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Repeat Dexamethasone implants (Ozurdex®-IVOM) for the treatment of non-infectious uveitis

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1. Table of contents

2. List of abbreviations

AC	Anterior Chamber
ACAID	Anterior Chamber-associated Immune Deviation
AU	Anterior Uveitis
BCVA	Best Corrected Visual Acuity
BRB	Blood Retinal Barrier
BM	Bone Marrow
CRT	Central Retinal Thickness
CME	Cystoid Macular Edema
ETDRS	Early Treatment for Diabetic Retinopathy Study
EXF	Extracellular Fluid
HLA	Human Leukocyte Antigen
IOL	Intraocular Lens
IOP	Intraocular Pressure
IGS	Irvine-Gass Syndrome
ICF	Intracellular Fluid
IVT	Intravitreal Therapy
IUSG	International Uveitis Study Group
KPs	Keratic Precipitates
logMAR	logarithm of Minimum Angel of Resolution
ME	Macular Edema
MTX	Methotrexate
MV	Macular Volume
NSAID	Non-Steroidal Anti-Inflammatory Agents
OCT	Optical Coherence Topography
ON	Optic Nerve
RPE	Retina Pigment Epithelium
SD	Standard Deviation
SUN	Standardization of Uveitis Nomenclature
TNF-α	Tumor Necrosis Factor- α
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
VKH	Vogt-Koyanagi-Harada
VMTS	Vitreomacular Traction Syndrome

3. Introduction of uveitis

3.1. Definition

The term uveitis encompasses inflammation of all intraocular structures, not only uvea, ciliary body and iris, but also anterior chamber, vitreous, retina and retinal vessels, papilla as well as retinal pigment epithelium. Various etiologies cause uveitis like infections, autoimmunity and tumors. [1, 2]

3.2. Classification

There are several ways to classify uveitis. An accurate classification is the first step to identify and diagnose any uveitic entity and it plays an important role to evaluate and determine the proper management and therapy of any uveitic case.

The commonest classification of uveitic diseases was published in 1987 by the International Uveitis Study Group (IUSG), which basically differentiates according to the anatomical site with the most intense inflammation. The anatomical classification is the first step for identification of uveitis entity and treatment.

The classification system is also supported from the Standardization of Uveitis Nomenclature (SUN). (Table 3.2.1 a, b)

Table 3.2.1 a

Anatomical classification according to SUN [3]		
	Primary inflammatory site	Uveitis types
Anterior Uveitis	Anterior chamber	Iritis Iridocyclitis Anterior cyclitis
Intermediate Uveitis	Vitreous +/- pars plana	Pars planitis Posterior cyclitis Hyalitis (Vitritis)
Posterior Uveitis	Retina and choroid	Focal, multifocal, diffuse Choroiditits Chorioretinitis Retinochoroiditis Retinitis Neuroretintis
Panuveitis [4]	All anatomical structures (Anterior chamber, vitreous, retina, choroid)	Endophthalmitis

Table 3.2.1 b		
Differential diagnosis for uveitis according to anatomical classification [5]		
Acute anterior uveitis	**Chronic anterior uveitis**	
Seronegative spondyloarthropathies Behçet's syndrome Herpetic (HSV, VZV, CMV) Glaucomatocyclitic crisis (Posner-Schlossman-syndrome) Post-streptococcal Tubulointerstitial nephritis and uveitis syndrome	Juvenile idiopathic arthritis Sarcoidosis Fuchs uveitis (persistent rubella infection) Syphilis Tuberculosis Herpetic	
Intermediate uveitis	**Posterior uveitis**	**Panuveitis**
Multiple sclerosis Idiopathic Sarcoidosis Lyme disease	Toxoplasmosis Toxocariasis Sarcoidosis Syphilis Tuberculosis Viral (HSV, VZV, CMV) Birdshot choroidopathy Ocular histoplasmosis Multifocal choroiditis/panuveitis Retinal vasculitis Cerebral vasculitis	VKH disease Behcet's disease Sympathetic ophthalmia Sarcoidosis Toxoplasmosis Toxocariasis Syphilis Tuberculosis Endophthalmitis

In 2005, SUN has presented an additional classification system according to the diagnostic terminology, outcome measures (VA outcome) [6] and grading schema of inflammation (anterior chamber cells and flares, vitreous haze). [7]

In 2008, the International Uveitis Study Group (IUSG) has presented a new classification system according to etiology. (Table 3.2.2)

Table 3.2.2	
Classification system according to IUSG	
Infectious	Viral, bacterial, parasitic, fungal
Non infectious	with positive or negative history of systemic associations
Masquerade	neoplastic, non-neoplastic [8]

Different aspects can be used to classify uveitis type. (Table 3.2.3 a-c)

Table 3.2.3 a

Classification according to duration and course of uveitis		
Time of onset	Sudden Insidious	
Duration	Limited Persistent	< 3 months duration > 3 months duration
Course	Acute Recurrent Chronic	Sudden onset and limited duration Repeated episodes with inactive interval without treatment > 3 months duration Persistent uveitis with relapse in < 3 months after discontinuing treatment

Table 3.2.3 b

Classification according to inflammatory type and clinical findings	
Type of inflammation	Granulomatous Non granulomatous
Lesion type	Focal Multifocal Disseminated Diffuse
Keratic precipitates type	Focal Central or peripheral Disciform Arlt triangle Stellate or diffuse
Other findings [9]	Synechiae Fibrin Nodules

Table 3.2.3 c

Other classification type factors	
Laterality	Unilateral or bilateral
Age of onset	infant, child, adolescent, young adult, elderly adult
Demographics	Sex, travel, race, occupation, residence location(s), immigration, other illnesses, hobbies, nutritional factors, stress and personality factors, pets
Social history	drug abuse, alcohol, smoking, sexual habits

Another etiopathological classification system divides uveitis in two main groups, granulomatous and non-granulomatous. (Table 3.2.4) This can differentiate the type of inflammation (involved cells) and the different clinical findings such as corneal endothelial keratic precipitates (KPs). KP have a different appearance in non-granulomatous (fine collection predominantly of granulocytes) than in granulomatous type (larger collection of macrophages and multinucleated cells with fatty appearance, mutton fat KP). This can be a diagnostic indicator and is helpful for the differential diagnosis. In granulomatous cases, typical iris and choroid changes such as iris nodules or choroidal and retinal granulomas may occur. [10]

Table 3.2.4

Classification according type of inflammation	
Non granulomatous inflammation	**Granulomatous inflammation**
HLA-B27 syndromes Behcet's disease Uveitis associated with multiple Sclerosis Juvenile idiopathic arthritis Syphilis Acute bacterial endophthalmitis	Sarcoidosis Sympathetic ophthalmia Uveitis associated with multiple sclerosis Lens-induced uveitis Intraocular foreign body Vogt–Koyanagi–Harada syndrome Chronic or persistent infections like syphilis, tuberculosis, viral infection with HHV 1-5 or rubella and fungal infections

3.3. Etiology

The identification of the etiology eye is most important for the correct management. Uveitis can be caused or associated with several etiological factors or diseases. Sometimes during the therapy of an uveitic eye, the exact etiology remains unknown but it is treated as a part of an etiologic category.

The etiological classification [11] is the following:

Infectious causes

This group can be classified according to the etiological pathogen or according to transmission route and the primary infection locus. (Table 3.3.1)

Table 3.3.1

Infection etiology according to the pathogenicity	
Bacteria	Treponema pallidum, Mycobacterium tuberculosis, Brucella, Mycobacterium leprae, Bartonella, Tropheryma whippelii
Fungi	Candida, Aspergillus, Fusarium, Cryptococcus, Coccidioides
Protozoa	Toxoplasma gondii, Toxocara canis, Taenia solium, Onchocerca volvulus
Viruses	Herpes simplex, Varicella zoster, Cytomegalovirus, Ebstein-barr virus, Human immunodeficiency virus, Measles and Rubella virus

Non-infectious causes (Table 3.3.2)

Table 3.3.2

Non-infectious uveitis [12]	
Autoimmune disease (associated with underlying disease)	HLA-B27 associated diseases: ankylosing spondylitis, reactive arthritis, psoriatic arthritis, bowel disease (Crohn's disease, ulcerative colitis) Psoriasis Juvenile idiopathic arthritis Multiple sclerosis (HLA-DR 15) Behcet's disease (HLA-B5 / B51) Sarcoidosis
Idiopathic	Acute posterior multifocal placoid pigment epitheliopathy Multiple evanescent white dot syndrome Multifocal choroiditis (Punctate inner choroiditis) Serpiginous choroiditis Birdshot chorioretinopathy Acute zonal occult outer retinopathy Presumed Ocular Histoplasmosis Syndrome

Masquerade syndromes (neoplastic) causes

Systemic hematological tumors, mainly malignant such as leukemia, lymphoma or even intraocular tumors such as retinoblastoma or melanoma of uvea may have uveitic manifestation. These cases can be also termed as masquerade syndromes

Traumatic or iatrogenic causes

Ocular injury (blunt or penetrating) may lead to uveitic presentation. This rarely can also happen after intraocular operation such as cataract, glaucoma or vitreoretinal operation. In rare cases medication may also cause an iatrogenic uveitis.

3.4. Macular edema

Macular edema (ME) is a common condition of central vision loss in the developed countries. It refers to an increase of retinal thickness at the macular area due to fluid accumulation. ME can also be defined as any pathological swelling of macula area.

During the clinical examination there are several signs and symptoms that can associated with ME. (Table 3.4.1)

Table 3.4.1
Clinical manifestation in ME eyes
Central vision distortion (blurry vision) with intact peripheral vision
Color vision distortion
Contrast sensitivity loss
Metamorphopsia best tested with Amsler chart [13]
Absence of foveal depression
Thickening fovea area
Absence of foveal reflex can be seen in eyes with macula thickness over 300μm [14]

Macular edema and fluid accumulation can general be differentiated into intracellular and extracellular [15] (Table 3.4.2). Clinically can be evaluated with different parameters (Table 3.4.3). There are several of these parameters that may be associated with different pathophysiological etiologies.

Table 3.4.2	
Classification of fluid accumulation in cellular level	
Intracellular (cytotoxic edema)	Due to changes of cellular ionic distribution
Extracellular	Due to changes of blood retinal barrier

Table 3.4.3	
Parameters of clinical evaluation in ME	
ME extent	Areas with increased retinal thickness
Central fovea status	Involvement of fovea (central area 500 μm)
ME distribution area	Focal or diffuse ME
Fluorescein leakage	In case of BRP dysfunction or changes
Vitreous status	Presence or absence of vitreal traction
Intra-retinal cyst	It is sign of ischemia (defect of perifoveolar capillaries and / or capillary area closure)
Localization of retinal thickness and cyst	Inner or outer retina
ME chronicity	Duration from initial diagnosis and response to therapy

Intracellular fluid (ICF) accumulation may be associated with several predisposing factors such as increased metabolic activity, Henle's layer radial arrangement, absence of inner foveal layer, reduce or absence of foveal blood supply.[16] This is mostly seen after ischemia, injury, toxic cell damage or inflammation.

Extracellular fluid (ECF) accumulation is more common and clinically more relevant. It is primarily associated with blood retinal barrier (BRB) breakdown. The tissue volume increases with fluid in retinal extracellular space. Retinal edema progression is secondary to blood retinal barrier (BRB) damage and depends on hydrostatic pressure and osmotic pressure difference gradients. [17]

Macular edema can be classified according to location of accumulated fluid in relation to anatomical retinal layer. (Table 3.4.4)

Table 3.4.4	
Classification of fluid accumulation in histopathological / retinal layer level	
Intraretinal	Fluid in neurosensory retinal layers
Subretinal	Fluid under RPE with separation from neurosensory retina
Combined	Fluid in intra- and subretinal compartment

Cystoid macular edema (CME) is a subtype of ME with similar characteristics clinically, in OCT and angiography. This neurosensory retinal layer change has a characteristic pseudocystic configuration and can cause a secondary distortion of the photoreceptor architecture.[18] This type of edema is termed as cystoids because of its appearance. Anatomically it is not a true cyst because it lacks an epithelial coating.

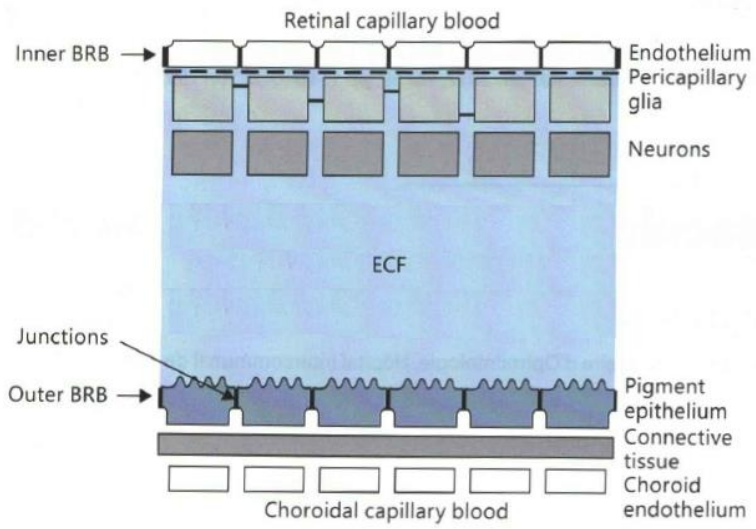
CME must be differentiated from subretinal edema and serous retinopathy. In serous retinopathy or serous retinal detachment there is a subretinal fluid accumulation which forces the neurosensory retina to separate from retinal pigment epithelium (RPE). It is categorized as atypical form of ME. [19] There are several conditions that present with this kind of macular edema: central serous chorioretinopathy (CSCR), retinal detachment and choroidal neovascular membrane belong to this group.[20]

The mechanism of intraretinal fluid accumulation is associated with inner and outer blood retinal barriers dysfunction leading to an abnormal permeability and fluid leakage from the perifoveal retinal capillaries. The inner blood retinal barrier constitutes of tight junction between retinal vessels (which pass through inner retina) and endothelial cells. Some inflammatory mediators (prostaglandins, protein kinase C, vascular endothelial growth fact, nitric ocide, leukotriennes, or other cytokines) may cause a dysfunctional barrier. [21] The outer blood retinal barrier is localized between adjacent RPE cells and is supported by tight junctions.

