmir/Turkey

Posters and Scientific Publications

Current intravitreal therapy and ocular hypertension: A Review.
Sudhalkar A, **Bilgic A**, Vasavada S, Kodjikian L, Mathis T, de Ribot FM, Papakostas T, Vasavada V, Vasavada V, Srivastava S, Bhojwani D, Ghia P, Sudhalkar A.
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Poster Presentations

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Book Chapters

Book: Intech-Open : Diabetic Eye Disease – From Therapeutic Pipeline to the Real World

Treatment Algorithm in Proliferative Diabetic Retinopathy.
From Protocols to the Real World

By Jesus Hernan Gonzalez-Cortes, Jesus Emiliano Gonzalez-Cantu, Aditya Sudhalkar, Sergio Eustolio Hernandez-Da Mota, **Alper Bilgic**, Javier Alan Garza-Chavarria and Jesus Mohamed-Hamsho

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Editorial and Reviewer Activities

Reviewer : European Journal of Ophthalmology , Therapeutic Advances in Ophthalmology, Clinical Ophthalmology, British Journal of Ophthalmology, Acta Scientific Ophthalmology, Indian Journal of Ophthalmology, Journal of Ophthalmology, Journal of Clinical Medicine, Journal of Fungi

Editorial Board Member : Journal of Ophthalmology, Acta Scientific Ophthalmology, BMC Ophthalmology

Regular Joining in Novartis und Roche Advisory Meetings

Acedemic Awards:

Vasavada V, Srivastava S, Vasavada V, Vasavada S, Vasavada AR, Sudhalkar A, Bilgic A.
Impact of fluidic parameters during phacoemulsification on the anterior vitreous face behavior: Experimental study**. Indian J Ophthalmology 2019;67:1634-7 has been selected for the AIOS-IJO Gold Award for the year 2019.**

Memberships:

- German Society of Ophthalmology
- German Society of Retinology
- American Academy of Ophthalmology
- European Society of Retina Specialists
- European Society of Cataract & Refractive Surgeons
- International Society of Refractive Surgery

Language Skills

German: advanced
English : advanced
Turkish : native language
Russian : basic knowledge
Spanish : basic knowledge

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Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.
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