An Overview of Dermatological indications of Isotretinoin Use

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Abstract

Background: The importance of retinol (vitamin A) was discovered during World War. The retinoid drug project was launched in 1968 to synthesize compounds similar to vitamin A by chemical manipulation of its molecule to improve clinical efficacy and safety. The use of these substances in therapy dates back some 3000 years to ancient Egypt, where liver was used to treat endemic night blindness. The modern history of retinoids, however, began in 1909 when an essential factor in the viability of an embryo in the fatty extract of the egg yolk, called vitamin A, was discovered. Retinoids finally were introduced into the treatment of dermatoses including photoaging more than two decades ago. While the use of isotretinoin has revolutionized the treatment of acne vulgaris, isotretinoin is increasingly recognized as a useful therapeutic option for many other cutaneous conditions. We review the evidence underlying the use of isotretinoin for a variety of dermatological indications including hidradenitis suppurativa, sebaceous gland pathology, rosacea, scarring alopecia, cosmetic dermatology, and non-melanoma skin cancer prophylaxis amongst other uses, and thus consider alternative uses within dermatology practice. The studies found benefit of isotretinoin, however most trials lacked statistical power and in many cases the use was limited to case series. Isotretinoin, if used within the correct cohort with appropriate pretreatment counseling regarding side-effects, is a well-tolerated medication with potential as either an adjunctive treatment or a second-line agent in those recalcitrant cases unresponsive to first-line therapy.

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Introduction

The importance of retinol (vitamin A) was discovered during World War. The retinoid drug project was launched in 1968 to synthesize compounds similar to vitamin A by chemical manipulation of its molecule to improve clinical efficacy and safety. The use of these substances in therapy dates back some 3000 years to ancient Egypt, where liver was used to treat endemic night blindness. The modern history of retinoids, however, began in 1909 when an essential factor in the viability of an embryo in the fatty extract of the egg yolk, called vitamin A, was discovered. Retinoids finally were introduced into the treatment of dermatoses including photoaging more than two decades ago **(1).**

Retinoids are chemically derived from vitamin A. They influence cellular division and differentiation of stratified structures of epidermis. Vitamin A (retinol), its provitamin (β-carotene) and its aldehyde (retinal) and acid (all-trans-retinoic acid ATRA) forms are all-natural retinoids and are involved in a wide variety of essential biological processes, such as vision, reproduction, vertebrate embryonic morphogenesis and organogenesis, cell growth arrest, cell differentiation, apoptosis, and immune regulation **(2).**

isotretinoin is 0.5 mg/kg/day which is continued for 4 weeks, following which the dose is escalated to 1 mg/kg/day which is maintained over the ensuing treatment course unless laboratory values and adverse clinical effects warrant dose adjustments. Treatment with ISO is continued till the cumulative dose of 120–150 mg/kg is attained. The FDA-approved dosing frequency is twice daily **(3).**

High-dose schedule with isotretinoin in acne:

It has been suggested that using higher daily doses of isotretinoin (>1 mg/kg/day) and obtaining a higher total cumulative dose of isotretinoin than what is recommended, produces a lower risk of acne relapse. Moreover, even when higher dosing of isotretinoin (mean daily dosing of 1.6 mg/kg/day) is utilized, the duration of therapy is not compressed when the standard cumulative dose is achieved but is continued for 5–6 months, obtaining a total cumulative dose of 290 mg/kg at the end of therapy **(4).**

Low-dose isotretinoin therapy:

Various authors have utilized isotretinoin at a dose lower than the conventional dose for acne vulgaris. Dosages have ranged from 0.14 mg/kg/day to 0.75 mg/kg/day and dispensed either as a daily dose, intermittent schedule, alternate day therapy or gradually increasing the dose. However, though after an initial course of remission of lesions, in most instances, there occurs a recurrence of acne, with retreatment becoming mandatory. It therefore becomes important to compensate for the lower dose of isotretinoin by extending the course of therapy to optimize the cumulative exposure to isotretinoin over the treatment course **(3).**

Warts:

Warts are common benign tumors caused by human papillomavirus (HPV) infection, which is acquired from direct contact with an infected individual or from the environment **(2).**

Oral isotretinoin is a world-wide, well-established therapeutic option for the treatment of moderate and severe acne vulagris. However, it is becoming more widely acknowledged as a viable, non-invasive treatment option for a variety of other

dermatological conditions, including warts **(2).**

The dose of oral isotretinoin in treatment of multiple recalcitrant common warts 0.5 mg/kg/day until complete clearance or for a maximum 3 month **(2).**

