Clinics in Dermatology (2016) **34**, 129–137

ELSEVIER

Clinics in Dermatology

Ocular changes induced by drugs commonly used in dermatology

Anna Turno-Kręcicka, PhD, MD[a,*], Andrzej Grzybowski, PhD, MD[b,c], Marta Misiuk-Hojło, PhD, MD[a], Eliza Patryn, PhD, MD[d], Karolina Czajor, MD[a], Małgorzata Nita, MD, PhD[e]

[a]*Department and Clinic of Ophthalmology, Wroclaw Medical University, Ul. Borowska 213, 50-556 Wrocław, Poland*
[b]*Department of Ophthalmology, Poznań City Hospital, Ul. Szwajcarska 3, 61-285 Poznań, Poland*
[c]*Department of Ophthalmology, University of Warmia and Mazury, Olsztyn, Poland*
[d]*Department of Ophthalmology, Academic Medical Center of the University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands*
[e]*Domestic and Specialized Medicine Centre "Dilmed", ul. Bohaterów Monte Cassino 3, 40-231 Katowice, Poland*

Abstract The use of many drugs in dermatologic diseases may cause ocular side effects. Some may regress after discontinuation of the therapy, but others persist or progress even after the cessation of treatment. This review presents four groups of commonly prescribed drugs—antimalarial medicines, glucocorticoids, retinoids, and psoralens + ultraviolet A (UVA) therapy—and discusses their possible ocular side effects.

The most significant complication of antimalarial drugs is retinopathy with the risk of permanent visual impairment. There are different recommendations for screening for this drug-related retinopathy. The most important ocular manifestations of steroid management are irreversible optic nerve damage in "steroid responders" (steroid glaucoma) and cataract. Some other side effects may disappear after discontinuation of the therapy. Retinoid-induced ocular side effects include ocular surface disease as well as retinal dysfunction. It is recommended to modify the therapy when night blindness occurs or after the decrease of color vision. Protective eyewear is sufficient to avoid ocular surface problems during psoralen + UVA therapy.

The knowledge of screening schemes and closer cooperation between physicians may decrease the risk of serious or irreversible ocular side effects.

Introduction

Many drugs widely used to treat nonophthalmology-related diseases are associated with ocular side effects, some of them potentially blinding. It is the responsibility of every clinician prescribing drugs with known ocular side effects to be fully aware of the ophthalmic implications and their incidence, pathogenesis, and current screening guidelines and to inform the patient of the potential risks of treatment. Patients and their physicians should understand that routine screening can help early damage detection, before severe vision loss.

This review focuses on ocular adverse effects induced by four groups of drugs commonly used in dermatology clinics: antimalarials, glucocorticoids, retinoids, and psoralens. We aim

* Corresponding author.
E-mail address: Turno@autograf.pl (A. Turno-Kręcicka).

http://dx.doi.org/10.1016/j.clindermatol.2015.11.012
0738-081X/

to familiarize practitioners with the potential ocular problems they might encounter in everyday practice as well as provide them with the suggested screening and management guidelines.

Antimalarials

Ocular toxicity of synthetic antimalarial drugs—chloroquine and its analogue, hydroxychloroquine—has been acknowledged for many years. Chloroquine was initially introduced as an antimalarial during the Second World War. Later, quinolones were found to be effective in the treatment of rheumatoid arthritis, lupus erythematosus, and other connective tissue disorders.[1,2]

First reports on chloroquine's ocular side effects emerged in the 1950s. Chloroquine-induced retinopathy was described in 1957, and chloroquine-related keratopathy was reported 1 year later.[3–5] Several further reports on retinal toxicity of antimalarials emerged in the 1960s and 1970s.[1,6,7] Chloroquine has nowadays largely been replaced by hydroxychloroquine, which is considered to be less toxic, although chloroquine is still used in some parts of the world.[8]

Ocular side effects of quinolones include keratopathy, ciliary body and ocular muscle imbalance, cataract, and the most significant complication, retinopathy.[9]

Nalixidic acid, a byproduct with antibacterial activity, was isolated during commercial production of chloroquine in 1962.[10] It was a precursor of recent fluoroquinolones, a widely used group of antimicrobials, deprived of specific ocular side effects characteristic for antimalarial drugs.[11]

Keratopathy

Quinolones may form deposits in the cornea, which can vary in form, ranging from diffuse punctate opacities to radial and vortex-like lines just inferior to the central cornea, and may become yellow or golden brown with continued use of the medication.[12,13] Quinolone keratopathy is often asymptomatic, with less than 50% of affected patients reporting visual disturbances, such as halos around light sources and photophobia.[9,12,13] *In vivo* confocal microscopy of hydroxychloroquine-related corneal deposits revealed the presence of intracellular inclusions concentrated in the basal epithelial layer and within the anterior and posterior stroma.[14,15] Corneal changes can develop as early as 2 to 3 weeks from the commencement of the treatment.[12]

The incidence of chloroquine keratopathy varies in different studies, ranging from 73% to 95% in patients taking full therapeutic dosage.[16–18] Chloroquine has been associated with more keratopathy than hydroxychloroquine, which may reflect a lower tissue accumulation or binding properties of the latter.[19] In a prospective study of 758 patients receiving hydroxychloroquine, corneal changes were reported in only 6 participants (0.8%).[20]

Corneal changes are completely reversible once the medication is discontinued regardless of the duration of therapy. Although they do not directly imply any retinal damage, they do suggest drug retention and reinforce the need for prophylactic screening. Quinolone keratopathy is usually not a reason to withdraw the medication.[12,21]

Ciliary body and ocular muscles

Long-term use of quinolones may lead to accommodation disturbances, manifesting in difficulties to quickly change focus, and/or ocular muscle imbalance resulting in diplopia or blurring. Dose reduction may be beneficial in case of persistent symptoms.[19,20]

Cataract

Posterior subcapsular lens opacities have been described in patients on chloroquine treatment.[12,22] No cataract formation had been reported in patients treated with hydroxychloroquine.[20,23]

