

Ocular Complications Associated with Systemic Medications Used in Allergy/Immunology Practice

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Abstract The repertoire of treatment options available to allergists and immunologists is ever increasing and with this comes the increased potential for these treatments to cause adverse ocular side effects. Corticosteroids remain the first line of treatment for most immunological disorders and physicians should be alerted to their extensive ocular morbidity profile. Patients requiring longer-term therapy may often receive immune modulators or newer biologic agents. While effective, these medications may have additional ocular side effects; as newer agents are more frequently used, some of these may not be previously documented. A number of patients will seek alternative or herbal remedies for these long-term conditions, often unknown to the treating physician; these too can cause harmful ocular morbidity. We review the latest information about the potential ocular side effects that may be encountered in treating patients with medications used in allergic and immunological disorders.

Keywords Ocular · Complications · Side effects · Allergy · Immunology · Systemic medications · Corticosteroids · Cataract · Glaucoma · Central serous chorioretinopathy · Antihistamines · Anticholinergics · Isotretinoin · Interferons · Methotrexate · Chloroquine · Hydroxychloroquine · Herbal remedies · Supplements

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Introduction

A number of conditions presenting to an allergist or immunologist have ophthalmic manifestations. Ocular symptoms and signs are not uncommon in conditions ranging from allergic rhinitis to severe immune mediated conditions like IgG4 disease. Additionally, a number of treatments used in the management of allergic and immunologic disease may have inadvertent ocular side effects with potentially sight-threatening consequences. It is important that both physicians and ophthalmologists have knowledge of these drugs and their ocular side effects. Understanding the ocular morbidity of these medications will aid the physician to monitor a patient's response to treatment. This article provides an overview of some of these medications and their potential ocular complications.

Corticosteroids

Corticosteroids, whether oral, inhaled or topically applied, are often the first line of treatment in allergic and autoimmune conditions. In many of these conditions, patients require prolonged treatment courses. These drugs have a well-documented profile of adverse effects including systemic hypertension, diabetes, osteoporosis and psychological disorders [1, 2]. These can lead to ocular complications such as hypertensive retinopathy and diabetic retinopathy.

Cataract

One of the earliest ocular side effects of corticosteroids was documented by Black et al. in 1960, who reported the development of posterior sub capsular cataracts (PSC) and glaucoma in patients on corticosteroids for rheumatoid arthritis [1]. Subsequently, these have been reported in both adults and

children, when using any form of corticosteroid preparation. The prevalence is influenced by the daily dose, cumulative dose, duration of treatment, patient age and patient ethnicity. Typically complications occur after at least 1 year of treatment with doses equal or higher than 10 mg per day of oral prednisone or its equivalent. The incidence of corticosteroid-induced cataracts reported in a number of randomized, controlled trials ranges from 6.4 to 38.7 % after oral corticosteroid use [2].

Inhaled corticosteroids (ICS) also have a significant impact on the eye, as detected in a large population-based epidemiological ocular health study (The Blue Mountains Eye Study). A higher, dose-dependent prevalence of both nuclear cataracts and PSCs was noted in subjects using inhaled corticosteroids therapy compared to others [3]. A recent meta-analysis has shown that the risk of cataracts is increased by about 25 % for each 1,000 mcg increase in the daily dose of beclomethasone dipropionate (BDP) or equivalent [4]. These findings reinforce the importance of prescribing the lowest effective dose of ICS therapy in both asthma and chronic obstructive pulmonary disease [5].

Patients developing cataract typically experience a gradual decrease in their visual acuity and also complain of glare and sensitivity to light. This may be more so for patients who are also diabetic, older or smokers. Ideally, patients should be monitored by ophthalmologists when using corticosteroids. Patients require cataract surgery should their cataracts become visually debilitating.

Glaucoma

Glaucoma is also a well-documented side effect of corticosteroid therapy and perhaps the most visually damaging as it can cause asymptomatic irreversible sight loss. Patients may present late in the disease after irreversible vision or visual field loss has taken place [6]. Glaucoma can occur with the use of topical, inhaled and oral corticosteroids [7, 8, 9]. A Canadian study showed that regular users of high dose ICS for 3 or more months were at an increased risk with an odds ratio (OR) of 1.44 (95 % confidence interval, 1.01–2.06) [10]. Ceasing ICS in patients with steroid-induced glaucoma can lead to lowering of the intraocular pressure (IOP) [11]. Prior to commencing a course of ICS, patients should be instructed to report any pre-existing or new glaucoma diagnoses. Family history of glaucoma, Afro-Caribbean race is also associated with a higher risk of developing glaucoma and should also be assessed. Patients who develop glaucoma may need long-term topical anti-glaucoma therapy, laser treatment or even surgery to control their IOP.

