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Research

Steroid-Induced Iatrogenic Glaucoma

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Abstract

Steroids in susceptible individuals can cause a clinical condition similar to primary open-angle glaucoma. Five percent of the population are high steroid responders and develop an intraocular pressure (IOP) elevation of more than 15 mm Hg above baseline. IOP elevation may occur as early as 1 day to as late as 12 weeks after intravitreal triamcinolone in 20–65% of patients. On average, 75% of eyes with steroid implants require IOP-lowering therapy at some point within 3 years of follow-up. The exact mechanism of steroid-induced glaucoma is not totally understood, but decreased trabecular meshwork outflow is regarded as the main cause of IOP elevation. High-risk patients who receive steroids should be monitored closely and if they develop elevated IOP, steroids with lower potency or steroid-sparing agents should be used. The IOP usually returns to normal within 2–4 weeks after stopping the steroid. About 1–5% of patients do not respond to medical therapy and need surgery. Trabeculectomy, trabeculotomy, shunt surgery, and cyclodestructive procedures are among the methods employed. Removal of residual sub-Tenon or intravitreal steroids may help hasten the resolution of the steroid response. Early results with anecortave acetate, an analog of cortisol acetate with anti-angiogenic activity, in controlling IOP have been promising.

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Introduction

The discovery of steroids was a major breakthrough in the treatment of various autoimmune and inflammatory diseases. Like other therapeutic agents, these medications have their own side effects, including ocular hypertension and iatrogenic glaucoma. The issue of steroid-induced iatrogenic glaucoma was first described in the 1950s with the observation of glaucoma in association with administration of systemic adrenocorticotropic hormones or topical and systemic steroids [1–3]. Armaly and Becker [4] and Becker [5] independently reported that the normal population could be divided into 3 groups based on their response to the topical administration of dexamethasone and bethamethasone: (1) high responders, 4–6% of the population, developed an intraocular pressure (IOP) above 31 mm Hg or a rise of more than 15 mm Hg above baseline; (2) moderate responders, approximately one third of the population, had IOPs between 20 and 31 mm Hg, or a pressure rise of 6–15 mm Hg; nonresponders, the remaining two thirds, had pressure increases of less than 6 mm Hg and IOPs of less than 20 mm Hg.

The most common routes of inducing iatrogenic hypertension or glaucoma are topical and intraocular or periocular administration. It can also occur after receiving systemic steroids, application to the skin, intranasally, or by inhalation [6].

With the advent of laser refractive surgery and post-operative steroid use, cases of severe IOP elevation have

been reported [7, 8]. Corneal-induced errors in IOP measurement, decreased corneal thickness and the accumulation of fluid beneath the Lasik flap may be possible reasons for the failure to recognize steroid-induced iatrogenic glaucoma [9, 10]. The current popular use of intravitreal triamcinolone acetonide (IVTA) for various vitroretinal diseases has led to an increased incidence of corticosteroid-induced ocular hypertension or glaucoma from IVTA [11–25]. As the list of indications and use of IVTA increases, the incidence of IOP elevation secondary to IVTA will be more common and more likely to be encountered by ophthalmologists. This review will address the issue of steroid-induced iatrogenic hypertension or glaucoma with an emphasis on the glaucoma associated with IVTA.

Timing of Response

The time frame when ocular hypertension begins depends on the specific drug, the dosage, the frequency and route of administration, and the susceptibility of the individual patient. The incidence of steroid-induced iatrogenic glaucoma or ocular hypertension following systemic therapies is much less common than following topical administration. Although an acute response has been reported with intensive systemic steroid therapy, the IOP response often occurs over years [26]. Bernstein and Schwartz [27] reported that patients who had been on systemic steroids for more than 4 years had significantly higher IOPs than those who had received systemic steroids for less than a year.

Although the majority of studies reported that IOP rises 3–6 weeks after the beginning of topical steroid use, some elevation of pressure can be found in most patients as early as the first or second week [28–31]. Armaly [28, 29] noted that normal patients developed the hypertensive effect of steroid at the end of the first week, with a mean increase in pressure of 19%. It almost never occurs sooner than 5 days [32]. Failure of IOP to increase after 6 weeks of steroid treatment is no assurance that it will not increase if treatment is continued [33].

There may be a delay in the onset of the increase in IOP of up to several months after corticosteroid injections [22, 34–36]. In Kalina's [36] study, 18 ocular hypertensions were seen after the subconjunctival injection of repository corticosteroid at a mean of 7.1 weeks (range: 1.5–16 weeks) and lasted for a mean duration of 3 months. Retrobulbar injection of triamcinolone acetonide resulted in an elevation of IOP at a mean of 5.2 weeks (range: 1–13

weeks) [37]. IOP elevation after IVTA usually occurs 1–2 months after injection [24, 38], but Smithen et al. [22] reported the occurrence at a mean of 100.6 days. However, Singh et al. [39] reported 3 cases of early and rapid increases in IOP within 1 week following an IVTA injection. All patients were pseudophakic, which may have allowed the medication to move into the anterior segment, causing physical obstruction of the trabecular meshwork. In 1 patient, a whitish deposit was observed in the inferior angle in gonioscopy. Vedantham [40] suggested that pseudophakic patients and those with prior vitrectomies should be followed closely. In addition, he suggested instructing these patients to sleep on their backs to prevent the migration of triamcinolone into the anterior chamber.

Different formulations of the same drug may have different effects on IOP. For example, triamcinolone acetonide sub-Tenon injection, a minimally water-soluble agent, can induce IOP elevations for as long as 6 months, but the diacetate form of the drug is moderately water soluble and thus tends to have a briefer effect on the IOP [41–43].

Risk Factors

The possibility of high response is greater in the following cases: patients with primary open-angle glaucoma (POAG) or glaucoma suspects, first-degree relatives with POAG [44], old age or age less than 6 years, connective tissue disease, especially rheumatoid arthritis in men [45], high myopia [46, 47], type 1 diabetes mellitus [37, 48], and angle recession glaucoma [49]. Patients with predisposing risk factors should be monitored more diligently when receiving corticosteroids.

Primary Open-Angle Glaucoma

Armaly [28, 29] reported that approximately one third of glaucoma suspects and more than 90% of patients with POAG experienced an IOP elevation greater than 6 mm Hg after receiving topical 0.1% dexamethasone for 4 weeks. Becker and Mills [50] also indicated that glaucoma or glaucoma suspect patients who received topical 0.1% betamethasone for 2–4 weeks demonstrated large, highly significant increases in IOP and exhibited decreased outflow facility during the treatment period. The IOP returned to baseline or normal in approximately 1 week after discontinuing the drops [50].

Whereas 18–36% of the general population shows a moderate increase in IOP after the topical administration of corticosteroids, 5–6% of the general population versus

46–92% of patients with POAG have a significant increase in IOP [28, 29, 50–52]. Studies of patients with secondary open-angle glaucoma generally do not find such a high response rate [53]. Other studies showed that simply having a first-degree relative with POAG could make one susceptible to being a high steroid responder [50, 54]. However, having POAG or a first-degree relative with POAG is not an absolute contraindication for steroid use because sometimes steroids are the most effective treatment modality. Given that patients who have undergone filtering surgery have an alternate outflow pathway, it is plausible that their IOP should be minimally affected by the administration of steroids. In a study by Oliver et al. [55] of 9 patients with prior glaucoma surgery who received IVTA, the mean difference between pre-IVTA and maximum post-IVTA IOP was 1 mm Hg. Only 2 patients required additional medication to control their IOP. Finally, some studies indicate that normal individuals classified as high steroid responders were more likely to develop glaucoma [56]. Testing for steroid responsiveness by topical agents to identify patients at risk of developing POAG has not become routine because of the variability in the extent of response and the potential risk to normal individuals [5].

Age

It has been demonstrated that the steroid IOP-increasing effect is greater in older compared with younger patients [28, 29, 38]. Infants and children under 10 years of age may have a marked IOP response although not all studies agree [57, 58]. A study by Lam et al. [59] on children who had had strabismus surgery showed that 71.2 and 59.2% of children receiving topical 0.1% dexamethasone (4 times per day and 2 times per day, respectively) developed IOP elevations greater than 21 mm Hg. In children who received dexamethasone 0.1% drops 4 times per day, the peak IOP was greater, the net increase in IOP was greater, and the time required to reach the peak IOP was less.

In an observational case series by Yamashita et al. [60] of 5 children with leukemia aged less than 6 years, the patients received systemic steroids with their systemic chemotherapy. An IOP rise greater than 21 mm Hg was observed in all patients. IOP increased to a mean maximum of 39.6 ± 7.2 mm Hg (range: 28–47). All patients achieved controlled IOP with antiglaucoma medications. One of the patients had glaucomatous optic neuropathy on the first exam. In their study on children below 10 years, Kwok et al. [61] concluded that the ocular hypertensive response to topical dexamethasone in children

occurs more frequently, more severely, and more rapidly than that reported in adults. Although older patients are at increased risk, the frequency of steroid responsiveness with age may occur in a bimodal distribution and children should be monitored closely.

Diabetes Mellitus

Becker et al. [62] reported that the steroid IOP-increasing effect was greater in diabetic patients . In a retrospective study of 49 patients who received one trans-Tenon retrobulbar injection of triamcinolone acetonide (20 mg), Hirooka et al. [37] reported that the only preoperative predictive factor for steroid responders was the presence of diabetes mellitus (multiple logistic regression analysis, odds ratio = 32.78, p = 0.006). In contrast, in a prospective study of 60 patients who received IVTA, Park et al. [21] found that diabetes mellitus had no correlation with IOP elevation.