Retinopathy

Retinal changes are the most important ocular manifestations of quinolone toxicity, because they may lead to progressive and permanent visual impairment, resulting in legal blindness. The American Academy of Ophthalmology and the Royal College of Ophthalmologists both have suggested the guidelines and techniques on screening to facilitate early detection of quinolone maculopathy before devastating changes develop.[21,24]

The earliest signs of retinal toxicity are fine pigmentary stippling of the macula and the loss of the foveal reflex, referred to as premaculopathy. A fully developed chloroquine retinopathy classically consists of a bilateral ring of depigmentation of the retinal pigment epithelium (RPE) surrounding the darker fovea, forming the so-called bull's-eye maculopathy, with the corresponding paracentral visual field defect.[9,19] With continued drug exposure, RPE atrophy and functional disturbances may spread over the entire fundus, with impairment of visual acuity and peripheral visual field and night vision loss. Vascular narrowing and segmental disc pallor may appear, giving rise to retinitis pigmentosa–like appearance. Once bilateral paracentral scotomas or bull's-eye maculopathy appear, no visual recovery may be expected; moreover, in some cases continued depigmentation and visual loss may progress for several years after the cessation of the treatment, which may reflect the drugs' long clearance period after discontinuation.[19,21,24,25]

The mechanism of retinal toxicity is not well understood; however, histopathologic studies of chloroquine retinopathy in humans revealed the destruction of rods and cones with sparing of the foveal cones. They suggested that photoreceptor degeneration is secondary to RPE changes.[19]

The incidence of quinolone retinopathy is nonetheless low. The risk of retinal toxicity is significantly higher with

Table 1 Criteria for low and high risk of retinopathy[21,26]

Criterion	Low risk	High risk
Dosage	<3 mg/kg/day chloroquine	>3 mg/kg/day chloroquine
	<250 mg/day chloroquine	>250 mg/day chloroquine
	<6.5 mg/kg/day hydroxychloroquine	>6.5 mg/kg/day hydroxychloroquine
	<400 mg/day hydroxychloroquine	>400 mg/day hydroxychloroquine
Cumulative dose	<1000 g hydroxychloroquine	>1000 g hydroxychloroquine
	<460 g chloroquine	>460 g chloroquine
Duration of treatment	<5 years	>5 years
Habitus	None	High fat level (unless dosage calculated for lean body mass)
Renal/liver disease	None	Present
Concomitant retinal disease	None	Present
Age	<60	>60

chloroquine, varying from 1-15%.[9] Chloroquine retinopathy has mostly occurred with high doses—above 3 mg/kg/day.[21] According to the Royal College of Ophthalmologists guidelines, chloroquine should only be considered if other drugs have failed to control the disease adequately.[24] Almost all cases of retinal toxicity with a lower dose of hydroxychloroquine occurred in individuals receiving treatment for more than 5 years.[19] The majority of reported cases concerned patients treated with doses higher than 6.5 mg/kg/day. New data show that the risk of toxicity increases toward 1% after 5 to 7 years of use, or a cumulative dose of 1000 g, of hydroxychloroquine.[26] In conclusion, the daily dosage and duration of treatment are thought to be the two most important risk factors for the development of retinal changes.[19,21,24]

The revised guidelines from the American Academy of Ophthalmology include[24,26] a baseline ophthalmologic assessment within the first year to document any other ocular diseases and to establish a record of the fundus appearance, the visual field, and acuity.[26] This examination should include best corrected visual acuity for distance and near, slit-lamp examination of the cornea and fundus, automated visual field Humphrey 10-2, and, additionally, one of these available tests: spectral domain optical coherence tomography, fundus autofluorescence, or multifocal electroretinogram.[26] The American Academy of Ophthalmology guidelines identify individuals with low and high risk of retinal toxicity. Criteria for low and high risk of retinopathy are shown in Table 1.

After baseline examination, patients should be reviewed on an annual basis after 5 years of therapy. Annual screening should be performed from the beginning by patients with high risk of retinopathy.[26] If suggestive visual symptoms or fundus changes are found, repeated fundal examination with Amsler grid and Humphrey field testing for confirmation should be performed. Further evaluation with fundus photography, fluorescein angiography, and multifocal electroretinogram can be considered. Doubtful cases should be reevaluated in 3 months' time. In confirmed cases of retinopathy, the treatment should be immediately stopped. Decision of the cessation of the treatment should, however, be made in conjunction with the prescribing physician after a careful consideration of the potential systemic implications. The American Academy of Ophthalmology recommends the further reevaluation 3 months after the diagnosis of retinopathy, and then annually until the condition is stable.[21]

The Royal College of Ophthalmologists does not currently support the introduction of a program of systematic screening for quinolone retinopathy.[24] The baseline visual acuity should be checked in dermatology or rheumatology clinic. If visual impairment is noted, the patient should be referred in the first instance to an optometrist who can subsequently refer the patient to an ophthalmologist if any abnormality is detected. Further examinations are at the discretion of the ophthalmologist. If the duration of treatment exceeds 5 years, an individual arrangement should be agreed with the ophthalmologist.[24] It should be explicitly explained to the patient that despite ophthalmologic monitoring, irreversible retinal damage could still occur.