Normally, there is equilibrium between the capillary filtration rate and rate of fluid removal from extracellular retina. Under physiological conditions RPE removes fluid from the retina. In case of any functional failure or any balance disruption, extracellular fluid accumulates within retinal layer in cystic form.[22] The outer plexiform and the inner nuclear layers are the main retinal layers where fluid accumulates. The outer plexiform layer is the initial layer of fluid accumulation due to anatomical position between retina and choroid where chorioretinal watershed area is present. Macula is more susceptible for fluid accumulation because of avascular zone, scarcity of Muller cells and vertical orientation of intraretinal fibers.[23] Initially the fluid accumulates in intracellular space of Muller cells, which may then rupture and cause extracellular accumulation. [24, 25] (Figure 3.4.2)

Figure 3.4.2

Inner and outer blood retinal barrier and associated locations[26]



Several risk factors can play a role to a disruption of homeostatic mechanism of eye. (Table 3.4.5) Any change between osmotic or hydrostatic force and retinal or choroidal vasculature can increase capillary permeability. [27, 28] Vitreous, retina, retinal pigment epithelium (RPE), choroid and vasculature play an important role in pathogenesis of ME.

Table 3.4.5

Retinal edema formation factors [29]
Blood retinal barrier permeability
Capillary hydrostatic pressure
Tissue hydrostatic pressure
Tissue osmotic pressure
Plasma osmotic pressure

CME induced by inflammatory process is the most common complication in uveitic eyes, independent from etiology or anatomical location of inflammation (but mostly posterior uveitis). This can lead to significant VA reduction. [30, 31] It is due to retinal vessels damage following release of inflammatory mediators like interferon-γ, interleukin-2 / -10, tumor necrosis factor-α, VEGF. This process compromises the BRB leading to macular swelling.[32,33]

There are several conditions and risk factors associated with fluid leakage and secondary ME formation.[34] The etiological classification of ME is categorized according to patho-mechanism of retinal dysfunction. (Table 3.4.6)

Table 3.4.6		
Cystoid macular edema associated diagnoses		
Vascular	Retinal	Diabetic retinopathy Retinal vein occlusion (branch or central) Retinal artery macroanuerysm [35] Radiation retinopathy Juxtafoveal retinal telangiectasis Coats'disease Retinopathy of prematurity Ocular ischemic syndrome
	Choroidal	Choroidal neovascularization (CNV) Hypertensive retinopathy [36]
Postoperative	Irvine-Gass syndrome Penetrating keratoplasty Scleral buckle Laser treatment [Argon or YAG (Yttrium-Aluminum-Garnet)] Cryotherapy	
Inflammatory	**Uveitis and Neuroretinitis** (Table 3.2.1b, 3.2.2 and 3.3.2)	
Medications	Table (3.4.8)	
Retinal dystrophies	Retinitis pigmentosa [37, 38] Autosomal dominant cystoids macular edema Gyrateatrophy Goldman Favre (enhanced S-cone syndrome) Juvenile X-linked retinoschisis	
Tractional	Epiretinal membrane (Macular pucker) Vitreomacular traction syndrome Vitreoretinal traction associated with myopia Macular hole	
Neoplastic (Tumor)	**Retinal**	Hemangiomas
	Choroidal	Melanoma Hemangioma Osteoma
Anatomical abnormalities	**Optic nerve**	Optic pit maculopathy [39] Opticdisc coloboma Morning glory disc anomaly
	Retina	Retinal detachment

Iatrogenic (postsurgical) or post traumatic

Pars-plana vitrectomy, glaucoma or cataract operation, penetrating keratoplasty and even laser procedures (such as capsulotomy), can cause changes in the retinal blood flow and produce an inflammatory reaction.[40] Irvine-Gass belongs to post-surgical inflammatory reaction after a cataract surgery, this occur in 20% of cataract operations or even more depending on duration of surgery and intra-operative complication. It usually manifests 6 to 10 weeks after surgery and resolves spontaneously in 95% of cases within 6 months and is the most common cause of VA reduction after a cataract surgery. [41, 42, 43, 44]. Uveitis[45], diabetic retinopathy[46], intra-operative vitreous loss [47] and intracapsular versus extracapsular surgery [48] are risk factor for Irvine-Gass ME formation

The IGS patho-mechanism is not fully understood, inflammatory intraocular mediators (histamine, prostaglandins, leukotrienes) play an important role in increased vessel permeability.

Another common condition for secondary ME is capsulotomy or panretinal photocoagulation. The associated mechanism is due to inflammatory mediator releasement or macular blood flow is increased and lead to transudation. [49] Capsulotomy related ME has a low incidence < 3% but may be increased if performed in early period after the cataract surgery.

Ocular immune privilege refers to several mechanisms that associated with regulation of ocular inflammation. Integrity of BRB is strongly associated with inflammatory process. The anterior chamber-associated immune deviation (ACAID) is strong enough to avoid any disruption of ocular immune privilege. An uni- or bilateral retinal laser therapy can cause a disruption of ACAID after changing the immune homeostasis and regulation system of both treated and non-treated eye. [50]

Medication

Several drugs can induce ME. (Table 3.4.8) The most common are the prostaglandin analogs which can lead to vascular instability and disruption of capillaries junctions due to pro inflammatory effects.[51] Other reports referred to epinephrine eye drops.[52] Nicotinic acid and Niacinmay can also induce ME with a daily dose over 1,5g. [53]

Table 3.4.8		
Medication associated with ME		
Benazalkonium chloride	Carmustine	Docetaxel
Epinephrine	Fingolimod	Glitazones
Niacin	Paclitaxel	Timolol
Prostaglandin analoges	Tamoxifen	

Intraocular neoplasms (tumors)

Any type (malignant or benign) tumor may associate with ME creation. The most common tumors are choroidal or retinal capillary haemangioma, choroidal melanomas and vasoproliferative tumors. ME is associated with RPE and/ or blood retinal barrier dysfunction due to choroidal mass compression effect.[54]

Tractional maculopathy

Macular pucker, vitreomacular traction syndrome (VMTS) and myopic macular schisis belong to this group. These conditions have mechanical tractional component that cause an intraretinal fluid accumulation. Tractional forces cause stress at the retinal area of Muller cells and contribute to release of inflammatory factors (vascular endothelial growth factor, basic fibroblastic growth factor, platelet derived growth factor). This can produce a disruption of blood retinal barrier with secondary separation of retinal layer and retinal pigment epithelium, Muller cells lyses, fluid leakage and finally edema. [55, 56, 57, 58] Epiretinal membrane is due to cell proliferation with an avascular fibrous membrane formation. Tractional forces can cause secondary ME that do not response to local therapy. In VMTS case there is an anterior vitreous detachment that attach the macular area and tractional forces of attached vitreous can cause ME.[59]

3.5. Uveitic complications

Uveitis is associated with intraocular complications such as cystoid macular edema[60], cataract formation [61] (inflammatory or steroid induced [62]) and secondary glaucoma [63] (inflammatory or steroid induced [64]). All of these complications may influence the final visual prognosis and may play an important role for management decision.

A conservative or surgical treatment may be indicated to treat intraocular uveitic complication and visual improvement secondarily. In case of early cataract formation, a cataract operation[65] with or without implantation of intraocular lens is the main treatment indication. In glaucoma cases, a primary conservative therapy with local or systemic medication may initial manage this condition and in severe or uncontrolled cases a laser or surgical treatment may be indicated. Most of the cases with CME respond well to topical or systemic steroids. [66]

3.6. Treatment strategies of inflammatory macular edema

Uveitic macular edema occur during active inflammation as well as in quiescent eyes. In order to treat ME inflammation has to be controlled as the first step. This includes the use of steroids, immunosuppressive agents as well as biologicals. In quiescent eyes with ME or in eyes in which ME persists even if inflammation is controlled, symptomatic treatment must be initiated. Different medications (Table 3.6.1) and routes of administration are available.[67]

Table 3.6.1
CME treatment options
Steroid therapy (local, topical, systemic or combined)
Non- steroidal anti-inflammatory drugs (local, topical, systemic or combined)
Carbonic anhydrase inhibitors (systemic)
Anti-vascular endothelial growth factor drug (intravitreal)
Steroid sparing immunosuppressive agents (intravitreal or systemic)
Macular grid laser [68]
Vitrectomy [69]

The route of administration may vary. The available routes for each substance are given in Table 3.6.2.

Table 3.6.2	
Classification of therapy according to administration route	
Local	Eye drops, ointments
Topical	Peri-ocular (retro- or para-bulbar), sub-conjunctival or intra-ocular injection
Systemic	Oral, intra-macular, intra-venous

Steroids

Steroid drugs are the most effective agents that can treat an inflammation process and subsequently the cystoid macular edema. The most potent agent is corticosteroid which has a broad effect in immune system, it targets to neutrophil transmigration and play a role to reduction of cytokine production. It has a primary anti-inflammatory action by prostaglandins and leukotrienes synthesis inhibition. In addition, the tight junctions of vascular endothelial cells are stabilized and thus leads to vessel sealing. [66]

Local steroids (eye drops)

Local steroids are mostly used in cases of anterior uveitis to control inflammation. Due to poor penetration of topically applied steroids to the posterior pole, a topical steroid therapy has no to mild effect on treatment of cystoid macular edema thus additional topical or systemic agents may be needed to treat the macular edema.[70]

Periocular steroids

Periocular administration allows for a better therapeutic concentration than local steroid therapy and it has a longer effect to because it acts as depot and penetration through the sclera is sufficient. The most common preparations are triamcinolone acetonide or methylprednisolone acetate. The periocular therapy is mainly indicated in unilateral or asymmetrical cases of intermediate or posterior uveitis, macular edema or in severe and resistance anterior uveitis. In case of bilateral posterior uveitis, a periocular therapy is considered as supplement to systemic therapy or if a systemic steroid therapy is contraindicated. Other possible indication is in patients with poor compliance with topical or systemic drugs. Sometimes a periocular steroid injection is used intra-operative to reduce post-operative inflammation and / or macula edema.

Secondary cataract formation[70, 71, 72, 73], globe penetration, elevation of IOP, refractory change from depot-mass effect, ptosis, subdermal fat atrophy, extraocular muscle paresis, optic nerve injury, retinal and choroidal vascular occlusion, cutaneous hypopigmentation are possible complication of a periocular steroid injection.

The periocular injection is made under local anesthetic like tetracaine or scandicaine. There are several possible anatomical regions of the injection, sub-conjunctival, peri- or retrobulbar anatomical region. [74]

Topical (intraocular or intravitreal) steroids [75]

Triamcinolone acetonide is a short acting steroid option in case of posterior uveitis and macula edema recalcitrant to other therapies. It has an effect of 3 months when is injected intravitreally in comparison to periocular injection that has an effect of 4 weeks. It has rapid macula edema response and it is more potent than other periocular triamcinolone injections. It can be used intra-operatively as prophylaxis in patient with risk of an inflammation and / or post-operative macula edema. The possible complications are the same as in any intrevitreal injection such as IOP elevation[76], cataract formation, endophthalmitis (sterile or infectious), hemorrhage and retinal detachment. [77, 78]

Slow-release implants such as Ozurdex® [79] (0.7mg Dexamethasone), Iluvien® [80, 81] (0.19mg fluocinolone acetonide) are useful in cases of posterior uveitis that have low response or are intolerant to other treatments. The implants are injected intravitreally via pars plana and have a slow release reservoir function for 3-4 months (Ozurdex®) to 2-3 years (Iluvien®). This can reduce the use of long term systemic therapy. The efficacy of intravitreal Dexamethasone implant (Ozurdex®) is five time more potent than topical triamcinolone acetonide. [82]

Table 3.6.3 shows the possible ocular side effects after use of local, peri- or intraocular steroids. These side effects are depending on the duration of administration and the dose.

Table 3.6.3
Ocular side effects after local, peri- or intraocular steroid therapy [83]
Cataracts
Glaucoma
Central serous retinopathy
Delayed wound healing and infection risk
Reactivation of herpes virus

Systemic steroids

Systemic steroids can be given orally or intravenously. They are indicated in intermediate and posterior uveitis. They are preferred in bilateral uveitic eyes with or without macular edema. Some studies have shown that systemic steroids induce resolution of macular edema faster than periocular steroids. [84]

Steroid therapy sometime is avoided as primary therapy in patient with high risk of adverse effects. [85]Steroid must be used with caution in diabetic patients, patient with peptic ulcers, osteoporosis, active systemic infections and psychosis on past steroid exposure.

Steroids are mostly used in acute conditions. Steroid sparing drugs may be added for chronic inflammation. [86]

Steroid treatment is started with a high dose and then to tapered slowly according to control of inflammation. Prednisolone is the most common preparation at an initial dose of 1-2mg/kg/day in single morning dose. Regular clinical follow ups are required during weekly dose tapering.

