Chapter III

Dexamethasone's Uses in Retinal Diseases

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Abstract

Steroids, having both anti-inflammatory and anti-angiogenic properties, are a useful therapeutic option in the treatment of retinal disease. Intravitreal steroids can be used in the treatment of various retinal conditions including diabetic and vasculo-occlusive macular edema, exudative macular degeneration, pseudophakic cystoid macular edema, and posterior uveitis. Although there are well known serious potential complications with intravitreal steroids, including glaucoma and endophthalmitis, recent studies have shown that intravitreal steroids may be used as a safe alternative to the practice of laser therapy for the treatment of macular edema secondary to diabetes or vein occlusions. Although there are several steroid formulations that may be used, this article focuses on the use of intravitreal dexamethasone. Dexamethasone

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is a potent anti-inflammatory agent that inhibits multiple inflammatory cytokines. Despite its established therapeutic benefit, side effects such as cataract formation and ocular hypertension/glaucoma raise concerns. Therefore, understanding the molecular and genetic effects of intraocular steroid treatments is of utmost importance and of clinical relevance. Our *in vivo* studies have elucidated several genes and pathways that are potentially altering the neuroprotective and/or neurodegenerative balance between glial and retinal ganglion cells during intravitreal steroid treatment, such as semaphorin signaling, a member of the neuronal axonal guidance signaling system. Furthermore, our more recent data results suggests that dexamethasone affects the balance of Th1, Th2 and Th17 cytokine production, which influences many pathological processes and plays both causative and protective roles in retinal disease.

Introduction

Steroids have both anti-inflammatory and anti-angiogenic properties, and thus are a mainstay therapeutic option in the ophthalmic practice. Intravitreal steroids can be used in the treatment of various potentially blinding retinal conditions including diabetic retinopathy, macular degeneration, vein occlusion, and non-infectious uveitis [1]. Despite the benefits of intravitreal steroids, there are several serious potential ocular complications—namely cataracts and glaucoma, that may require surgical intervention or even result in permanent vision loss. These complications limit the use of intravitreal steroids in certain patient populations. Although there are well known serious potential complications with intravitreal steroids, studies have shown that intravitreal steroids may be used as a safe alternative to the standard practice of laser therapy for the treatment of macular edema secondary to diabetes or vein occlusions [2]. Although there are several steroid formulations that may be used, this article focuses on the use of intravitreal dexamethasone, both in solution and implant-form.

Mechanism of Action

Endogenous Glucocorticoid Signaling

The main role in regulating signaling by glucocorticoid receptor (GR) is played by the hypothalamic-pituitary-adrenal axis. Neural, endocrine and

cytokine signals are controlled via this axis which secretes the glucocorticoid, cortisol, in humans and corticosterone, in mice [3] and refs therein). The glucocorticoid receptor is a member of the nuclear steroid receptor superfamily (with mineralocorticoid, thyroid hormone, retinoic acid and vitamin D receptors) [4], and has a high affinity for cortisol. The GR is ubiquitously expressed in tissues, and regulates tissue specific gene expression of a multitude of target genes. These genes are involved in a diverse array of physiologic functions, such as tissue development, homeostatic regulation, suppression of inflammation and stress response induced by noise, restraint, hypoglycemic or immune challenge [5] and references therein). Figure 1 illustrates some of those pathways.

The GR can be functionally divided in several domains: a N-terminal transcription activation domain, a central DNA binding domain with Zn-fingers and a C-terminal ligand/steroid hormone binding domain. The glucocorticoid receptor is coded by only one gene with nine exons, evolutionarily highly conserved [6], but it has a multitude of variants present in the cells. First there are splice variants, which generate variants at the mRNA level. The main proteins translated from them are GRalpha, and a C-terminal variant GRbeta, which has a deletion of ligand/steroid hormone binding domain, that likely has a dominant negative effect on GRalpha. Less abundant and with less understood function are GRdelta, mainly expressed in cancer and GRgamma, with additional Arg in the DNA binding domain [7, 8]. Furthermore, there are multiple proteins translated from GRalpha transcripts, that use alternative translation initiation sites, and the GR is subject to a variety of posttranslational modifications, which adds to even larger diversity of GR proteins [8]. The GR protein variants have been shown to have differential activity on gene regulation, and have also been shown to have cell type specific differential expression.