Central Serous Chorioretinopathy (CSC)

CSC is a less well-recognised complication of corticosteroid use. Patients present with a central scotoma with a varying amount of reduced visual acuity, often associated with

dyschromatopsia, micropsia and reduced contrast sensitivity. They may also experience a hypermetropic shift in their refraction resulting in blurred vision. The aetiology of CSC is unknown, but it is probably caused by either a focal dysfunction in retinal pigment epithelium (RPE) cells and/or altered permeability of the choroidal vasculature leading to localised accumulation of subretinal fluid. This is often self-limiting but can recur in about one-third of patients, and in chronic cases can cause permanent visual damage [12•]. There are several documented cases of CSC caused by exogenous steroid use including intranasal [13], topical skin and oral preparations [14]. CSC can be a challenging management problem in patients such as steroid-dependent patients following organ transplantation.

Patients on long-term corticosteroids and their physicians need to be aware of these complications and patients require referral for ophthalmic examinations for timely detection of ocular complications from corticosteroids. Even patients using over-the-counter intranasal or topical corticosteroid treatments are at risk and should be educated about these side effects.

Antihistamines and Anticholinergics

Medications with anticholinergic properties affect the eye by interfering with the cholinergic innervation of the lacrimal gland, iris muscle or ciliary muscle. Systemic antihistamines and anticholinergics, commonly used to treat allergy, can cause dry eye or exacerbate dry eye symptoms.

Tear film aqueous and mucin production is decreased in patients treated with systemic antihistamines. This leads to decreased tear production and reduced tear film breakup time leading to symptoms of dry eye [15]. Animal studies have also demonstrated a 20–60 % reduction of tear fluid associated with chlorpheniramine, a common over-the-counter antihistamine [16]. Patients may experience varying degrees of dryness, irritation, foreign body sensation, light sensitivity and itching when using systemic antihistamines. This can have a considerable impact on visual function, daily activities and quality of life. Patients may require supplementation with topical ocular lubricants for the symptomatic relief of their dry eye symptoms.

In patients with allergic conjunctivitis, these agents often provide insufficient symptomatic relief of ocular surface discomfort due to the induced tear-film dysfunction and excessive ocular surface drying [17••]. In one study, oral loratadine and cetirizine hydrochloride induced signs and symptoms associated with ocular dryness, including increased corneal and conjunctival staining, decreased tear film break-up time and increased ocular discomfort in healthy individuals. Loratadine induced significantly more conjunctival staining than cetirizine hydrochloride [18]. The poor efficacy of oral agents in ocular

allergy suggests a topical approach to treatment is more successful in improving the quality of life of patients suffering from allergic conjunctivitis and/or rhinitis [19].

First-generation oral antihistamines can have potent antimuscarinic, anti- α -adrenergic and antiserotonin effects leading to mydriasis, photophobia, and diplopia [20].

Isotretinoin and Other Retinoids

Isotretinoin (13-*cis* retinoic acid) is a synthetic retinoid compound approved for the treatment of nodular cystic acne unresponsive to conventional acne therapy [21].

It is one of the most effective therapeutic agents for acne with an excellent long-term remission rate [22]; it has also been used to treat systemic lupus erythematosus [23]. However, isotretinoin is a potential teratogenic drug with serious adverse effects such as depression, suicidal thoughts, and pancreatitis. Isotretinoin causes dry eye, probably by reducing Meibomian gland secretions. These glands normally secrete a lipid outer layer onto the tear film to prevent excessive evaporation of the aqueous component of tears, and disturbed secretion results in rapid break-down of the tear film. Although this may be bothersome to patients, it does not cause serious ocular pathology when low doses are used for a limited time and is reversible after discontinuation [24]. Rarely, patients treated with retinoids can develop a chronic, severe, recalcitrant dry eye syndrome.

More seriously, there has been a report of macular haemorrhage associated with isotretinoin use in a 19-year-old female with acne. The authors postulate that tissue plasminogen activator stimulation in retinal endothelial cells resulted in fibrinolytic activity that may have caused the hemorrhage [25].

There have also been reports of raised intracranial pressure with isotretinoin use that can lead to papilloedema. Chronic papilloedema may result in irreversible optic nerve injury with axonal damage causing loss of peripheral vision [26].