Glucocorticoids

Glucocorticoids remain the most important agents for managing allergic, immunobullous, and collagen vascular

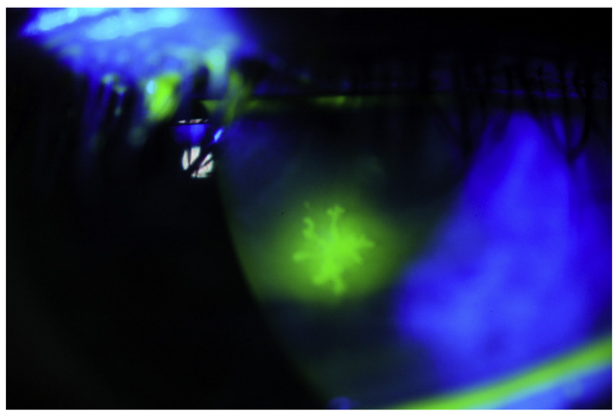

Fig. 1 Ophthalmologic examination: Fluorescein staining of the corneal herpetic infiltration after general steroid therapy.

diseases in dermatology; however, they are also associated with numerous and frequent adverse effects.[27] It is, therefore, important for prescribing physicians to have a sufficient knowledge of the side effects of these drugs (Figure 1). Systemic glucocorticoids have been associated with glaucoma, cataract formation, and central serous chorioretinopathy.[28]

Systemic absorption and adrenal suppression after topical steroids treatment have been confirmed[29,30] and are not only limited to the super potent class of topical glucocorticoids.[31] What is very interesting is that patients with severe atopic dermatitis (AD) have low basal cortisol values without steroid treatment history. The suppression of the hypothalamic-pituitary-adrenal axis is probably connected with disease activity. Its recommended to measure basal and follow-up serum cortisol levels in patients with severe AD during treatment and to provide appropriate supplementation during stressful situations (eg, fever, operation) if needed.[32] Factors that play a role in developing side effects include: state of the skin barrier, body site involved, disease extent, age, use of occlusion, amount of steroid applied, and duration of treatment.[33] Children, due to a higher ratio of the total body surface area to body weight, are more sensitive to systemic reactions during treatment with topical steroids.[34] There are case reports published on topical steroid–induced glaucoma and cataract during dermatologic treatment, however, related only to long-term use of steroids on the eyelids and periorbital region.[35] It seems that the application of steroids on distal parts of the body is safe and connected with no risk of ophthalmic complications. It is recommended to screen for glaucoma and cataract patients using high cumulative amounts of topical glucocorticoids (especially on eyelids) or oral glucocorticoids.[36] Practitioners should keep in mind during recommendation of steroid therapy on the face and eyelids that the penetration of topical glucocorticoids is 300 times greater through the eyelid than on other body sites.[37] Also, the penetration of corticosteroids through the skin of AD patients is 2 to 10 times greater than through healthy skin due to defective epidermal barrier.[38] It is always important to estimate the risk/benefit ratio when using potent topical glucocorticoids, but unjustified fear of ocular side effects of topical corticosteroids may lead to undertreatment of disease. Other therapeutic options like immunosuppressive drugs also have a wide spectrum of side effects.

Glaucoma

Glucocorticoid-induced ocular hypertension and secondary iatrogenic open-angle glaucoma are serious side effects of glucocorticoid therapy, because they may result in irreversible optic nerve damage. Steroid-induced intraocular pressure (IOP) elevation typically occurs within a few weeks from the beginning of the steroid therapy. Patients with an elevated IOP on chronic corticosteroid therapy can remain asymptomatic until irreversible glaucomatous optic nerve damage occurs. Induction of ocular hypertension after corticosteroid administration is limited to the so-called steroid responders. Approximately 18-36% of the general population are corticosteroid responders, increased from 46% to 92% in patients with primary open-angle glaucoma.[39–41] Glaucoma formation has also been reported in patients using topical facial steroids to the periorbital region.[42–44]

Patients with primary open-angle glaucoma also exhibit increased peripheral sensitivity of glucocorticoid receptors, which may enhance local glucocorticoid action in the eye and exacerbate the adverse effects of glucocorticoids.[45]

Children are more susceptible[46] to the development of steroid-induced increased intraocular pressure due to the structural and functional immaturity of trabecular meshwork.[47]

In most cases, IOP lowers spontaneously to the baseline within a few weeks to months after the discontinuation of steroids. The IOP elevation may, however, persist even after stopping the therapy. Patients whose underlying condition necessitates the continued use of corticosteroids despite the elevated IOP should be treated identically to those with primary open-angle glaucoma.[40]

Cataract

Formation of cataract, usually in the form of posterior subcapsular lens opacities (Figure 2), is a known complication of systemic corticosteroid therapy with an incidence of 22-58%. Present data do not allow clear establishment of the relationship between cataract formation and the dose of glucocorticoids or the duration of therapy.[48–51] Individual susceptibility to side effects of corticosteroids seems to be the most important factor in drug-induced cataract formation.[52]

AD is an independent risk factor of developing cataract, with the incidence of cataract in patients with AD between 5% and 38%.[53] Anterior subcapsular cataract is more specific to AD, but posterior subcapsular opacities are more common.[54] The postulated risk factors for lens opacities in AD patients include high levels of serum lipids and decreased superoxide dismutase activity[55]; infantile onset of AD; family history of AD, asthma, or

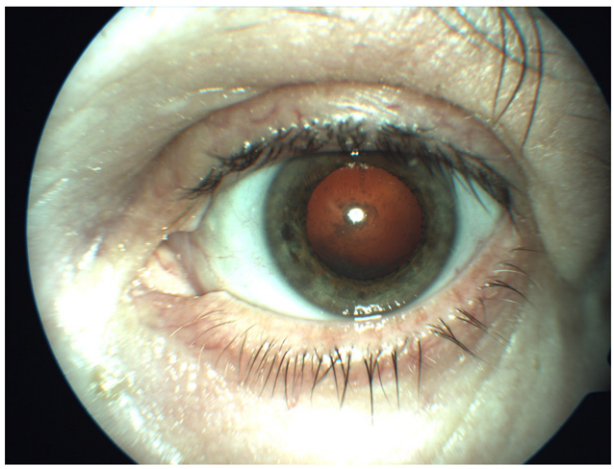

Fig. 2 Steroid-induced subcapsular cataract.

hay fever; systemic glucocorticoids use; and elevated lipid peroxide levels.[54]

