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Steroid-Induced Iatrogenic Glaucoma

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Steroid-induced ocular hypertension · Glaucoma · Intravitreal drug delivery

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 antiangiogenic activity, in controlling IOP have been promising.

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 postoperative steroid use, cases of severe IOP elevation have

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

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

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 non-glaucomatous 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 subconjuctival 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 brimobidine 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.

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