Glucocorticoid hormone (GH) gets inside of cells by diffusion. GH diffuses across plasma membrane, binds to glucocorticoid receptors in the cytoplasm, and promotes its dissociation from chaperone proteins i.e., heat-shock proteins. Activated GRs can dimerize and translocate to the nucleus, where they bind to glucocorticoid response elements (GREs) in the promoter of glucocorticoid responsive genes, resulting in change in their transcription. This results in the increase of the transcription of genes that act to suppress inflammation, i.e. interleukin-1 receptor antagonist. Additional level of tissue specific regulation occurs from interaction of GR-GH complex with other, tissue specific transcription factors, such as proinflammatory NF-kappa B [9, 10], ICAM, or TNF∂ and MAPK pathways [11-14].
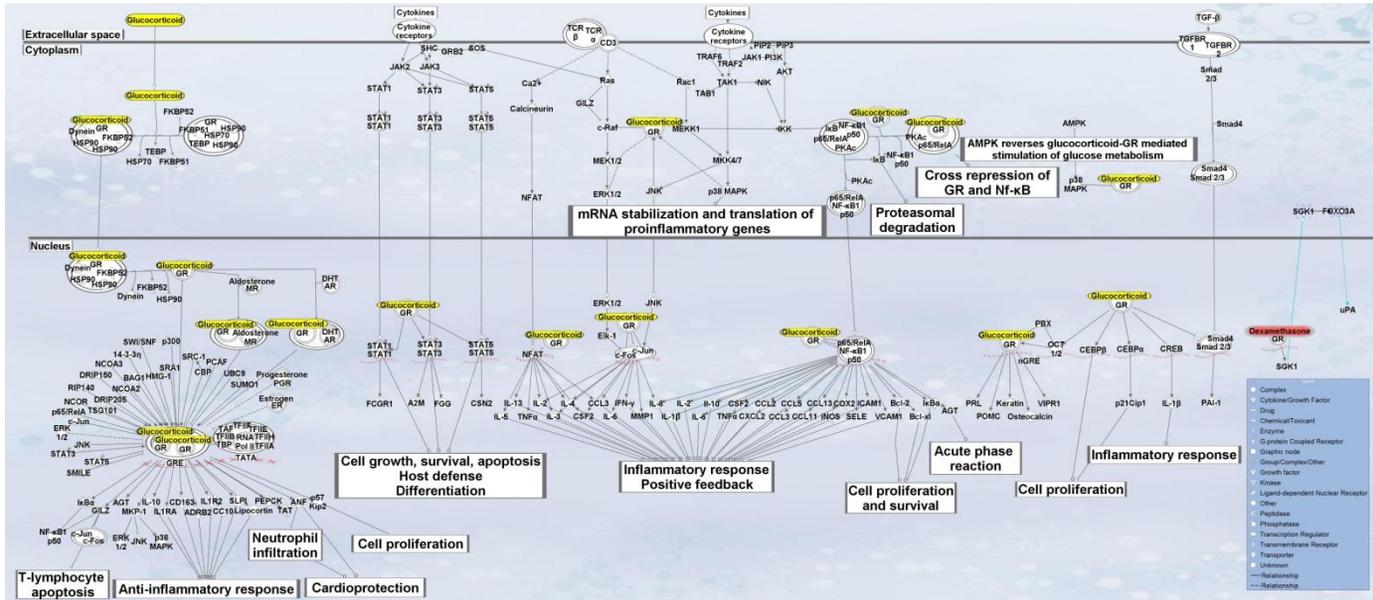
Figure 1. Glucocorticoids and glucocorticoid receptors are involved in regulation of a diverse array of biological pathways and physiologic functions.

These two mechanisms 1) direct transcriptional activation by binding to GRE and 2) interaction with other transcription factors, are often referred as classical GR mechanisms of action. Third, so called "rapid action" mechanism acts via so called non-genomic pathways, through membrane-associated receptors, such as G protein coupled receptors (GPRCs) and second messengers which activate several signal transduction pathways [15, 16]. And, yet, there are additional epigenetics modes of action that include histone deacetylation, leading to suppression of gene expression [11-13] and methylation. Systemic use of steroids has been shown to result in genome-wide alterations in promoter methylation [17, 18]. Some of these multiple modes of action of GR are depicted in Figure 2.

Synthetic Glucocorticoids

The synthetic glucocorticoids are the most potent anti-inflammatory agents known, but their use is limited owing to the range and severity of their side-effects. Although their structure is based on natural GR ligands, their chemical structure has been changed slightly to optimize therapeutic potential and minimize adverse reactions [19]. The studies of the structure of the ligand binding domain of the GR have shown that even subtle changes to the ligand structure alter the final conformation of the ligand–receptor complex, with dramatic consequences for the whole protein conformation, and function of the receptor [20-22].
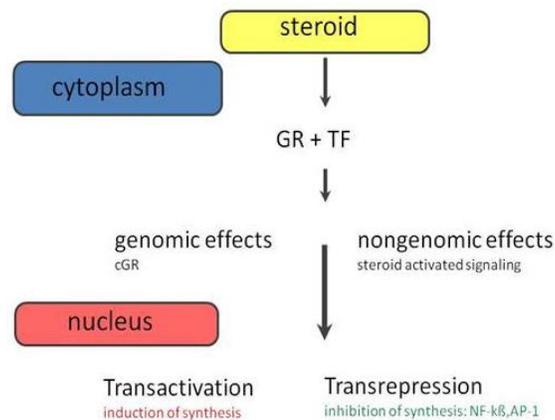

Figure 2. Multiple modes of action of glucocorticoids in the cell.

Expression Analysis of Dexamethasone in Ocular Tissue

While dexamethasone has a very efficient anti-inflammatory clinical effect, complications such as cataract formation and steroid induced glaucoma are common. The results of our study showed that while glucocorticoids stimulated many of anti-inflammatory and neuroprotective genes, they also upregulate immune response genes, likely of glial origin, that may cause tissue damage and apoptosis. Microarray gene expression studies on steroid-induced glaucoma have shown that steroids induce dose dependent, differential gene profiles in human trabecular meshwork (TM) cells [23-26]. Currently, the TM epithelium is considered to be the target tissue and the myocilin gene, which is expressed mainly in TM, the top candidate gene for the development of steroid-induced glaucoma. The myocilin protein clogs the TM that causes increased intraocular pressure (IOP) [27]. Although an elevated IOP is a significant risk factor for the development of glaucoma, it is important to note that sight-threatening effects of glaucoma are not necessarily coming from increased IOP but from retinal and optic nerve neurodegeneration.

