

Corticosteroid-induced glaucoma: a review of the literature

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Abstract

The intraocular pressure rise that can complicate the use of topical or systemic corticosteroid has been recognised for 50 years. More recently, following isolation of the myocilin gene (previously known as the trabecular meshwork inducible glucocorticoid response or TIGR gene), there has been renewed interest in this steroid-responsive phenomenon. Furthermore, the currently fashionable use of injectable intraocular steroids in the management of clinically significant subretinal fluid and macular oedema has resulted in an increased incidence. Animal studies, cell biology, molecular biology, and an improved knowledge of genetics have provided a better understanding of the mechanisms behind the response. The purpose of this review is to describe the risk factors for developing corticosteroid-induced glaucoma, to discuss the underlying mechanisms and genetics of the condition and to present management options.

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Introduction

A rise in intraocular pressure (IOP) can occur as an adverse effect of corticosteroid therapy. If the ocular hypertensive effect is of sufficient magnitude, for an adequate duration, damage to the optic nerve (steroid-induced glaucoma) may ensue. In 1950, McLean¹ reported a rise in IOP induced by systemic administration of adrenocorticotrophic hormone (ACTH). After 4 years, Francois² described the first case of elevated IOP induced by local administration of steroid (cortisone). Since that time, investigators

have maintained an interest in this particular form of secondary ocular hypertension/glaucoma, both in its own right and in providing possible insights into the aetiology of certain types of open-angle glaucoma (OAG).

It has long been known that IOP fluctuates diurnally and it has been postulated that this may be linked to cortisol levels.³ The peak in diurnal IOP occurs at around 0700 hours and the trough during the early evening, the daily fluctuation in IOP correlating closely with plasma cortisol levels.³ Furthermore, cases have been described of raised IOP secondary to adrenal gland hyperplasia^{4,5} and although direct cause and effect has not been proven, it is known that there is no diurnal IOP variation in patients who have had their adrenals removed.³

A corticosteroid-induced IOP rise has been shown to occur with various methods of steroid administration (see *Methods of administration*, below), but is most commonly identified as a complication of topical corticosteroid application with drugs such as dexamethasone or prednisolone. In responsive patients, the IOP typically rises after several weeks of continual corticosteroid therapy and returns to normal following cessation of such therapy.²

The purpose of this review is to describe the risk factors for developing corticosteroid-induced glaucoma, including the effect of preparation type, to discuss the underlying mechanisms, and genetics of the condition and to present management options.

Risk factors

Although only partially understood, a number of risk factors for developing corticosteroid-induced glaucoma or ocular hypertension have been identified.

History of glaucoma/glaucoma suspect

In 1963, Becker and Mills⁶ demonstrated that patients who had glaucoma, or had been

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diagnosed as glaucoma suspects, had marked IOP rises in response to several weeks' exposure to topical corticosteroids. The IOP for the glaucoma group rose from a mean of 16.9 to 32.1 mmHg and that for the glaucoma suspect group rose from a mean of 17.1 to 28.3 mmHg. However, in the normal group the IOP rose much less, from a mean of 13.6 to only 18.2 mmHg, with patients in this group falling into two distinct populations; those who showed a moderate increase and those who showed none. Patients who responded to the steroids were also shown to have a reduced outflow facility during the period of steroid treatment. The IOP for all the patients studied returned to their baseline or to a normal level after cessation of the steroid treatment.

Age

In the same year (1963), Armaly^{7,8} showed that the ocular hypertensive response to topical dexamethasone was due to a reduction in aqueous outflow, this outweighing a smaller reduction in aqueous production. Armaly reported that the steroid-induced effect was greater in older compared with younger eyes, and greater in glaucomatous compared with nonglaucomatous eyes.