The table 3.6.4 shows dose and administration route of common steroids.

Table 3.6.4			
Administration route and doses of common used steroid agents			**Duration of anti - inflammatory effect**
Triamcinolone acetonide	Intravitreal	2–4 mg	1-3 months
	Periocular or retrobulbar	40mg	4-6 weeks
Dexamethasone implant (Ozurdex®)	Intravitreal	0.7mg	3-5 months
Fluocinolone acetonide implant (Iluvien®)	Intravitreal	0.19 mg	2-3 years
Prednisone	Oral	1–2 mg/kg/day	1-2 days
Methylprednisolone	Intravenous	1g over 1-2 h	1-2 days

Systemic steroid therapies cause adverse effects during administration. The side effects (Table 3.6.5) mainly depend on the dose and the duration of administration.

Table 3.6.5		
Side effect of steroid therapy[87]		
Fluids, electrolytes	**Musculoskeletal**	
Sodium retention, potassium loss Fluid retention Hypokalemic alkalosis Hyperosmolar coma	Muscle weakness Steroid induced myopathy Osteoporosis Femoral and humeral heads aseptic necrosis Tendon rupture	
Endocine	**Neurologic**	**Gastrointestinal**
Menstrual irregularities Cushingoid state Growth suppression in children Hirsutism Adrenocortical pituitary axis suppression Diabetes	Convulsions Headaches Hyperexcitability Moodiness Psychosis Mental changes	Nausea Dyspepsia Increased appetite Peptic ulcer Intestine perforation Pancreatitis
Dermatologic	**Other**	**Ophthalmologic**
Poor wound healing Easy bruisability Increased sweating	Weight gain Thrombo-embolism Infection reactivation	Table 3.6.3

Prostaglandin inhibitors and non-steroid anti- inflammatory drugs (NSAID) (topical and systemic)

Prostaglandin inhibitors can be used in some ocular inflammatory conditions. In some cases NSAID can reduces the severity and the recurrences of uveitis (mostly AU) when administrated in combination with steroids. NSAIDs are not used as first line therapy in uveitic patient (with or without macular edema) because of low effectivity as single agent in intraocular inflammation conditions. [88]

The most commonly used agent is diclofenac either as local or systemic agent. It is commonly used after capsulotomy or cataract operation to reduce the risk of any inflammatory response and secondary macula edema (Irvine-Gass-syndrome). [89, 90, 91]

NAISDs are anti-inflammatory agents that inhibit pro- inflammatory prostaglandins, thromboxane and cyclo-oxygenase production. [92, 93] Some studies have showed that Bromfenac and Nepafenac also have a therapeutic value for the treatment of macular edema. [94, 95, 96]

Carbonic anhydrase inhibitors (Acetazolamide) and Somatostatin analogues

Acetazolamide is a carbonic anhydrase inhibitor. The inhibition of carbonic anhydrase primary reduces aqueous humor production and also facilitates net-transport of water from the retina through the retinal pigment epithelium (RPE) into the choroid. Several studies have showed the effectiveness of acetazolamide as treatment for cystoid macular edema. [97, 98, 99]

Other studies have shown that somatostatin analogues such as Octreotide may reduce inflammatory macular edema in uveitic eyes by restoration of inner blood retinal barrier.[100, 101]

Vascular endothelial growth factor inhibitors (intravitreal)

Vascular endothelial growth factor is upregulated in inflammation and has a pro-inflammatory effect. It plays an important role in angiogenesis and retinal vascular permeability. [102103104] These effects cause macular edema. Intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) such as ranibizumab, aflibercept and bevacizumab suppress macular edema. The effect of VEGF-inhibitors in inflammatory macular edema[105, 106, 107, 108] are much less potent and therefore only second or third line therapy in the treatment of uveitic macular edema. In some cases secondary retinal vascularization develops during an uveitic inflammatory process[109], in those cases an anti-VEGF intravitreal injection plays an primary

or additional role to treat the macular edema as well as the neovascularization. The source of VEGF in inflammation seems to be T-lymphocytes. [110]

Steroid sparing immunosuppressive or antimicrobial / antiviral agents

Steroid sparing immunosuppressive drugs such as antimetabolites and biologicals are mostly used in cases of severe uveitic, bilateral involvement, non-infectious etiologies in patient with inadequate response to steroid therapy. It is also indicated in patient with systemic steroid intolerance, side effect[111, 112] or in chronic disease that a prolonged or high daily dose of steroid is needed. The main administration route is systemic and in some cases also topical. [113]

Immunosuppressive[114, 115, 116, 117] or anti-microbial or anti-viral therapies have no direct effect on cystoid macular edema but help secondarily by reducing inflammation. The most common immunosuppressive agents are summarized in table 5.5.7.

Immunosuppressive agents are generally given for 2-3 years after induction of uveitis remission and then tapered. Some patients may require a prolong therapy to control active disease.

Table 3.5.7

Commonest steroid sparing immunosuppressive agents	
Antimetaboloites	Azathioprine
	Methotrexate (MTX)[118]
	Mycophenolat emofetil
Calcineurin inhibitors	Ciclosporin
	Tacrolimus
Biological blockers	Interleukin receptor antagonists
	Tumor necrosis factor-α antagonists

Macular grid laser coagulation and pars plana vitrectomy

The effect of macular grid laser coagulation and pars plana vitrectomy have been studied for several years and have shown some effect on macular edema reduction. Both methods are not primarily indicated. [119, 120, 121]

4. Goal of the study

The aim of this study is to evaluate the clinical outcomes of 4 parameters (Visual acuity, central macular thickness, macular volume and intraocular pressure) after repeated intravitreal injection of 0.7 mg Dexamethasone implant (Ozurdex®) in defined follow up intervals. This retrospective analysis includes only eyes with cystoids macular edema with non-infectious uveitis.

5. Material and methods

5.1. Visual acuity (VA)

The visual acuity (VA) level in uveitic eyes depends on several factors. Any pathological change that can decrease the transparency of the cornea, anterior chamber, lens and vitreous can reduce the VA. Any retinal clinical change such as macular edema, infiltration, scaring or necrosis can lead to a significant VA disturbance. In addition, the optic nerve pathology can also play an important role to VA level. Any VA disturbance should be evaluated to identify cause and appropriate treatment. [122, 123]

Testing VA is also an important tool to assess functional changes and one of the most important features for indication to therapy and follow ups.

Distance and near vision should be tested with the best correction. Distance VA is mostly used as primary test but near VA sometime may improve earlier than the distance VA such in patient with chronic macular edema. [124, 125]

The VA is the ability of the eye to perceive and resolve an object and its details. The minimum angle of resolution (MAR) (Figure 5.1.1) is the angle between two objects in order to be resolved correctly on the retina. The minimum angle of resolution also depends on brightness and contrast of presented test objects. These parameters are standardized according to DIN-norms (58220).[126]

Decimal visual acuity is calculated as the reciprocal of the minimal angle of resolution, which is the smallest recognized gap in the Landolt ring given in arcminute.

$$\text{Decimal VA} = \frac{1}{\text{smallest recognized gap in the Landolt ring given in arcminute}}$$

It is possible to calculate the Log(MAR) from the decimal VA using the following formula:

$$\text{Log(MAR)} = -\text{Log (decimal VA)}$$

The advantage of Log(MAR) is that it is an logarithmic scale, which reflects the psychometric perception of vision. For instance: an doubling in visual acuity indicates a halving of the minimum angle of resolution. On a decimal scale this could be an increase of visual acuity from 0.1 to 0.2 or from 0.5 to 1.0 resulting in different numeric differences. On the logarithmic Log(MAR) scale this would be expressed as an increase by –0.3 independent of

the initial visual acuity. In the above example the Log(MAR) would increase from 1.0 to 0.7 or from 0.3 to 0.0. Unfortunately the Log(MAR) scale is an inverted scale due to the minus in the formula, indicating better visual acuity by lower digits. The other major advantage of Log(MAR) scale is that is allows to mathematically calculate average or changes in VA. Due to the logarithmic psychometric perception this would not be allowed on the decimal scale. (Table 5.1.1)

Figure 5.1.1

MAR (Minimum Angle of Resolution) [127]

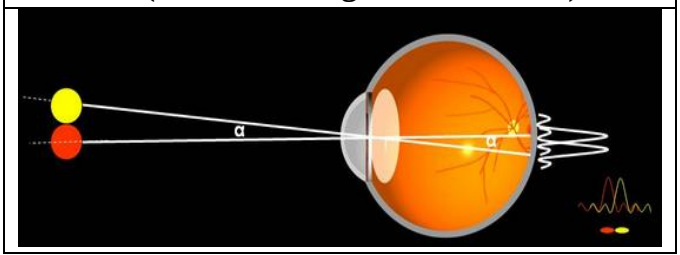


Table 5.1.1

Visual Acuity Scales [128]

Decimal	LogMAR
0.01	2.00
0.025	1.60
0.05	1.30
0.10	1.00
0.125	0.90
0.16	0.80
0.20	0.70
0.25	0.60
0.32	0.50
0.4	0.40
0.5	0.30
0.63	0.20
0.80	0.10
1.00	0.00
1.25	-0.10
1.60	-0.20
2.0	-0.30
2.5	-0.40

In this study the visual acuity has been tested in predefined intervals. The best corrected visual acuity has been taken according to decimal VA method (DIN-norms: 58220). The values have been later converted to log MAR for the further statistical analysis.

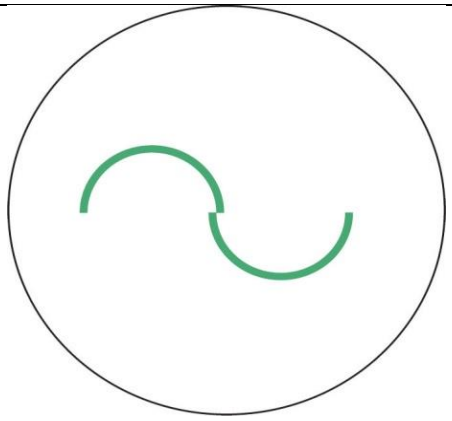
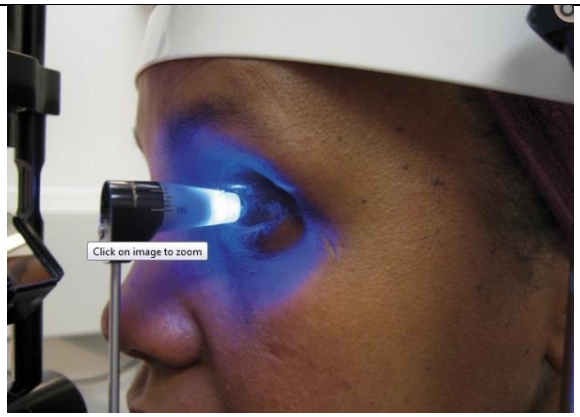
5.2. Intraocular pressure (IOP) measurement

Intraocular pressure (IOP) is the pressure of the fluid inside the eye. It is a main diagnostic indicator to identify any type of glaucoma and the glaucoma therapy is based on IOP regulation. The normal IOP values are range from 8-21mmHg, with a normal average of 16 +/- 2.5mmHg. Several factors can influence the IOP, such as age, race, genetics, obesity, blood pressure, exercise, Valsalva, posture, time of day, drugs, hormones, eye lid closure and any refractive error. [129]

There are several methods to measure the intraocular pressure. The gold standard method is the Goldmann applanation tonometry (Table 5.2.1).

Table 5.2.1

Steps of Goldmann applanation tonometry [130]	
I	Installation of local anesthetic eye drops with fluorescein dye
II	Set the blue filter of slit beam and shine onto the tonometer head with bright light. This show the fluorescein rings
III	Tonometer head should have perpendicular position to the eye and then move it forward until prism attach gently the central cornea
IV	Calibrate dial on the tonometer until the two margins of fluorescein semi rings meet each other in horizontally S shape and then note the reading on the dial

Applanation tonometry rings with Goldmann prism	**Applanation tonometry**
	

All measurements of the intraocular pressure in our study are based on the Goldmann applanation method.

5.3. Ocular coherence tomography (OCT)

OCT allows for measurement of vitreal, retinal and choroidal thickness in a non-invasive procedure (Table 5.3.1). It uses an interferometric method. This non-contact method can create a tomographic image of all retinal layers and can examine retinal areas with a sectional resolution of 10-15 microns.[131] It is a similar technique as the ultrasound, except that the image is created by reflection and backscattering of a laser beam. Any reflective property change between the tissues can be determined with this technique which is based on time domain or spectral domain protocols (Table 5.3.2). [132, 133]

Table 5.3.1
OCT Functions [134]
Measures retinal thickness
Measures retinal nerve fiber layer (RNFL)
Measures retinal volume
Creates retinal map
Isolates and creates maps of internal limiting membrane and retinal pigment epithelium
Measures optic disk parameters
Displays 3-dimensional views
Provides C-scan (en face) analyses, creating a section plane horizontally in tissue
Offers RPE fit function

Table 5.3.2
Spectral domain OCT protocols [135, 136]
Resolution of 3 micrometer
OCT images continuously in a 6mm area
20.000-40.000 scans per second
2 as well as 3 dimensional images

It is the standard method in many retinal diseases (Table 5.3.3) such as macular edema (including the anatomical location of edema), macular pucker, macular hole, epiretinal gliosis, vitreo-macular traction, macular degeneration, neurosensory retinal or retinal pigment epithelium pathologies or detachments. OCT has the capability to monitor and compare any progression of the macular disease (macular thickness, retinal volume) as in cases of macular edema therefore it is an important tool to evaluate the efficacy of treatment and further management (Table 4). [137, 138] OCT has a limitation in eyes with a media opacity such vitreous hemorrhage, corneal scars or mature cataract. The quality of the OCT imaging depends on machine operator, patient cooperation, media clarity and type of OCT machine.