Central serous chorioretinopathy

Central serous chorioretinopathy (CSCR) is a relatively common retinal disease in which a serous detachment of the neurosensory retina occurs at the macula over an area of leakage through the RPE (Figure 3). It typically affects young and middle-aged men with type A personalities. Patients typically suffer from acute symptoms of visual impairment and metamorphopsia. Other symptoms include decreased central vision and a positive scotoma, loss of color saturation, and contrast sensitivity. The pathology most likely begins with a nonspecific disturbance of the choroidal circulation. The elevated levels of circulating cortisol and epinephrine are thought to affect the autoregulation of the choroidal circulation, causing a spasm of the choroidal vasculature and altering the permeability and perfusion.[56,57]

To date, many cases of central serous chorioretinopathy have been described during or after treatment with glucocorticoids for various systemic or ocular conditions.[58–60] The biggest consecutive case series of 50 patients with CSCR so far showed that 52% of patients with CSCR had used exogenous steroids within 1 month of presentation compared with 18% of control participants. All patients in this study experienced spontaneous resolution of their disease when the glucocorticoids were discontinued.[60]

Retinoids

Synthetic retinoids are the treatment of choice for severe recalcitrant nodular acne as well as for disorders of cornification and psoriasis and are widely used in dermatology. Their mode of action involves the reduction of sebum exertion, comedogenesis, and the colonization of the pilosebaceous duct with *Propionibacterium acnes*. Therapeutic effectiveness of retinoids is also related to the inhibition of chemotaxis, leukocyte migration, and inflammation[61]; however, this group of drugs is associated with a variety of adverse reactions, usually involving the skin and mucous membranes but also nervous, respiratory, genitourinary, and gastrointestinal systems.[62] Retinoid side effects are generally preventable or manageable through routine monitoring, dose adjustments, and proper patient selection.

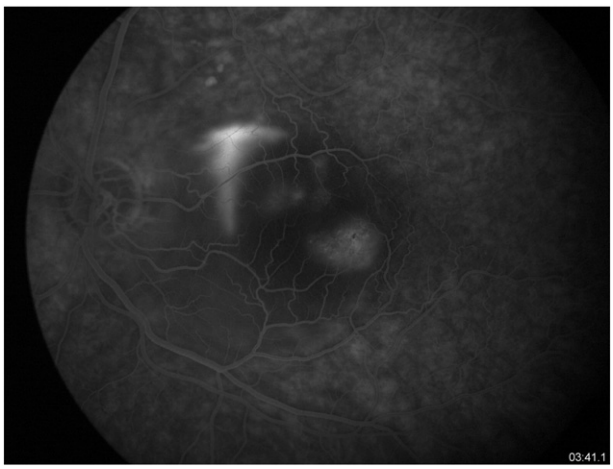

Fig. 3 Fluorescein angiography: Central serous chorioretinopathy—leakage of the dye under sensory retina, with marked disturbances of vision as the result.

Isoretrinoin

Isoretrinoin (13-cis retinoic acid), the first-generation synthetic vitamin A derivative was introduced in the 1980s. Its potent and multidirectional action in skin diseases, including acne vulgaris, rosacea, and seborrheic dermatitis, is well known, but adverse effects are relatively common. The systemic use of isotretinoin as a monotherapeutic agent in acne has experienced a drawback now from the first-line to the second-line treatment.

Typical ocular side effects of isotretinoin can be divided between changes to the eyelids (Figure 4) and the surface of the cornea (Figure 5) and lacrimal abnormality, refractive changes, abnormal retinal function, and papilledema. The most common complaint of patients on isotretinoin treatment is itchiness, photophobia, eye pain, burning, and gritty feeling or visual disturbance occurring with days up to a few months after the commencement of the therapy. The former may be due to ocular surface disease, whereas the latter is due to retinal function changes and refractive damage, corneal opacities, and lens opacities. Decreased color vision and permanent loss of dark adaptation were also reported as possible isotretinoin use side effects.[63,64]

Ocular surface diseases

In retrospective cohort study of 14,682 adolescents and young adults, the most common adverse side effects attributed to isotretinoin were conjunctivitis, hordeolum, chalazion, blephar-

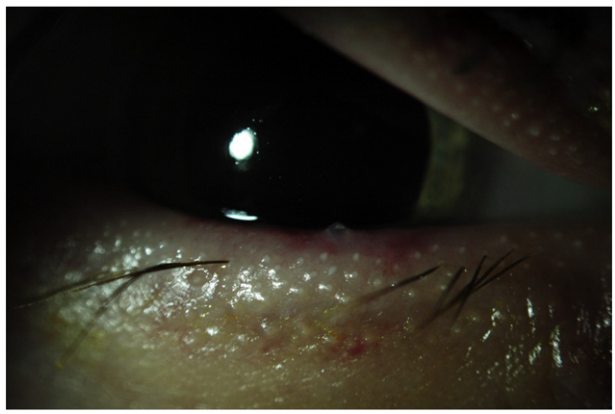

Fig. 4 Chronic blepharoconjunctivitis with loss of eyelashes.

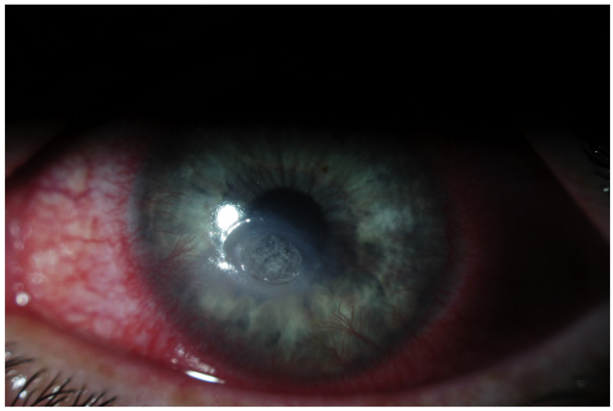

Fig. 5 Corneal ulcer, a typical complication of dry eye syndrome.

itis (Figure 6), and dry eye, which occur usually at the third to fifth weeks of therapy.[64] These pathologic conditions may be secondary to Meibomian gland dysfunction connected with isotretinoin therapy, with atrophy of Meibomian glands and their reduced density and hyposecretion.[65]

