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Side effects of retinoid therapy on the quality of vision

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Retinoids are compounds chemically related to vitamin A, which are frequently used in dermatological practice (1). They are characterized by numerous mechanisms of action leading to normalization of keratinocyte proliferation and maturation. They have anti-seborrhoeic, immunomodulatory and anti-inflammatory effects (1, 2). A number of side effects to retinoid treatment have been recorded; one group of such side effects relates to eyes and vision. Dry eye syndrome and blepharoconjunctivitis are the most common side effects, appearing in 20–50 % of patients treated with retinoids. They often contribute to the occurrence of other side-effects such as eye discomfort and contact lens intolerance. Due to the widespread use in clinical practice, the adverse effects, including ocular side effects, should be studied. To confirm the variety of adverse effects of retinoids, several case reports of rare side-effects are presented.

Keywords: retinoids, isotretinoin, adverse effects, eyes, acne

Retinoids are compounds chemically related to vitamin A (1, 2); they can be presented through 3 generations (2):

(*i*) first generation, which includes alitretinoin (9-*cis*-retinoic acid), retinaldehyde, retinol, isotretinoin (13-*cis*-retinoic acid), tretinoin (*trans*-retinoic acid);
(*ii*) second generation, whose representatives are acitretin and etretinate;
(*iii*) third generation, which includes adapalene, arotinoid, arotinoid ethyl, methyl sulfone arotynoid, bexarotene, tazarotene.

Mechanisms of action of vitamin A derivatives *inter alia* rely on:

(*i*) reducing the expression of matrix metalloproteinases (MMP) such as collagenases 1-4, gelatinases A and B, stromelysins and others, which participate in skin inflammatory processes; (3)

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(*ii*) blocking the activity of 3α-hydroxysteroid dehydrogenase of retinol (2);
(*iii*) inhibiting the transcription factor-activator protein 1 (AP-1) (2);
(*iv*) blocking the cell-division cycle (2);
(*v*) inducing apoptosis of sebocytes as well as their stem cells and precursor cells of the sebaceous glands, which result in a long-lasting effect of retinoids (4).

Retinoids affect human cells at the stages of embryogenesis, reproduction, regulation of inflammatory process, cell growth and differentiation (5). As ligands, they modify the DNA transcription through interaction with the retinoic acid receptors (RAR) and retinoid-X-receptors (RXR) – nuclear receptors that serve as transcription factors (1, 5). After ligand binding, dimerisation of receptors and interaction with DNA, co-activators are recruited and RNA elongation is performed (5). By inhibiting growth-stimulating signals and activating downstream signaling they regulate apoptosis and cell differentiation in pre-cancerous and cancerous lesions (5). The anti-inflammatory and anti-bacterial action can be seen in the influence on immune response to *Propionibacterium acnes* through reducing the expression of the toll-like-receptor 2 (TLR2) on immune system cells responsible for pro-inflammatory cytokines production (4, 5). All these mechanisms lead to the normalization of keratinocyte proliferation and maturation, immunomodulatory and anti-inflammatory effects of these medicaments (5).

The use of systemic retinoids is widespread. Acitretin is used orally in patients with severe and erythrodermic psoriasis vulgaris resistant to other therapies, generalized and localized pustular psoriasis, severe congenital ichthyosis, Darier's disease, pityriasis rubra piliaris, recalcitrant lichen planus and palmoplantar keratoderma (1, 7, 8). Alitretinoin is effective in severe chronic hand eczema (5, 8). Tretinoin is used in acute promyelocytic leukemia treatment (1). Bexarotene is approved for the cutaneous T-cell lymphoma therapy and it demonstrates promising effects in some cancers like non-small cell lung cancer. It is

Table I. Guidelines of care for the management of acne vulgaris (10)

Acne	Mild	Moderate	Severe
First choice	BP or topical retinoid or topical combination therapy*	Topical combination therapy* or oral antibiotic + topical retinoid + BP or oral antibiotic + topical retinoid + BP + topical antibiotic	Oral antibiotic + topical combination therapy*: or oral isotretinoin
Alternatives	Add topical retinoid or BP or alternative retinoid or topical dapsone	Alternative combination therapy or alternative oral antibiotic or add oral combined contraceptive or oral spironolactone (females) or oral isotretinoin	Alternative oral antibiotic or add oral contraceptive or oral spironolactone (females) or oral isotretinoin

BP – benzoyl peroxide
* Topical combination therapy: BP + antibiotic or BP + retinoid or BP + retinoid + antibiotic

also used in mycosis fungoides and Sézary syndrome in combination with other forms of therapy (9). The effectiveness of isotretinoin in the treatment of acne was first observed in 1970. In 1982, the Food and Drug Administration (FDA) approved its oral form as a drug used for acute forms of nodular acne (6). Actually, isotretinoin is mainly administrated to treat severe acne vulgaris according to recommendations for the use of retinoids in acne, which are contained in ref. 10 and presented in Table I. Less frequent indications include hidradenitis suppurativa, selected cases of acne rosacea and some other hyperkeratotic dermatological conditions (2).