Genetic Susceptibility

It has been suggested that a genetic difference exists between corticosteroid responders and nonresponders and that patients who show an increase in IOP have a different or more sensitive corticosteroid receptor. Some researchers tried to explain this genetic susceptibility by a monozygotic autosomal mechanism. It was suggested that medium responders were heterozygous while high responders were homozygous [5, 63, 64].

Mueller et al. [65] retrospectively studied 63 eyes of 55 patients who received posterior sub-Tenon corticosteroid injections (80 mg methylprednisolone acetate, or 40 mg triamcinolone acetonide). All patients had been treated previously with topical or systemic corticosteroids and did not experience an excessive increase in IOP. Some patients had received multiple injections, and in none of them was IOP elevation detected. The nonresponders seemed to be immune to high doses of steroids in the long run. However, Schwartz et al. [66] found no significant difference in the frequency of steroid-induced IOP elevation between monozygotic and dizygotic twin groups. This may suggest that an environmental factor may influence the steroid response.

Several genes have been shown to be upregulated in dexamethasone-treated trabecular meshwork cells, and the most extensively studied represents the protein myocilin [67–69]. Mutations of the myocilin gene are one cause of autosomal dominant juvenile- and adult-onset POAG, but the mechanism by which mutant myocilins cause disease is poorly understood [70]. In animal studies, the investigators could not find statistically signifi-

cant evidence of a link between myocilin gene mutations or myocilin overexpression and steroid-induced IOP elevation [71–73]. Further studies are necessary to enhance our understanding of the role of genetics in steroid-induced iatrogenic glaucoma.

Connective Tissue Disease and Sex

In a study of 34 patients with connective tissue disease, mainly rheumatoid arthritis, who used 0.1% dexamethasone drops in one eye for 6 weeks, Gaston et al. [45] reported a higher incidence of positive steroid response than would be expected in a normal population. Additionally, most of the male patients were responders. Five patients (15% of the total) were high responders (a rise in IOP to 32 mm Hg or more). They were all male. Seven patients (20%) were intermediate responders (IOP between 25 and 31 mm Hg); 4 (57%) were male and 3 were female. Twenty-two patients (65%) were nonresponders (IOP 24 mm Hg or less); 2 (9%) were male and 20 were female.

Mixed results have been obtained regarding the effect of sex on IOP elevation after IVTA injection. In a study of 147 patients, male sex [11] and in another study of 82 patients, female sex [16] were risk factors for IOP elevation in patients who received 4 mg IVTA. More studies are necessary to determine if sex can be regarded as a risk factor.

High Myopia

Although it has been demonstrated that patients with high myopia have a greater risk of increased steroid response [47, 49], in a prospective, noncomparative study of 60 patients who received 4 mg IVTA, Park et al. [21] found that high myopia had no correlation with IOP elevation.

Mode of Administration

Topical Steroids

In most cases, corticosteroid glaucoma or ocular hypertension are caused by drops or ointments instilled in the eye. In a series with 34 cases of steroid-induced iatrogenic glaucoma, topical steroid use was the most frequent (73.5%) mode of administration [74]. Tragically, many cases of steroid-induced glaucoma are produced by treatment for trivial conditions such as contact lens discomfort or red eye. Because of the widespread availability and effectiveness of combination steroid-antibiotic eyedrops, the general medical community routinely prescribes these drops for red eye. Although the majority develops

Table 1. Anti-inflammatory and IOP elevations for different topical steroid preparations

Corticosteroid preparation	Rise in IOP (mm Hg)	Anti-inflammatory potency
Dexamathasone 0.1%	22 ± 2.9	24
Prednisolone 1.0%	10 ± 1.7	2.3
Fluorometholone 0.1%	6.1 ± 1.4	21
Hydrocortisone 0.5%	3.2 ± 1.0	1
Tetrahydrotriamcinolone 0.25%	1.8 ± 1.3	1.4
Medrysone 1.0%	1.0 ± 1.3	1.7

no problem following a short course, the susceptible groups are at risk, especially if prescriptions for the drugs may be refilled.

There is evidence that topical steroids are absorbed systemically. When one eye is treated with topical steroids, the contralateral untreated eye may be affected by the systemically absorbed steroid [75, 76]. The amount of steroid reaching the eye is probably less with systemic therapy than with topical application and it may explain the higher frequency of IOP elevation with topical steroids compared to systemic forms [77]. Fluoromethalone and medrysone are less potent topical corticosteroids, but they have also been shown to produce an elevated IOP with much less risk. The risk of producing an elevated IOP with the new corticosteroids rimexolone and loteprednol is comparable to fluorometholone (table 1) [78]. Difluprednate, a difluorinated prednisolone derivative, penetrates the corneal epithelium rapidly and effectively. Difluprednate does not use benzalkonium chloride as a preservative, but is preserved with sorbic acid, which has been shown to cause little irritation or damage to ocular tissue and is recommended for sensitive eyes [79]. In a multicenter, randomized, double-masked, parallel-group, placebo-controlled trial on 438 patients with unilateral ocular surgery, 111 received difluprednate 2 times a day, 107 received difluprednate 4 times a day, and 220 received a placebo 2 or 4 times a day. A clinically significant IOP rise (defined as ≥10 mm Hg from baseline and ≥21 mm Hg overall) was observed in 3 patients (3%) in both difluprednate groups and 2 patients (1%) in the placebo group [80]. Elevated IOP was effectively controlled with topical medication. In another randomized trial on 182 patients, 3 subjects (3.7%) in the difluprednate group had a clinically significant IOP rise (≥10 mm Hg from baseline and ≥21 mm Hg overall) compared to the placebo group [81].

Table 2. Frequency of different IOP in individuals treated with systemic steroid

Authors	Patients (number)	Mean age (years)	Sex	Mean steroid dosage (mg/kg)	Mean duration of treatment (years)	Patients (%)		
						IOP <20 mm Hg	IOP 20–31 mm Hg	IOP >31 mm Hg
Lee [86]	13	57	7 female 6 male	18	4.4 (1–6)	54	46	0
Bernstein and Schwartz [27]	48	50	35 female 13 male	16	3.5 (0.2–11)	76	24	0
Hovland and Ellis [85]	26	26	10 female 16 male	24	1.25–2.5	69	29	2

Figures in parentheses are ranges.

Long-term steroid creams, lotions and ointments applied to the face, eyelids, or at distant sites may raise the IOP, as so may systemically administered corticosteroids [27, 34, 46, 82–84].

Systemic Steroids
Although glaucoma is also observed in Cushing's syndrome with the production of excess endogenous steroids, the likelihood of IOP elevation with systemic steroids is less than the topical route. Generally, groups of patients being treated with long-term systemic steroids showed higher mean IOPs, as well as an increased number of individuals with higher pressures than are present in the normal population (table 2) [27, 85, 86]. This has been confirmed by comparing steroid-treated patients to the normal population with no steroid treatment or to a group of patients with a similar disease but without steroid treatment [27, 87]. With systemic steroids, there was evidence for both an increase in flow, especially upon short-term administration, and a decrease in the facility of outflow [77, 88]. In patients who are steroid responders, pressure elevations with systemic steroid use average approximately 60% of those produced by topically applied steroids [89]. One study found a 10% incidence of ocular hypertension in renal-transplant patients receiving steroids [90]. Tripathi et al. [33] found a significant relationship between IOP and the dose of corticosteroid (1.4 mm Hg increase in mean IOP for each 10 mg increase in the average daily dose of prednisone) administered.

Ng et al. [91] reported the use of a dose-tapering regimen of dexamethasone was associated with a transient increase in IOP in preterm very low birth-weight (<1,500 g) infants. The IOP at week 1, while the infants were receiving the maximum dose of dexamethasone (0.6 mg/kg/day), was significantly higher than the pretreatment IOP at week 0 (average: 19.7 vs. 16.4 mm Hg, respectively, p < 0.0001), and when the infants were receiving the minimum dose of dexamethasone (0.15 mg/kg/day) at week 3 (19.7 vs. 15.8 mm Hg, p < 0.0001), and also 5 weeks after discontinuance of dexamethasone (19.7 vs. 16.0 mm Hg, p < 0.0001).

Steroid Inhalers
A large cross-sectional, population-based study found that the use of inhaled steroids was associated with an increased risk of IOP elevation only in subjects reporting a first-degree relative with a family history of glaucoma [92]. In another study by Bui et al. [93], a significant reduction in IOP was observed after discontinuing nasal steroids in patients with glaucoma. Studies on the nonglaucomatous patients have not revealed IOP elevation after using various forms of steroid inhalers [94, 95]. As the administered dose of steroid is not high with inhalers, it is logical that we see an increase in the IOP only in susceptible patients.

Intravitreal Steroids
Intravitreal corticosteroids are a recent therapeutic modality that are being used increasingly to treat various edematous and neovascular intraocular conditions. Triamcinolone acetonide is the most commonly used intravitreal steroid. The usual dose is 4 or 20 mg (the latter is more commonly used in Europe). Recently, Chuang et al. [96] reported that the incidence of secondary ocular hypertension was not significantly different between 2 versus 4 mg IVTA (38.9 vs. 50%, p = 0.36). However, patients who received 4 mg had a higher proportion of long-term antiglaucoma medication usage (5.6 vs. 40.6%, p < 0.001).

