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Review Article

Oral isotretinoin: beyond acne – a review of its use in cosmesis

口服異維甲酸：暗瘡以外的美容治療使用的綜述

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Oral isotretinoin is the first generation U.S. Food and Drug Administration (FDA) approved retinoid introduced for severe nodulocystic acne. It exerts its effects on anti-inflammatory, immunomodulatory and anti-seborrhoeic pathways. There is clear and extensive evidence in its efficacy in acne treatment. Newer studies are under way to explore its use beyond the confines of acne. In this paper, we studied the role of isotretinoin in improving the following primary cosmetic conditions: acanthosis nigricans, seborrhoea, ichthyosis, rosacea and photoageing. Publications were sourced from Pubmed/Medline and OVID. Isotretinoin was found to be promisingly effective in improving cosmetic outcomes in the above conditions.

口服異維甲酸是美國食品和藥物管理局（FDA）批准用來治療嚴重結節囊腫性痤瘡的第一代維甲酸。它通過抗炎、免疫調節和抗脂溢性等機理發揮其療效。目前在痤瘡治療中，其療效有著明確和廣泛的證據。現時較新的研究，正在探討其痤瘡以外的用途。在本文中，我們會探討口服異維甲酸在改善下列影響基本儀容的情況中可扮演的角色，包括黑棘皮病、皮脂溢、魚鱗癬、玫瑰痤瘡和光老化。參考的醫學文獻源自 Pubmed 、 Medline 及 OVID 。總括來說，異維甲酸予人期望能有效地改善上述各種情況的美容效果。

Keywords: Cosmesis, isotretinoin, retinoids, review

關鍵詞：美容效果、異維甲酸、維甲酸、綜述

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Introduction

Retinoids are a class of biologically potent metabolites, chemically derived from vitamin A and retinols. Retinols, in turn, are a dietary derived, alcoholic form of vitamin A. Absorbed from the gastrointestinal system, they exert their effects through diverse biological processes in humans,

ranging from vision, cell growth and apoptosis[1] and immunomodulation.

Retinoids are formed through *in vivo* enzymatic conversion of retinol. The latter is first absorbed in the gastrointestinal tract, forming complexes with cellular retinol binding protein. The majority of retinol (50-80%) is contained in the liver. Specific retinol-binding proteins are needed to bind these hydrophilic retinols in the plasma for systemic circulation.[2] At the cellular level, metabolic oxidative transformation occurs to generate retinaldehyde and retinoic acid isomers, all-*trans* (tretinoin), 9-*cis* and 13-*cis* (isotretinoin). Binding at nuclear receptors-retinoic acid receptors (RAR) and retinoid X receptor (RXR)[3] regulates transcription and downstream gene expression of keratinocytes and fibroblasts.

Retinoic acid is a classical retinoid which exerts a baseline physiological effect in the skin for cellular proliferation and turnover. Increased pharmacological doses will thus augment its biological effects, paving the way for new systemic and topical therapies for diseased skin.

Since its inception, there have been many new retinoids derived, and these can be broadly grouped into three generations (Non-aromatic, mono-aromatic, polyaromatic).

Isotretinoin

Isotretinoin is derived through the modification of the polar end group and polyene side chain of vitamin A compound. First introduced in the 1980s, extensive clinical experience has been gathered in relation to its use. Oral isotretinoin is the first generation U.S. Food and Drug Administration (FDA) – approved retinoid introduced for severe nodulocystic acne. The recommended daily dose is 0.5-1.0 mg/kg, with a total recommended cumulative dose of 120-150 mg/kg.[4] Recent studies in Southeast Asia have shown efficacy and better tolerability at lower daily doses of 0.3-0.4 mg/kg/day.[5]

Mechanism of action

Isotretinoin, unlike other retinoids, is less lipophilic. Bioavailability of isotretinoin is 25%, with a half-life of 20 hours. It is extensively metabolised to 13-*cis*-4-oxo-retinoic acid and all-*trans*-retinoic acid. Isotretinoin exerts its effect through cellular surface receptors, mediating the metabolism of sex hormones and endogenous retinoids. Clinical effects observed with the use of isotretinoin include hypoplasia of sebaceous glands and reduction of sebum production. This is instrumental in acne treatment, for which seborrhoea has been implicated.