Many conditions may be treated with the topical form of vitamin A derivatives. Topical tretinoin is effective in acne therapy but is also used in other skin disorders, including premature skin aging induced by ultraviolet light, actinic keratosis and other less described conditions, *e.g.*, lesions of oral mucosa, hypertrophic scarring, pigmentation disorders (11). Topical alitretinoin is administrated in Kaposi's sarcoma patients with human immunodeficiency virus (HIV) infection. Some other retinoids, such as adapalene, may be used in acne vulgaris and tazarotene in combination with topical corticosteroids in psoriasis (1). Topically used retinoids differ in the potential to induce local side-effect, irritation, erythema and in particular exfoliation of skin (5). The wide range of substances allow the physician to make selection for an individual patient in search of the best tolerance. In our opinion, it is valid for clinicians to select the most suitable medicament but it is also important to pay attention to systemic uptake of retinoids applied onto skin, especially on extensive areas of the body. Shiva *et al*. (12) pointed out that external application of isotretinoin causes its penetration into the circulatory system. We expect that it may demonstrate systemic activity, as well as cause systemic side-effects. The same authors showed that the tolerance elevates when specific new solid-lipid nanoparticles of isotretinoin are used. Moreover, such form of isotretinoin can prevent its systematic uptake.

The most commonly used oral retinoid in dermatological practice is isotretinoin, it will therefore be the basis of discussion regarding the adverse effects of vitamin A derivatives, paying particular attention to the ocular symptoms.

ADVERSE OCULAR EFFECTS

Isotretinoin is an effective and generally well tolerated drug (6, 13). Many of the adverse effects can be predicted before they occur (13). The most common side-effects rarely reach the severity that could require discontinuation of treatment and they disappear a short time after the cessation of therapy (13).

The adverse effects of isotretinoin therapy, in dependence on the frequency of occurrence, are shown in Table II (2).

Analyzing 1,741 reports of possible ocular adverse effects induced by isotretinoin Fraunfelder *et al*. (13) divided them into the following categories according to World Health Organization (WHO) in the Causality Assessment Guide of Suspected Adverse Reactions: "certain," "probable/likely," "possible," "unlikely," "conditional/unclassified," and unassessible/unclassifiable". Section "certain" includes: abnormal meibomian gland secretion, blepharoconjunctivitis, corneal opacities, decreased dark adaptation, photophobia, decreased tolerance to contact lenses, decreased vision, increased tear osmolality, myopia, ocular discomfort, ocular sicca (dry eye syndrome), pseudotumor cerebri (when adminis-

Table II. Adverse effects of isotretinoin therapy and frequency of occurrence (ref. 2)

Frequency of occurrence	Adverse effects of isotretinoin
Very common (>1/10)	Cheilitis, dryness, peeling, itching, redness of the skin; features resembling hand eczema; increase of transaminases; increase of triglycerides; muscle and joint pain; decreased exercise tolerance; decreased high-density lipoprotein; dry eye; irritation of the eye; blepharitis; conjunctivitis; night vision disturbances; anemia; accelerated erythrocyte sedimentation rate; thrombocytopenia; thrombocytosis
Common (>1/100)	Neutropenia, headache, epistaxis, dryness of nose mucus membrane, increase of the cholesterol and glucose concentration, hematuria, proteinuria
Rare (>1/10.000)	Allergic skin reactions, anaphylactic reactions, depression, anxiety, aggression, mood swings, hair loss
Very rare (<1/10.000)	Bacterial infections of the skin and mucous membranes, lymphadenopathy, diabetes, hyperuricemia, abnormal behavior, suicidal ideation, pseudotumor cerebri (when administrated simultaneously with oral tetracycline), drowsiness, seizures, blurred vision, cataract, color vision disorder, intolerance of contact lenses, keratitis, photophobia, impaired hearing, allergic vasculitis, Wegener's granulomatosis, pancreatitis, hepatitis, fulminant acne, exacerbation of acne, hirsutism, nail dystrophy, paronychia, hyperpigmentations, photosensitivity, myositis and arthritis, tendonitis, increase of creatine phosphokinase

trated simultaneously with oral tetracycline), keratitis and teratogenic ocular abnormalities. Most of these symptoms are reversible and pass after discontinuation of retinoid treatment (13). The list of side effects is long but, in our experience, the most common ocular adverse effects are the dry eye syndrome and blepharoconjunctivitis. They occur in 20–50 % of patients taking the drug, usually 3–5 weeks after initiation of the therapy (2, 14).