Table 3. Studies on IOP elevation after IVTA injection

Authors	Patients and eyes (numbers)	Definition of IOP elevation	Average follow-up (months)	Prevalence of IOP elevation	Risk factors	Dose of IVTA	No response to medical therapy and underwent surgery
Roth et al. [13]	929 eyes of 841 patients	>21 mm Hg	14	24% in 12 months, 28% in 24 months	– glaucoma – young age (10-year increase in age was associated with a 16% reduction in risk) – IOP elevation after first IVTA injection	4 mg	1%
Lau et al. [11]	147 eyes	>6 mm Hg increase in baseline IOP	2.5	43.5%	– male sex – young age <55 years	4 mg	6.8%
Vasconcelos-Santos et al. [25]	150 eyes	>21 mm Hg	7.7	32%	– glaucoma – baseline IOP >16 mm Hg	4 mg	–
Im et al. [15]	14 eyes	>24 mm Hg	1	43%		4 mg	none
Yamamato et al. [16]	82 eyes of 69 patients	>5 mm Hg increase in baseline IOP	6	34.1%	– female sex – age <60 years	4 mg	2.4%
Baath et al. [17]	233 eyes of 192 patients		9.5	31.3% needed medical therapy		4 mg	1%
Kramar et al. [18]	85 eyes		4	5–9 mm Hg in 32% ≥10 mm Hg in 30%	–	4 mg	none
Gregori et al. [19]	40 eyes	≥10 mm Hg	12	24%			5%
Konstantopoulos et al. [20]	114 eyes of 108 patients	>28 mm Hg		30%		4 mg	1%
Rhee et al. [12]	570 eyes of 536 patients	>30% increase in baseline IOP	12	50 and 65% that received second injection	– baseline IOP >16 mm Hg – second IVTA injection	4 mg	1%
Park et al. [21]	60 eyes	>21 or 5 mm Hg increase in baseline IOP	6.1	43.3%	– age <60 years	4 mg	1%
Smithen et al. [22]	89 eyes	>24 mm Hg	100 days	40%	– baseline IOP >15 mm Hg	4 mg	none
Bakri et al. [23]	43 eyes of 38 patients	>5 and >10 mm Hg increase in baseline IOP	3	49 and 28%	–	4 mg	none
Jonas et al. [24]	305 eyes of 272 patients	>21 mm Hg	–	41.2%	– younger age	20 mg	1%

IVTA limits the impact of corticosteroids to ocular tissues, thereby minimizing the side effects associated with systemic steroid therapy. Additionally, the issues of drug penetration and bioavailability are eliminated. The reported frequency of IOP elevation varies from 20 to 65% (table 3) [22]. This wide range of values might be explained by the IVTA dose, variation between definitions of IOP elevation, length of follow-up, sample size, and whether patients have previously received IVTA injections or not. Several reports have suggested the higher frequency of IOP elevation in younger patients, higher baseline IOP, intravitreal injection compared to sub-Tenon injection and increased triamcinolone acetonide dosage [21, 97–99]. Although IOP elevation commonly occurs as early as 1 day to as late as 12 weeks after the initial treatment, the IVTA has been reported to be present intraocularly in measurable concentrations up to 1.5 years after intravitreal injection [100].

In order to predict the possibility of a post-IVTA IOP rise, Breusegem et al. [101] conducted a topical dexamethasone provocative test (4 drops a day for 4 weeks) before IVTA injection. A steroid response after the dexamethasone test or after IVTA was defined as an IOP increase of ≥6 mm Hg. In dexamethasone responders, the IOP elevation after IVTA was 17.0 ± 7.8 versus 5.0 ± 4.4 mm Hg in dexamethasone nonresponders (p = 0.005). This test had a low sensitivity, a high specificity, a high positive predictive value and a moderate negative predictive value. Interestingly, all test responders demonstrated high IOP increases after intraocular repository-steroid injection.

The highest IOP elevation within the first 24 h after IVTA injection occurs within 10 min, and to combat this rise, some perform anterior chamber paracentesis [102, 103]. However, one anterior chamber paracentesis for treating an IOP spike after IVTA precipitated an episode of malignant glaucoma [104].

In a meta-analysis, it was shown that there was a tendency toward a higher increase in IOP in patients with uveitis and patients with central retinal vein occlusion [24].

Intravitreal Sustained-Release Steroid Implants

Intravitreal steroid implants are designed for controlling intraocular inflammation due to noninfectious posterior-segment uveitis or macular edema due to vascular accidents [105, 106]. Through three trials of the fluocinolone acetonide implantation, a total of 584 eyes received a single implant at one of two dosages: 0.59 or 2.1 mg. At 1 year, the IOP was elevated to above 30 mm Hg in 36.9 and 40.7% of eyes treated with the 0.59-mg and 2.1-mg implants, respectively. At 2 and 3 years, these values were 46.4 and 55.2% and 51.2 and 59.0%, respectively [106–109]. The incidence of elevated IOP with the fluocinolone acetonide implant has been higher than that with IVTA injections [106]. One explanation for this may be exposure to sustained corticosteroid levels throughout the implant's 30-month lifespan, whereas the eyes treated with IVTA injections are exposed to fluctuating corticosteroid levels every 3 months.

Overall, 75% of eyes receiving the fluocinolone acetonide implant required IOP-lowering therapy at some point within the course of the 3-year study. More than one third of the eyes (36.6%) required IOP-lowering surgery. The most common surgery employed was trabeculectomy (76.2%) and 20.6% received glaucoma drainage devices as first-line treatment. Other employed surgical therapies included cyclodestructive procedures and nonpenetrating glaucoma surgeries [107].

A major complication of surgical intervention for high IOP in these patients was the high prevalence of hypotony (42.5%) that was defined as IOP < 5. The prevalence of hypotony in eyes that received the implant but did not require IOP-lowering surgery was 35.4%. Therefore, it is likely that eyes receiving the fluocinolone acetonide implant were predisposed to low IOP independent of IOP-lowering filtrating surgery [107]. In the study by Callanan et al. [106], the frequency of IOP-lowering surgery began to increase by postimplantation week 12 for implanted eyes and month 27 for fellow eyes.

In two identical, multicenter, masked, randomized, 6-month, sham-controlled clinical trials on patients with central or branch retinal-vein occlusion, a total of 1,267 patients received intravitreal dexamethasone implants [105]. The percentage of dexamethasone implant-treated eyes with an IOP of ≥ 25 mm Hg peaked at 16% at month 2 but was not different from sham by month 6. Studies with longer follow-up periods are necessary to determine the effect of this implant on the IOP.

Mechanism

Trabecular meshwork accounts for nearly 90% of aqueous humor drainage from the eye. Although the proposed mechanism of corticosteroid-induced IOP elevation is increased resistance to aqueous flow via this route, the precise mechanism is still unknown [110]. Krishnan et al. [111] obtained complete success with viscocanalostomy in lowering IOP and because the stripping of the juxtacanalicular tissue and the inner endothelial lining of Schlemm's canal relieved the steroid-induced resistance to aqueous outflow, the obstruction to aqueous outflow in steroid-induced glaucoma seems to lie predominantly in the juxtacanalicular tissue and the endothelium of Schlemm's canal. Based on the histopathologic study of 2 patients who had trabeculectomy because of uncontrolled IOP after IVTA, the ultrastructural changes in the trabecular meshwork resembled those with glaucoma after topical corticosteroid treatment [112]. There are a number of observations that can be summarized as follows.

Trabecular Meshwork Extracellular Matrix

The effect of steroids on the trabecular meshwork extracellular matrix may be due to altered rates of protein synthesis, or to protein degradation, or a combination of both. This results in increased deposition of glycosaminoglycan, elastin, fibronectin, laminin, and type IV collagen as part of the extracellular matrix secondary to increased production and decreased destruction because of inhibition of several trabecular meshwork matrix metalloproteinases [81–83]. Additionally, dexamethasone is known to inhibit the phagocytic abilities of trabecular meshwork cells so that debris accumulates within the drainage channels [113].

Gene Expression

Myocilin was the first glaucoma gene (GLC1A) to be mapped and identified and was a glaucoma candidate

gene because of its expression in the trabecular meshwork and its induction by steroids [114–116]. The myocilin gene product, known as myocilin or trabecular meshwork-inducible glucocorticoid response (TIGR) protein, is distributed intracellularly as well as in the extracellular matrix of the normal and glaucomatous trabecular meshwork [117]. Myocilin gene mutations are responsible for juvenile open-angle glaucoma and 3–5% of cases of POAG [118, 119]. Mutations of this gene appear to produce a dysfunctional secretion of the translated protein in trabecular meshwork cells, leading to decreased aqueous outflow [120]. A more than 100-fold increase in myocilin gene expression has been reported after exposure to dexamethasone [121]. However, a recent study of human trabecular meshwork cells that were cultured in the presence of ophthalmic steroids did not show that myocilin gene overexpression is associated with an increase in IOP [122]. More studies are needed to explain the variations in the myocilin gene and their role in steroid-induced glaucoma.

Trabecular Meshwork Cells

Trabecular meshwork cells have glucocorticoid receptors, and the activation of these receptors by steroids alters the structure and protein expression of trabecular meshwork cells [79]. Steroids have been shown to alter trabecular meshwork cell morphology by causing an increase in nuclear size and DNA content [113, 123].

In a study of the effects of steroids on junctional protein expression and cytoskeleton organization in primary human trabecular meshwork cultures, it was shown that dexamethasone increased the protein levels of zonula occludens-1 and connexin 43 in trabecular meshwork cells, which are thought to be closely related to fluid flow resistance. Dexamethasone also altered the F-actin architecture and promoted cross-linked actin network formation [124]. F-actin interacts with zonula occludens-1 to help intercellular tight junction assembly, in which the tightness and distribution of the tight junctions influence the outflow rate of aqueous humor. F-actin is also organized to respond to cell contraction and to participate in generating forces responsible for the continued development and maintenance of tension. It has been shown that dexamethasone induces F-actin expression and enhances the mediated contraction of trabecular meshwork cells [125, 126]. Contraction of the trabecular meshwork reduces the intercellular spaces and thus reduces the outflow of aqueous humor [127].