Further studies have investigated the *in vivo* and *in vitro* effects of isotretinoin. Studies have demonstrated its immunomodulatory effects involving interleukins and immunoglobulins. Its pharmacokinetics at the cellular level has also been employed in antineoplastic treatment through gene transcription, modification and modulation of cell proliferation rate.[6]

The anti-inflammatory, immunomodulatory, anti seborrhoeic effects of oral isotretinoin have piqued curiosity regarding its use beyond the confines of acne. Studies have previously established its use, albeit limited, in non-acne dermatological conditions such as rosacea, psoriasis, pityriasis rubra pilaris.

List 1. Conditions with demonstratable responsiveness to isotretinoin

a. Acanthosis nigricans
b. Condylomata acuminata
c. Darier's disease
d. Granuloma annulare
e. Hidradenitis suppurativa
f. Ichthyosis
g. Photoageing
h. Pityriasis rubra pilaris
i. Psoriasis
j. Rosacea
k. Seborrhoea/Seborrhoeic dermatitis
l. Wound healing/Keloid formation

In this paper, we studied the role of isotretinoin in improving the following primary cosmetic conditions:
a. Acanthosis nigricans
b. Seborrhoea
c. Ichthyosis
d. Rosacea
e. Photoageing
f. Keloid formation

Methods

A multi-database search was conducted in July 2014 using publications sourced from Pubmed/Medline and OVID. The search was limited to the English language with the following keywords: aesthetic, cosmetic, isotretinoin, dermatology, non-dermatology, acanthosis nigricans, photoageing, rosacea, ichthyosis and keloid.

Abstracts were examined and full text articles for appropriate papers were reviewed. The selected literature fulfilled at least one of the following criteria:
- Use of oral isotretinoin in non-acne-related dermatological conditions
- Case reports and case series of novel use of isotretinoin in specific populations
- Publications supporting *in vivo* or *in vitro* use of isotretinoin in cosmesis or aesthetics.

Acanthosis nigricans

Acanthosis nigricans (AN) is often described as a hyperpigmented, velvety rash commonly localised to the axillae, neck and perineum. Eight subtypes of AN have been described, with obesity-associated, non-malignant AN being the most common. Diabetes mellitus and increased insulin resistance have been commonly implicated in the development of AN in such patients.

Activation of certain receptors in the skin (fibroblast growth factor receptor, tyrosine kinase, epidermal growth factor receptor, insulin-like growth factor receptor) have been demonstrated to accelerate epidermal cell proliferation, accounting for the characteristic features of AN.

Two case reports have reported the successful use of oral isotretinoin in the treatment of AN,[7,8] one of which employed concomitant therapy with metformin. Using a stepwise escalation approach, both cases demonstrated at least 50% improvement (flattening, lightening) in the AN lesions. A third study explored the use of topical tretinoin in the treatment of AN to satisfactory effect.[9]

AN is a fairly common cosmetic concern amongst Asians (personal observation). We believe a head to head comparison of efficacy between oral isotretinoin and topical tretinoin is warranted. More objective descriptors and instruments of quantification of AN are also needed.

Seborrhoea

Seborrhoea of the face predisposes to acne development, and in itself is a nuisance to many patients. Physicians often employ a combination of sebum-absorbing topical agents, keratolytics and chemical peels, but the effects are often transient and incomplete.

Oral isotretinoin has been reported in a small study group of 11 patients to effectively control seborrhoea. Different dosages of isotretinoin were used. The dosage ranged from 2.5 mg three times a week, 2.5 mg daily and 5 mg daily in the study by Geissler et al.[10] Even higher doses were employed by King et al (0.1 mg/kg-1 mg/kg)[11] and Geiger et al (20 mg/day).[12] A dose-dependent trend was not shown to be significant in the control of seborrhoea. In a study utilising the *in vitro* human sebocyte model by Zouboulis et al,[13] retinoids demonstrated efficacy in inhibiting both proliferation and differentiation of sebocytes. Oral isotretinoin remains one of the most active and potent compounds, with effects seen through its extension of maturity period of basal sebocytes.