Blepharoconjunctivitis and meibomitis were reported in 37% of patients on isotretinoin therapy.[66] Hordeolum and chalazion are common consequences of chronic blepharitis. Meibomian gland dysfunction typically leads to insufficient secretion of lipids into the tear film and, as a result, to increased evaporation of tears and tear film instability, resulting in damage of the ocular surface epithelium. The presence of isotretinoin and its metabolites in the tear film may directly irritate the corneal surface.[64] Ocular surface and tear-film changes in treated patients should be monitored routinely by conjunctival impression cytologic examination, anesthetized Schirmer test, rose bengal staining, and tear breakup time monitoring. Keratoconjunctivitis sicca observed during the isotretinoin therapy is characterized by the reduction in the density of goblet cells in impression cytologic testing, an early sign of squamous metaplasia of the epithelium and the secondary reduction in the mucin layer of the tear film.[67] Significant reductions in values for the anesthetized Schirmer test and tear breakup time have been observed in patients treated with 0.8 mg/kg isotretinoin.[67] In this group of patients, rose bengal staining also has been used to detect dead or degenerated epithelial cells of the corneal and conjunctival epithelium, and marked changes have been found. In conclusion, ocular surface epithelia and the preocular tear film can be markedly affected in these patients, resulting in dry eye syndrome. Dermatologists who prescribe isotretinoin should also prescribe ocular lubricants, as well as preservative-free artificial tears, and should cooperate with ophthalmologists when ocular symptoms progress or persist. Eye dryness is related to the isotretinoin dose and disappears 1 month after the discontinuation of treatment. Severe keratoconjunctivitis sicca may be associated with the risk of secondary serious corneal problems, such as corneal ulceration, herpes simplex virus activation, vascularization, and corneal opacification.

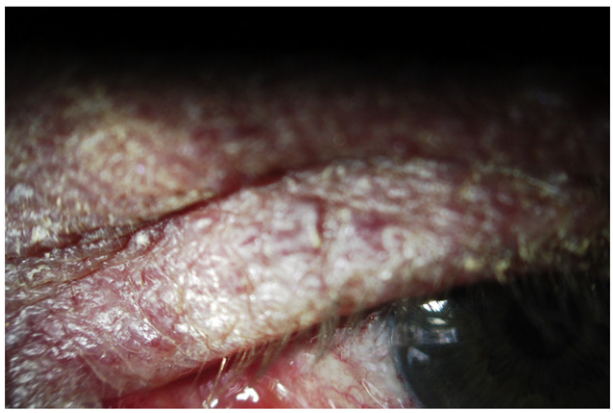

Fig. 6 Chronic blepharitis—red, edematous, painful margins of the eyelids.

Refractive changes

Visual disturbances associated with isotretinoin are related to corneal steeping and peripheral corneal edema and, as a result, to corneal aberrations with temporal or permanent myopic shift.[68,69] The mechanism underlying corneal edema is unclear and may be connected with the presence of isotretinoin in the tear film.[67]

Abnormal retinal function

Impaired night vision and decreased color vision have been associated with isotretinoin in a number of studies.[66,68] Isotretinoin may interfere with vitamin A metabolism in the visual cycle by inhibiting ocular retinol dehydrogenases. Abnormal retinal function could be assessed by electroretinography. Risk factors for these ocular complications include hypovitaminosis A and low retinol binding protein level. All patients on isotretinoin treatment should be encouraged to promptly report changes in their night vision, and patients such as pilots and drivers should be examined before and during therapy, including electroretinography and vitamin A and retinol binding protein blood levels. Although night blindness is a rare complication of retinoid use, it may persist after the discontinuation of the treatment. It is, therefore, recommended that the medication be discontinued on the first signs of night blindness or decreased color vision.

Papilledema

Published data suggest that retinoid use may be associated with intracranial hypertension and papilledema.[70] The average time of symptom onset was 2 to 3 months from the commencement of the treatment.[70] It is recommended to consider the discontinuation of the isotretinoin treatment in patients who develop otherwise unexplained headaches or blurred vision.

Dosages

The severity of isotretinoin side effects may be dose related. In one study, researchers reported significantly more pronounced eye dryness in the group of 26 patients receiving

high-dose (>0.5 mg/kg/day) systemic isotretinoin compared with 25 patients treated with low-dose (<0.5 mg/kg/day). One month after the completion of the treatment, there was no difference between the two groups.[61] Isotretinoin was originally indicated for the management of severe nodulocystic acne, at a dose of 1 to 2 mg/kg/day to a cumulative dose of 120 to 150 mg/kg, usually over 4 to 5 months. The recommended dose of isotretinoin has changed significantly, with lower and more intermittent dosage regiments. The low dose is suggested to be 0.15 to 0.4 mg/kg/day, with a total cumulative dose of <120 mg/kg; for example, 10 to 20 mg/day is usually sufficient for most patients with acne vulgaris.[62]

The most serious systemic adverse effect of the drug is teratogenicity; the most common appear to be cheilitis, eczema, and tiredness.[62]

It is important that a patient should be informed of the potential ocular adverse effects, and a follow-up visit to the ophthalmologist should be advised about 4 months after the beginning of isotretinoin therapy.