Oral isotretinoin has shown promising efficacy and safety for the treatment of plane warts in many studies. Nofal and colleagues conducted a study to evaluate the efficacy and safety of a combination of oral isotretinoin and Candida antigen versus either agent alone in the treatment of multiple plane warts. They found that Candida antigen, oral isotretinoin of dose 0.3 mg/kg/day and a combination of both represent potential effective and safe modalities for the treatment of plane warts **(2).**

Rosacea:

Oral isotretinoin has shown to be effective, particularly in treating papulopustular rosacea, although beneficial properties of isotretinoin have also been seen in erythematotelangiectatic rosacea and phymatous rosacea. In rosacea, isotretinoin reduces cutaneous blood flow and also diminishes the size and number of sebaceous glands in the prefibrotic stage. Apart from facial rosacea, isotretinoin has also been employed in the treatment of extra facial rosacea (EFR) (excluding ocular rosacea). The most effective dosing for rosacea is 20 mg/day or 0.3 mg/kg/day **(3).**

In many studies, 20 mg of ISO was administered to rosacea patients for 4 months and then gradually tapered over the next 6 months till an end dose of 20 mg/week was obtained. This dosing schedule demonstrated significant improvements within the first month of treatment for both papulopustular lesions and the erythematous component of rosacea **(5).**

Pityriasis rubra pilaris:

There have been mixed reports with isotretinoin in PRP. isotretinoin can be employed as a first-line therapy for PRP with a higher level of efficacy compared to ultraviolet B (UVB), topical calcipotriol, keratolytics, azathioprine, methotrexate, and cyclosporine. In several studies, the dosage employed ranged from 1 to 1.5 mg/kg/day employing 20mg/day of isotretinoin in children and 40 mg/day of isotretinoin in adults **(6).**

Psoriasis:

isotretinoin in psoriasis can be considered a therapeutic option in women with childbearing potential who wish to avoid long-term use of contraceptives following acitretin for almost 2–3 years, in view of its shorter half-life. As isotretinoin modulates inflammatory cells and keratinocyte hyperproliferation and differentiation, it has been shown to be of value in psoriasis. isotretinoin probably has been shown to be most effective in managing pustular psoriasis with dose 1.5 mg/kg/day **(7).**

Hidradenitis suppurativa:

Although isotretinoin has not been included in the treatment guideline of HS, there have been reports supporting the use and efficacy of isotretinoin in HS. **(8)**

Moreover, there are certain patient characteristics that influence a good therapeutic response with isotretinoin in HS,with those with lower weight, female gender, and those associated with acne ***(9).***

Generalized granuloma annulare:

Generalized GA is characterized by widespread annular papules, plaques, and nodules which are particularly recalcitrant to various treatments. There have been many individual case reports demonstrating isotretinoin may improve GA symptoms via its antiproliferative effect and inhibition of collagen synthesis. Several case reports describe the successful use of isotretinoin (in doses of 0.5–1 mg/kg/day, 30–50 mg once daily, or 30–40 mg twice daily for 8–16 weeks) **(10).**

Darier's disease:

A genetic dermatosis, with extensive areas of hyperkeratotic papules and plaques. Case reports and a review article reported improvement with isotretinoin at daily doses of 0.2-0.7 mg/kg **(11).**

The most efficacious dose is typically found between 0.5 and 1.0mg/kg/day. Symptomatic improvement is often reported within 2 to 4 weeks of therapy. Due to the chronic nature of this disorder, a continual low maintenance dose has also been demonstrated that long-term use of isotretinoin with cumulative doses of up to 1075mg/kg did not cause significant radiological abnormalities. However, vigilance is required to avoid complications of long-term isotretinoin therapy **(6).**

Cutaneous lupus erythematosus:

Both isotretinoin and acitretin have been used successfully in patients with various forms of lupus erythematosus (LE). Recurrence of the lesions after completion of the treatment is a limiting factor ***(12).***

Several trials utilizing isotretinoin (0.15 mg/kg/day and then increased to 0.5 mg/kg/day) for cutaneous lupus erythematosus (CLE) demonstrated both clinical improvement and histological improvement in 86.9% of the 24 patients with CLE **(6).**