Other factors

It has been reported that there is a greater risk of corticosteroid response in patients with certain types of connective tissue disease,⁹ type I diabetes,¹⁰ a first-degree relative with primary open-angle glaucoma (POAG),^{11–13} or high myopia.^{14,15} Other steroid-induced ocular effects that have been reported include an increase in corneal thickness and a slight mydriasis, but these changes have not been shown to correlate with an ocular hypertensive response.^{16,17}

Type of preparation

Methods of administration

Elevation in IOP has been associated with both topical and systemic administration of corticosteroid. Since Francois^{2,18} described the pressure rise after topical use, and Bernstein *et al*¹⁹ described the response to systemic corticosteroids, others have described corticosteroid-induced ocular hypertension following other methods of administration.

Steroid-induced ocular hypertension has been reported in association with topical application to the eyelids,²⁰ chronic nasal or inhaled steroid,²¹ subconjunctival, and sub-Tenon's injection of steroid.²²

Cubey²⁰ described the case of a 22-year-old man who had developed corneal oedema secondary to an elevated IOP of 60 mmHg, caused by nightly application of fluocinolone acetonide for 7 years. The associated glaucoma was refractory to medical therapy despite cessation of steroid therapy, and he eventually required bilateral glaucoma filtration surgery.

Garbe *et al*²¹ described a case-control study in which patients were recruited from a health insurance database. The odds ratio of patients who had a recent diagnosis of ocular hypertension or OAG was calculated in patients using nasal or inhaled corticosteroids relative to nonusers. The ratio was then adjusted for age, sex, diabetes, systemic hypertension, and use of ophthalmic or systemic steroids. Users of nasal corticosteroids were shown to be at increased risk of ocular hypertension or glaucoma with an odds ratio of 1.44.

More recently, there has been renewed interest in the use of injectable intraocular steroids in the management of clinically significant subretinal fluid and macular oedema,²³ this includes the novel method of combining intravitreal triamcinolone with the use of photodynamic therapy.²⁴ These new techniques involve the use of a repository steroid injection and, while there is an increasing body of evidence to suggest this can improve visual outcome in these patients,^{23,24} it should be remembered that the depot steroid cannot easily be removed. Fortunately, although it has been shown that depot intravitreal administration of triamcinolone can produce IOP rises,²⁵ the majority of affected patients have been controlled with topical ocular hypotensive therapy, although intractable glaucoma has been reported.²⁶

Different preparations

Cantrill *et al*²⁷ have reported differences in the level of steroid response in known high responders to steroid for different preparations and found that the higher the steroid potency the greater the ocular hypertensive effect (see Table 1).

Herschler²⁸ investigated 12 patients who demonstrated a steroid response to injected corticosteroid and showed that the duration and severity of response was inversely related to preparation solubility—this was despite 10 of the patients having had extensive topical treatment prior to the injection without a pressure rise. Herschler's findings implied that topical corticosteroid treatment could not be used as a screening method to exclude any subsequent pressure response with depot steroid injections.

Table 1 IOP elevations for different steroid preparations

Preparation	Average pressure rise (mmHg)
Dexamethasone 0.1%	22.0±2.9
Prednisolone 1.0%	10.0±1.7
Dexamethasone 0.005%	8.2±1.7
Fluoromethalone 0.1%	6.1±1.4
Hydrocortisone 0.5%	3.2±1.0
Tetrahydrotriamcinolone 0.25%	1.8±1.3
Medrysone 1.0%	1.0±1.3