Changes in the microstructure of the trabecular meshwork (cross-linked actin network formation) and cell activities may lead to the decreased proliferation, migration and phagocytosis of the trabecular meshwork cells [76, 80]. All these cause the diminished cellularity of the trabecular meshwork seen in patients with steroid-induced glaucoma and the progressive accumulation of extracellular debris and increased aqueous outflow resistance.

Clinical Picture and Differential Diagnosis

Steroid-induced glaucoma can occur with any form of steroid administration. Patients with steroid-induced glaucoma have relatively few symptoms. These patients do not complain until they notice visual disturbances: blurred vision or signs of visual-field defect. Glaucoma may be discovered by chance during an ophthalmological checkup. If the IOP is not measured at the initial stages when there are no glaucomatous optic nerve head findings, misdiagnosis is not unusual. The blurred vision is caused by corneal edema if the IOP has risen to the point of compromising corneal function and may be associated with halo. It may even be due to a posterior subcapsular cataract. The IOP rise is generally gradual and painless, but a few patients may experience ocular or brow ache [26, 128].

The typical manifestation of steroid induced-glaucoma in adults is similar to POAG. Even in patients with high IOP, the eyes are remarkably white. However, some patients may present with a pale disk, often not typically excavated at the onset, and the uncharacteristically deteriorated visual field resembling the findings after an acute angle-closure attack. This picture develops when the IOP reaches high values rapidly. Elderly patients who received corticosteroid treatment in the past may present as cases of normal-tension glaucoma. They have experienced IOP elevation and glaucomatous optic-nerve damage while being on steroids and, years later, present off steroid with normal IOP and glaucomatous optic neuropathy. Because these eyes are generally asymptomatic, diagnosis relies on appropriate recognition and monitoring of patients at risk [129].

Of the reported complications of steroids that may accompany steroid-induced glaucoma are mydriasis and ptosis. In cases with unilateral steroid-induced glaucoma, mydriasis and ptosis may be striking; otherwise, as they are not severe, they may not be evident [130].

In a pediatric series reported by Yamashita et al. [60], no patient had symptoms, even the one who had an IOP of 47 mm Hg. The clinical picture in infants with steroid-induced glaucoma resembles congenital glaucoma [57].

Management

The most effective treatment for corticosteroid-induced glaucoma is its prevention through judicious use of steroids. In this regard, education of the patient and physician about the potential ocular complications of steroids is necessary. Failure of IOP elevation after 6 weeks of therapy is no assurance that an individual will not develop an increase in IOP if steroid administration is continued. For this reason, patients who are on steroids, specially the topical form, should have regular follow-up examinations to prevent iatrogenic glaucomatous optic-nerve damage [33].

IOP Monitoring

Recognition of the condition is the most important step in its management. When patients are put on steroids, particularly with potent topical steroids and periocular injections, the physicians should monitor them thoroughly. This includes baseline IOP measurement, mostly to rule out preexisting glaucoma. IOP monitoring should initially occur at 2 weeks and then every 4–6 weeks for 2–3 months, and then every 6 months after an initial response has been ruled out. In the case of IVTA injection, in addition to the above-mentioned measurements, IOP should be checked on the injection day and first week [129].

Discontinuance of Steroids

The steroid-induced IOP increase is usually short-lived and reversible by discontinuance of therapy if the drug has not been used for more than a year. It is likely to result in permanent IOP elevation if steroid therapy has been continued for 18 months or more [32]. The IOP usually returns to normal within 2–4 weeks after discontinuing the steroid [131]. In cases with repository-steroid injection and high IOP, the residual subconjunctival or intraocular steroid may be removed [28, 86–88]. In the two cases with very high IOP described by Agrawal et al. [132], the removal of the intravitreal corticosteroid by vitrectomy reversed the elevated IOP. However, the potential surgical complications of vitrectomy, including rhegmatogenous retinal detachment, proliferative vitreoretinopathy, and induction of cataract, have to be considered against the risk-benefit profile of other treatment modalities, such as laser trabeculoplasty and trabeculectomy or shunt surgery. However, some reports document continued IOP elevation, even long after withdrawal of the steroid [21, 89]. Additionally, the removal of the repository steroid will also result in a reduction in the drug's desired effect.

If the drug should be continued, it must be used in a lower concentration or replaced by weaker corticosteroids, or antiglaucoma agents should be commenced to control the high IOP. In the case of topical steroids, loteprednol can be a suitable alternative since it undergoes hydrolysis in the cornea and aqueous humor to become an inactive derivative and thus may not have a marked effect on the IOP [133]. Rimexolone 1% is a topical steroid designed so as not to elevate IOP, but IOP increase has been reported, even though it is rare [32]. Systemic steroids can be replaced by steroid-sparing agents such as systemic nonsteroidal anti-inflammatory agents [134].

Medical Management

It may not be possible to discontinue the steroid, and the elevated IOP should be managed medically or surgically. The medical management of these cases is essentially the same as for POAG. Nearly all patients who develop steroid-induced iatrogenic glaucoma can be controlled with topical antiglaucoma therapy [18, 31]. Sihota et al. [74] reported that in 25 of 34 patients (73.5%), IOP could be controlled by topical medications alone. At 6, 12, and 18 months' follow-up, 22 (64.7%), 33 (97.1%), and all 34 (100%) patients were off treatment, respectively. In a study by Gillies et al. [95], of 75 patients who received 4 mg IVTA, it was shown that with the criterion of treating any IOP above 25 mm Hg, 21 (28.0%) required treatment with topical glaucoma therapy. A single medication was sufficient in 18 (85.7%) patients, whereas the other 3 (14.3%) required 2 medications to control IOP. Topical glaucoma treatment was discontinued in 52.4% at the 6-month follow-up and in 71.4% after a mean period of 8 months (range: 1.5–32 months). Eight percent of eyes that did not receive glaucoma medication before IVTA continued to require glaucoma medication at the last study visit (3-year study duration).

Another study revealed that the patient who was managed with topical glaucoma medications for elevated IOP after IVTA injection no longer needed antiglaucoma agents about 6 months after the injection [135]. Overall, as the ocular hypertensive effect of repository steroids decreases, the majority of patients need to receive antiglaucoma medications for just 6 months after steroid injection.

All available antiglaucoma medications can be used in these patients, beginning with aqueous humor suppressants. These include β-blockers, followed by either α_2 agonists or topical carbonic anhydrase inhibitors.

Topical β-blockers are a popular first-line agent for treating this type of glaucoma and are categorized as well-tolerated drugs in patients with uveitis [136].

The α_2 agonist brimodidine is an often effective drug for treating steroid-induced iatrogenic glaucoma and can be used in patients with intraocular inflammation [129].

Carbonic anhydrase inhibitors are also regarded as effective agents in this condition. Acetazolamide is frequently used for the short-term control of high IOP, and the topical forms can be used for a more prolonged period. They are also regarded as potent and effective agents in controlling IOP in patients with uveitis [136].

Prostaglandin analogues have been reported to induce uveitis and are relatively contraindicated in patients who have developed high IOP after using steroids to control ocular inflammation [137]. However, this agent, as well as miotics, may be effective, particularly as an additive agent. Although prostaglandin analogues may not be the first choice, they can be helpful in some situations in which further IOP lowering is required.

Laser Trabeculoplasty

Rubin et al. [138] reported 7 patients who underwent selective laser trabeculoplasty (SLT) for increased IOP after IVTA. The mean preoperative IOP of 38.4 ± 7.3 with 4 medications decreased postoperatively to 23.9 at 3 months (p < 0.006) with 3.9 medications, and 15.7 at 6 months (p < 0.001) with 2.4 medications. Four patients had a second SLT procedure. Two patients failed after the third-month visit: one had pars plana vitrectomy and lensectomy and the other underwent Ahmed valve implantation.

In another study, SLT was performed on 4 patients under 47 years with elevated IOP after a sub-Tenon injection of triamcinolone acetonide which could not be maintained within normal limits by antiglaucoma medications. In 3 eyes, the mean IOP before the SLT was 28.7 mm Hg and the postoperative mean IOP was 15.3 mm Hg at 6 months without antiglaucoma medications. In 1 patient, the IOP increased to 40 mm Hg at 4 weeks after SLT, and the patient underwent trabeculotomy [139].

Five patients who received argon laser trabeculoplasty for increased IOP after IVTA achieved normal IOP within the first postoperative month [140, 141]. The advantages of laser trabeculoplasty are numerous when considering the possible hazards of trabeculectomy, including anesthesia, hypotony, cataract, and endophthalmitis. It is also a time-efficient and cost-effective procedure when compared with filtering surgery [141, 142]. Another advantage of this procedure, in contrast to filtering procedures that increase the turnover and wean off the effect of steroids, is keeping the intraocular steroid so that its therapeutic effect does not cease. Although the IOP drop

after laser trabeculoplasty in patients who have intraocular steroids could also be due to the waning of the steroid effect, this procedure can reduce IOP until the steroid-induced hypertensive effect disappears [141, 143]. Laser trabeculoplasty may be considered as a primary option for steroid-induced ocular hypertension when considering the ocular and systemic adverse effects of antiglaucoma agents.

Surgical Management

If the patient's IOP is very high or remains elevated for a significant period of time, surgical intervention should be considered. Although most patients with steroid-induced elevated IOP can be treated systemically or topically, about 1–5% with intractable glaucoma must still undergo surgery to normalize their IOP [15, 97]. Also, if the patient is expected to have repeated exposure to steroids, surgery may be the best solution so steroids can then be used more freely. However, Muecke and Brian [144] reported a case with several episodes of steroid-induced ocular hypertension (above 50 mm Hg) when challenged with topical steroid on two occasions despite having a functional Molteno shunt and having received maximal hypotensive medication after each steroid challenge. Moreover, in a prospective study of 87 eyes of 52 patients with POAG, a significant steroid-induced rise in IOP in the 4 weeks after trabeculectomy was observed in 23% of eyes [145]. The patients who need to receive steroids in any form after glaucoma surgery for steroid-induced iatrogenic glaucoma need to be monitored regularly.