Biologic Agents

Biologic agents are being used with increasing frequency to treat autoimmune and other immune-mediated diseases. Commonly used agents with known ocular side effects include T cell blocker abatacept, tumour necrosis factor (TNF)- α inhibitors infliximab, etanercept, and adalimumab, antilymphocyte antibodies rituximab and alemtuzumab, interleukin-2 receptor blocker daclizumab and recombinant interferon (IFN)- α .

Abatacept

Abatacept is used to treat diseases like SLE and psoriasis. It has been reported to cause ocular irritation, pruritus, blurred

vision and visual disturbances in a small number of patients, which may be related to allergic conjunctivitis or other ocular surface disturbances [27, 28].

Rituximab

Rituximab (RTX) is a human/murine chimeric monoclonal antibody (mAb) that specifically targets the transmembrane protein CD20 on B cells [29]. In a clinical study concerning the efficacy of rituximab in 222 patients with lymphoma, 9 of them reported ocular side effects, including conjunctivitis, transient peri-ocular oedema, a burning sensation, and transient visual problems. Only one patient developed severe visual loss, but the aetiology was unknown [30].

Tumour Necrosis Factor- α Inhibitors

Etanercept and infliximab have a low incidence of ocular side effects reported in the published literature. There have been cases described of optic neuritis and multiple sclerosis with infliximab therapy [31]. Optic neuropathy and optic neuritis have been reported with both infliximab and adalimumab [32–34]. Ceasing treatment must be considered should any optic nerve toxicity occur. In addition activation of scleritis has been documented. [35, 36]. Etanercept has also been reported to cause uveitis. Etanercept therapy is associated with a significantly greater number of reported uveitis cases compared with infliximab and adalimumab in two medication side effect registries. These results are consistent with previous studies and suggest that this relationship is drug specific and not related to TNF inhibitors as a whole [37]. Another concern with TNF- α inhibitors is the reactivation of tuberculosis or other infections. Testing for tuberculosis prior to therapy is recommended and should include a detailed history of travel, tuberculosis exposure, symptoms such as chronic cough and weight loss, a chest X-ray, tuberculin skin testing and interferon gamma assay [38, 39].

Interferons

Interferons are antiviral glycoproteins naturally produced by most cells in the body in response to intracellular (e.g. viral) infections that modulate the activity of the immunological system. Recombinant IFN- α has been approved for its antiviral effects and the inhibition of cell proliferation, and has been used in autoimmune diseases such as multiple sclerosis and uveitis. The mechanism of action in autoimmune diseases is yet to be fully elucidated. IFN- α can cause interferon retinopathy, consisting of retinal microvascular changes, cotton-wool spots and intraretinal haemorrhages [40, 41]. Although these may be dramatic in appearance and can resemble hypertensive or diabetic retinopathy, they resolve on cessation of the medication and rarely cause permanent visual loss.

Methotrexate

Methotrexate may cause non-specific ocular symptoms such as periorbital oedema, ocular pain, blurred vision, photophobia, conjunctivitis, Meibomian gland dysfunction and decreased reflex tear secretion. It has also been reported to cause optic neuropathy, probably related to folate deficiency [42]. Folate supplementation when co-administered with methotrexate minimizes its adverse effects and may therefore prevent this potential complication. If recognised early, optic nerve damage can be reversed if methotrexate is ceased and appropriate folate supplementation is administered promptly [43].

Chloroquine and Hydroxychloroquine

Chloroquine and hydroxychloroquine are used to treat rheumatoid arthritis, discoid and systemic lupus erythematosus, and collagen and dermatologic diseases. Hydroxychloroquine is now dominant clinically as it has a lower side effect profile [44, 45] and chloroquine use is rare. Despite this, hydroxychloroquine has been associated with many ocular toxic effects including keratopathy, ciliary body dysfunction, lens opacities, outer retinal damage and pigmentary retinopathy.

The damage to the retina manifests as a pigmentary mottling around the macula leading to a characteristic ‘bulls eye maculopathy’ with abnormalities in retinal electrophysiological function. Patients present with visual field defects, decreased visual acuity and colour-vision defects. Early changes are subtle and may be not clinically obvious. In later stages of toxicity, irreversible atrophy of the RPE and overlying retina can spread to involve the entire fundus. Early detection and prompt discontinuation of medication may limit retinal toxicity at an initial stage; however, when established, retinal toxicity is generally irreversible and may be progressive despite discontinuation of medication. Toxicity is dose-related; the risk of toxicity is low if the daily dose is less than 6.5 mg/kg/day and the cumulative dose is less than 1,000 g [46•]. Currently, it is recommended that automated fields using the Humphrey visual field analyser 10–2 protocol are performed in conjunction with at least one of: multifocal electroretinogram, spectral domain optical coherence tomography and fundus autofluorescence at baseline and then at least once a year after the first 5 years of treatment [47••]. Screening should be commenced earlier in high risk cases, including those on a high dosage, and with low lean body mass or poor renal function. Screening guidelines are still evolving and there are multiple published protocols. At present, physicians should work closely with