Timing of response

Topical steroids have been shown to produce a steroid response over a period of weeks in both normal⁷ and glaucomatous eyes^{8,27} and Armaly showed this with provocation testing administering dexamethasone eye drops three times a day to the right eye for 4 weeks, using the left eye as a control.^{7,8} Weinreb *et al*²⁹ have reported that, although rare, a more acute onset rise can occur within hours of starting intensive topical dexamethasone. In addition, an acute onset response has been reported in association with intensive systemic steroid therapy, although the IOP response to systemic steroids typically occurs over a much longer period, often years.¹⁸ Francois¹⁸ found the incidence of steroid glaucoma following systemic treatment to be much less common than following topical treatment. In addition, Francois¹⁸ reported that the time of onset of the IOP elevation was dependent on corticosteroid potency, the effect being seen within weeks with potent drugs and only after several months with the weaker agents. Bernstein and Schwartz³⁰ examined the long-term effects of systemic steroids and found that there was an increase in IOP in a group of patients treated with systemic steroid when compared to an age- and sex-matched control group. Furthermore, it was reported that those who had been on systemic steroids for more than 4 years had significantly higher IOPs than those who had been on systemic steroids for less than a year.³⁰

Suggested mechanisms of the corticosteroid response

Corticosteroids are believed to decrease outflow by inhibiting degradation of extracellular matrix material in the trabecular meshwork (TM), leading to aggregation of an excessive amount of the material within the outflow channels and a subsequent increase in outflow resistance.³¹ Two patterns of extracellular deposition have been described in the TM of steroid-induced glaucoma patients; fingerprint-like deposition of material in the uveal meshwork, and

accumulation of fine fibrillar material in the juxtacanalicular region.³²

Francois¹⁸ and Armaly⁷ both suggested that the response might be due to an alteration of the metabolism of mucopolysaccharides, leading to their accumulation in the TM. It was proposed that corticosteroids, which stabilise lysosomal membranes, could reduce the release of lysosomal hyaluronidase, this resulting in a relative inhibition of hyaluronate depolymerisation. The subsequent accumulation of mucopolysaccharides could, it was suggested, cause retention of water ('biological oedema') and subsequent narrowing of the trabecular spaces.

Support for a steroid-induced effect within the outflow channels has come from animal studies, experiments with cultured human TM cells and perfusion-cultured donor eye models.

In rabbit eyes glucocorticosteroid receptor concentration has been shown to be high in ocular tissue³³ and intravenously administered steroid has been found to bind specifically to the nuclei of cells in the outflow channels,³⁴ in a similar manner to the binding of dexamethasone reported to occur in cultured human TM cells.³⁵ Glucocorticoids have been shown to alter TM cell morphology by causing an increase in nuclear size and DNA content.^{32,36} A further study has shown that steroids also induce proliferation and activation of the endoplasmic reticulum, Golgi apparatus, and increase deposition of extracellular matrix material.³⁷

The amounts of glycosaminoglycans, elastin, and fibronectin have been shown to increase in tissue culture preparations in response to dexamethasone treatment while the levels of tissue plasminogen activator, stromelysin,³⁸ and the activity of several TM metalloproteases^{32,39} have been shown to fall. Furthermore, excessive accumulation of glycosaminoglycans has been identified in human trabecular meshwork specimens obtained from steroid-responders,⁴⁰ confirming similar findings in a rabbit model.⁴¹

In support of the evidence for extracellular matrix deposition, dexamethasone treatment has also been shown to inhibit TM cell arachadonic acid metabolism³⁵ and reduce phagocytic activity.^{42,32} TM cells have phagocytic properties, the function of which is to clear the outflow channels of debris. A steroid-induced inhibition of phagocytosis within the meshwork could result in accumulation of channel debris and decreased facility of outflow,⁴³ so contributing to steroid-induced glaucoma. Structural changes in the TM cells have also been proposed.^{36,44} Clark *et al*⁴⁴ discovered that dexamethasone caused cross-linkage of actin fibres, leading to the formation of networks within cultured

human TM cells. The actin network structure was reversible following cessation of corticosteroid administration to the cultures. It was suggested that the response might be mediated by the TM glucocorticoid receptor. However, the effect of such an alteration of cellular cytoskeleton on TM cell function remains unclear.