In a series, 9 out of 34 patients with steroid-induced iatrogenic glaucoma (26.5%) required surgery. The mean baseline IOP in the eyes requiring surgery was 49.67 ± 13.28 mm Hg, and in the eyes managed medically 30.36 ± 7.51 mm Hg (p = 0.002). In addition, patients ≤20 years old with greater glaucomatous optic neuropathy were more likely to need surgery [74].

The most commonly employed surgery in patients with virgin conjunctiva is trabeculectomy; otherwise, shunt implantation or cyclodestructive procedures may be preferred. Repository-steroid removal (excision in the case of sub-Tenon deposits and vitrectomy in the IVTA) and a glaucoma procedure can be performed in one session when the IOP drop does not seem to be controlled by steroid removal [146].

Vitrectomy

Agrawal et al. [132] reported the successful outcome of vitrectomy in 2 patients that had an IOP of 70 after

IVTA. The IOP returned to below 21 within the first postoperative week with no antiglaucoma medications. However, pars plana vitrectomy is a more invasive intervention than trabeculectomy or shunt surgery, and the therapeutic effect of steroids stops. In addition, up to 3% of steroid responders may have irreversible elevations of IOP [26].

Filtering Procedures

In a case series of 3 eyes of 3 patients with elevated IOP after IVTA, trabeculectomy augmented with 5-fluouracil controlled the IOP to less than 18 mm Hg without antiglaucoma medications, with a median follow-up of 9.5 months [147]. Krishnan et al. [111] reported a series of 3 patients who developed refractory glaucoma secondary to IVTA and were successfully treated with viscocanalostomy.

Trabeculotomy

Contrary to other types of adult glaucoma, trabeculotomy has been reported to be effective in adult patients with steroid-induced iatrogenic glaucoma [139, 148]. Honjo et al. [148] studied 14 eyes in 7 patients with a history of topical or systemic corticosteroid treatment before the rise of IOP and underwent trabeculotomy as the first surgical procedure. After an average follow-up of 60.6 ± 33.5 months, the IOP in all of the 14 eyes was well controlled below or equal to 21 mm Hg at the final examinations.

Shunt Implantation

Seven eyes of 5 patients underwent fluocinolone acetonide implantation and Ahmed valve placement in a single surgical session. The average IOP decreased from 27.3 mm Hg at baseline to 14.6 mm Hg 12 months after the combined surgery (p = 0.01). One eye did not maintain target IOP and underwent the placement of a second glaucoma tube shunt 4.4 months after the initial surgery, with subsequent appropriate IOP control [149].

Eyes with active inflammation or conjunctival scarring from previous surgery will benefit particularly from the use of a shunt implantation. Another consideration for implant selection is plate size. In eyes with fluocinolone acetonide implants, larger plate size may result in a higher risk of hypotony. An implant with a smaller plate size, such as the Ahmed implant, is probably less likely to cause chronic hypotony in patients with uveitis and steroid implants [106]. In patients with IVTA and high IOP, Ahmed valve implantation has proven to be effective [39, 138].

Future Therapies

Anecortave acetate is an analog of cortisol acetate that lacks the typical anti-inflammatory and immunosuppressive properties of glucocorticoids. Anecortave acetate functions as an antiangiogenic agent, inhibiting blood vessel growth by decreasing extracellular protease expression and inhibiting endothelial cell migration. Its angiostatic activity does not seem to be mediated through any of the commonly known pharmacological receptors [150–152]. In a case series, a total of 8 eyes of 7 subjects with medically uncontrolled IOP following intravitreal or sub-Tenon injections of triamcinolone acetonide received an anterior juxtascleral depot of 3% anecortave acetate solution. To administer the drug in the juxtascleral area after instilling topical anesthesia and inserting a lid speculum, the patients were advised to look upward. Then, using a 33-gauge needle on a tuberculin syringe, 0.8–1.0 ml of a 30 mg/ml suspension (24–30 mg) of anecortave was injected into the anterior sub-Tenon space in the inferior fornix approximately 4 mm from the limbus with the needle parallel to the limbus slowly over 1–2 min. The mean baseline IOP had reduced from 39.9 mm Hg by 34.5% (14.1 mm Hg, p = 0.003) at the 1-month follow-up. Four eyes required surgical intervention despite a decrease in IOP because of a markedly elevated initial IOP and the degree of preexisting glaucomatous optic neuropathy. No adverse effects were observed [92].

In a prospective interventional case series of 28 uncontrolled glaucoma (mainly uveitic/steroid-induced glaucoma), Prata et al. [153] showed that a single juxtascleral depot injection of anecortave acetate (24–30 mg) resulted in a significant IOP reduction for at least 3 months in 11 patients (39.2%). This series also sustained no complication. The mechanism underlying this anecortave effect is unclear [92–94], but these studies provide a basis and model not only for studying the mechanism of steroid-induced glaucoma but also of POAG and evaluating potential therapies.

Conclusion

The exact mechanism of steroid-induced glaucoma is not yet known. The genetics are not fully understood. Contrary to the postulation of simple Mendelian inheritance, steroid-induced glaucoma seems to be induced by a number of gene locus interactions and environmental factors. The responses of normal, suspect or glaucomatous patients to steroids differ. The lowest pressure eleva-

tion after steroid use has been observed in normal patients, while the highest has been observed in patients with glaucoma. Data from several studies indicate that the response of IOP to steroids appears to be dependent upon mean initial pressure. Susceptible patients should be identified early enough and monitored closely to prevent irreversible optic nerve damage. Discontinuance of the steroid or resection of the remainder of the repository steroid may be of benefit to the patient. The majority of cases with steroid-induced iatrogenic glaucoma can be controlled successfully by topical glaucoma medications.

The high incidence of elevated IOP is a significant complication with intravitreal fluocinolone acetonide implants but can be managed in most patients with IOP-lowering eye drops or surgery. However, surgery is associated with a high frequency of postoperative hypotony.

About 1–5% of patients with steroid-induced iatrogenic glaucoma do not respond to medical therapy and need surgery to normalize their IOP. Trabeculectomy, trabeculotomy, shunt surgery, and cyclodestructive procedures are among the surgeries employed and can be combined with vitrectomy in patients who have IVTA to remove the remainder of the steroid. Early results of anecortave acetate, an angiostatic steroid, in controlling IOP have been promising. Further studies on the mechanism of steroid-induced glaucoma, genetics, and the potential role of anecortave acetate can improve our understanding of this sight-threatening complication of steroids to advance their medical and surgical management.

Disclosure Statement

Neither author has any conflicts of interest associated with the work presented in this article.

References

1 Woods AC: Clinical and experimental observation on the use of ACTH and cortisone in ocular inflammatory disease. Trans Am Ophthalmol Soc 1950;48:259–296.
2 Covell LL: Glaucoma induced by systemic steroid therapy. Am J Ophthalmol 1958;45:108–109.
3 Goldmann H: Cortisone glaucoma. Arch Ophthalmol 1962;68:621–626.
4 Armaly MF, Becker B: Intraocular pressure response to topical corticosteroids. Fed Proc 1965;24:1274–1278.
5 Becker B: Intraocular pressure response to topical corticosteroids. Invest Ophthalmol 1965;4:198–205.
6 Urban RC Jr, Dreyer EB: Corticosteroid-induced glaucoma. Int Ophthalmol Clin 1993;33:135–139.
7 Shaikh NM, Shaikh S, Singh K, Manche E: Progression to end-stage glaucoma after laser in situ keratomileusis. J Cataract Refract Surg 2002;28:356–359.
8 Morales J, Good D: Permanent glaucomatous visual loss after photorefractive keratectomy. J Cataract Refract Surg 1998;24:715–718.
9 Samuelson TW: Refractive surgery in glaucoma. Curr Opin Ophthalmol 2004;15:112–118.
10 Hamilton DR, Manche EE, Rich LF, Maloney RK: Steroid-induced glaucoma after laser in situ keratomileusis associated with interface fluid. Ophthalmology 2002;109:659–665.
11 Lau LI, Chen KC, Lee FL, Chen SJ, Ko YC, Liu CJ, Hsu WM: Intraocular pressure elevation after intravitreal triamcinolone acetonide injection in a Chinese population. Am J Ophthalmol 2008;146:573–578.

12 Rhee DJ, Peck RE, Belmont J, Martidis A, Liu M, Chang J, Fontanarosa J, Moster MR: Intraocular pressure alterations following intravitreal triamcinolone acetonide. Br J Ophthalmol 2006;90:999–1003.
13 Roth DB, Verma V, Realini T, Prenner JL, Feuer WJ, Fechtner RD: Long-term incidence and timing of intraocular hypertension after intravitreal triamcinolone acetonide injection. Ophthalmology 2009;116:455–460.
14 Vasconcellos JP, Melo MB, Costa VP, Tsukumo DM, Basseres DS, Bordin S, Saad ST, Costa FF: Novel mutation in the MYOC gene in primary open glaucoma patients. J Med Genet 2000;37:301–303.
15 Im L, Allingham RR, Singh I, Stinnett S, Fekrat S: A prospective study of early intraocular pressure changes after a single intravitreal triamcinolone injection. J Glaucoma 2008;17:128–132.
16 Yamamoto Y, Komatsu T, Koura Y, Nishino K, Fukushima A, Ueno H: Intraocular pressure elevation after intravitreal or posterior sub-Tenon triamcinolone acetonide injection. Can J Ophthalmol 2008;43:42–47.
17 Baath J, Ells AL, Crichton A, Kherani A, Williams RG: Safety profile of intravitreal triamcinolone acetonide. J Ocul Pharmacol Ther 2007;23:304–310.
18 Kramar M, Vu L, Whitson JT, He YG: The effect of intravitreal triamcinolone on intraocular pressure. Curr Med Res Opin 2007;23:1253–1258.