Dry eye is caused by atrophic changes in meibomian glands (15, 16) as well as modification of the tear film composition (15). Meibomian glands are tarsal sebaceous glands responsible for the production of meibum, an oily substance, the most superficial layer of the tear film that protects it from evaporation and dysfunctions (15). Lambert and Smith (16) studied the impact of retinoids on the morphological cell structure. They found that isotretinoin inhibits the differentiation of meibomian acinar cells and stimulates proliferation of the epithelium lining the ducts and acini causing their thickening. Mathers *et al.*'s examination (17) of the meibomian gland morphology and tear osmolality showed that during retinoid treatment the meibomian glands become significantly less dense, atrophic and the osmolality of the tear film increases. Nevertheless, these changes had no impact on the Schirmer test results used to assess the secretion of tears.

Meibomian gland excretion prevents excessive evaporation of the aqueous layer of the tear film and secures film osmolality and stability. Thus, dysregulation causes secondary dryness and irritation of the most external structures of the eye: conjunctiva and cornea (18). In our opinion, this might be assumed as an indirect effect of retinoid acid whereas direct action should also be taken into consideration. It is caused by the presence of the drug and its metabolites in the tear film (14), which may directly provoke its instability, hence dryness and irritation. We emphasize that both of these mechanisms are predis-

posed to ocular adverse effects such as conjunctivitis, blepharitis, intolerance of contact lenses and photophobia.

Neudorfer *et al*. (18) conducted a retrospective cohort study involving 14,682 adolescents and young adults with a recommended daily dose of isotretinoin of 0.5–1.0 mg kg^{-1}, to a cumulative dose of 120 to 150 mg kg^{-1}. Adverse ocular effects were measured within 1 year after the first dispensed isotretinoin prescription. In group I, with new users of isotretinoin for acne, 13.8 % of the patients reported adverse ocular effects; in group II, with acne but without isotretinoin treatment 9.6 %, and in group III, which was a control group, 7.1 %. During a one-year follow-up period, the first group showed a significantly increased risk of ocular symptoms. This significantly increased risk was not found in the second group. The dry eye risk was reported in 0.7, 0.2 and 0.1 % of patients in the respective groups.

In the Bergler-Czop study (2), out of 155 patients treated with oral isotretinoin because of different forms of acne (examined before qualifying for treatment, at the beginning of treatment, and during the 3rd and the 6th months of treatment), dry eye was observed in 50 % of patients during later treatment periods.

Karalezli *et al*. (14) conducted a prospective clinical study examining 50 patients treated with isotretinoin at a daily dose of 0.8 mg kg^{-1}. The patients underwent a full ophthalmologic examination before treatment, during treatment (on the 30th and 120th day), at the end of treatment, and 30 days after the treatment. The average results of the Schirmer test performed at each examination time point did not differ significantly, while the mean anesthetized Schirmer test and tear breakup time (TBUT, which reflects the stability of the tear film) results decreased. The scores of ocular surface disease index (OSDI, which assesses the symptoms associated with the dryness of eyes and their effects on vision) were elevated.

Cumurcu *et al*. (19) compared how the high-dose and low-dose isotretinoin treatments affect the vision. A group of 26 patients were treated with the high dose (> 0.5 mg kg^{-1} daily) of the drug and 25 patients with the low dose (< 0.5 mg kg^{-1} daily). Ophthalmological examination took place before the treatment, on the 45th and 90th day of treatment and one month after treatment. The authors did not observe any statistically significant difference between these two groups in the results of the Schirmer test with anesthesia. The duration of TBUT on days 45 and 90 was significantly shorter in the group taking the higher dose of retinoid, with no difference in the results before and after the treatment.