Table 5.3.3		
Anatomical OCT interpretation and associated diseases [139]		
Preretinal	**Intraretinal**	**Subretinal**
Posterior vitreous detachment	Macula edema	RPE detachment
Vitreomacular traction	IGS	RPE tear
Epiretinal membrane	Retinal exudates	**Choroid**
Pseudo- lamellar- or macular hole		CNV

The anatomical regions of macula area are listed in Table 5.3.4 and figure 5.3.1. [140, 141]

Figure 5.3.1

Macular regional map

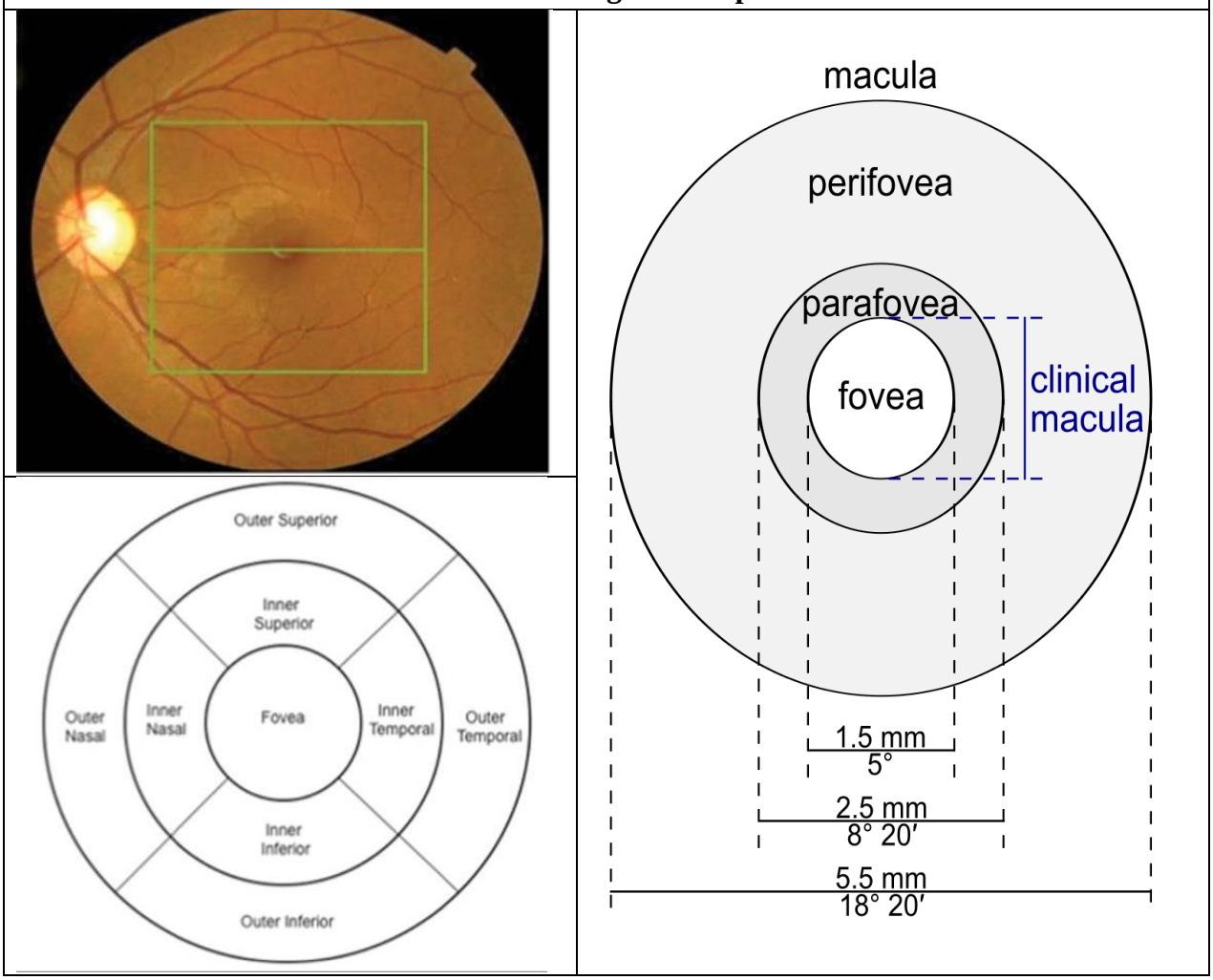


Table 5.3.4			
Macula anatomical regions		**Diameter of macula**	
Fovea	1.55 mm	Anatomical macula diameter	5.5-6 mm
Foveal avascular zone	0.5 to 0.6 mm		
Foveala	0.35 mm	Clinical macula diameter (Fovea)	1.5 mm
Umbo	0.15 mm		

The normal values of macular thickness and macular volume are listed in Tables 5.3.5. Normally, the thinnest part of macula is the central fovea area and the thickest part is within 3 mm diameter from the central macula to peripheral macula and then there is a further decreasing of thickness toward peripheral macula. The temporal part of macula is thinner than nasal part. [142, 143, 144, 145]

Table 5.3.5

Normal macular thickness		**Normal macular volume by OCT**	
Region	**Mean +/- SD**	Total macular volume	3.04 +/- 0.14 mm^3
Fovea (500 μm radius)	212±20	Central subfield volume	0.2122 +/- 0.017 mm^3
Center			
Automatically determined	182 ±23		
Manually determined	170 ± 18		
Inner ring (1,5 mm radius)	255 ± 17		
Superior	260 ±15		
Inferior	251 ±13		
Temporal	267 ± 16		
Nasal			
Inner ring (3 mm radius)			
Superior	239 ± 16		
Inferior	210 ± 13		
Temporal	210 ± 14		
Nasal	246 ± 14		

Overall, the mean CSF volume is 0.2122 +/- 0.017 mm^3. Mean total volume (including all subfields) is 3.0382 +/- 0.1432 mm^3. Among the ETDRS subfields (central fovea, inner macula and outer macula), the outer nasal quadrant had the maximum volume (0.3386 +/- 0.016 mm^3). The retinal volume did not show significant difference with age (P = 0.33), gender (P = 0.2) or race (P = 0.42). [145]

Normative values for total macular volume and volume in each subfield in otherwise healthy eyes were established using Spectralis SD-OCT. Based on these data, the present study proposes the guidelines for normal CSF volume to be 0.2122 mm^3 for future studies using macular volume measurements with Spectralis SD-OCT. Macular volume data in various

conditions like macular edema and response to treatment will be of more importance than retinal thickness in clinical practice as well as a parameter for future clinical trials for treatment of such diseases.

In this study, the central macular thickness and the macular volume have been monitored with the help of the OCT, Spectralis, Heidelberg Engineering GmbH. All the measurements have been performed using the same technique and the same OCT equipment. The central retinal thickness (CRT) value is referred to the central foveal area.

5.4. Intravitreal injection procedure

Intravitreal injection of 0.7 mg Dexamethasone implant is performed in aseptic condition. It has a special delivery system with a preload, single use applicator (Figure 5.4.1 and 5.4.2). Gloves, drape and eyelid speculum should be in sterile condition. The procedure is under local anesthesia. Prior to intravitreal injection, a prophylactic antibiotic local therapy is instilled. The periocular skin and the conjunctiva is disinfected and washed with 5% povidone iodine prior to the injection. [146] [147]

Figure 5.4.1

Procedure of 0.7 mg Dexamethasone implant injection [148]

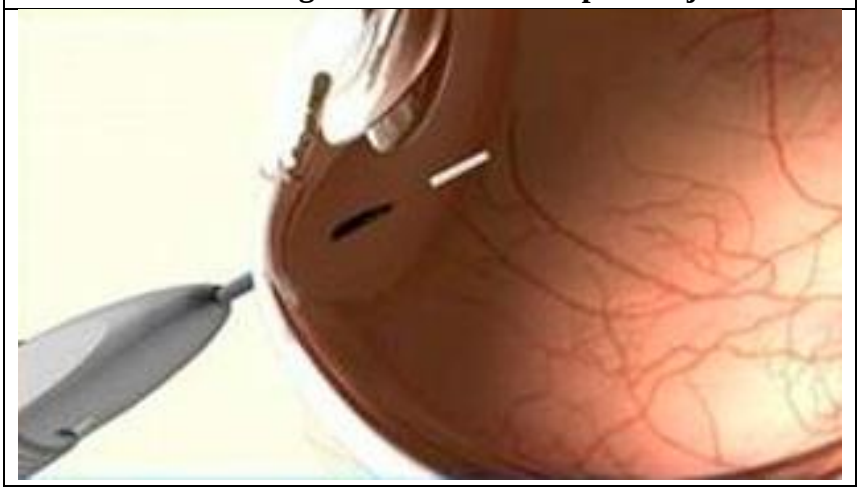
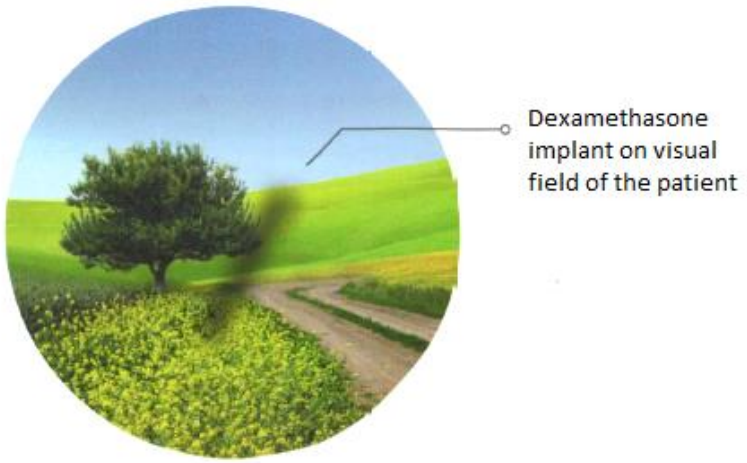


Figure 5.4.2

Dexamethasone implant in visual field [149]



The administration of 0.7 mg Dexamethasone implant has the following steps:

1) The long axis of the applicator is hold parallel to the limbus.

2) The applicator is injected 1mm into the sclera at an oblique angle and hold parallel to the limbus.

3) The applicator is then redirected towards the vitreous cavity. This will create as sclera tunnel. Then the needle enters into the vitreous cavity.

4) The injection button is pressed slowly until a click.

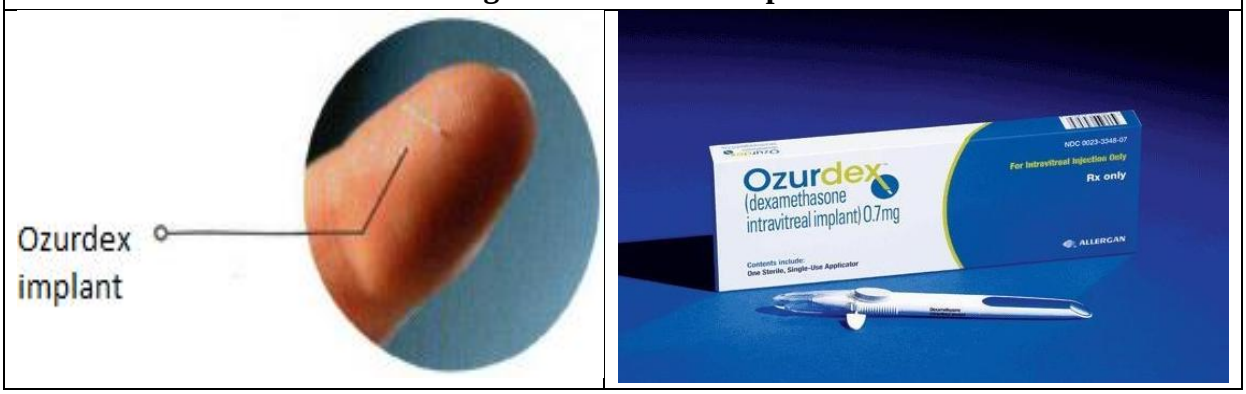
5) The applicator should be removed in the same direction as it has been entered.[150]

5.5. Ozurdex® Implant

Ozurdex® (Allergan, Irvine, CA, USA) [151] is a single use, slow release drug of 0.7 mg Dexamethasone approved by the European Medicines Agency (EMA) [152] (Figure 5.5.1). It is a biodegradable, tiny solid rod shape implant that is injected into vitreous of the eye and it has a solid polymer sustained release drug delivery system [153] and constituted of an intravitreal polyglactin (poly D,L-lactide-coglycolide) polymer matrix without a preservative. Dexamethasone itself has a white colored crystalline powder poorly soluble in water. Dexamethasone implant can dissolve natural over months as the copolymer matrix degrades to glycolic acid and lactic acid, which are metabolized to carbon dioxide and water [154] and does not need to be removed chirurgical. Dexamethasone implant has a minimal systemic absorption.

Figure 5.5.1

0.7 mg Dexamethasone implant



Pharmacologically, Dexamethasone is an inflammatory suppressor that acts as inhibitor of prostaglandin and pro-inflammatory cytokines (such as interleukins, tumor necrosis factor-α, interferon γ) which are associated with decreased edema, fibrin deposition, inflammatory cells migration and capillary leakage. Dexamethasone acts as a corticosteroid.