19 Gregori NZ, Rosenfeld PJ, Puliafito CA, Flynn HW Jr, Lee JE, Mavrofrides EC, Smiddy WE, Murray TG, Berrocal AM, Scott IU, Gregori G: One-year safety and efficacy of intravitreal triamcinolone acetonide for the management of macular edema secondary to central retinal vein occlusion. Retina 2006;26:889–895.
20 Konstantopoulos A, Williams CP, Newsom RS, Luff AJ: Ocular morbidity associated with intravitreal triamcinolone acetonide. Eye (Lond) 2007;21:317–320.
21 Park HY, Yi K, Kim HK: Intraocular pressure elevation after intravitreal triamcinolone acetonide injection. Korean J Ophthalmol 2005;19:122–127.
22 Smithen LM, Ober MD, Maranan L, Spaide RF: Intravitreal triamcinolone acetonide and intraocular pressure. Am J Ophthalmol 2004;138:740–743.
23 Bakri SJ, Beer PM: The effect of intravitreal triamcinolone acetonide on intraocular pressure. Ophthalmic Surg Lasers Imaging 2003;34:386–390.
24 Jonas JB, Degenring RF, Kreissig I, Akkoyun I, Kamppeter BA: Intraocular pressure elevation after intravitreal triamcinolone acetonide injection. Ophthalmology 2005;112:593–598.
25 Vasconcelos-Santos DV, Nehemy PG, Schachat AP, Nehemy MB: Secondary ocular hypertension after intravitreal injection of 4 mg of triamcinolone acetonide: incidence and risk factors. Retina 2008;28:573–580.
26 Francois J: Corticosteroid glaucoma. Ann Ophthalmol 1977;9:1075–1080.

27 Bernstein HN, Schwartz B: Effects of long-term systemic steroids on ocular pressure and tonographic values. Arch Ophthalmol 1962;68:742–753.

28 Armaly MF: Effect of corticosteroids on intraocular pressure and fluid dynamics. I. The effect of dexamethasone in the normal eye. Arch Ophthalmol 1963;70:482–491.

29 Armaly MF: Effect of corticosteroids on intraocular pressure and fluid dynamics. Il. The effect of dexamethasone in the glaucomatous eye. Arch Ophthalmol 1963;70:492–499.

30 Becker B, Mills DW: Corticosteroids and intraocular pressure. Arch Ophthalmol 1963;70:500–507.

31 Carnahan MC, Goldstein DA: Ocular complications of topical, peri-ocular, and systemic corticosteroids. Curr Opin Ophthalmol 2000;11:478–483.

32 American Academy of Ophthalmology: Basic and Clinical Science Course, Section 2: Fundamentals and Principles of Ophthalmology. San Francisco, American Academy of Ophthalmology, 2008, p 419.

33 Tripathi RC, Kirschner BS, Kipp M, Tripathi BJ, Slotwiner D, Borisuth NS, Karrison T, Ernest JT: Corticosteroid treatment for inflammatory bowel disease in pediatric patients increases intraocular pressure. Gastroenterology 1992;102:1957–1961.

34 Herschler J: Intractable intraocular hypertension induced by repository triamcinolone acetonide. Am J Ophthalmol 1972;74:501–504.

35 Helm CJ, Holland GN: The effects of posterior subTenon injection of triamcinolone acetonide in patients with intermediate uveitis. Am J Ophthalmol 1995;120:55–64.

36 Kalina RE: Increased intraocular pressure following subconjunctival corticosteroid administration. Arch Ophthalmol 1969;81:788–790.

37 Hirooka K, Shiraga F, Tanaka S, Baba T, Mandai H: Risk factors for elevated intraocular pressure after trans-Tenon retrobulbar injections of triamcinolone. Jpn J Ophthalmol 2006;50:235–238.

38 Jones R, 3rd, Rhee DJ: Corticosteroid-induced ocular hypertension and glaucoma: a brief review and update of the literature. Curr Opin Ophthalmol 2006;17:163–167.

39 Singh IP, Ahmad SI, Yeh D, Challa P, Herndon LW, Allingham RR, Lee PP: Early rapid rise in intraocular pressure after intravitreal triamcinolone acetonide injection. Am J Ophthalmol 2004;138:286–287.

40 Vedantham V: Intraocular pressure rise after intravitreal triamcinolone. Am J Ophthalmol 2005;139:575; author reply 576.

41 Herschler J: Increased intraocular pressure induced by repository corticosteroids. Am J Ophthalmol 1976;82:90–93.

42 Kalina PH, Erie JC, Rosenbaum L: Biochemical quantification of triamcinolone in subconjunctival depots. Arch Ophthalmol 1995;113:867–869.

43 Goldstein DA, Fiscella RG, Tessler HH: Biochemical quantification of triamcinolone in subconjunctival depots. Arch Ophthalmol 1996;114:363–364.

44 Davies TG: Tonographic survey of the close relatives of patients with chronic simple glaucoma. Br J Ophthalmol 1968;52:32–39.

45 Gaston H, Absolon MJ, Thurtle OA, Sattar MA: Steroid responsiveness in connective tissue diseases. Br J Ophthalmol 1983;67:487–490.

46 Spaeth GL, Rodrigues MM, Weinreb S: Steroid-induced glaucoma: A. Persistent elevation of intraocular pressure. B. Histopathological aspects. Trans Am Ophthalmol Soc 1977;75:353–381.

47 Podos SM, Becker B, Morton WR: High myopia and primary open-angle glaucoma. Am J Ophthalmol 1966;62:1038–1043.

48 Becker B: Diabetes mellitus and primary open-angle glaucoma. The XXVII Edward Jackson Memorial Lecture. Am J Ophthalmol 1971;71:1–16.

49 Spaeth GL: Traumatic hyphema, angle recession, dexamethasone hypertension, and glaucoma. Arch Ophthalmol 1967;78:714–721.

50 Becker B, Mills DW: Corticosteroid and intraocular pressure. Arch Ophthalmol 1963;70:500–507.

51 Becker B, Mills DW: Elevated intraocular pressure following corticosteroid eye drops. JAMA 1963;185:884–886.

52 François J, Heintz-De Bree C, Tripathi RC: The cortisone test and heredity of early open-angle glaucoma (in French). Bull Soc Belge Ophtalmol 1965;141:576–581.

53 Becker B: The effect of topical corticosteroids in secondary glaucoma. Arch Ophthalmol 1964;72:769–771.

54 Reichle ML: Complications of intravitreal steroid injections. Optometry 2005;76:450–460.

55 Oliver A, Gao H, WuDunn D, Peracha MO, Cantor LB: Intravitreal triamcinolone injection in patients with surgically controlled glaucoma. Arch Ophthalmol 2006;124:1788–1790.

56 Kitazawa Y, Horie T: The prognosis of corticosteroid-responsive individuals. Arch Ophthalmol 1981;99:819–823.

57 Kass MA, Kolker AE, Becker B: Chronic topical corticosteroid use simulating congenital glaucoma. J Pediatr 1972;81:1175–1177.

58 Ohji M, Kinoshita S, Ohmi E, Kuwayama Y: Marked intraocular pressure response to instillation of corticosteroids in children. Am J Ophthalmol 1991;112:450–454.

59 Lam DS, Fan DS, Ng JS, Yu CB, Wong CY, Cheung AY: Ocular hypertensive and anti-inflammatory responses to different dosages of topical dexamethasone in children: a randomized trial. Clin Experiment Ophthalmol 2005;33:252–258.

60 Yamashita T, Kodama Y, Tanaka M, Yamakiri K, Kawano Y, Sakamoto T: Steroid-induced glaucoma in children with acute lymphoblastic leukemia: a possible complication. J Glaucoma 2010;19:188–190.

61 Kwok AK, Lam DS, Ng JS, Fan DS, Chew SJ, Tso MO: Ocular-hypertensive response to topical steroids in children. Ophthalmology 1997;104:2112–2116.

62 Becker B, Bresnick G, Chevrette L, Kolker AE, Oaks MC, Cibis A: Intraocular pressure and its response to topical corticosteroids in diabetes. Arch Ophthalmol 1966;76:477–483.

63 Armaly MF: Statistical attributes of steroid hypertensive response in the clinically normal eye. I. The demonstration of three levels of response. Invest Ophthalmol 1965;4:187–197.

64 Becker B, Hahn KA: Topical corticosteroids and heredity in primary open-angle glaucoma. Am J Ophthalmol 1964;57:543–551.

65 Mueller AJ, Jian G, Banker AS, Rahhal FM, Capparelli E, Freeman WR: The effect of deep posterior subTenon injection of corticosteroids on intraocular pressure. Am J Ophthalmol 1998;125:158–163.

66 Schwartz JT, Reuling FH, Feinleib M, Garrison RJ, Collie DJ: Twin study on ocular pressure following topically applied dexamethasone. Il. Inheritance of variation in pressure response. Arch Ophthalmol 1973;90:281–286.

67 Alward WL: The genetics of open-angle glaucoma: The story of GLC1A and myocilin. Eye (Lond) 2000;14:429–436.

68 Polansky JR, Nguyen TD: The TIGR gene, pathogenic mechanisms, and other recent advances in glaucoma genetics. Curr Opin Ophthalmol 1998;9:15–23.