Clark *et al*⁴⁵ went on to demonstrate histological and pressure changes in steroid treated, perfusion-cultured human eyes. IOP was measured using a pressure transducer within the eye, so that the measurement was not affected by corneal thickness. In those eyes in which there was a pressure increase, morphological changes included; thickened trabecular beams, decreased intertrabecular spaces, thickened juxtacanalicular tissues, and increased amounts of amorphous granular extracellular material. In another perfusion-cultured human eye model glycosaminoglycan deposition in the meshwork increased with increasing duration of steroid exposure.⁴⁶

It is hoped that recent advances in novel molecular genetic methods will allow a better understanding of the mechanisms causing the steroid-induced glaucoma. By gene deletion or overexpression studies, the exact role of individual genes responsible for the modulation of meshwork extracellular material may be identified in the near future.³⁸

Genetics

Several authors have proposed a genetic susceptibility for corticosteroid glaucoma.^{6–8} In 1964, Becker and Hahn¹² suggested that patient response to corticosteroids could be explained by a monogenic autosomal mechanism. Armaly⁴⁷ and Becker,¹¹ in refining this, suggested that medium responders were heterozygotes while high responders were homozygotes.

Francois¹⁸ argued against this simplistic theory, and tested both parents and children of glaucoma patients. It was hypothesised that parents of high-response glaucoma patients should show at least a medium response according to the theory. He tested six parents of glaucoma patients and five of the six showed a negative response. Children of glaucoma patients, it was proposed, would all show a medium response, but when 87 were tested, only 29 showed a response. Schwartz *et al*⁴⁸ found no significant difference in the frequency of corticosteroid response between monozygotic and dizygotic twin groups—this perhaps implying that there is an environmental influence on the development of a corticosteroid response.

Palmberg *et al*⁴⁹ have offered an explanation for the apparent discrepancy in findings, by investigating the

reproducibility of the corticosteroid response. Patients were divided into three groups depending on their pressure response to topical corticosteroid therapy. The low-response group showed a pressure rise of less than 6 mmHg, the intermediate group showed a rise of 6–15 mmHg, while the high-response group had a rise of >15 mmHg. The testing was repeated using either the ipsilateral eye or the contralateral eye and the pressure response reassessed. The concordance value for the total population studied over the two tests was 73%, which was significantly higher than expected by chance (47%). However, it was noted that the intermediate and low-response groups did show quite large degrees of crossover. Concordance values were examined for each of the individual subgroups. The high-response group showed a marked difference in the concordance (79%) and chance (6%) values. The intermediate group had a concordance (74%) that was closer to chance (36%), but still statistically higher, while the low-response group showed no statistical difference (concordance 71%, chance 58%). The authors felt that while topical testing had limited effectiveness in whole populations, it did show good reproducibility in the high-response group. It was suggested that the less-than-perfect reproducibility might explain to an extent the low concordance identified in Schwartz's twin study. Indeed, in the twin study, of the four identical twins who were high responders, one set were both high responders, and the other two were twins of intermediate responders, and none were twins of low responders.

Several genes have been shown to be upregulated in dexamethasone-treated TM cells,⁵⁰ including genes representing a serine protease inhibitor (alpha-1-antichymotrypsin), a neuroprotective factor (pigment epithelium-derived factor), an antiangiogenesis factor (cornea-derived transcript factor 6) and a prostaglandin synthase (prostaglandin D2 synthase) enzyme. However, the most extensively studied gene is that representing the protein myocilin (initially referred to as TM-inducible glucocorticoid response or TIGR, gene product),^{51,52} the gene being identical to GCL1A and now referred to as the myocilin gene.^{53,32} The myocilin gene, which is a 55 kDa protein, has been shown to be induced in human cultured TM cells after exposure to dexamethasone for 2–3 weeks. The role of myocilin in corticosteroid-induced ocular hypertension has been proposed because: (1) it is highly expressed in trabecular cells exposed to glucocorticoids, (2) the delay in its expression is similar to the delay in the pressure rise in glucocorticoid-treated eyes and (3) the dose required to cause the protein expression is similar to that required to raise IOP.³² Linkage analysis of a large single family with juvenile onset POAG has shown that mutations in a gene on chromosome 1q are responsible for most cases of