Table 1 Guidelines for monitoring patients on hydroxychloroquine

Risk factors	Duration of use	>5 years
	Cumulative dose	
	HCQ	>1,000 g (total)
	CQ	>460 g (total)
	Daily dose	
	HCQ	>400 mg/day (>6.5 mg/kg ideal body weight for short individuals)
	CQ	>250 mg/day (>3.0 mg/kg ideal body weight for short individuals)
	Age	Elderly
	Systemic disease	Kidney or liver dysfunction
	Ocular disease	Retinal disease or maculopathy
Time of examination	Baseline examination within first year of use	
	Annual screening after 5 years of use	
Recommended screening procedures	Dilated retinal examinations are important for Ocular detection of associated retinal disorders, but examination should <i>not</i> be relied on for screening (low sensitivity).	
	Automated visual field	White 10-2 threshold testing. Interpret with a low threshold for abnormality, and retest if abnormalities appear.
	In addition, if available, perform one or more of the following objective tests	
	SD-OCT	Rapid test that can be done routinely; can show abnormalities very early, even before field loss
	mfERG	Valuable for evaluation of suspicious or unreliable visual field loss; may show damage earlier than visual field testing
	FAF	May validate other measures of toxicity; can show abnormalities earlier than field loss

(Adapted from Marmor et al. [47••])

their ophthalmologists to determine the best available screening protocol for their patients. Table 1 summarizes the best practice guidelines by the American Academy of Ophthalmologists.

Herbal Remedies and Supplements

Herbal medicines and nutritional supplements are being used by a large segment of the population, often without strong evidence on efficacy or safety. Therefore, clinicians must remain vigilant in recognizing adverse ocular reactions as well as inquiring whether these alternative treatments are being used, as patients frequently do not disclose this information to their physicians. There a variety of different compositions which are largely untested and unregulated but are consumed by large numbers of the patient population.

Chamomile

Chamomile (*Matricaria chamomilla*) is used as a treatment eye irritation, styes, epiphora, and inflammation [48]. However, when the tea is applied topically around the eye, it can paradoxically cause a severe conjunctivitis. In one study, angioedema occurred in two patients. All subjects had a history of seasonal allergic rhinitis [49]. Physicians should recognize the possibility of *Matricaria chamomilla* sensitivity in cases of what appears to be allergic conjunctivitis, especially in patients who already have an atopic history.

Datura

Datura is used to treat asthma, bronchitis, influenza, and coughs as well as allergic conjunctivitis. The leaves contain alkaloids in extremely varying concentrations that are anticholinergic and parasympatholytic. These can cause unintended prolonged dilated pupils [50].

Ginkgo Biloba

The flower and seeds of this herb make one of the words most popular herbal remedies. It acts as a platelet aggregation inhibitor with a similar mechanism of action to aspirin. It is also used orally to treat asthma by inhibiting bronchoconstriction. It can exacerbate or cause a tendency to bleed, resulting in numerous case reports of subarachnoid haemorrhage, hyphaema and retrobulbar haemorrhage [51, 52].

Licorice

Licorice (*Glycyrrhiza glabra*) root derives some of its medicinal properties from the isoflavonoid glabridin. Glabridin inhibits cyclooxygenase activity and has both anti-inflammatory and

antiplatelet effects. Ocular side effects are reported to be similar to those experienced with an ocular migraine without headache possibly due to induced vasospasm [53].

Ma Huang

Ephedra sinica (Ma Huang) and some other species of oriental *Ephedra* are used as herbal bronchodilators. *Ephedra* has been used to treat allergy as well because of its action on the sympathetic nerves. Ocular side effects include mydriasis and blurred vision.

Conclusions

The repertoire of treatment options is ever increasing, and with this comes the potential risks of adverse events. Corticosteroids remain the mainstay or initial treatment of a majority of these diseases and physicians should be alert to their side effect profile. Patients requiring longer-term therapy may often receive immune modulators or newer biologic drugs. These also have potential side effects that physicians should be aware of, and, with increasing use of these agents, more are being reported. A number of patients will seek alternative or herbal remedies and physicians should remember to ask about their use as patients often do not volunteer this information.

The list of medications or side effects in this article is by no means exhaustive, but serves to bring attention to the potential ocular complications a physician may encounter in treating patients with these agents.

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