69 Lo WR, Rowlette LL, Caballero M, Yang P, Hernandez MR, Borras T: Tissue differential microarray analysis of dexamethasone induction reveals potential mechanisms of steroid glaucoma. Invest Ophthalmol Vis Sci 2003;44:473–485.

70 Liu Y, Vollrath D: Reversal of mutant myocilin non-secretion and cell killing: implications for glaucoma. Hum Mol Genet 2004;13:1193–1204.

71 Zillig M, Wurm A, Grehn FJ, Russell P, Tamm ER: Overexpression and properties of wild-type and Tyr437His mutated myocilin in the eyes of transgenic mice. Invest Ophthalmol Vis Sci 2005;46:223–234.

72 Gould DB, Miceli-Libby L, Savinova OV, Torrado M, Tomarev SI, Smith RS, John SW: Genetically increasing Myoc expression supports a necessary pathologic role of abnormal proteins in glaucoma. Mol Cell Biol 2004;24:9019–9025.

73 Fingert JH, Clark AF, Craig JE, Alward WL, Snibson GR, McLaughlin M, Tuttle L, Mackey DA, Sheffield VC, Stone EM: Evaluation of the myocilin (MYOC) glaucoma gene in monkey and human steroid-induced ocular hypertension. Invest Ophthalmol Vis Sci 2001;42:145–152.

74 Sihota R, Konkal VL, Dada T, Agarwal HC, Singh R: Prospective, long-term evaluation of steroid-induced glaucoma. Eye (Lond) 2008;22:26–30.

75 Levene R, Wigdor A, Edelstein A, Baum J: Topical corticosteroid in normal patients and glaucoma suspects. Arch Ophthalmol 1967;77:593–597.

76 Spiers F: Topical steroids and intraocular pressure. I. Clinical investigation on the reactions of 93 outpatients to monocular steroid provocation and to subsequent water-drinking test. Acta Ophthalmol (Copenh) 1965;43:735–745.

77 Schwartz B: The response of ocular pressure to corticosteroids. Int Ophthalmol Clin 1966;6:929–989.

78 Stewart RH, Kimbrough RL: Intraocular pressure response to topically administered fluorometholone. Arch Ophthalmol 1979; 97:2139–2140.

79 Jamal KN, Callanan DG: The role of difluprednate ophthalmic emulsion in clinical practice. Clin Ophthalmol 2009;3:381–390.

80 Korenfeld MS, Silverstein SM, Cooke DL, Vogel R, Crockett RS: Difluprednate ophthalmic emulsion 0.05% for postoperative inflammation and pain. J Cataract Refract Surg 2009;35:26–34.

81 Smith S, Lorenz D, Peace J, McLeod K, Crockett R, Vogel R: Difluprednate ophthalmic emulsion 0.05% (durezol) administered two times daily for managing ocular inflammation and pain following cataract surgery. Clin Ophthalmol 2010;4:983–991.

82 Cubey RB: Glaucoma following the application of corticosteroid to the skin of the eyelids. Br J Dermatol 1976;95:207–208.

83 Zugerman C, Saunders D, Levit F: Glaucoma from topically applied steroids. Arch Dermatol 1976;112:1326.

84 Alfano JE: Changes in the intraocular pressure associated with systemic steroid therapy. Am J Ophthalmol 1963;56:245–247.

85 Hovland KR, Ellis PP: Ocular changes in renal transplant patients. Am J Ophthalmol 1967;63:283–289.

86 Lee PF: The influence of systemic steroid therapy on the intraocular pressure. Am J Ophthalmol 1958;46:328–331.

87 Lindholm B, Linner E, Tengroth B: Effects of long-term systemic steroids on cataract formation and on aqueous humour dynamics. Acta Ophthalmol 1965;43:120–127.

88 Diotallevi M, Bocci N: Effect of systemically administered corticosteroids on intraocular pressure and fluid dynamics. Acta Ophthalmol (Copenh) 1965;43:524–527.

89 Feiler-Ofry V, Godel V, Stein R: Systemic steroids and ocular fluid dynamics. 3. The genetic nature of the ocular response and its different levels. Acta Ophthalmol (Copenh) 1972;50:699–706.

90 Adhikary HP, Sells RA, Basu PK: Ocular complications of systemic steroid after renal transplantation and their association with HLA. Br J Ophthalmol 1982;66:290–291.

91 Ng PC, Lee CH, Tam BS, Wong SP, Lam HS, Kwok AK, Fok TF: Transient increase in intraocular pressure during a dose-tapering regime of systemic dexamethasone in preterm infants. Ophthalmology 2008;115:e7–e14.

92 Mitchell P, Cumming RG, Mackey DA: Inhaled corticosteroids, family history, and risk of glaucoma. Ophthalmology 1999; 106:2301–2306.

93 Bui CM, Chen H, Shyr Y, Joos KM: Discontinuing nasal steroids might lower intraocular pressure in glaucoma. J Allergy Clin Immunol 2005;116:1042–1047.

94 Behbehani AH, Owayed AF, Hijazi ZM, Eslah EA, Al-Jazzaf AM: Cataract and ocular hypertension in children on inhaled corticosteroid therapy. J Pediatr Ophthalmol Strabismus 2005;42:23–27.

95 Gillies MC, Simpson JM, Billson FA, Luo W, Penfold P, Chua W, Mitchell P, Zhu M, Hunyor AB: Safety of an intravitreal injection of triamcinolone: results from a randomized clinical trial. Arch Ophthalmol 2004;122:336–340.

96 Chuang LH, Yeung L, Wang NK, Shen-Lih Chen H, Ku WC, Lai CC: Secondary ocular hypertension after intravitreal injection with 2 mg or 4 mg of triamcinolone in retinal vein occlusion. J Ocul Pharmacol Ther 2010;26:325–328.

97 Inatani M, Iwao K, Kawaji T, Hirano Y, Ogura Y, Hirooka K, Shiraga F, Nakanishi Y, Yamamoto H, Negi A, Shimonagano Y, Sakamoto T, Shima C, Matsumura M, Tanihara H: Intraocular pressure elevation after injection of triamcinolone acetonide: a multicenter retrospective case-control study. Am J Ophthalmol 2008;145:676–681.

98 Jonas JB, Kreissig I, Degenring R: Intraocular pressure after intravitreal injection of triamcinolone acetonide. Br J Ophthalmol 2003;87:24–27.

99 Iwao K, Inatani M, Kawaji T, Koga T, Mawatari Y, Tanihara H: Frequency and risk factors for intraocular pressure elevation after posterior sub-Tenon capsule triamcinolone acetonide injection. J Glaucoma 2007;16: 251–256.

100 Jonas JB: Intraocular availability of triamcinolone acetonide after intravitreal injection. Am J Ophthalmol 2004;137:560–562.

101 Breusegem C, Vandewalle E, Van Calster J, Stalmans I, Zeyen T: Predictive value of a topical dexamethasone provocative test before intravitreal triamcinolone acetonide injection. Invest Ophthalmol Vis Sci 2009; 50:573–576.

102 Bakri SJ, Pulido JS, McCannel CA, Hodge DO, Diehl N, Hillemeier J: Immediate intraocular pressure changes following intravitreal injections of triamcinolone, pegaptanib, and bevacizumab. Eye (Lond) 2009; 23:181–185.

103 Dwinger MC, Pieper-Bodeewes I, Eter N, Holz FG: Variations in intraocular pressure (IOP) and necessity for paracentesis following intravitreal triamcinolone injection. Klin Monbl Augenheilkd 2005;222:638–642.

104 Heatley CJ, Lim KS, Siriwardena D, Barton K: Malignant glaucoma as a complication of intravitreal triamcinolone acetonide. Acta Ophthalmol Scand 2006;84:712–713.

105 Haller JA, Bandello F, Belfort R Jr, Blumenkranz MS, Gillies M, Heier J, Loewenstein A, Yoon YH, Jacques ML, Jiao J, Li XY, Whitcup SM: Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. Ophthalmology 2010;117:1134–1146, e1133.

106 Callanan DG, Jaffe GJ, Martin DF, Pearson PA, Comstock TL: Treatment of posterior uveitis with a fluocinolone acetonide implant: three-year clinical trial results. Arch Ophthalmol 2008;126:1191–1201.

107 Bollinger KE, Smith SD: Prevalence and management of elevated intraocular pressure after placement of an intravitreal sustained-release steroid implant. Curr Opin Ophthalmol 2009;20:99–103.

108 Goldstein DA, Godfrey DG, Hall A, Callanan DG, Jaffe GJ, Pearson PA, Usner DW, Comstock TL: Intraocular pressure in patients with uveitis treated with fluocinolone acetonide implants. Arch Ophthalmol 2007;125:1478–1485.

109 Jaffe GJ, Martin D, Callanan D, Pearson PA, Levy B, Comstock T: Fluocinolone acetonide implant (Retisert) for noninfectious posterior uveitis: thirty-four-week results of a multicenter randomized clinical study. Ophthalmology 2006;113:1020–1027.

110 Clark AF, Wordinger RJ: The role of steroids in outflow resistance. Exp Eye Res 2009;88:752–759.

111 Krishnan R, Kumar N, Wishart PK: Viscocanalostomy for refractory glaucoma secondary to intravitreal triamcinolone acetonide injection. Arch Ophthalmol 2007; 125:1284–1286.

112 Kubota T, Okabe H, Hisatomi T, Yamakiri K, Sakamoto T, Tawara A: Ultrastructure of the trabecular meshwork in secondary glaucoma eyes after intravitreal triamcinolone acetonide. J Glaucoma 2006;15:117–119.