The main indication of the 0.7 mg Dexamethasone implantation are non-infectious inflammatory eye conditions, a macula edema associated to a central or branch retinal vein occlusion and a macula edema due to diabetic retinopathy.

The Ozurdex® implant has some advantages over orally cortisone therapy. There is a minimal systemic absorption and has not any significant interaction.

The implant of 0.7 mg Dexamethasone has an action with an improvement of clinical findings up to 12 weeks then followed by a gradual declination. The overall efficacy is less than 24 weeks.[155] Other study has shown that in cases of macular edema associated with diabetes mellitus there is a functional and anatomical improvement with a duration of 4 months. [156]

A retrospective study of diabetic patients has showed that after repeated injection of 0,7mg Dexamethasone intravitreal implant there is no effect on HbA1c or renal function. But some transient changes of lipid profile (LDL cholesterol level) have been reported. [157]

It can be used in children (off label), during pregnancy (off label) or lactation. Repeated injections for long term use are safe.

The main contraindications of the 0.7 mg Dexamethasone implant are any peri- or intra ocular infection, glaucoma patients with progressive disease, patients with associated cortisone

responding glaucoma, any condition of anatomical malformation of posterior lens capsule and in rare cases, patient with allergy to its ingredients.

The main identified risks after 0.7 mg Dexamethasone implant are mentioned in table 5.5.1.

Table 5.5.1	
Complication after 0,7 mg Dexamethasone implantation[158]	
Endophthalmitis (Infectious / non-infectious)	Increased intraocular pressure
Retinal detachment or retinal tear	Posterior subcapsular cataract
Implant dislocation	Implant misplacement
Increase risk of secondary eye infection due to bacteria, fungi or viruses	Retinitis secondary to reactivation of latent viral infection
Vitreous hemorrhage or detachment	Rare systemic effects such as infection, healing impairment, hypertension

5.6. Statistics

The data of this study have been collected and analyzed initially with Microsoft® Office Excel 365. The statistical analysis was performed and based on SPSS Statistics 25 (IBM, Armonk, NY, USA). Differences between two groups were determined by students-T-Test. In more than two groups an ANOVA with Bonferroni post hoc test was used. A p-value of <0.05 was regarded as statistically significant.

6. Results

The study was conducted at the department of Ophthalmology of Ludwig Maximilians University in Munich, Germany and is a retrospective analysis of a total of 55 eyes of 44 patients with an active non-infectious uveitis. Baseline patient characteristics are depicted in Table 6.1.

Table 6.1

Review and characteristics of patient and eyes treated with intravitreal Dexamethasone implant in noninfectious uveitis

Patients	44		
Eyes	55		
Sex	Male 15 (34%)	Female 29 (66%)	
Age (years ± range)	Male	60 [32-84]	
	Female	59 [23-89]	

In total 157 injections were conducted. Each eye has received 2 (at least) to 5 intravitreal injections of 0.7 mg Dexamethasone implant. Table 6.2 is to summarize the study patient drop and lost to follow up characteristics after the second injection.

Table 6.2

Number of Dexamethasone implants pro eye

Total implants	157 Dexamethasone implants	
Implants pro eye	1 and 2 Dexamethasone implants	55 eyes
	3 Dexamethasone implants	28 eyes
	4 Dexamethasone implants	11 eyes
	5 Dexamethasone implants	8 eyes

The uvetic macula edema was the indicator parameter for the decision of intravitreal injection administration and was identified with OCT imaging. All patients underwent clinical and laboratory testing for exclusion of an infectious cause of uveitis (Table 6.3). As this study was conducted in a real life retrospective settings some patients have received additional topical and/or systemic medication, but did not receive any other intravitreal medication during this study (Table 6.4).

Table 6.3			
Summary of diseases according to anatomical SUN classification [159]			
Anterior uveitis	17 eyes	Iritis	2 eyes
		Iridocyclitis	15 eyes
Intermediate uveitis	12 eyes	Hyalitis	1 eye
		Posteriorcyclitis	11 eyes
Posterior uveitis	20 eyes	Papillitis / Papillophlebitis	2 eyes
		Choroiditits	1 eye
		Vasculitis	6 eyes
		Chorioretinitis	11 eyes
Panuveitis	6 eyes		
Summary of diseases according to etiological classification			
Idiopathic	34 patients (44 eyes)	HLA B27 (+)	1 patient
Sarcoidosis	3 patients (4 eyes)	Raynaud's syndrome	1 patient
Behcet's disease	2 patients	Psoriasis	1 patient
B cell lymphoma	1 patient	Birdshot	1 patient

Table 6.4		
Therapies prior to Dexamethasone implant		
Topical	**Periocular steroids**	33 Pt (40 eyes)
	Intravitreal anti-VEGF	4 Pt (4 eyes)
Therapies prior to and during time of Dexamethasone implant		
Local	**Steroids**	30 patients (32 eyes)
	Anti-inflammatory [NSAID]	3 patients
Systemic	**Steroids**	27 patients
	Acetazolamide (Diamox)	21 patients
	Immunosuppressants	(25 patients)
	> Methotrexate	7 patients
	> Ciclosporin	6 patients
	> Adalimumab	4 patients
	> Azathrioprine	3 patients
	> Mycophenolate	3 patients
	> Interferon α2	1 patient
	> Chemotherapy (Carboplatin)	1 patient

Visual acuity, central macular thickness and macular volume were the primary parameters that have been studied and monitored. Additionally, intraocular pressure was measured as secondary parameter. The response to the Dexamethasone implant was measured by change in all parameters during follow ups of each injection of 0.7mg Dexamethasone implant.

The monitoring and analysis of all clinical parameters was based on four follow ups intervals that have been set for an statistical analysis. Generally, the patient were seen at first, third and fifth month after the injection. The injection day was defined as the initial point of time of all intervals and it was counted as the starting point of each follow up of each injection. The time of each follow up after each injection is defined in Table 6.5.

Table 6.5

Overview of time intervals of follow ups after each Dexamethasone implant injection

Day of injection	Visit: V 1
4 weeks follow up after the injection ± 1 week	Visit: V 2
3 months follow up after the injection ± 2 weeks	Visit: V 3
5 months follow up after the injection ± 1 months	Visit: V 4

6.1. Visual acuity

The initial BCVA of all 55 eyes (V1.1), before any 0.7 mg Dexamethasone implant, had a mean ± standard deviation (SD) value of 0.78 ± 0.43 logMAR. In the predefined interval of four weeks and after the first 0.7 mg Dexamethasone implantation (V1.2), there was a statistically significant improvement to 0.55 ± 0.42 logMAR. A mild visual deterioration to 0.63 ± 0.47 logMAR has observed at the three months follow up (V1.3). By the last follow up at five months (V1.4) after 0.7 mg Dexamethasone injection, BCVA showed a further worsening to 0.73 ± 0.42 logMAR.

In all 55 eyes, a second 0.7 mg Dexamethasone implant was inserted. The clinical response was similar to the first 0.7 mg Dexamethasone implant. The BCVA at the time of the second 0.7 mg Dexamethasone implant (V2.1) had a mean value of 0.80 ± 0.45 logMAR. Four weeks later (V2.2) the mean BCVA has an improvement to 0.59 ± 0.44 logMAR with a mild reduction of mean VA of 0.61 ± 0.47 logMAR after a post injection interval of three months (V2.3). Finally at the post injection interval of five months the mean VA was 0.75 ± 0.53 logMAR which shows a significant BCVA deterioration.

Similar results have seen in the 28 eyes that continue to receive the third 0.7 mg Dexamethasone implant. The initial mean BCVA at the time of third injection (V3.1) was 0.83 ± 0.49 logMAR with a further melioration of mean BCVA to 0.66 ± 0.52 logMAR 1 month after the third injection (V3.2). At the time of three months (V3.3) after the third injection shows again a similar mild worsening of mean BCVA of 0.70 ± 0.77 logMAR. The last predefined follow up of five months (V 3.4), has showed again a reduction of mean VA at level of 0.85 ± 0.63 logMAR.

Mean BCVA of the fourth and fifth injection showed similar results, however with a lower statistical significance than the first three injections because of the small number of cases.

11 eyes have received a fourth intravitreal 0.7 mg Dexamethasone implant. The first measurement of mean BCVA at the day of injection (V4.1) was 0.72 ± 0.76 logMAR. A further statistical improvement of mean BCVA to 0.54 ± 0.40 logMAR was seen at the time of one month (V4.2). 0.80 ± 0.9 logMAR was the mean BCVA in period of three months after fourth injection (V4.3). Five months follow up (V4.4) shows again a worsening of mean VA to 0.70 ± 0.38 logMAR.

The last VA measurements have been monitored in eight (8) eyes after the fifth injection of 0.7 mg Dexamethasone implant. The first time point of injection day (V5.1) had a mean BCVA of 0.87 ± 0.97 logMAR. There again was an improvement of mean BCVA to 0.78 ± 1.1 logMAR in one month follow up (V 5.2). At the follow up of three months (V 5.3) was seen an improvement of mean BCVA (in comparison to other four0.7 mg Dexamethasone implants, probably due to insufficient data and reduced number of cases) to 0.28 ± 0.16 logMAR. The last predefined interval of five months (V 5.4), has showed again a significant decrease of mean BCVA to 0.60 ± 0.46 logMAR (Diagram 6.1.1).

Diagram 6.1.1

VA mean and SD (logMAR / months) of all injection during follow ups

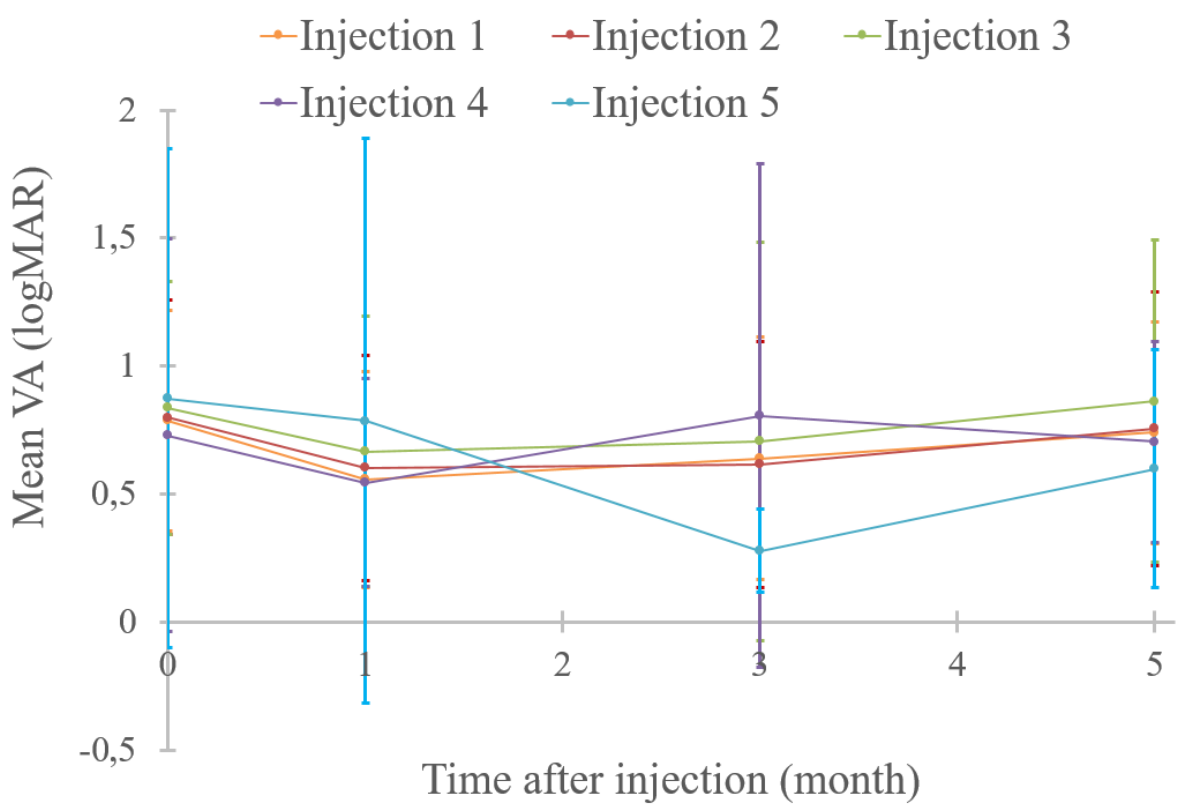
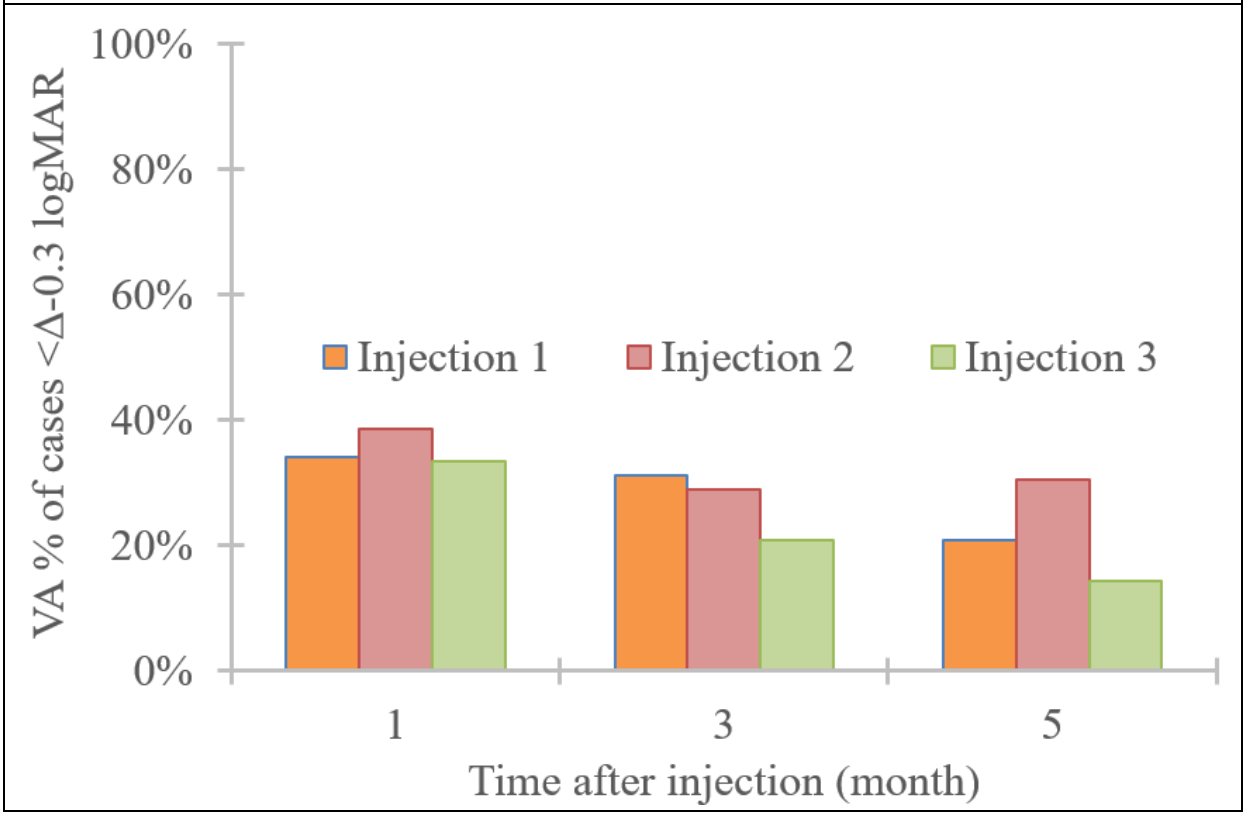