autosomal dominant juvenile onset POAG. This gene, previously called the TIGR gene, produces the protein myocilin. Different mutations within myocilin lead to widely variable glaucoma phenotypes⁵⁴ involved in both juvenile and adult onset POAG.⁵⁵ The role of myocilin remains poorly understood and experiments altering its expression have provided conflicting results. In perfused human anterior segment cultures, recombinant myocilin increased outflow resistance, while viral-mediated transfer of myocilin in TM cells caused an overexpression of myocilin and lead to reduction in outflow resistance.⁵⁶

Mice that have been genetically engineered to overexpress myocilin have not shown an increase in intraocular pressure.^{57,58} In monkeys, Fingert *et al*⁵⁹ could not find statistically significant evidence of a link between myocilin mutations and steroid-induced ocular hypertension.⁵⁹

Further investigation of myocilin and other steroid-induced gene products is needed to enhance our understanding of the role that steroids play on TM cells and outflow resistance. Of equal importance will be the findings of future genetic studies that may aid clinicians in being able to predict more accurately those patients most likely to develop steroid-induced glaucoma.

Clinical aspects

The clinical features of corticosteroid glaucoma are similar to those of POAG, with the exception that patients with corticosteroid-responsive glaucoma have a history of significant corticosteroid use. The elevated IOP, induced as part of the corticosteroid response, increases the risk of optic nerve fibre damage, leading to characteristic visual field and optic nerve changes indistinguishable from those associated with POAG.

As with all iatrogenic conditions, prevention is ideal. Health-care professionals should aim to prevent or minimise the chance of inducing irreversible damage by paying careful attention to patients' medical histories and with judicious use of steroids. It is particularly important, whenever possible, to avoid use of steroids in patients with pre-existing glaucoma, since these patients are prone to steroid-responsiveness and may be tipped into a state of significant visual loss by such therapy. In all situations, when steroid therapy cannot be avoided, the choice of drug should be of one that has a therapeutic effect at the lowest possible dose, administered by the safest route, minimising the risk of all potential adverse effects. The typically insidious nature of progressive steroid-induced glaucoma

requires careful monitoring of patients at risk to identify any early changes that would necessitate a change in management.

Patients at higher risk than average (see risk factors above)

POAG	First-degree relative with POAG
Glaucoma suspect	High myopia
Previous steroid response	Type I diabetes
Increasing age	Connective tissue disease (eg Rha)

Management of corticosteroid-induced glaucoma (see also Appendix A)

Monitoring of IOP

A baseline measurement of IOP should be taken prior to commencement of corticosteroid therapy. Patients on topical therapy should then have their IOP measured again 2 weeks after initiation of treatment, then every 4 weeks for 2–3 months, then 6-monthly if therapy is to continue.

Patients undergoing intravitreal triamcinolone should be monitored for several months following the steroid injection. Smithen *et al*⁶⁰ found that 40.4% of patients receiving triamcinolone show a pressure rise to greater than 24 mmHg over at an average of 100 days after treatment.

Ideally, patients requiring long-term systemic corticosteroid therapy should have glaucoma screening and those receiving 10 mg or more of prednisolone daily should have their IOP checked at 1, 3, and 6 months and 6 monthly thereafter. Glaucoma screening can be performed by optometrists in the community, or in local ophthalmic departments should there be a suspicion of established glaucoma.

Cessation of corticosteroid treatment

It is ideal to ensure that the suspected corticosteroid is responsible for the glaucoma and if glaucoma is established (and especially if progressive), use of the corticosteroid should be stopped. The chronic corticosteroid response resolves in 1–4 weeks, whereas the rare acute response may resolve within a few days of steroid cessation.²⁹ In the case of repository corticosteroids, the steroid may have to be surgically removed.²⁸ If cessation of steroid therapy is not possible, then methods of reducing the effects of the corticosteroid need to be considered.