Etretinate

The oral retinoid etretinate is characterized by the safety profile similar to isotretinoin, it may potentially be retinotoxic. According to some authors, despite prolonged treatment in high doses, there was no evidence of ocular side effects associated with the drug[71]; however, in rare instances, like other retinoids, etretinate may cause intracranial hypertension.[70]

Acitretin, the active retinoid metabolite, has replaced etretinate in retinoid therapy of psoriasis due to the more favorable pharmacokinetic profile. Mucocutaneous side effects associated with the therapy may include blepharoconjunctivitis and dry eye, but in short-term therapy with oral acitretin (1 mg/kg/day) after 1 and 2 months no statistically significant deterioration in the visual acuity and tear film function were observed.[70] Dose-response studies have established the dose dependence of its side effects. It is recommended to initiate the therapy at low doses (10-25 mg/day) and, if necessary, gradually increase the dose until optimal effect is achieved.[72] Acitretin may rarely cause intracranial hypertension and papilledema.[70]

Topical retinoids

First-generation tretinoin, isotretinoin, and synthetic third-generation adapalene and tazarotene have favorable safety profiles and are used as the first-line treatment in most types of noninflammatory and inflammatory acne. They are suitable as long-term medications, with no ocular adverse effects.[73]

PUVA therapy

Since its development in 1974, photochemotherapy using ultraviolet A radiation with oral psoralen (PUVA) has been broadly used in the management of chronic inflammatory or lymphoproliferative skin diseases.[74] PUVA therapy has been suggested to cause transient ocular surface problems, such as conjunctival hyperemia and corneal superficial epithelial defects. The biggest concern regarding PUVA therapy, however, was linked to its alleged potential for inducing irreversible lens opacities. Cataract formation associated with PUVA therapy has been documented in experimental animal models. Some case reports suggest that PUVA also may increase the risk of lens abnormalities in humans.[75–78]

From 1977 to 2004, the PUVA follow-up study has periodically monitored the ocular status of 1237 cohort members, including eye examinations, finding no significant relation between the risk of developing a lens abnormality and the level of exposure to PUVA among persons using eye protection.[79] In the one of studies, 198 patients underwent 10 years of PUVA therapy with no cataract formation, lens opacities, or impairment of visual acuity reported.[80] Also, experimental studies have suggested that a dosage of psoralen producing threshold skin reaction is insufficient to induce lens changes—5- to 10-fold more UVA light is required to produce lens changes than to induce minimal skin reaction.[81]

Short- and long-term ocular side effects of PUVA therapy were investigated in 82 patients who refused to wear UVA-blocking sunglasses after the treatment. Conjunctival hyperemia developed in 20 cases, and decreased lacrimation in 21 cases was reported. Lens opacities did not develop in any patient.[82] In other study, conjunctival squamous metaplasia in PUVA-treated patients was reported.[83]

It is, therefore, recommended that all patients undergoing PUVA wear UVA-blocking opaque goggles during the irradiation; furthermore, UVA-opaque wraparound sunglasses should be worn for 24 hours after drug ingestion. Transparent glasses with limited UVA transmission should be worn after the 24-hour period following drug ingestion and indoors during the first 24 hours.[81] With the proper eye protection, the risk of developing ocular side effects during PUVA therapy is negligible.

Conclusions

Several group of drugs broadly used in dermatology are associated with ocular side effects. The best practice requirements imply that it is the duty of every physician to be fully aware of prescribed drugs' adverse effects. It is also the physician's responsibility to inform the patient as to the potential risks of the recommended treatment and to ensure appropriate preventive and screening methods implementation.

References

1. Giles CL, Henderson JW. The ocular toxicity of chloroquine therapy. *Am J Med Sci.* 1965;249:230-235.
2. Rynes RI. Antimalarial drugs in the treatment of rheumatological diseases. *Br J Rheumatol.* 1997;36:799-805.