Diagram 6.1.2 represents the percentage of those cases that during follow up of the first three injections had an improvement of less than -0.3 logMAR. During the fourth and fifth injections were insufficient cases to review an accurate result.

The percent of cases that had a BCVA difference of < - 0.3 logMAR between the day of injection and four week follow interval during first three injections were 34 % (first injection), 38.6 % (second injection) and 33.3% (third injection). This difference of logMAR during the three month follow up were observed in 31 % (first injection), 28.9 % (second injection) and 20.8 % (third injection) cases. During the last follow up at month 5 it was 20.8 %, 20.4 % and 14.2 % respectively.

Diagram 6.1.2

% of cases that had an VA < Δ - 0.3 logMAR during each follow up of first three injections



6.2. Optical coherence tomography

Central retinal thickness (diagram 6.2.1 and figure 6.2.1) and macular volume (diagram 6.2.2 and figure 6.2.2) were followed up as the main anatomical study parameter for pharmacological response.

After the first injection there was a statistically significant decrease in central retinal thickness from 540 mm ± 189 mm to 287 mm ± 107 mm ($p<0.001$) and macular volume from 10.6 mm^3 ± 2.1 mm^3 to 9.22 mm^3 ± 1.2 mm^3 ($p=0.002$) after 4 weeks of follow up. From baseline to three month this difference was still significant ($p<0.001$ for CRT and $p=0.002$ for MV). After five month the Dexamethasone implant did not exhibit any statistically significant effect on central retinal thickness and macular volume anymore ($p=0.09$ and $p=0.82$ respectively).

The same pattern was observed for the second injection with a statistical significant effect at the time of 4 weeks ($p<0.001$ for CRT and $p<0.001$ for MV) and 3 months ($p<0.001$ for CRT and $p=0.025$ for MV) but the effect is diminished after five months ($p=0.45$ for CRT and $p=0.93$ for MV).

In detail, the point time of V2.1 referred to the time of second 0.7 mg Dexamethasone implant, the CRT and MV measurement at this point was recorded as 507 mm ± 195 mm and 10.7 mm^3 ± 1.7 mm^3. At four weeks (±) follow up (V2.2) a notable improvement to 280 mm ± 137 mm and 9.2 mm^3 ± 1.2 mm^3 was seen. At the three months (± 2 weeks) control (V2.3), CRT and MV has been recorded as 318 mm ± 91.5 mm and 9.7 mm^3 ± 1.1 mm^3. The final follow up of CRT and MV values of second injection of 0,7 mg Dexamethasone implant (V2.4) were 446 mm ± 168 mm and 10.2 mm^3 ± 1.7$mm^3$and it had a similar worsening of OCT values as during the last follow up (V1.4) of the first injection of 0,7 mg Dexamethasone implant.

Also after the third injection a statistically significant improvement of CRT and MV was seen ($p=0.001$ for CRT and $p=0.044$ for MV at the time of first follow up). Whereas the findings of the third and fifth month follow ups showed a reduction of effectiveness with p values of $p= 0.031$ (CRT) / $p=0.39$(MV) and $p=0.92$ (CRT) / $p=1.0$ (MV) respectively.

The CRT and MV values at the time of the third injection of 0.7 mg Dexamethasone implant (V3.1) were 476 mm ± 181 mm and 10.3 mm^3 ± 2.4 mm^3. The next time point V3.2 revealed measurements of 281 mm ± 86.1 and 8.8 mm^3 ± 1.2 mm^3, respectively, which demonstrated again an improvement of OCT values. V3.3 reported again and mild increase of CRT and MV

values to 328 mm +/- 104 mm and 9.3 mm^3 ± 1.2 mm^3. The last follow up V3.4 showed an obvious worsening of CRT and MV values with 549 mm ± 239 mm and 10mm^3 ± 1.5 mm^3.

After the fourth and fifth 0.7 mg Dexamethasone implant similar results of mean and SD values of CRT and MV were recorded, but had lower accuracy as the first three injections due to lower number of clinical cases.

The CRT and MV measurement of V4.1 after the fourth 0.7 mg Dexamethasone injection was recorded as 568 mm ± 257 mm and 10mm^3 ± 1.8 mm^3. A repeated improvement of mean CRT and MV was seen four weeks (± 1 week) after (V4.2) with mean and SD values of 253 mm ± 64 and 8.5 mm^3 ± 1.6 mm^3. The V4.3 follow up showed a mild worsening of mean and SD CRT and MV to 341 mm ± 95 mm and 8.9 mm^3 ± 1.5mm^3. The final follow up of fourth injection of 0.7 mg Dexamethasone implant again demonstrated worsened measurements as high as 493 mm ± 156 mm and 10.3 mm^3 ± 2.1 mm^3, respectively.

The measurement at the fifth 0.7 mg Dexamethasone injection were recorded in 8 eyes. The mean and SD results of CRT and MV at time point V5.1 was 547 mm ± 180 mm and 10.4 mm^3 ± 3.1 mm^3. The V5.2 mean and SD values appeared again better as 325 mm ± 186 mm and 9.4 mm^3 ± 2.5mm^3 with a mild worsening at the point of V5.3 with values of 412 mm ± 178 mm and 10.2 mm^3 ± 1.3mm^3. Lastly the mean and SD of CRT worsened again as 498 mm ± 171 mm with a change of MV mean and SD values to 9.6 mm^3 ± 0.4 mm^3.

Figure 6.2.1

All OCT-CRT follow ups during an injection of Dexamethasone implant

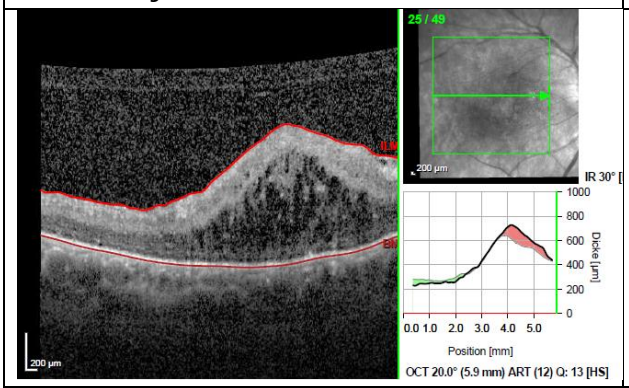
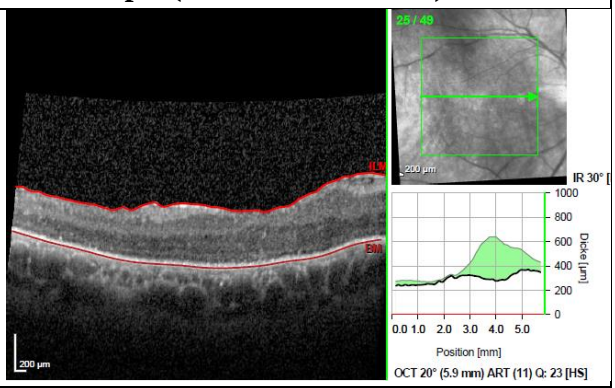
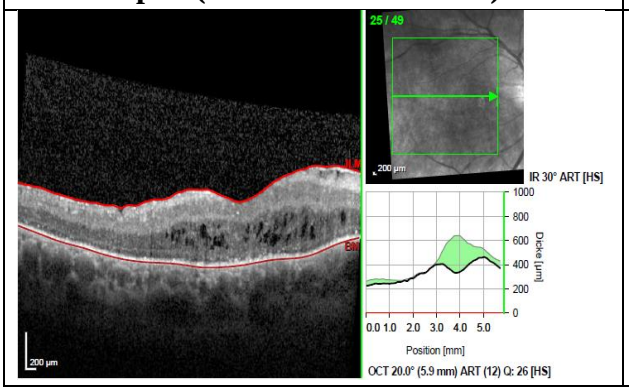
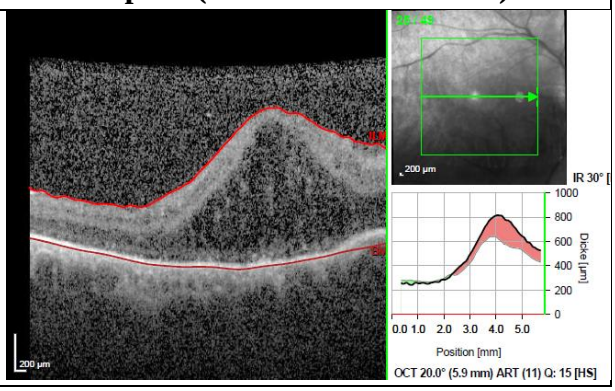
Date of injection	**Follow up I (4 weeks +/- 1 week)**
	
Follow up II (3 months +/- 2 weeks)	**Follow up III (5 months +/- 1 month)**
	

Diagram 6.2.1

CRT mean and SD (microns/months) of all injection during follow ups

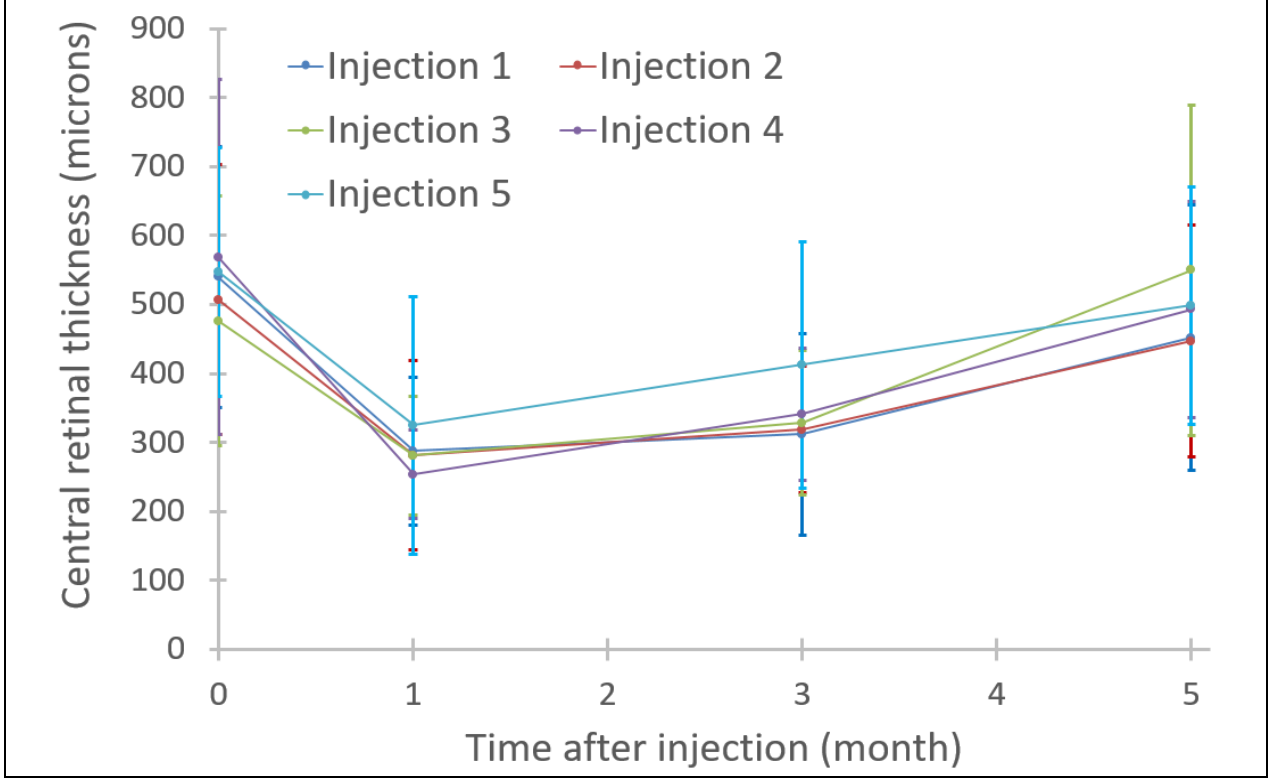
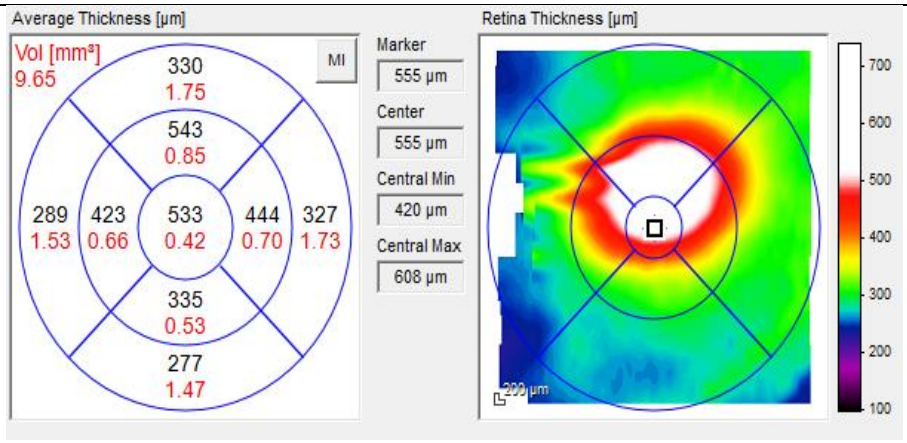