We did genomics expression analysis of Dex and TAA intravitreal injections in the mouse retinas at clinically relevant time points of 1 week and 1 month. More than 1500 genes were found to be differentially expressed at the level of 99% statistical significance. Furthermore, statistical analysis for each of the time points separately identified groups of genes that are common and similarly regulated for both steroids as well as a set of unique genes differentially regulated by each steroid. [28]. For example, in week 1 postinjection, common upregulated genes for both dexamethasone and triamcinolone were stress response proteins and genes with a role in immune response and apoptosis, members of TGFβ receptor signaling and TNFα signaling cascade, as well as Semaphorin signaling, which VEGF signaling is part of. Besides the common ones, dexamethasone uniquely activated retinal glia macrophages and genes that are regulated by NFkappaB and p53, while triamcinolone's week 1 targets were primarily genes from the folate pathway and dopamine metabolism. Pathway analysis demonstrated that some of the biological pathways activated are unique for each steroid, although even in the pathways that are common, different set of genes might be affected differently by different steroid. For example, both dexamethasone and triamcinolone activated Semaphorin signaling pathway, but one week after dexamethasone treatment we observed upregulation of ligands Sema3, Sema4, and Sema5a, on the glial side, and Plexins A and A2 receptors on the neuronal side. One week after TAA injection we observed upregulation of Sema4 and Sema3, while

Plexins A and A2 were downregulated. Our results, and results of several other investigators [23-26, 29], demonstrate that each steroid has discrete specificity both clinically and biologically. Small differences in the structure can result in targeting different sets of genes, or different biological pathways. We will discuss the significance of these observations a bit later.

Several of the genes we identified upregulated by dexamethasone are identical or related to the genes identified by microarray analysis of DBA/J mouse, a mouse glaucoma model [30, 31]. Although, it still remains to be seen whether upregulation of these genes have a protective or damaging effect on retinal and optic nerve degeneration as well as glaucoma development.

One of the top pathways identified was 'Semaphorin Signaling in Neurons'. Semaphorins are signaling molecules that act as neuronal as well as vascular growth guidance molecules. Disregulation of this pathway can lead to inhibition and/or apoptosis of neuronal tissue, as well as disregulated growth of vascular tissue. In addition to their role in axonal guidance, semaphorins also have a major role in immune response. At one week after dexamethasone treatment we observed upregulation of several of Sema ligands (Sema3, Sema4, and Sema5a) expressed on glial cells, and their Plexin receptors (A and A2), expressed on the neuronal side. Semaphorin 4A has an important role in the visual system development, and Sema4A mouse knockout develops severe retinal degeneration [32]. Sema3A has been found to be secreted by ischemic neurons in the avascular retina in the response to the pro-inflammatory cytokine IL-1beta, thus preventing vascular regeneration in proliferative retinopathies [33]. The role of Sema3E in eye therapy is still being worked out: both inhibition of Sema3E protein [34] as well as intravitreal application [35] are being considered for therapeutic anti-angiogenesis. Sema5A, upregulated one week after dexamethasone injection, has been shown to promote angiogenesis by increasing endothelial cell proliferation, migration, and decreasing apoptosis in vitro [36].

There was upregulation of somatostatin receptor Sstr2 1 week post injection. Somatostatin signaling regulates glutamate release in the retina [37], and it has been suggested that Sstr2 has an anti-angiogenic role in retina [38] therefore its upregulation of Sstr2, might be a result of the protective effect of dexamethasone against inflammation.

At one month post-injection of dexamethasone we observed upregulation Aryl-hydrocarbon receptor (AhR). It has been shown that Ahr has a regulatory role for small heat shock proteins induced in retina and other tissues of the eye [39]. Several human retinal dystrophies such as Leber congenital amaurosis,

juvenile retinitis pigmentosa and dominant cone-rod dystrophy are mapped to AhR pathway [40, 41].
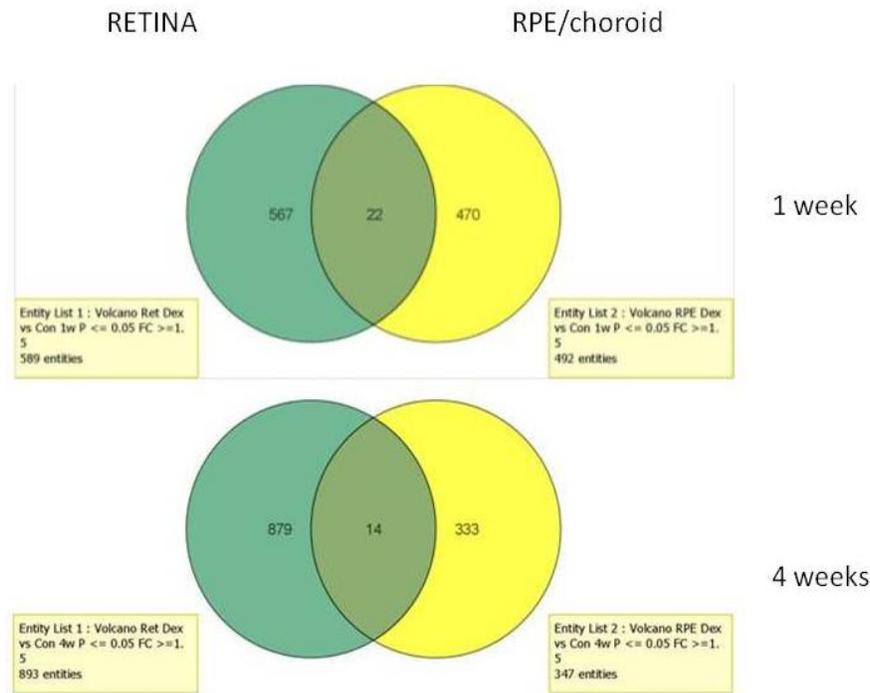

Figure 3. Tissue specific differences in the gene expression in response to intravitreal dexamethasone application in the mouse eye.

Members of the AhR family play critical roles in a broad range of biological functions including regulation of circadian rhythm, neurogenesis, hypoxia response and drug metabolism.

Our focus in data interpretation was on genes with known neuroprotective vs. neurodegenerative effects and/or known role in ophthalmic or neurodegenerative diseases. We have identified several genes and pathways that appear to be affected by intravitreal dexamethasone injections. Perhaps modulation of some of these potential targets in combination with steroid intravitreal therapy will in the future lead to reduced side-effects.