113 Wordinger RJ, Clark AF: Effects of glucocorticoids on the trabecular meshwork: towards a better understanding of glaucoma. Prog Retin Eye Res 1999;18:629–667.

114 Sheffield VC, Stone EM, Alward WL, Drack AV, Johnson AT, Streb LM, Nichols BE: Genetic linkage of familial open angle glaucoma to chromosome 1q21-q31. Nat Genet 1993;4:47–50.

115 Stone EM, Fingert JH, Alward WL, Nguyen TD, Polansky JR, Sunden SL, Nishimura D, Clark AF, Nystuen A, Nichols BE, Mackey DA, Ritch R, Kalenak JW, Craven ER, Sheffield VC: Identification of a gene that causes primary open angle glaucoma. Science 1997;275:668–670.

116 Polansky JR, Fauss DJ, Chen P, Chen H, Lutjen-Drecoll E, Johnson D, Kurtz RM, Ma ZD, Bloom E, Nguyen TD: Cellular pharmacology and molecular biology of the trabecular meshwork inducible glucocorticoid response gene product. Ophthalmologica 1997;211:126–139.

117 Tawara A, Okada Y, Kubota T, Suzuki Y, Taniguchi F, Shirato S, Nguyen TD, Ohnishi Y: Immunohistochemical localization of MYOC/TIGR protein in the trabecular tissue of normal and glaucomatous eyes. Curr Eye Res 2000;21:934–943.

118 Alward WL, Fingert JH, Coote MA, Johnson AT, Lerner SF, Junqua D, Durcan FJ, McCartney PJ, Mackey DA, Sheffield VC, Stone EM: Clinical features associated with mutations in the chromosome 1 open-angle glaucoma gene (GLC1A). N Engl J Med 1998;338:1022–1027.

119 Fingert JH, Heon E, Liebmann JM, Yamamoto T, Craig JE, Rait J, Kawase K, Hoh ST, Buys YM, Dickinson J, Hockey RR, Williams-Lyn D, Trope G, Kitazawa Y, Ritch R, Mackey DA, Alward WL, Sheffield VC, Stone EM: Analysis of myocilin mutations in 1703 glaucoma patients from five different populations. Hum Mol Genet 1999;8: 899–905.

120 Clark AF, Steely HT, Dickerson JE Jr, English-Wright S, Stropki K, McCartney MD, Jacobson N, Shepard AR, Clark JI, Matsushima H, Peskind ER, Leverenz JB, Wilkinson CW, Swiderski RE, Fingert JH, Sheffield VC, Stone EM: Glucocorticoid induction of the glaucoma gene MYOC in human and monkey trabecular meshwork cells and tissues. Invest Ophthalmol Vis Sci 2001;42: 1769–1780.

121 Rozsa FW, Reed DM, Scott KM, Pawar H, Moroi SE, Kijek TG, Krafchak CM, Othman MI, Vollrath D, Elner VM, Richards JE: Gene expression profile of human trabecular meshwork cells in response to long-term dexamethasone exposure. Mol Vis 2006;12:125–141.

122 Sohn S, Hur W, Choi YR, Chung YS, Ki CS, Kee C: Little evidence for association of the glaucoma gene MYOC with open-angle glaucoma. Br J Ophthalmol 2010;94:639–642.

123 Weinreb RN, Mitchell MD, Polansky JR: Prostaglandin production by human trabecular cells: in vitro inhibition by dexamethasone. Invest Ophthalmol Vis Sci 1983;24:1541–1545.

124 Zhuo YH, He Y, Leung KW, Hou F, Li YQ, Chai F, Ge J: Dexamethasone disrupts intercellular junction formation and cytoskeleton organization in human trabecular meshwork cells. Mol Vis 2010;16:61–71.

125 Fanning AS, Jameson BJ, Jesaitis LA, Anderson JM: The tight junction protein ZO-1 establishes a link between the transmembrane protein occludin and the actin cytoskeleton. J Biol Chem 1998;273:29745–29753.

126 Clark AF, Wilson K, McCartney MD, Miggans ST, Kunkle M, Howe W: Glucocorticoid-induced formation of cross-linked actin networks in cultured human trabecular meshwork cells. Invest Ophthalmol Vis Sci 1994;35:281–294.

127 Wiederholt M: Direct involvement of trabecular meshwork in the regulation of aqueous humor outflow. Curr Opin Ophthalmol 1998;9:46–49.

128 Weinreb RN, Polansky JR, Kramer SG, Baxter JD: Acute effects of dexamethasone on intraocular pressure in glaucoma. Invest Ophthalmol Vis Sci 1985;26:170–175.

129 Kersey JP, Broadway DC: Corticosteroid-induced glaucoma: a review of the literature. Eye (Lond) 2006;20:407–416.

130 Goldmann H: Cortisone glaucoma. Int Ophthalmol Clin 1966;6:991–1003.

131 Tripathi RC, Parapuram SK, Tripathi BJ, Zhong Y, Chalam KV: Corticosteroids and glaucoma risk. Drugs Aging 1999;15:439–450.

132 Agrawal S, Agrawal J, Agrawal TP: Vitrectomy as a treatment for elevated intraocular pressure following intravitreal injection of triamcinolone acetonide. Am J Ophthalmol 2004;138:679–680.

133 Novack GD, Howes J, Crockett RS, Sherwood MB: Change in intraocular pressure during long-term use of loteprednol etabonate. J Glaucoma 1998;7:266–269.

134 Brennan KM, Brown RM, Roberts CW: A comparison of topical non-steroidal anti-inflammatory drugs to steroids for control of post cataract inflammation. Insight 1993;18:8–9, 11.

135 Jonas JB, Kreissig I, Degenring R: Secondary chronic open-angle glaucoma after intravitreal triamcinolone acetonide. Arch Ophthalmol 2003;121:729–730.

136 Moorthy RS, Mermoud A, Baerveldt G, Minckler DS, Lee PP, Rao NA: Glaucoma associated with uveitis. Surv Ophthalmol 1997;41:361–394.

137 Smith SL, Pruitt CA, Sine CS, Hudgins AC, Stewart WC: Latanoprost 0.005% and anterior segment uveitis. Acta Ophthalmol Scand 1999;77:668–672.

138 Rubin B, Taglienti A, Rothman RF, Marcus CH, Serle JB: The effect of selective laser trabeculoplasty on intraocular pressure in patients with intravitreal steroid-induced elevated intraocular pressure. J Glaucoma 2008;17:287–292.

139 Yuki K, Inoue M, Shiba D, Kawamura R, Ishida S, Ohtake Y: Selective laser trabeculoplasty for elevated intraocular pressure following subtenon injection of triamcinolone acetonide. Clin Ophthalmol 2010;4: 247–249.

140 Ricci F, Missiroli F, Parravano M: Argon laser trabeculoplasty in triamcinolone acetonide induced ocular hypertension refractory to maximal medical treatment. Eur J Ophthalmol 2006;16:756–757.

141 Viola F, Morescalchi F, Staurenghi G: Argon laser trabeculoplasty for intractable glaucoma following intravitreal triamcinolone. Arch Ophthalmol 2006;124:133–134.

142 Drake M: Complications of glaucoma filtration surgery. Int Ophthalmol Clin 1992; 32:115–130.

143 Chen WL, Tsai YY, Chiang CC, Lin JM: Argon laser trabeculoplasty for late glaucoma after intravitreal triamcinolone. Acta Ophthalmol 2009;87:238–239.

144 Muecke J, Brian G: Steroid-induced ocular hypertension in the presence of a functioning Molteno seton. Aust N Z J Ophthalmol 1995;23:67–68.

145 Thomas R, Jay JL: Raised intraocular pressure with topical steroids after trabeculectomy. Graefes Arch Clin Exp Ophthalmol 1988;226:337–340.

146 Kaushik S, Gupta V, Gupta A, Dogra MR, Singh R: Intractable glaucoma following intravitreal triamcinolone in central retinal vein occlusion. Am J Ophthalmol 2004;137: 758–760.

147 Jonas JB, Degenring RF, Kamppeter BA: Outcome of eyes undergoing trabeculectomy after intravitreal injections of triamcinolone acetonide. J Glaucoma 2004;13:261.

148 Honjo M, Tanihara H, Inatani M, Honda Y: External trabeculotomy for the treatment of steroid-induced glaucoma. J Glaucoma 2000;9:483–485.

149 Malone PE, Herndon LW, Muir KW, Jaffe GJ: Combined fluocinolone acetonide intravitreal insertion and glaucoma drainage device placement for chronic uveitis and glaucoma. Am J Ophthalmol 2010;149: 800–806, e801.

150 D'Amico DJ, Goldberg MF, Hudson H, Jerdan JA, Krueger DS, Luna SP, Robertson SM, Russell S, Singerman L, Slakter JS, Yannuzzi L, Zilliox P: Anecortave acetate as monotherapy for treatment of subfoveal neovascularization in age-related macular degeneration: twelve-month clinical outcomes. Ophthalmology 2003;110:2372–2383; discussion 2384–2375.

151 Schmidt-Erfurth U, Michels S, Michels R, Aue A: Anecortave acetate for the treatment of subfoveal choroidal neovascularization secondary to age-related macular degeneration. Eur J Ophthalmol 2005;15: 482–485.

152 Clarke MS: Anecortave acetate. Ophthalmology 2004;111:2316; author reply 2316–2317.

153 Prata TS, Tavares IM, Mello PA, Tamura C, Lima VC, Belfort R Jr: Hypotensive effect of juxtascleral administration of anecortave acetate in different types of glaucoma. J Glaucoma 2010;19:488–492.