Alternative corticosteroid formulations

Topical treatments can be changed to preparations such as fluoromethalone 0.1% or rimexolone 1%, which are claimed to have less effect on IOP,²⁷ or in certain situations to nonsteroidal anti-inflammatory drugs (NSAIDs). For patients prescribed systemic corticosteroids, introducing or increasing steroid-sparing agents such as cyclophosphamide or methotrexate may allow the corticosteroid dosage to be reduced. Steroid-sparing medications have their own significant adverse effects and they require extensive monitoring, so their use should be discussed with a physician unless the ophthalmologist has specific experience with such medications.

Irreversible steroid-induced ocular hypertension/glaucoma

In about 3% of cases, and in particular when there is a family history of glaucoma and/or chronic use of steroid (at least 4 years), the ocular hypertensive response has been shown to be irreversible.^{18,61} The management of such cases is no different from that for POAG.

Medical antiglaucomatous therapy

Miotics Corticosteroid-induced glaucoma has appeared to be relatively refractory to miotics while the steroid has still been used.¹⁷ Furthermore, in addition to being less popular than more modern agents, miotics are also contraindicated in inflamed eyes (ie those that may require topical steroid therapy) since they can exacerbate the formation of posterior synechiae.⁶²

Beta-blockers Topical beta-blockers can be used to control corticosteroid-induced glaucoma,⁶² preferably following cessation of steroid therapy and are a popular first-line agent for the condition.

Prostaglandin analogues Concomitant latanoprost has been shown to be as effective as cessation of therapy in controlling the IOP rise associated with corticosteroids⁶³ so can be useful if steroid treatment must be continued. However, latanoprost has been reported to induce uveitis^{64,65} and is relatively contraindicated in eyes with uveitic glaucoma. Latanoprost has been shown to cause cystoid macular oedema in certain pseudophakic eyes in the early postoperative period (when steroids are likely to have been prescribed),⁶⁵ so caution should be exercised when prescribing prostaglandin analogues in such eyes.

Alpha agonists Brimonidine can be useful in many patients with steroid-induced glaucoma, although there

have been reports of brimonidine-induced uveitis in a minority of patients.⁶⁶

Carbonic anhydrase inhibitors Oral acetazolamide is an effective short-term treatment for the control of IOP in all forms of glaucoma, including that induced by corticosteroids. Over longer periods, the side effect profile of acetazolamide tends to make it poorly tolerated and it is contraindicated in certain patients, such as those with renal impairment. However, topical carbonic anhydrase inhibitors (dorzolamide and brinzolamide) are of use in the control of IOP due to corticosteroid-induced glaucoma.⁶²

Argon laser trabeculoplasty (ALT)

This treatment has been tried both before and after commencing corticosteroid therapy and has not been shown to be effective in preventing corticosteroid-induced pressure rises.⁶⁷ Galin et al attempted to prevent a corticosteroid response in myopic eyes undergoing radial keratotomy by using ALT. It was reported that when ALT was performed prior to therapy with topical corticosteroid, 28% of the patients developed a pressure rise of 6 mmHg or more,⁶⁷ which was similar to the rises reported by Becker and Mills⁶ for 'normal' eyes that had not undergone ALT.

Filtration surgery

Trabeculectomy remains an effective treatment for glaucoma in those patients who have a persistently raised IOP following cessation of corticosteroid therapy and are refractory to medical therapy.⁶⁸ However, as always, the adverse consequences of trabeculectomy or other forms of drainage surgery should be considered in relation to the potential benefits.