When we examined gene expression profile of the RPE at the same time points (unpublished data), we found strong tissue specific expression and response to intravitreal dexamethasone application. Figure 3 illustrates dramatic differences between these two tissue types.

Immune Response Regulation by Dexamethasone and Implications for Treatment of Retinal Disease

Glucocorticoids can regulate inflammatory and autoimmune response by directly suppressing innate and cellular immune response. There are two main types of cellular immune response – Th1 being cell-mediated, while Th2 is humoral-mediated immunity. Some of the typical cytokines that represent mediators of these actions are IL-12 for Th1, IL-4 for Th2 and IL-17 for Th17. Franchimont et al have shown that dexamethasone selectively inhibits IL-12 inducible IFN-gamma secretion and Stat4 phosphorylation, in both NK and T-cells, without altering IL-4 phosphorylation. This might be one of the mechanisms by which dexamethasone shift immune response from cellular (Th1) to humoral (Th2) [42]. One of the early relevant finding for eye research was that repeated pre-treatment with dexamethasone was able to suppress early and late phase of topically induced ocular anaphylaxis in rats [43].

Relatively recently, a novel type of Th cells has been described, and its importance is steadily growing – Th17, T-cells which selectively produces pro-inflammatory cytokines, such as IL-17, IL-21 and IL-22. Th17 cells are now known to play an important role in the pathogenesis of inflammation and autoimmune diseases [44]. Figure 4 illustrates these three branches of immune system and their interaction.
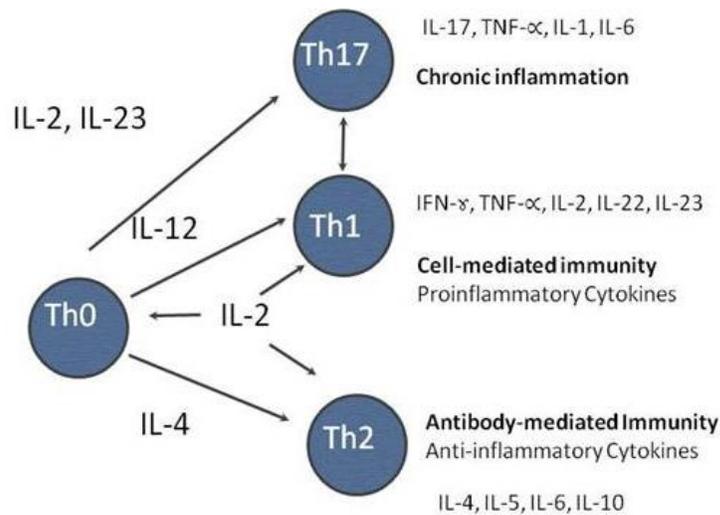

Figure 4. The schematics of the Th1, Th2 and Th17 branches of immune system and their interactions.

Table 1. Retinal diseases have differential disregulations of Th1/Th2/Th17 branches of immune system

Retinal Diseases	Th1 (IL-1, IL-2)	Th2 (IL-4, IL-6, IL-10)	Th17 (IL-17, IL-22)
CME		+ [52]	
DME	+ [53]	++ [49, 53]	
RVO		++ [49, 54, 55]	+ [55]
AMD	+ [56]	++ [56]	+ [57]

In addition to cytokines, induction of TGFbeta-1 and retinoic acid-related orphan receptor-gammat (RORgammat) lead to differentiation of Th-17 cells in mice. Role of dexamethasone is still controversial. There is report that dexamethasone can inhibit the release of IL-17 likely by inhibiting RORgammat expression and blocking Th17 differentiation in asthmatic Balb/c mice [45]. On the other hand, in a model of chronic allergic airway inflammation in Th17-deficient mice in T cells, where Th-17 cells induce airway remodeling independent of Th2 response, Zhao et al. showed that dexamethasone inhibited eosinophilia, present in acute inflammation, but not neutrophilia, hallmark of chronic disease, and enhanced Th17 development in vitro [46].

Our results suggests that there may be a preference between steroids as to which branch of immune system they act upon, as well as tissue specificity (Smit-McBride et al, manuscript in submission). The main branches of the immune system are represented on the Figure 4. The clinical evidence is mounting suggesting that the cytokine signaling produced by CD4+ T helper (Th) cells may be an important determinant of clinical pathology in a variety of diseases in which steroids are being tested (Table 1). The disturbance of the balance of Th1/Th2 cytokine production is an underlying cause of neural damage in several neurologic diseases, while restoration promotes neuroprotection [47-51]. The finding of differential gene expression and tissue specific effects of different steroids may have clinical implications for treatment of retinal disease. Furthermore, it may allow the development of new generations of steroids that do not have the adverse effects and have more specific targeting. Additionally, biomarkers for determining who may be at risk for the adverse effects, are being identified and may reduce these complications for future use.

Clinical Usage of Dexamethasone

Popular Formulations of Dexamethasone

Although there are several steroid formulations that may be used, this article focuses on the use of intravitreal dexamethasone. Dexamethasone is a potent anti-inflammatory agent that inhibits multiple inflammatory cytokines. Dexamethasone has a relatively short half-life (3.5 hours), but is 5 times more potent than other steroid formulations, including intravitreal triamcinolone. Intravitreal dexamethasone comes in a 4mg/ml solution, and may be injected in the vitreous space at a dosage of 0.4 mg.