With regard to the recurrence of seborrhoea post treatment, the strongest evidence lies in acne-related studies. Recurrence of seborrhoea was observed at 16 weeks post-treatment cessation.[14] Another study with a two-year follow-up period reported a 87% recurrence of seborrhoea post-treatment.[15] In this study, 52% of patients experienced recurrence of acne lesions at one year post-treatment.

Patients suffering from severe seborrhoea may therefore benefit from a course of oral isotretinoin, when topical agents have been unsuccessful. Isotretinoin given at a lower dose or reduced dosing frequency seems to be sufficient for these patients.

Ichthyosis

Ichthyosis is a rare group of skin disorders with manifestations of fish-like scales and hyperkeratosis with sites of inflammation. Encompassing both inherited and acquired forms, it varies in severity, time of onset and body surface area involved, ranging from ichthyosis vulgaris, to the harlequin type. A French epidemiological paper revealed a prevalence of 4.5 cases/million for lamellar ichthyosis and 1.9 cases/million for both congenital ichthyosiform erythroderma and syndromic ichthyosis.[16]

A systematic review examined six randomised controlled trials exploring various treatment options in inherited ichthyosis.[17] Although topical agents such as calcipotriol, liarozole cream have demonstrated promise, the trials involved study subjects in relatively small numbers. A superior treatment option was not conclusively established. Literature on isotretinoin use in ichthyosis is scanty. Chang and Reyes highlighted a case of an infant with harlequin ichthyosis treated with long-term isotretinoin.[18] The infant was 9 months old at the time of study, having been treated with isotretinoin since day 7 of birth. A review of 45 cases showed that mortality occurred in 44% of patients, with death usually taking place in the first 52 days.[19]

A multicentre study evaluating 40 subjects with lamellar ichthyosis and epidermolytic hyperkeratosis demonstrated improvement in scaling, erythema, crusting and induration in >90% of subjects over 16 weeks at a maximum dose of 4 mg/kg/day oral isotretinoin.[20] Cessation of treatment resulted in symptomatic disease recurrence.

We postulate that oral isotretinoin bears promise in the cosmesis treatment of ichthyosis vulgaris, a common cosmetic genodermatosis. The ideal dosing regime remains to be elucidated.

Rosacea and rhinophyma

Rosacea is an inflammatory skin disorder characterised by vasomotor changes; inflammatory development of papules and pustules; and lymphoedema. These skin manifestations are intermittent and recurrent. Four subtypes have been described: erythemato-telangiectatic, papulo-pustular, phymatous and ocular. It typically affects fair-skinned young to middle-aged females.

A multitude of aetiological factors have been implicated. A genetic component has been postulated, with the disequilibrium in innate immune system, ultraviolet radiation, lifestyle factors (inadequate exercise, excessive stress) and infectious organisms – *Demodex* mites,[21] being contributory causes. This is a relatively well-studied condition with diverse treatment options, including topical and oral anti-inflammatory agents and antibiotics, phototherapy[22] and retinoids.[23] Previous reviews have documented the efficacy of topical metronidazole, azelaic acid and doxycycline.[24] With regard to ocular rosacea, ciclosporin 0.5% ophthalmic emulsion may be effective.

Oral isotretinoin represents an alternative treatment strategy. A study by Plewig et al demonstrated a clear histologically-proven benefit in 13 patients with treatment-refractory rosacea.[25] Up to 1 mg/kg/day was used and the longest

treatment duration was 28 weeks. Postulations of treatment efficacy centre on sebaceous gland reduction and an anti-inflammatory effect by isotretinoin. A large multi-centre, randomised, controlled German trial involving 573 subjects provides further evidence that isotretinoin is as effective as doxycycline, with a quarter of them achieving complete remission.[26] The clinically effective dose was established at 0.3 mg/kg/day. Further studies reported clinical relapse within eight weeks after the cessation of treatment.[27]

There is growing evidence that oral isotretinoin is a viable non-surgical option for the management of severe rosacea, and particularly, rhinophyma.[28] A 25-year-old male with an eight-year history of rhinophyma was started on oral isotretinoin 20 mg/day, titrating to a maximum dose of 120 mg/day, and achieved partial reduction in nasal volume. Other authors have called for oral isotretinoin as a worthwhile non-surgical means of rhinophyma treatment.