It seems unlikely that a steroid response occurs following successful filtration surgery, although Thomas and Jay⁶⁹ described a small group of patients undergoing trabeculectomy in whom it appeared that an ocular hypertensive response developed to postoperative steroid. They described an increase in IOP in 17% of the postoperative eyes at around 4 weeks following surgery. However, during a later challenge only three of eight previous 'responders' showed a further rise, this inducing some doubt as to whether there was a true effect of the corticosteroid or simply an effect of postoperative inflammation.

Although rarely necessary, excision of depot periocular or intraocular steroid may be indicated in patients

refractory to medical therapy.^{70–72} With the increasing popularity of intravitreal triamcinolone injections,^{23,24} vitrectomy may prove useful in preventing glaucoma in selected cases.

Uveitic glaucoma

Uveitic glaucoma provides a particular therapeutic challenge. A significant minority (10%) of patients with uveitis show a rise in IOP.⁷³ Although IOP often falls in an acutely inflamed eye (due to a reduction in aqueous production and a four-fold increase in uveo-scleral outflow),⁷⁴ a rise occurs if this effect is exceeded by obstruction of the TM outflow pathway.⁷⁵ An increase in outflow resistance can be due, in part, to the increase in aqueous protein content, accumulation of cellular debris in the TM, angle closure through anterior synechiae formation and, in addition, an iatrogenic corticosteroid response.

For individual patients, it is rarely possible to determine which of these factors is most important and it differs significantly between eyes.⁷⁵

Corticosteroids remain the mainstay of therapy for uveitis in controlling inflammation, but monitoring of IOP is critical. With respect to corticosteroid responsiveness, the management of uveitic glaucoma can be difficult because it is usually impossible to determine whether an elevation in IOP is due to the steroid therapy or the uveitic disease process itself. The principles of management, therefore, are to minimise the use of steroid appropriately and apply standard antiglaucomatous therapy. First-line therapy for lowering IOP in eyes with uveitis is usually with a beta-blocker, carbonic anhydrase inhibitors or adrenergic agonists being used as second-line agents.⁷⁵ Prostaglandins have been used successfully in the management of uveitic glaucoma, but their use is cautioned, since they may exacerbate intraocular inflammation.^{64,65} After episodes of uveitis complicated by elevation in IOP requiring therapy, cessation of the antiglaucomatous therapy (as well as the steroid) should be considered, particularly if a temporary corticosteroid response is suspected.

Future therapies

Glucocorticoid receptor blockers have been proposed as useful potential therapeutic agents for treating corticosteroid-induced glaucoma. Mifepristone (RU 486-6), a peripheral progesterone blocker with antiglucocorticoid properties, has been shown to reduce IOP in both normotensive⁷⁶ and

corticosteroid-induced ocular hypertensive rabbits.⁷⁷ However, this mode of therapy has not yet been used in human subjects.

Southren et al^{78,79} have inhibited dexamethasone-induced ocular hypertension in rabbits using tetrahydrocortisol. However, Clark et al⁸⁰ believe that the action of tetrahydrocortisol is not due to its action as a glucocorticoid antagonist but due to a direct effect that alters the dexamethasone-induced TM changes.

Conclusions

Although there has been marked progress in the last few years in understanding the mechanisms behind corticosteroid-induced glaucoma, further research needs to be undertaken. The genetics are not fully understood, and it appears that a number of gene loci interact in controlling the corticosteroid-induced glaucoma response rather than it following simple Mendelian inheritance. Better identification of patients at risk of corticosteroid-induced IOP rises would allow them to be more closely monitored than others. It is important to identify those patients who have a corticosteroid-induced pressure rise early enough to prevent them from developing permanent visual loss. In most cases, corticosteroid-induced glaucoma can be treated successfully by topical antiglaucoma therapy,⁶³ although cessation of corticosteroid therapy is the ideal course of action.

It is possible that further development of nonsteroidal anti-inflammatory therapies will provide effective alternatives to corticosteroids. It is also hoped that a full understanding of the steroid-induced response may result in the development of novel therapies for the treatment of other types of glaucoma, including POAG.

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Appendix A: management principles