Despite the anti-inflammatory benefits of dexamethasone, the short half-life of 3 hours limits the clinical use. This limitation is addressed via a biodegradable dexamethasone implant—Ozurdex (DEX implant, Allergan, Inc., Irvine, CA). Ozurdex delivers an extended release of dexamethasone via an intravitreal injection to modulate various macular and retinal disorders. The implant is made of a solid polymer (Novadur™, Allergan, Irvine, CA, USA), that initially releases a burst of dexamethasone to achieve a therapeutic concentration followed by a lower sustained release of the drug. Ozurdex allows a longer duration of pharmacological effect with lower administration frequency compared to other intravitreal steroids. The benefits of Ozurdex may last up to 6 months in the eye, but clinicians often report a shorter duration of action. It should be noted that the FDA has approved the use of intraocular steroids only for a select number of conditions [1]. Ozurdex was approved as first line therapy for macular edema secondary to vein occlusions in 2009, and for treatment of non-infectious uveitis in 2010 [58]. However, retinal clinicians often use Ozurdex "off label" to treat a wider range of ocular disorders, namely macular edema from diabetic retinopathy or post-surgical cystoid macular edema.

Clinically Usage of Steroids Based on Disease

Endophthalmitis

Intraocular dexamethasone was first used in the 1970s to reduce the inflammatory response in the treatment of bacterial endophthalmitis in conjunction with antibiotic therapy. Endophthalmitis is a severe inflammation of the eye secondary to contaminating microorganisms introduced during

surgery, penetrating trauma, or endogenous spread. Despite appropriate therapeutic intervention, bacterial endophthalmitis frequently results in visual loss, and potentially loss of the eye. The first line of therapy remains intravitreal antibiotics or vitrectomy surgery (EVS study [97]); however, dexamethasone is often added as an adjunct to the antibiotic regimen based on its rapid mechanism of action for modulating the inflammatory response. Currently, intravitreal dexamethasone's role in combating the destructive inflammatory response in endophthalmitis remains controversial, as the literature provides conflicting results. In 1974 Graham and Peyman described the beneficial addition of intravitreal dexamethasone to antibiotic therapy in the rabbit model for reduction of the inflammatory response in the anterior and posterior chambers, vitreous, retina, and choroid [59]. Intravitreal dexamethasone has been used as an adjunct to intravitreal antibiotics in the management of bacterial endophthalmitis—namely in cases with gram-negative endophthalmitis [60]. In the rabbit model, Streptococcus pneumonia infected eyes treated with vancomycin and dexamethasone had significantly less intraocular inflammation and more preservation of retinal tissue than untreated eyes or eyes treated with vancomycin alone [61]. Clinically, several authors showed favorable visual results when dexamethasone was used in the treatment of post-cataract endophthalmitis [62, 63]. A recent study demonstrated that intravitreal dexamethasone improved vision without prolonging infection in patients with bleb-induced endophthalmitis, a particularly severe form of endophthalmitis [64]. However, other studies have shown no difference in the visual acuity of eyes treated with and without dexamethasone [65] and some studies have even shown negative visual results [66]. In 2004, 43% of retina specialists reported that they use intravitreal dexamethasone in conjunction with intraocular antibiotics to treat postsurgical endophthalmitis [67].

Trauma

Intraocular steroids have also been used to modulate the inflammatory response in surgical and nonsurgical trauma. The ultimate success rate of vitreoretinal surgery is limited by development of proliferative vitreoretinopathy (PVR). Stages of vitreoretinal scarring include cellular activation, proliferation, extracellular matrix elaboration and remodeling, and contraction [68]. Anti-inflammatory agents such as dexamethasone and other corticosteroids have been used to limit the process of vitreo-retinal scarring. A

single intravitreal injection of 1 mg of dexamethasone has shown to reduce the rate of development of tractional retinal detachment and retinal neovascularization in rabbits after injection of homologous fibroblasts. [69]. Subconjunctival dexamethasone injection at the conclusion of intraocular surgery and frequent topical corticosteroid treatment are commonly used techniques for prophylaxis against postoperative inflammation and fibrin formation [68]. However, intravitreal dexamethasone (0.8 mg) at the end of vitrectomy for complicated diabetic retinopathy did not successfully reduce intraocular inflammation, flare, or fibrin formation [70]. Another study by Chalam et al showed that patients who received 0.4mg of intravitreal dexamethasone at the end of vitrectomy surgery for proliferative diabetic retinopathy or macular puckers showed significant reduction in postoperative inflammation as measured by aqueous cell and flare intensity on postoperative day 1, 10, and 90 [71].

Exudative Macular Degeneration

Intravitreal dexamethasone is also used in clinical practice as a part of adjuvant therapy to treat wet macular degeneration. Wet macular degeneration, a potentially blinding ocular condition, is a multi-factorial condition that involves neovascularization, vascular leakage, and inflammation. A triple therapy approach to wet macular degeneration that addresses these pathologies can be employed when more traditional methods (i.e. repeated anti-VEGF agents) have failed. Triple therapy consists of reduced-fluence photodynamic therapy, an anti-VEGF agent, and dexamethasone. The range of dexamethasone dose used ranges from 200-800 micrograms per injection. Several recent studies [72-74] have shown that triple therapy may reduce the total number of injections needed in some patients and stabilize vision in those patients who do not respond to single therapy with anti-VEGF agents. A recent study demonstrated that the combination of intravitreal anti-VEGF with dexamethasone and full-fluence photodynamic therapy provided visual and anatomic improvement and a good safety profile [75]. Patients who received triple-therapy required a lower number of total injections and a longer interval of time before repeat injections were necessary. Of note, no adverse effects of intravitreal dexamethasone were observed in the mean follow up period of 14 months. A study investigating quadruple therapy for macular degeneration (low-fluence PDT, followed 24 h later by a 0.4-ml core pars plana vitrectomy with intravitreal injection of 0.8 mg dexamethasone and 1.25 mg

bevacizumab) showed sustained visual improvement over 14 months, without any adverse side-effects of dexamethasone [76]. Although the standard treatment of wet macular degeneration remains monthly anti-VEGF injections, intravitreal dexamethasone may be an important adjuvant treatment for some patients.