Another frequently observed adverse effect of therapy is blepharoconjunctivitis. Karalezli *et al*. (14) observed blepharitis in 36 % of patients 1 month after the cessation of treatment. It was accompanied by dysfunction of meibomian glands, hyperemia and vascularization of the lid margin. In the Fraunfelder *et al*. (13), 15 % of patients had blepharoconjunctivitis during isotretinoin treatment.

Neudorfer *et al*. (18), in the previously mentioned study, recorded the following incidence of conjunctivitis after a 1-year observation period: 4.0 % in group I (new users of isotretinoin for acne), 2.4 % in group II (patients with acne but without isotretinoin treatment), and 1.9 % in the group III (control group), while blepharitis was observed in particular groups in 1.0, 0.2 and 0.2 %, respectively.

Night and color vision disturbances are among the most serious side-effects of retinoids (20). Night vision abnormalities are most likely associated with the fact that isotretinoin inhibits retinol dehydrogenase, which leads to the reduction of 11-*cis*-retinal and

thus causes functional impairment of rod photoreceptors (2, 20). Toxic doses of isotretinoin do not cause histological loss of rod cells, but even a single dose of the drug causes slower recovery of rod signaling and rhodopsin regeneration for several days (21). Rare cases have been reported of irreversible night vision disturbance, which seems to be an idiosyncratic reaction not related to the dose (20).

Mollan *et al*. (22) examined 47 patients treated with oral isotretinoin in the past. They underwent standard electroretinograms (ERG), which measure the electrical responses to standardized stimuli of various cell types in retina, and the Goldmann-Weekers dark adaptation test (DA), which represents the ability of eye to adapt to darkness. Thirteen patients had ERG changes showing night vision disturbances, and 2 of them had also abnormal DA.

Fraunfelder and colleagues (13) conducted a study of 1,741 patients and noted decreased dark adaptation in 8 % of them.

SOME CLINICAL CASES

Corneal steepening (23). – A 39-year-old female patient, taking isotretinoin (20 mg kg^{-1} daily) for seven and a half weeks, experienced blurred vision, transient loss of some parts of her visual field, dry eyes, peeling and erythema of the face and lips. Examination revealed a number of abnormalities, including conjunctival hyperemia, punctate corneal staining and meibomian gland dysfunction. Corneal topography showed changes in the shape of cornea – corneal steepening more intensified in peripheral parts. Refraction of eyes showed no significant changes compared to previous results of the patient. After cessation of isotretinoin treatment, the reported symptoms disappeared and corneas returned to normal structure after 7 and a half weeks.

Premacular hemorrhage (24). – A 19-year-old female patient, receiving oral isotretinoin (30 mg kg^{-1} daily) for 4 months, reported a sudden and painless loss of vision in her left eye. The patient underwent additional tests including ophthalmoscopy (eye fundus examination), fluorescent angiography and optical coherence tomography (OCT), which showed premacular hemorrhage. Anamnesis, further examinations (in search of the source) and the fact that the hemorrhage occurred during isotretinoin therapy and disappeared after cessation of the treatment, with no other predisposing factors, indicate that the hemorrhage was an adverse effect of acne treatment.

Autoimmune thyroiditis and ocular myasthenia gravis (25). – A 19-year-old male patient, treated with oral isotretinoin (1 mg kg^{-1} daily) for 6 months, experienced a sudden episode of right eye ptosis, which passed spontaneously after 2 weeks. Following the next week of therapy, ptosis of the left eye appeared and also subsided spontaneously. After another 2 weeks, the patient experienced eye ptosis again, accompanied by double vision. Medical history and additional tests indicated thyroiditis with antibodies against thyroid-stimulating hormone (TSH) receptors and ocular myasthenia gravis, which was confirmed by a good response to steroidotherapy with prednisolone (40 mg daily) and pyridostigmine (360 mg daily). Simultaneous absence of the factors causing or predisposing to these diseases and the fact that isotretinoin may cause other autoimmune diseases (such as Crohn's disease and Guillain-Barre syndrome) indicate their relationship with isotretinoin treatment.

CONCLUSIONS

Due to the widespread use in clinical practice, the adverse effects of retinoids, including ocular effects, should be studied thoroughly. This is particularly important because of the fact that many of the adverse effects of these drugs can be predicted (13), which suggests the need for systematic control of patients treated with vitamin A derivatives. The frequency of ocular side effects compels practitioners to consider periodic ophthalmological controls, particularly in patients with initial ocular symptoms (*e.g.*, dry eye syndrome). Such controls would provide the possibility of treating or reducing these adverse effects.

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