There is sufficient evidence for the use of oral isotretinoin in severe rosacea. Newer studies are now being conducted for optimal dosing and duration of isotretinoin treatment, with 0.3 mg/kg having a fine balance between efficacy and side-effect/risk profile.[29]

Photoageing

Photoageing is a degenerative process involving epidermal and dermal layers of the skin. Cumulative and prolonged ultraviolet A (UVA) and ultraviolet B (UVB) exposure have been implicated. UVA has a longer wavelength (315-40 nm) with deeper penetrance, in contrast to UVB (290-315 nm). The pathophysiology of photoageing includes intracellular matrix metalloproteinase-1 (MMP-1) activation and hence increased collagenolytic activity, activation of lysosomal protease cathepsin K in fibroblasts which augments elastin degradation, reactive oxygen species damage to DNA, causing DNA instability and cellular damage, as well as telomere shortening with consequent shortening of cellular life cycle leading to apoptosis.[30]

Photoageing manifests clinically as skin wrinkling, pigmentation, dryness and laxity. Current treatment options include sun/UV protection and topical retinoids. Retinols retard photoageing through epidermal thickening, promoting collagen production and inhibiting proteolysis from MMP-1.

Previous non-controlled trials have demonstrated efficacy of isotretinoin using a varied-dosing 10-20 mg three times a week regime for a maximum of 2-3 months.[31] Two recent studies by Bagatin et al cited the safe and relatively effective use of oral isotretinoin in photoageing.[31,32] A randomised controlled trial of 32 menopausal or sterilised women achieved mild improvement in fine wrinkling morphologically and amelioration in skin elasticity after receiving isotretinoin 20 mg three times weekly over a three month period. Histological results were largely comparable between both intervention arm and control arm of sunscreen and moisturiser. A significant reduction of epidermal p53 expression was observed in the isotretinoin arm. p53 has been identified has an inducer of ageing, with its chronic activation associated with a loss of subcutaneous fat and xerosis.[33]

A follow-up randomised controlled study of 24 subjects in 2014 compared the efficacy of isotretinoin against 0.05% topical retinoids, using the following outcome measures: quality of life indices, patient, clinical and histopathological assessments. Clinical improvement was noted in both groups, with a histologically-proven reduction in elastosis and an increase in collagen. Neither treatment, however, was significantly superior.[32]

Isotretinoin was shown to have an excellent safety profile in all the studies. With non-inferior results compared to conventional sunscreen/ moisturisers, or topical retinoids, it is a viable option in the treatment of photoageing.

Postsurgical keloid formation

There have been case reports and series of patients on treatment with isotretinoin developing keloids and hypertrophic scars after dermal procedures (laser, abrasion).[34] This was postulated to be due to isotretinoin affecting skin cell metabolism, leading to dysfunctional collagen production. These lesions remain steroid-responsive.

A systematic review by Abdelmalek challenged the notion of the use of isotretinoin being an absolute contraindication for dermal procedures.[35] While some patients cited in case series developed keloids within two to four months post procedure, they were known to have a predisposition for keloid formation.

Since then, studies in animal models, have demonstrated normal wound healing and the safe use of isotretinoin periprocedure in both animal and human subjects in dermabrasion and full thickness wounds.[36,37] A further interventional study of seven subjects who underwent dermabrasion for atrophic acne scars revealed normal wound healing.[38] Keloid formation may therefore represent an idiosyncratic reaction.

A study by Gencoglan et al shed light on this issue through analysis of mast cell infiltration at wound sites in rats.[39] Retinoids promoted epithelisation and collagen production, increasing wound healing rates.

At this moment, positive evidence for normal wound healing pertained mainly to topical tretinoin.[40] A cautious approach should be undertaken in normal subjects on oral isotretinoin who are undergoing dermal procedures. Further studies on inflammatory responses mediated by isotretinoin on wound healing should be undertaken.

Conclusion

The extensive clinical experience with isotretinoin has shown its effectiveness in improving cosmetic outcomes in seborrhoea, rosacea, ichthyosis, acanthosis nigricans and photoageing.

Large multicentre, randomised, controlled and long-term prospective studies need to be undertaken to further delineate its efficacy, optimal dosing regimes and duration, long term safety and maintenance of efficacy upon drug withdrawal in the various conditions.

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