Diabetic Macular Edema

Diabetic macular edema is a visually-threatening eye disorder that is often a challenge to treat. Thermal laser photocoagulation remains the only FDA approved treatment for diabetic macular edema. However, thermal laser is not an ideal treatment option for patients who have vascular leakage within the foveal-avascular zone, who have a significant amount of macular edema, or who have had an inadequate response to past laser therapy. Although the FDA has not approved the use of Ozurdex for the treatment of diabetic macular edema, it is increasingly becoming a popular therapeutic option, especially in post-vitrectomized eyes [77]. Increased production of inflammatory mediators and vascular permeability factors contribute to diabetic macular edema, and these processes are stabilized by corticosteroids [78]. Several studies have shown Ozurdex's benefit at reducing macular edema and vascular leakage [77, 78]. One study found that the dexamethasone implant improved visual acuity for up to 6 months in patients with macular edema due to a variety of causes including diabetic retinopathy [79]. In a subgroup analysis of 171 eyes with persistent diabetic macular edema, the dexamethasone implant resulted in improvement in best corrected visual acuity at three months, but this was lost after 180 days - and steroid treatment groups had an increased incidence of elevated IOP [80]. A study in patients' who were status post vitrectomy showed that a dexamethasone implant resulted in statistically and clinically significant improvements in both vision and vascular leakage from diabetic macular edema, with an acceptable safety profile [77]. It is important to note, however, that the benefit of intravitreal dexamethasone tapered from week 1 to week 26 of the study.

Retinal Vein Occlusion

Retinal vein occlusion is second to diabetic retinopathy as a cause of vision loss from an underlying retinal vascular disorder. Retinal vein occlusion

leads to vision loss from macular edema and ocular ischemia. The FDA approved the use of Ozurdex in the treatment of vein occlusions based on two identical, multicenter, masked, randomized, 6-month, sham-controlled clinical trials that included 1267 patients with vision loss from BRVO or CRVO [80]. Haller et al. showed the safety and efficacy of the dexamethasone intravitreal implant compared with sham control. Improvement in mean best corrected visual acuity was greater in the DEX implant groups compared with sham at all follow-up visits (P< or =0.006) over 6 months. The dexamethasone implant reduced the risk of vision loss and improved the speed and incidence of visual improvement in eyes with macular edema secondary to BRVO or CRVO. Further, the incidence of DEX implant-treated eyes with IOP of > or =25 was not different from sham by day 180, and there were no patients that required cataract surgery at 6 months.

Haller et al. then extended the study design for 6 more months (in an open-label extension of the study) [80]. She reported that out of the 1256 patients included in the study-extension, 997 patients required a second treatment of Ozurdex implant based on decreased visual acuity or increase in macular thickness at day 180. Over the 12 month study period, patients who received either a single or repeat treatment of DEX implant had improved visual acuity and decrease in macular edema compared to sham. The rates of complications between the groups that received one implant injection versus two implant injections were similar, except the group that received two injections had a higher rate of cataract formation at the end of study period (29.8% versus 5.7%). Other recent studies have also demonstrated the safety and efficacy of the Ozurdex implant in treatment of vein occlusions [80-82].

In our experience, we have found dramatic improvements in macular edema in patients with retinal vein occlusions. For example, in our practice we saw a 64 year old male with a history of a vein occlusion with significant macular edema with count finger vision that did not improve with 5 prior intravitreal anti-VEGF injections (Figure 5). He received an Ozurdex injection, and two months after the injection he experienced a significant decrease in macular edema and improvement in vision to 20/200 (Figure 6). At the two month follow up, he did not have an elevated intraocular pressure.

Although Ozurdex is the first FDA approved pharmacologic treatment for vein occlusions, work still needs to be done to determine the best frequency of drug administration. Haller et al. demonstrated effectively of Ozurdex implant with either one or two intravitreal injections over a 12 month period. Qureques et al. demonstrated that repeated intravitreal Ozurdex on a "per-needed' basis (with a retreatment interval <6 months) had benefits in the treatment of ME

due to RVO [81]. Matonti et al. reported a case of a 75 year old female who benefited from a series of four Ozurdex injections over 17 months [83]. Although Ozurdex remains the only FDA approved treatment of macular edema from central retina vein occlusions, it is interesting that in a recent 2012 Membership Survey of Preferences and Trends by the American Society of Retinal Specialists, 36% of US/Canadian members and 50% of international members reported not having experience with use of the drug. Interestingly, about a quarter of all members in the survey reported that Ozurdex is more effective than Triamcinolone in treating central retinal vein occlusions.
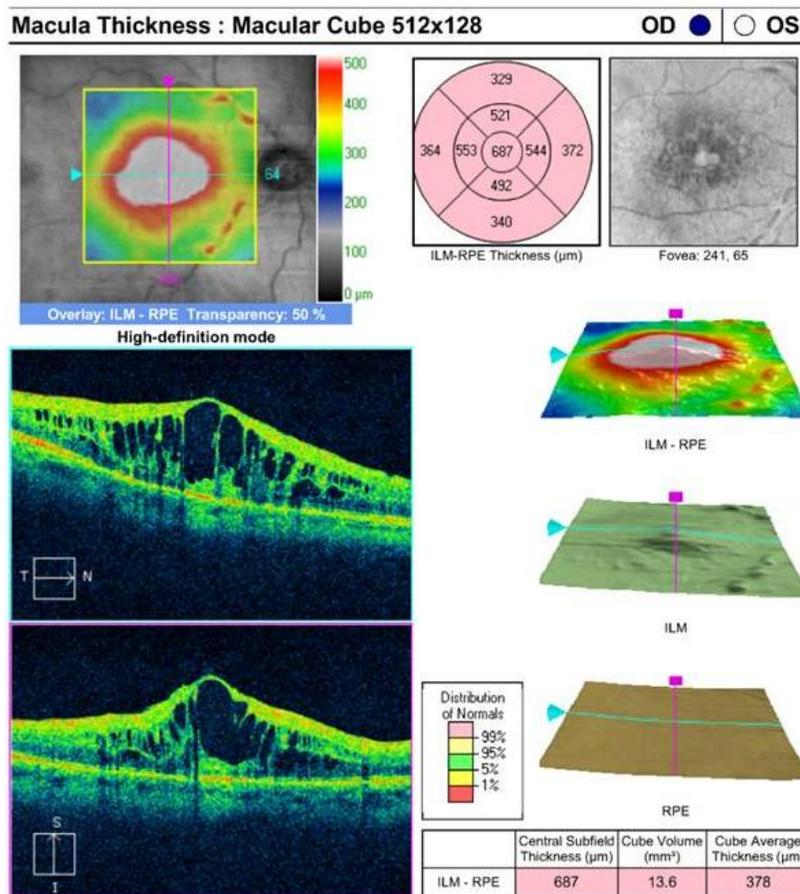