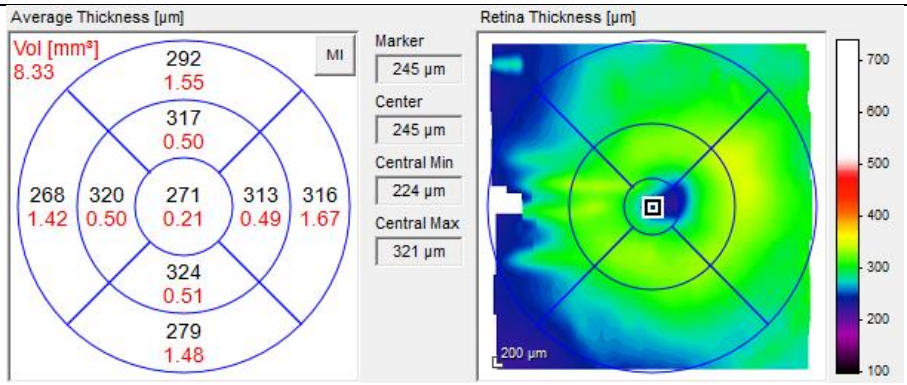
Figure 6.2.2

All OCT-MV follow ups during an injection of Dexamethasone implant

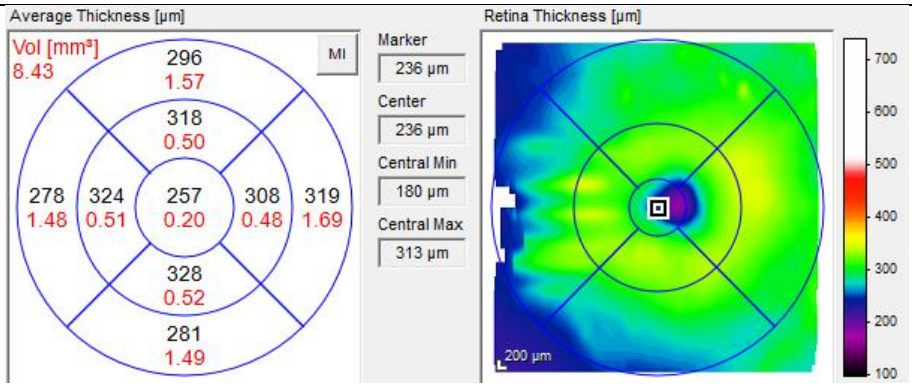
Date of injection



Follow up I (4 weeks +/- 1 week)



Follow up II (3 months +/- 2 weeks)



Follow up III (5 months +/- 1 month)

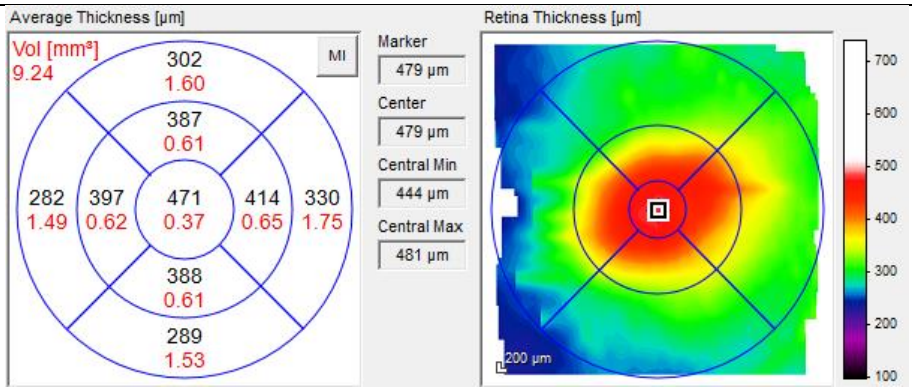
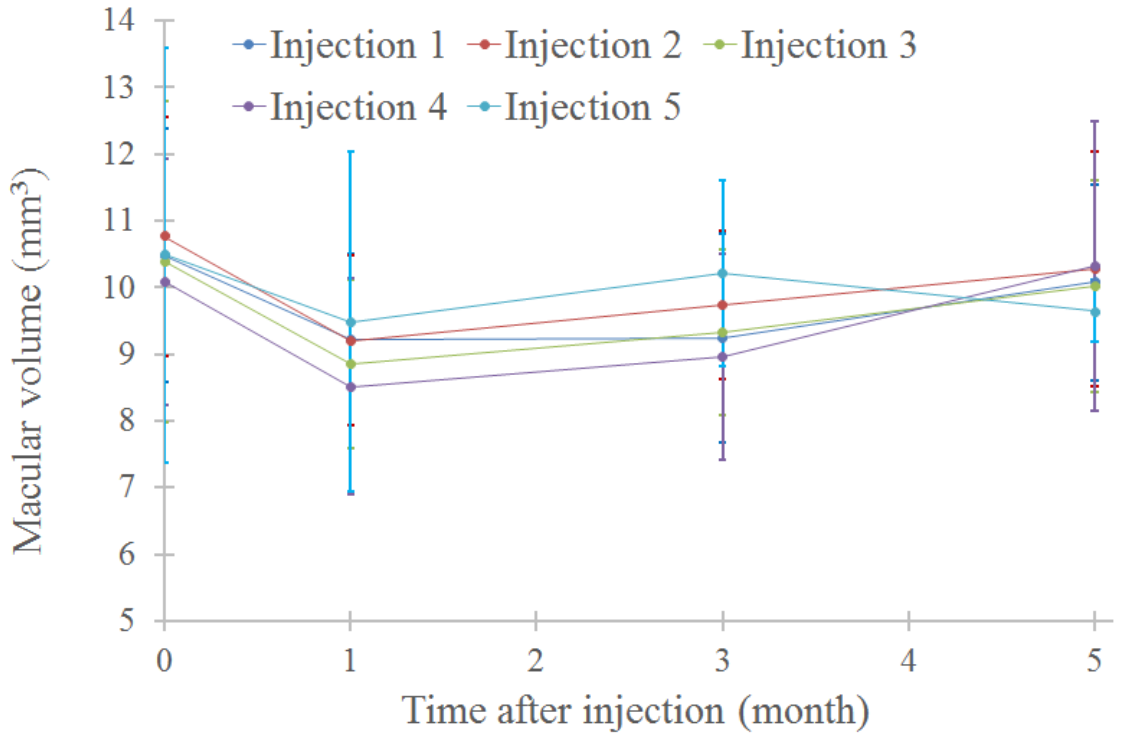


Diagram 6.2.2

MV mean and SD (mm^3/months) of all injection during follow ups



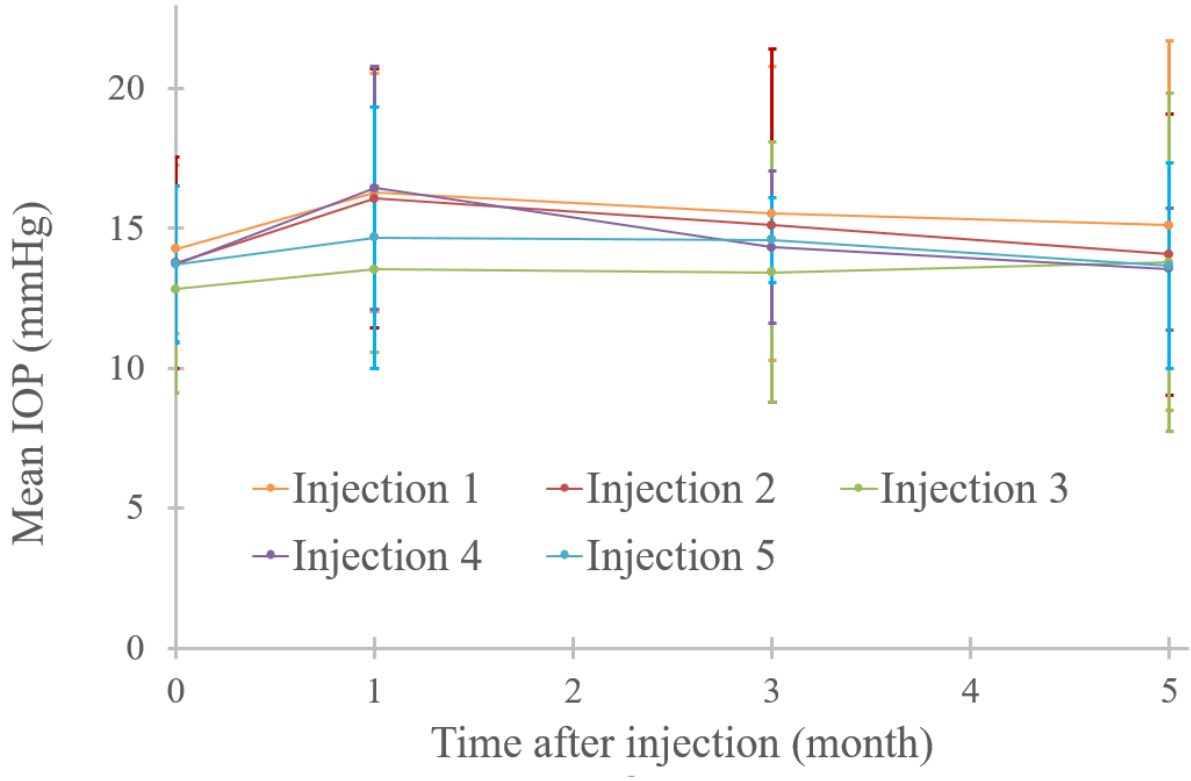
6.3. Intraocular pressure

The intraocular pressure (IOP) in this study was monitored as a secondary parameter. In our cohort there was limited information about any possible additional local or systemic anti-glaucomatous prescription which might have been prescribed in the outpatient setting, in between the predefined follow up intervals that take place at our department. This lack of detailed information impedes interpretation of IOP values.

The mean and standard deviation of all five injections is summarized in diagram 6.3.1.

Diagram 6.3.1

Mean values (mmHg) and standard deviation of IOP during 5 Dexamethasone implants



After injections a major IOP increase was observed in the fourth week of follow-up with a slow decline at the next time points. Since the standard deviation of IOP-measurements varies widely between individuals it is also important to analyze the percentage of eyes that showed an increase of 10 mmHg of more at different time points.

After injection 1 at the post injection time of four weeks an IOP elevation of more than 10 mmHg was observed in 8.6 % of the cases. The second follow up at month three after injection showed that in 4.5 % of the cases the IOP increased by more than 10 mmHg. After five months of follow up 4.3% of cases showed an IOP elevation of more than 10mmHg.

The clinical results during the second injection seemed to be similar as during the first injection. 12.1 % of cases had an IOP elevation more than 10 mmHg at four weeks interval after the second injection. Later, at time point of three months has observed an IOP improvement and only 5.7 % had an IOP increase over 10 mmHg. Finally at the time of five months the cases with IOP >10mmHg were reduced to 2.3 %.

During third injection and at the time of four weeks follow there was no case with IOP elevation over 10mmHg, this is a comparable result to the first two injections and is ascribed to intensified usage of anti-glaucomatous medications. At three months interval after third injection an IOP increase of more than 10 mmHg was seen in 4.3 % cases. This was similar to the increase during the first two injections. Lastly, there were 10.5 % of cases with elevation of IOP over 10 mmHg after a post injection follow up time of five month. (Diagram 6.3.2 and Table 6.3.1).