3. Cambiaggi A. Unusual ocular lesions in a case of systemic lupus erythematosus. *AMA Arch Ophthalmol.* 1957;57:451-453.
4. Hobbs HE, Calnan CD. The ocular complications of chloroquine therapy. *Lancet.* 1958;i:1207-1209.
5. Hobbs HE, Sorsby A, Freedman A. Retinopathy following chloroquine therapy. *Lancet.* 1959;i:478-480.
6. Marks JS. Chloroquine retinopathy: is there a safe daily dose? *Ann Rheum Dis.* 1982;41:52-58.
7. Carr RE, Henkind P, Rothfield N, et al. Ocular toxicity of antimalarial drugs. Long-term follow-up. *Am J Ophthalmol.* 1968;66:738-744.
8. Finbloom DS, Silver K, Newsome DA, et al. Comparison of hydroxychloroquine and chloroquine use and the development of retinal toxicity. *J Rheumatol.* 1985;12:692-694.
9. Spiteri MA, James DG. Adverse ocular reactions to drugs. *Postgrad Med J.* 1983;59:343-349.
10. Lesher GY, Froelich EJ, Gruett MD, et al. 1,8-naphthyridine derivatives. A new class of chemotherapeutic agents. *J Med Pharm Chem.* 1962;91:1063-1065.
11. Sable D, Murakawa GJ. Quinolones in dermatology. *Clin Dermatol.* 2003;21:56-63.
12. Bernstein HN. Ophthalmologic considerations and testing in patients receiving long-term antimalarial therapy. *Am J Med.* 1983;75:25-34.
13. Hollander DA, Aldave AJ. Drug-induced corneal complications. *Curr Opin Ophthalmol.* 2004;15:541-548.
14. Ma X, He L, He D, et al. Chloroquine keratopathy of rheumatoid arthritis patients detected by in vivo confocal microscopy. *Curr Eye Res.* 2012;37:293-299.
15. Dosso A, Rungger-Brändle E. In vivo confocal microscopy in hydroxychloroquine-induced keratopathy. *Graefes Arch Clin Exp Ophthalmol.* 2007;245:318-320.
16. Cullen AP, Chou BR. Keratopathy with low dose chloroquine therapy. *J Am Optom Assoc.* 1986;57:368-372.
17. Jeddi A, Ben Osman N, Daghfous F, et al. The cornea and synthetic antimalarials. *J Fr Ophtalmol.* 1994;17:36-38.
18. Easterbrook M. Is corneal deposition of antimalarial any indication of retinal toxicity? *Can J Ophthalmol.* 1990;25:249-251.
19. Yam JCS, Kwok AKH. Ocular toxicity of hydroxychloroquine. *Hong Kong Med J.* 2006;12:294-304.
20. Grierson DJ. Hydroxychloroquine and visual screening in a rheumatology outpatient clinic. *Ann Rheum Dis.* 1997;56:188-190.
21. Marmor MF, Carr RE, Easterbrook M, et al. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy: a report by the American Academy of Ophthalmology. *Ophthalmology.* 2002;109:1377-1382.
22. Cumming RG, Mitchell P. Medications and cataract. The Blue Mountains Eye Study. *Ophthalmology.* 1998;105:1751-1758.
23. Rynes RI. Ophthalmologic safety of long-term hydroxychloroquine sulfate treatment. *Am J Med.* 1983;75:35-39.
24. Scientific Department, The Royal College of Ophthalmologists. Ocular toxicity and hydroxychloroquine: guidelines for screening. Available at:, www.rcophth.ac.uk/core/core_picker/download.asp?id=165&filetitle=Ocular+Toxicity+and+Hydroxychloroquine%3A+Guidelines+for+Screening+2009 2009. [Accessed 05 Nov 2013].
25. Kazi MS, Saurabh K, Rishi P, et al. Delayed onset chloroquine retinopathy presenting 10 years after long-term usage of chloroquine. *Middle East Afr J Ophthalmol.* 2013;20:89-91.
26. Marmor MF, Kellner U, Lai TYY, et al. Revised recommendations on screening for chloroquine and hydroxychloroquine retinopathy. *Ophthalmology.* 2011;118:415-422.
27. Summey BT, Yosipovitch G. Glucocorticoid-induced bone loss in dermatologic patients: an update. *Arch Dermatol.* 2006;142:82-90.
28. Carnahan MC, Goldstein DA. Ocular complications of topical, peri-ocular, and systemic corticosteroids. *Curr Opin Ophthalmol.* 2000;11:478-483.
29. Gilbertson EO, Spellman MC, Piacquadio DJ, et al. Super potent topical corticosteroid use associated with adrenal suppression: clinical considerations. *J Am Acad Dermatol.* 1998;38:318-321.
30. Levin C, Maibach HI. Topical corticosteroid-induced adrenocortical insufficiency: clinical implications. *Am J Clin Dermatol.* 2002;3:141-147.
31. Schlessinger J, Miller B, Gilbert RD, et al. An open-label adrenal suppression study of 0.1% fluocinonide cream in pediatric patients with atopic dermatitis. *Arch Dermatol.* 2006;142:1568-1572.
32. Haeck IM, Timmer-de Mik L, Lentjes EGWM, et al. Low basal serum cortisol in patients with severe atopic dermatitis: potent topical corticosteroids wrongfully accused. *Br J Dermatol.* 2007;156:979-985.
33. Charman C, Williams H. The use of corticosteroids and corticosteroid phobia in atopic dermatitis. *Clin Dermatol.* 2003;21:193-200.
34. Hengge UR, Ruzicka T, Schwartz RA, et al. Adverse effects of topical glucocorticosteroids. *J Am Acad Dermatol.* 2006;54:1-15.
35. McLean CJ, Lobo RF, Brazier DJ. Cataracts, glaucoma, and femoral avascular necrosis caused by topical corticosteroid ointment. *Lancet.* 1995;345:330.
36. Haeck IM, Rouwen TJ, Timmer-de Mik L, et al. Topical corticosteroids in atopic dermatitis and the risk of glaucoma and cataracts. *J Am Acad Dermatol.* 2011;64:275-281.
37. Feldmann RJ, Maibach HI. Regional variation in percutaneous penetration of 14 C cortisol in man. *J Invest Dermatol.* 1967;48:181-183.
38. Turpeinen M, Lehtokoski-Lehtiniemi E, Leisti S, et al. Percutaneous absorption of hydrocortisone during and after the acute phase of dermatitis in children. *Pediatr Dermatol.* 1988;5:276-279.
39. Clark AF, Wordinger RJ. The role of steroids in outflow resistance. *Exp Eye Res.* 2009;88:752-759.
40. Jones III R, Rhee DJ. Corticosteroid-induced ocular hypertension and glaucoma: a brief review and update of the literature. *Curr Opin Ophthalmol.* 2006;17:163-167.
41. Tripathi RC, Parapuram SK, Tripathi BJ, et al. Corticosteroids and glaucoma risk. *Drugs Aging.* 1999;15:439-450.
42. Sahni D, Darley CR, Hawk JLM. Glaucoma induced by periorbital topical steroid use—a rare complication. *Clin Exp Dermatol.* 2004;29:617-619.
43. Aggarwal RK, Potamitis T, Chong NH, et al. Extensive visual loss with topical facial steroids. *Eye (Lond).* 1993;7(Pt 5):664-666.
44. Katsushima H. Corticosteroid-induced glaucoma following treatment of the periorbital region. *Nippon Ganka Gakkai Zasshi.* 1995;99:238-243.
45. Stokes J, Walker BR, Campbell JC, et al. Altered peripheral sensitivity to glucocorticoids in primary open-angle glaucoma. *Invest Ophthalmol Vis Sci.* 2003;44:5163-5167.
46. Ng JS, Fan DS, Young AL, et al. Ocular hypertensive response to topical dexamethasone in children: a dose-dependent phenomenon. *Ophthalmology.* 2000;107:2097-2100.
47. Remé C, D'Epinay SL. Periods of development of the normal human chamber angle. *Doc Ophthalmol.* 1981;51:241-268.
48. Urban Jr RC, Cotlier E. Corticosteroid-induced cataracts. *Surv Ophthalmol.* 1986;31:102-110.
49. Adhikary HP, Sells RA, Basu PK. Ocular complications of systemic steroid after renal transplantation and their association with HLA. *Br J Ophthalmol.* 1982;66:290-291.
50. Veenstra DL, Best JH, Hornberger J, et al. Incidence and long-term cost of steroid-related side effects after renal transplantation. *Am J Kidney Dis.* 1999;33:829-839.
51. Matsunami C, Hilton AF, Dyer JA, et al. Ocular complications in renal transplant patients. *Aust N Z J Ophthalmol.* 1994;22:53-57.
52. Skalka HW, Prchal JT. Effect of corticosteroids on cataract formation. *Arch Ophthalmol.* 1980;98:1773-1777.
53. Chen CC, Huang JL, Yang KD, et al. Atopic cataracts in a child with atopic dermatitis: a case report and review of the literature. *Asian Pac J Allergy Immunol.* 2000;18:69-71.
54. Bair B, Dodd J, Heidelberg K, et al. Cataracts in atopic dermatitis: a case presentation and review of the literature. *Arch Dermatol.* 2011;147:585-588.
55. Niwa Y, Iizawa O. Abnormalities in serum lipids and leukocyte superoxide dismutase and associated cataract formation in patients with atopic dermatitis. *Arch Dermatol.* 1994;130:1387-1392.
56. Bouzas EA, Karadimas P, Pournaras CJ. Central serous chorioretinopathy and glucocorticoids. *Surv Ophthalmol.* 2002;47:431-448.
57. Prünte C, Flammer J. Choroidal capillary and venous congestion in central serous chorioretinopathy. *Am J Ophthalmol.* 1996;121:26-34.