Figure 5. Optical coherence tomography (OCT) image of macula in patient with cystoid macular edema from a retina vein occlusion.
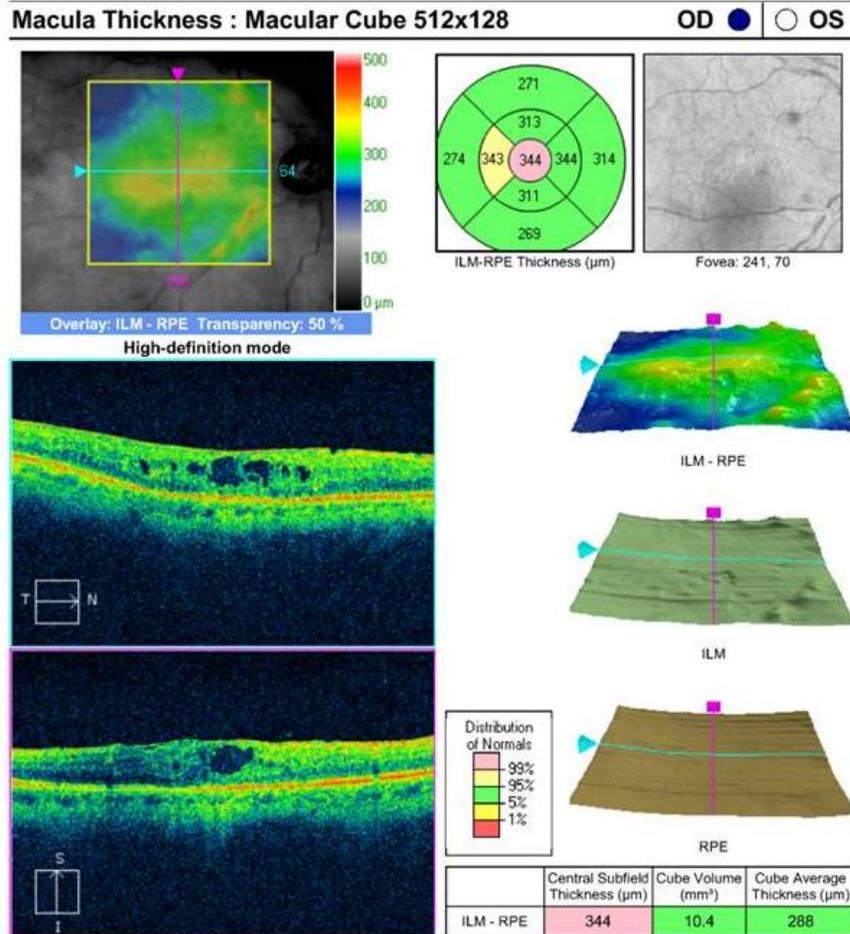
Figure 6. OCT image of patient in Figure 5, 2 months after intravitreal injection of Ozurdex steroid implant.

Pseudophakic Cystoid Macular Edema

Despite advances in modern cataract surgery, pseudophakic cystoids macular edema (PCME) remains a common problem that may cause vision loss during the post-operative period. Several treatment options are available, but most clinicians use a step-wise treatment approach that starts with topical medical treatment (topical NSAIDS and steroids) and may progress to surgical intervention, namely pars plana vitrectomy. In cases of severe or refractory

cystoids macular edema, subtenon's or intravitreal steroids are commonly employed [84]. Some clinicians use steroid implants the first-line of treatment in PCME [85]. The Ozurdex implant would have a role in treating PCME, especially in vitrectomized eyes. Unfortunately, to our knowledge, there are no published randomized clinical trials to compare intravitreal dexamethasone to other established treatment modalities [86].

Noninfectious Uveitis

Uveitis is responsible for 30,000 new cases of legal blindness annually in the Western world [87]. Topical, systemic, periocular, and intravitreal corticosteroids play an important role in the treatment of noninfectious forms of uveitis and they are the first-line treatments in this condition. They offer the advantage of direct delivery to the site of inflammation while minimizing and avoiding a host of systemic side effects seen with oral and intravenous administration of corticosteroids. Systemic steroids are associated with fluid retention, hypertension, hyperglycemia, greater susceptibility to infections, osteoporosis, mood alteration, and psychosis. In posterior uveitis macular edema is often the main source of vision loss. Intravitreal treatment directly targets this site and may be used as monotherapy or in conjunction with systemic immunosuppression depending on the absence or presence of extraocular manifestation the underlying auto immune condition. In chronic cases of posterior uveitis serial intravitreal treatments may be necessary.