Diagram 6.3.2

% of cases that had an IOP elevation < 10mmHg during each follow up of all injections

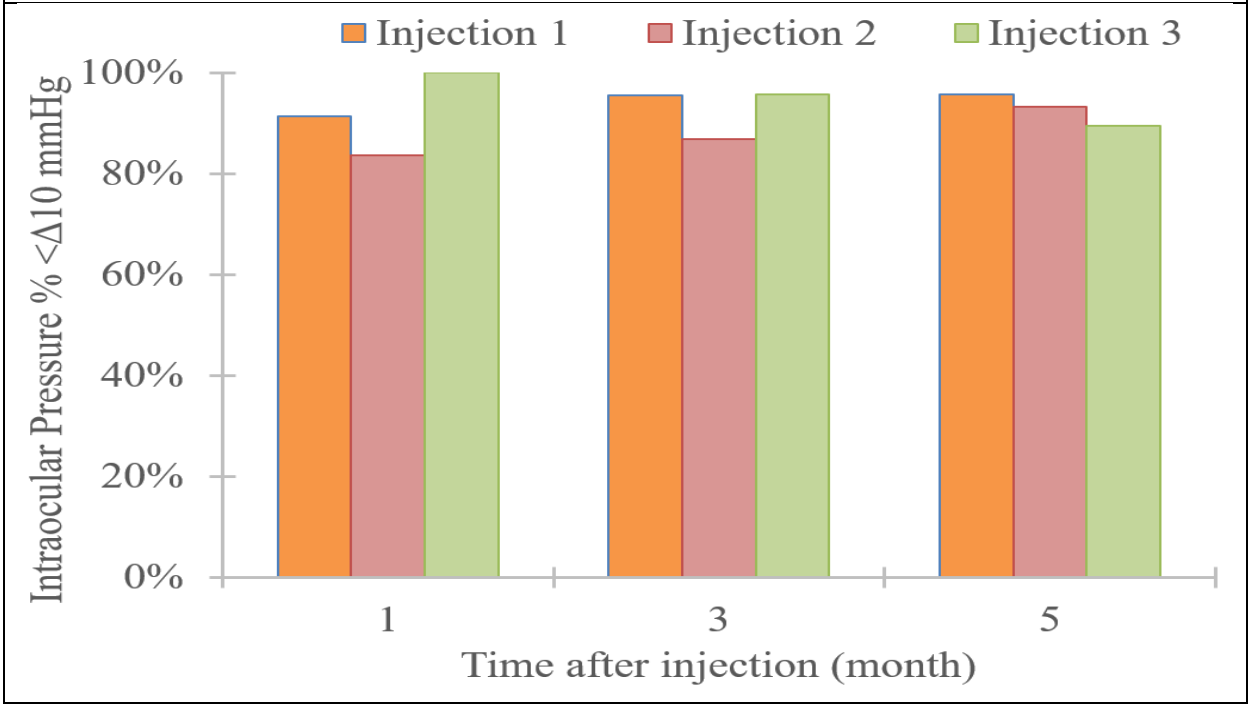


Table 6.3.1		
% of cases with IOP elevation > 10 mmHg after each Dexamethasone implant during all follow ups of the first three injections		
IOP V1.2	**IOP V1.3**	**IOP V1.4**
8.6 %	4.5 %	4.3 %
IOP V2.2	**IOP V2.3**	**IOP V2.4**
12.1 %	5.7 %	2.3 %
IOP V3.2	**IOP V3.3**	**IOP V3.4**
0 %	4.3 %	10.5 %

During fourth and fifth injections were not enough accurate measurable values due to least cases.

The percent of the cases that had an elevation of IOP value > 10mmHg from time of first injection to all follow ups and even the time of each re-injection is listed in Table 6.3.2.

Table 6.3.2										
% of cases with IOP elevation > 10 mmHg from day of first Dexamethasone implant to all follow ups and time of re-injections										
IOP V1.2	**IOP V1.3**	**IOP V1.4**	**IOP V2.1**	**IOP V2.2**	**IOP V2.3**	**IOP V2.4**	**IOP V3.1**	**IOP V3.2**	**IOP V3.3**	**IOP V3.4**
8.6 %	4.5 %	4.3 %	1.9%	6.9%	5.2%	4.4%	3.5%	0%	8.6%	10.5%

A general evaluation of our measurements showed a similar result during all five injection of 0.7 mg Dexamethasone implant. The maximal mean value IOP elevation difference was 0.7 mmHg to 2.7 mmHg at the time point of four weeks (± 1 week) after the injection. 0.6 mmHg to 1.3 mmHg was the maximal mean value IOP elevation difference at the time point of three months (± 4 weeks). Finally the mean value difference at the time point of V4, five months (± 1 month), was between - 0.1 mmHg to 1 mmHg, this difference is not an important IOP change. It is likely due to lack of Dexamethasone action.[160]

6.4. Cataract surgery and other associated factors

In addition to the main parameters of this study (VA, central retinal thickness, macular volume and IOP), the lens status was recorded since corticosteroids as well as inflammation cause cataract. Prior to the initiation of 0.7 Dexamethasone therapy, 28 eyes were pseudophakic already. Four (4) eyes were already aphakic prior the first injection of 0.7 mg Dexamethasone implant and only one (1) has to proceed to a secondary IOL implantation during the follow ups period. In 23 eyes mild to advanced cataract was recorded and 15 of these 23 eyes underwent cataract surgery during the study period. Only 8 eyes (34.8 %) have kept the physiological lens during this study (Table 6.4.1). The correlation between cataract operation and number of injection of 0.7 mg Dexamethasone implant is listed in table 6.4.2.

Table 6.4.1	
Lens status prior Dexamethasone treatment	
Aphakia	4
Phakia	23
Pseudophakia	28
Cataract operation or secondary IOL implantation during Dexamethasone treatment	
Cataract operation during IVOMs	15
IOL implantation in aphakic eyes during IVOMs	1

Table 6.4.2	
Cataract operation in correlation to number of injection	
IVOM 1	7 Eyes underwent to cataract operation
IVOM 2	6 Eyes underwent to cataract operation
IVOM 3	1 Eyes underwent to cataract operation
IVOM 4	1 Eye underwent to cataract operation

The cataract formation of the 15 eyes and subsequent cataract operation with implantation of an artificial intraocular lens (IOL) was due to steroid as side effect. Other important factor of secondary cataract formation was the inflammation.

7. Discussion

In this retrospective study, we have examined the clinical long term outcomes of patients with non-infectious uveitis and cystoids macular edema after repeated injections of 0.7 mg Dexamethasone implant. Our clinical results were the following:

(1) BCVA was always improved to a maximum at 4 weeks (± 1 week) after every injection of 0.7 mg Dexamethasone implant and slowly deteriorated to the level of pre injection time point. This BCVA improvement occurred regularly after each injection, independently of injection number except during the fifth injection, probably due to the small number of cases. A remarkable point was that BCVA has the best value at pre injection time point of fourth injection if we compared to the first three initial pre injection time points.

(2) Our result shows that the central macular retinal thickness was minimal at 4 (± 1 week) after each intravitreal injection of 0.7 mg Dexamethasone implant with a slow worsening during the following months and with mild central retinal thickness increasement at the time point of 3 months (± 2 weeks). Finally at the time point of 5 months the macular thickness was identical to the pre injection time point. This effect was seen after each injection of 0.7 mg Dexamethasone implant independently to injection number and it had similar result during all of five injections.

(3) During the second and the third injection, the initial central retinal thickness at the pre injection time point was gradually reduced in comparison to the initial central retinal thickness of first injection at pre injection time point. This effect was not seen during the fourth and fifth pre injection time point, but we have seen a mild elevation of initial central retinal thickness in comparison to the second and third pre injection central macular thickness. This is possible due to chronic inflammatory process with subsequent post inflammatory changes of anatomical structure of macula or due to reduced cases during the fourth and fifth injection.

(4) The result of intraocular pressure have shown that during the first and second injection there was an elevation of intraocular pressure at the time point of 4 (± 1 week) weeks and a mild improvement with a reduction of IOP at the time point of 3 (± 2 week) months. Finally the IOP values at the time point of 5 (± 1 months) months returned to the pre injection time. This noticeable IOP change at time point 4 (± 1 week) weeks, was not seen during the third injection, most likely due to prescribed anti-glaucomatous therapy after IOP complication

during the first two injection. During the fourth injection there was again an IOP elevation. We speculate that this depends on the additional use of anti-glaucomatous drugs.

(5) The lens opacity and a possible subsequent cataract operation during injections period has been studied and monitored as secondary finding. This analysis has showed a remarkable result. 65,2 % of 23 eyes have proceeded to an early cataract operation with implantation of an artificial IOL during the time of our study after repeated injections of 0.7 mg Dexamethasone implant and only 34.8 % have kept the physiological lens during this time. The lens opacity during our study was correlated with BCVA values but it was independently to the improvement of the other clinical condition such as of central retinal thickness and macular volume.

(6) The BCVA was a functional parameter in this study and could be related to central macular thickness as an anatomical factor. In addition to central retinal thickness other secondary factors such as early cataract (in phakic eyes), secondary cataract, cataract surgery, epiretinal gliosis, anatomical changes from chronic inflammatory process and chronic elevation of intraocular pressure with secondary glaucoma (due to cortisone respond or due to chronic inflammation) contribute to the final clinical result of visual acuity.

Several studies have focused on different treatments of non-infectious uveitis with cystoids macular edema. The efficacy, safety side effect and clinical response of 0.7 mg Dexamethasone implant has been discussed in several reports with different points of view.

The study Intravitreal Dexamethasone implant for the treatment of macular edema in chronic non-infectious disease has shown that the Dexamethasone implant is an effective treatment additional to systemic therapy with steroids or immunomodulator and require a further investigation to set the Dexamethasone implant as single therapy for chronic uveitic macular treatment. This study had monitored two main parameters CRT and BCVA. There was an improvement of CRT in 91.4% of cases and the BCVA was better in 80% of all eyes three months after the 0.7 mg Dexamethasone implantation. Additionally there was similar clinical improvement in CRT and BCVA after repeated injections of 0.7 mg Dexamethasone implantation. The treatment success was reported to be between third and sixth month after the injection. [161]

In our study, during the first injection there was a significant improvement of CRT in 98% cases during the follow up time of four weeks. The BCVA increased in 86% of cases during the time point of four weeks after the first injection. Both studies have the same therapeutic

indication for macular edema in non-infectious uveitic eyes but all cases of our study have received a repeated injection in comparison to this study that a repeated injection was occurred in 28.5%. The repetition of implant at the same eye has shown similar effect in both studies with melioration of clinical findings.

The CHROME study have tested the efficacy and safety of single or multiple intrvitreal 0.7 mg Dexamethasone implant in cases with macular edema due to uveitis, vein thrombosis, diabetes mellitus. The parameters were BCVA, CRT, IOP and cataract surgery and have been monitored ≥ 3 months after injection. In the subgroup of uveitis patients the study had concluded that the 0.7 mg Dexamethasone implant as single or combined therapy resulted in anatomical and functional improvement in cases with chronic macular edema and of cases had a repeated second and third injection. All cases had a significant improvement of BCVA and a decrease of central retinal thickness. 22.7% of uveitic eyes had an IOP elevation to ≥ 10 mmHg. 29.8% of eyes underwent to cataract surgery. [162]

In our study 65.2 % of eyes have proceeded to cataract operation. The difference to the CHROME-study is that in our study, the cases have received at least two up to five injections in comparison to 1 to 3 injections.

8. Summary

The intravitreal 0.7 mg Dexamethasone implant (Ozurdex®) in eyes with non-infectious uveitis demonstrated a significant improvement in visual acuity and central retinal thickness with peak effect at four weeks after implantation. A further stabilization was observed until the third month but five months post implantation the efficacy was lost.

Additionally, ocular side effect such as mild transient elevation of intraocular pressure and cataract formation was reported during this study. In both cases after a proper management with anti-glaucomatous drugs or cataract operation have shown an improvement of clinical findings and visual acuity.

Thus, the 0.7 mg Dexamethasone implant can be used safely as standard therapy in cases of non-infectious uveitis with macular edema with a satisfactory result to controlling the disease in functional and anatomical point of view but requires repeated administration and tight control of side effects.

9. Zusammenfassung

Das intravitreale 0.7 mg Dexamethasone Implantat (Ozurdex®) bei Augen mit nicht-infektiöser Uveitis, zeigt eine deutliche Verbesserung des Visus und der zentralen Netzhaudicke, mit einer Maximalwirkung vier Wochen nach der Implantation. Eine weitere Stabilisierung wurde bis zum dritten Monat nach der Implantation festgestellt jedoch war fünf Monate nach der Implantation keine Wirksamkeit mehr sichtbar.
Außerdem wurden während dieser Studie Nebenwirkungen, wie zum Beispiel eine leichte transiente Erhöhung des intraokulären Augendrucks und eine Kataraktformation festgestellt. In beiden Fällen war, nach geeigneter anti-glaukomatöser Therapie oder Katarakt-Operation, eine Verbesserung der klinischen Befunde und des Visus zu vermerken.

Zusammenfassend kann das 0.7 mg Dexamethason-Implantat bei nicht-infektiöser Uveitis mit Makulaödem mit einem zufriedenstellenden Ergebnis zur Kontrolle der Erkrankung in funktioneller und anatomischer Hinsicht sicher als Standardtherapie eingesetzt werden. Es erfordert jedoch eine wiederholte Verabreichung und strenge Verlaufskontrollen, um mögliche Nebenwirkungen frühzeitig zu erkennen.

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11. Curriculum vitae

Aus datenschutzrechtlichen Gründen wird in dieser Fassung der Dissertation mein Lebenslauf nicht dargestellt.

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