Isotretinoin of dose 0.2-1 mg/kg/day was indicated as an option for refractory cases of subacute LE, chronic LE, and hyperkeratotic forms. However, adverse events and faster relapse are more frequent, and contra indicated in association of LE and Sjogren's syndrome **(11).**

Condylomata accuminata:

Oral isotretinoin has been implemented in hopes that its immunomodulatory properties might aid in the treatment of this condition. It has been utilized in two forms: monotherapy and in combination with interferon alpha (INFα). The available studies suggest that combination therapy may be a reasonable option in cases of recalcitrant CA **(6).**

Disseminate and recurrent infundibulofolliculitis:

It is a clinical condition characterized clinically by hundreds of skin-coloured follicular papules resembling goose bumps. It may last for months to years and may be pruritic. isotretinoin (0.5 mg/kg/day) for 16 weeks has been tried, but evidence for the efficacy of ISO is anecdotal **(3).**

Acanthosis nigricans:

One study of isotretinoin 3 mg/kg/d leading to clearance of acanthosis nigricans (AN). However reported relapse of lesions on stopping treatment and emphasized importance of maintenance treatment. Another report was of improvement with sustained maintenance of AN lesions on combination therapy of isotretinoin and metformin **(13).**

Lichen planus:

Many studies reported isotretinoin for treating both oral, valvular and cutaneous lichen planus. The dose given here was 0.25-1 mg/kg/day the improvement observed within 2 months without relapses. Systemic isotretinoin at a dose of 0.5-1 mg/kg/day has also been reported to be effective in severe lichen planus involving the oral mucosa and skin, witnessed in several patients **(14).**

Photoaging:

Although topical tretinoin is generally accepted as a cosmetically beneficial medication for photo-damaged skin, oral isotretinoin is not. However, the studies reported that there is a significant cosmetic improvement in wrinkles, thickness and color of the skin, size of pores, skin elasticity, tone, reduction in pigmented lesions and mottled hyperpigmentation with isotretinoin administered at 10–20 mg 3 times a week over 2 months along with rejuvenation cosmetic procedures when compared to using both treatments individually **(6).**

Precancerous Cutaneous Conditions:

Actinic keratosis:

Many studies reported the use of oral isotretinoin (10–20 mg/day) for photodamaged skin, one study reports isotretinoin 20 mg/day combined with topical 5-fuorouracil cream actinic keratosis lesions regressed completely **(14).**

Leukoplakia:

Few encouraging studies involving isotretinoin's use in leukoplakia. That the patients achieved clinical improvements after three months of isotretinoin (1–2mg/kg/day) use. However, many patients experienced significant toxicity and required a dose reduction. Further, more than half of the patients relapsed within three months. In other study induction therapy (1.5mg/kg/day for three months) followed by a low maintenance dose of isotretinoin (0.5mg/kg/day for 9 months) the patients responded effectively. In the low-dose maintenance phase, isotretinoin achieved better relapse free state **(6).**

Cutaneous T-cell lymphoma:

Oral isotretinoin monotherapy for Cutaneous T-cell lymphoma (CTCL) ranged from 0.5 to 2 mg/kg/day, with 1–2 mg/kg/day for 2–3 months being most effecting in lesion clearance, and Combined therapy of isotretinoin (1 mg/kg/day) along with IFN-α have demonstrated a great response in patients with Stage I and Stage II cutaneous T cell lymphoma **(14).**

Squamous cell carcinoma:

The combination of isotretinoin and IFN-α has also proven valuable in squamous cell carcinoma (SCC) of the skin, with success rates ranging from 17% to 68%. Recently other studies reported isotretinoin (1 mg/kg/day) in combination with daily radiotherapy also reported a rapid reduction in tumor size **(6).**

Resistant dermatophytosis:

Recent study used Combination therapy of oral isotretinoin (20 mg/day) with itraconazole (200 mg/day) 6 weeks has demonstrated to be effective with resistant dermatophytosis secondary to Trichophyton (rubrum and mentagrophytes). The patient shows mycological cure and even after 6 month follow up no relapse **(15).**

Erythema dyschromicum perstans:

Erythema dyschromicum perstans (EDP) is a disorder of pigmentation characterized by asymptomatic, symmetrically distributed ashy grey patches. There have been a number of treatments for EDP with minimal success. Several authors have demonstrated the beneficial effects of ISO in EDP. The possible mechanism of isotretinoin here could be based on its anti-inflammatory and immunomodulatory properties **(16).**

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