Intravitreal dexamethasone has the advantage of office-based implantation procedure with topical anesthesia. A 26-week trial was performed studying single treatment with 0.7-mg DEX implant and 0.35-mg DEX implant compared to a control sham group [88]. Proportion of eyes with a vitreous haze score of zero at week 8 was 47% with the 0.7-mg DEX implant, 35% with the 0.35% DEX implant, and 12% with the sham groups. At all time points, the proportion of eyes with improvement in vitreous haze was greater in the dexamethasone treated groups, seen in over 90% by 6 weeks compared with 46% of sham-treated eyes. Less than 10% of eyes receiving the 700 μg implant had an intraocular pressure rise of over 25 mm Hg at any point, and no patient had progression of cataracts. In a comparison based series, Arcinue et al evaluated the efficacy and safety of the flucinolone acetonide (Retisert) implant compared with the dexamethasone (Ozurdex) implant in 27 eyes that noninfectious uveitis [89]. Of note, Ozurdex is implanted in the eye in the office-setting, but the Retisert implant requires surgical intervention in the

operating room with sedation. No significant differences were seen in terms of improvement in inflammatory score and best-corrected visual acuity (BCVA) in both groups. Eyes with the Ozurdex were 5 times more likely to receive a second implant compared to Retisert (P=0.02). No eyes in the Ozurdex group needed additional glaucoma medications, surgery, or laser compared to 44% of eyes in the Retisert group.

Toxoplasmosis

Kishore and Peyman in 2001 described a new method of management of toxoplasmic retinochoroiditis by using intravitreal injections of clindamycin (1mg/0.1ml) and dexamethasone (1mg/0.1ml) [90]. A lower dose of intravitreal dexamethasone (0.4 mg/0.1 ml) in combination with a higher dose of clindamycin (1.5 mg/0.1 ml) has also shown to be effective for treatment of zone 1 toxoplasmic retinochoroiditis in cases of intolerance to oral medication, contraindication to oral medication secondary to pregnancy, and lack of response and progression of disease despite oral antimicrobial and anti-inflammatory treatment [91].

Complications

Chronic administration of steroids can have systemic and local side effects. Topical, periocular, and intravitreal treatment of ocular disorders limits the systemic side effects and there is minimal systemic absorption following local administration of steroids [1]. However, the risk of local side effects such as cataract formation, increased intraocular pressure, and development of glaucoma may not be avoided [92]. Each technique for delivery of corticosteroid to the eye may also present its own inherent risks. Periocular steroid treatment carries a risk of inadvertent globe penetration, extraocular muscle injury, ptosis, and local skin depigmentation [87]. The risks of intravitreal injection include endophthalmitis, retinal detachment, vitreous hemorrhage, and the risk of cataract formation and IOP elevation is higher with intravitreal administration of corticosteroids.

Despite the known benefits of reducing inflammation in several macular diseases, intravitreal glucocorticoids may lead to progression of cataracts and development of steroid-induced glaucoma that are unique to this drug-class. Studies on steroid-induced glaucoma have shown that corticosteroids induce

dose-dependent, differential gene profiles in human trabecular meshwork cells, revealed by microarray technology [23, 25]. Microarray analysis has also shown that intravitreal corticosteroids may upregulate immune response genes, likely in glial cells that may cause damage to retinal neural tissue [28].

In the landmark Haller et al. study the percentage of DEX implant-treated eyes with IOP of > or =25 mmHg peaked at 16% at 60 days in the Dex-treated group, but there was no difference from the sham control group at day 180 [93]. Statistically significant side effects of the dexamethasone treated group not found in the sham group also included eye pain and anterior chamber cells. It is important to note that although there were no significant differences between the rate of cataract formation between the treated and the sham control group, the study length was only 6 months. In Haller et al.'s extension follow up of 12 months [94], cataract progression occurred in 90 of 302 phakic eyes (29.8%) that received 2 DEX implant 0.7 mg injections versus 5 of 88 sham-treated phakic eyes (5.7%). At 12 months, 10.3% of patients who received two dexamethasone injections required IOP-lowering medications. When using Ozurdex for uveitis patients, the incidence of cataract progression reported was 15% with the 0.7-mg DEX implant, 12% with the 0.35-mg DEX implant, and 7% of the sham control group (P>0.05). Throughout the 26 week study, the percentage of eyes in the 0.7mg DEX implant group requiring IOP lowering medication was 23% and no eyes required incisional surgery as intervention for elevated IOP.

Some unique complications have been reported using the DEX implant as compared to the DEX solution. Reports of anterior dislocation of the DEX implant have been noted. In some cases repositioning has been successful by dilation of the eye and placement of patient in supine reclined position [95]. The risk of anterior chamber migration of the DEX implant is increased in cases of prior vitrectomy with prone positioning of patient in dilated state. Iris claw lenses and zonular rupture increase the risk of this complication, and in patients without integrity of the zonules and the posterior capsule there is a potential risk of anterior chamber migration of the DEX implant [96].

Conclusion

1.   Dexamethasone has tissue-specific effects on gene expression in retina and RPE tissue.

2. Dexamethasone has different effects on tissues whose effects are modulated by different glucocorticoid receptor interactions. The biological effects of steroids are then mediated through several mechanisms involving, genomic and non-genomic effects with subsequent transactivation or transrepression. Lastly, epigenetic effects of steroids are emerging as important determinants of action.

3. Dexamethasone clinically has a short half-life, but is highly potent. The biodegradable implant Ozurdex, allows for sustainable delivery in the vitreous and lasts 4-6 months.

4. Dexamethasone affects clinically relevant pathways involving inflammation, proliferation, apoptosis, and oxidative stress.

5. The primary clinical side effects of dexamethasone use include cataracts formation and glaucoma.

6. Dexamethasone has clinically been used to treat cystoid macular degeneration from surgery, retinal vein occlusion, exudative age-related macular degeneration and diabetes. Other uses include treatment of non-infectious uveitis.

7. Ozurdex has been FDA approved for the treatment of retinal vein occlusions and non-infectious uveitis. Ongoing studies are exploring the possible usefulness of Ozurdex in the treatment of diabetic macular edema.

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