58. Polak BC, Baarsma GS, Snyers B. Diffuse retinal pigment epitheliopathy complicating systemic corticosteroid treatment. *Br J Ophthalmol.* 1995;79:922-925.
59. Spraul CW, Lang GE, Lang GK. Retinal pigment epithelial changes associated with systemic corticosteroid treatment: report of cases and review of the literature. *Ophthalmologica.* 1998;212:142-148.
60. Carvalho-Recchia CA, Yannuzzi LA, Negrão S, et al. Corticosteroids and central serous chorioretinopathy. *Ophthalmology.* 2002;109:1834-1837.
61. Cumurcu T, Sezer E, Kilic R, et al. Comparison of dose-related ocular side effects during systemic isotretinoin administration. *Eur J Ophthalmol.* 2009;19:196-200.
62. Rademaker M. Adverse effects of isotretinoin: a retrospective review of 1743 patients started on isotretinoin. *Australas J Dermatol.* 2010;51:248-253.
63. Weleber RG, Denman ST, Hanifin JM, et al. Abnormal retinal function associated with isotretinoin therapy for acne. *Arch Ophthalmol.* 1986;104:831-837.
64. Neudorfer M, Goldshtein I, Shamai-Lubovitz O, et al. Ocular adverse effects of systemic treatment with isotretinoin. *Arch Dermatol.* 2012;148:803-808.
65. Lambert RW, Smith RE. Pathogenesis of blepharoconjunctivitis complicating 13-cis-retinoic acid (isotretinoin) therapy in a laboratory model. *Invest Ophthalmol Vis Sci.* 1988;29:1559-1564.
66. Fraunfelder FW. Ocular side effects associated with isotretinoin. *Drugs Today.* 2004;40:23-27.
67. Karalezli A, Borazan M, Altinors DD, et al. Conjunctival impression cytology, ocular surface, and tear-film changes in patients treated with systemic isotretinoin. *Cornea.* 2009;28:46-50.
68. Fraunfelder FT, Fraunfelder FW, Edwards R. Ocular side effects possibly associated with isotretinoin usage. *Am J Ophthalmol.* 2001;132:299-305.
69. Santodomingo-Rubido J, Barrado-Navascués E, Rubido-Crespo MJ. Drug-induced ocular side-effects with isotretinoin. *Ophthalmic Physiol Opt.* 2008;28:497-501.
70. Fraunfelder FW, Fraunfelder FT. Evidence for a probable causal relationship between tretinoin, acitretin, and etretinate and intracranial hypertension. *J Neuroophthalmol.* 2004;24:214-216.
71. Pitts JF, Mackie RM, Dutton GN, et al. Etretinate and visual function: a 1-year follow-up study. *Br J Dermatol.* 1991;125:53-55.
72. Ling MR. Acitretin: optimal dosing strategies. *J Am Acad Dermatol.* 1999;41:S13-S17.
73. Thielitz A, Gollnick H. Topical retinoids in acne vulgaris: update on efficacy and safety. *Am J Clin Dermatol.* 2008;9:369-381.
74. Rai R. Phototherapy: an update. *Indian J Dermatol Venereol Leprol.* 2009;75:634-637.
75. Lerman S, Megaw J, Gardner K. Psoralen-long-wave ultraviolet therapy and human cataractogenesis. *Invest Ophthalmol Vis Sci.* 1982;23:801-804.
76. Boukes RJ, Van Balen AT, Bruynzeel DP. A retrospective study of ocular findings in patients treated with PUVA. *Doc Ophthalmol.* 1985;59:11-19.
77. Lafond G, Roy PE, Grenier R. Lens opacities appearing during therapy with methoxsalen and long-wavelength ultraviolet radiation. *Can J Ophthalmol.* 1984;19:173-175.
78. Koch HR, Beitzen R, Kremer F, et al. 8-methoxypsoralen and long ultraviolet effects on the rat lens: experiments with high dosage. *Graefes Arch Clin Exp Ophthalmol.* 1982;218:193-199.
79. Malanos D, Stern RS. Psoralen plus ultraviolet A does not increase the risk of cataracts: a 25-year prospective study. *J Am Acad Dermatol.* 2007;57:231-237.
80. Abdullah AN, Keczkes K. Cutaneous and ocular side-effects of PUVA photochemotherapy—a 10-year follow-up study. *Clin Exp Dermatol.* 1989;14:421-424.
81. Glew WB, McKeever G, Roberts WP, et al. Photochemotherapy and the eye: photoprotective factors. *Trans Am Ophthalmol Soc.* 1980;78:243-254.
82. Calzavara-Pinton PG, Carlino A, Manfredi E, et al. Ocular side effects of PUVA-treated patients refusing eye sun protection. *Acta Derm Venereol Suppl (Stockh).* 1994;186:164-165.
83. Söker S, Nergiz Y, Cakmak S, et al. The demonstration of changes in bulbar conjunctiva surface epithelium in the psoriatic patients treated with PUVA. *Ann Ophthalmol (Skokie).* 2008;40:94-98.