HIGH AND LOW DOSE ORAL ISOTRETINOIN IN THE TREATMENT OF ACNE VULGARIS

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ABSTRACT:

Background: Acne is the common skin disease in the general population, highly affected in adolescents with an 85% prevalence rate. Due to the chronicity, the disease has a considerable impact on patients’ physical and psychological health. Certain medications may aggravate acne and interact with the prescribed drugs, and a family history of severe acne determines a more protracted course. The duration of the disease, past and present response to therapy, and skin type are factors which guide therapeutic decisions. Grading of acne should be attempted, focusing on the severe lesions present and, on the presence, or psychological scarring. Patients with moderate to severe inflammation acne are also candidate for treatment with oral isotretinoin.

Although isotretinoin is a very effective medication for the treatment of acne, its association with several complications necessitates the precise selection of patients.

I. ACNE VULGARIS

Acne vulgaris affects the adolescents, women more frequently than men (1). It is temporary and can be resolves by the mid-20s but more severe cases take longer and it can persist into adult years in 50% of individuals (2).

The acne has clinical features as seborrhea, non-inflammatory and inflammatory lesions, nodules and cysts comprise sever nodulocystic acne and various degrees of scarring. The distribution of acne corresponds to the highest density of pilosebaceous units which including face, neck, upper chest, shoulders, and back) (3).

Multiple factors contribute to the pathogenesis of acne, all of which give rise to the development of antiacne treatments. (50,51) Among these therapeutic agents, isotretinoin is considered the most effective drug available by suppressing sebaceous gland activity. Although approved by the US Food and Drug Administration for the treatment of nodulocystic acne in 1982, isotretinoin is increasingly encouraged for managing patients with moderate to severe acne. (32,53).

However, there are many cases of acne that are unresponsive to isotretinoin therapy, and it needs to careful use and monitoring because of unwanted side-effects. (53,54) To overcome these things, not only various dose regimens are being introduced but also an effort to develop new alternatives in reducing sebum is being made

II. ISOTRETINOIN

Isotretinoin is termed 13-cis-retinoic acid (13-CRA) and considered a retinoid approved by U.S. Food and Drug Administration for the treatment of severe nodulocystic acne. Isotretinoin exerts its biological action by serving as retinoic acid and/or 9-CRA isomers can efficiently activate retinoic acid receptors (4).

Mechanism of action:

Isotretinoin interferes with the cellular processes as the gene transcription (5). FoxO1 and FoxO3 are p53r target genes for isotretinoin, and there are apoptosis-promoting transcription factors. In a recent RNAseq analysis, Kovács et al. noted that gene expression changes were mostly related to altered growth factors and other differentiation pathways, which has the key role in sebocytes differentiation and not the lipid metabolism (5).
Isotretinoin is the only therapy that impacts on all of the major aetiological factors implicated in acne. It achieves this remarkable efficacy by cellular differentiation, cell survival and apoptosis. With enhancement of targeted genetic expression, isotretinoin has a peripheral biological effect. Isotretinoin also reduces androgen receptor gene expression and reduction of testosterone levels and has antiproliferative effect on stromal cells of the ovary (6). Isotretinoin represents is potent therapeutic agent in treatment of acne (6).

Isotretinoin also has anti-inflammatory effect through suppression of mTORC1 in a subgroup of isotretinoin-responsive patients (7). The anti-inflammatory role of isotretinoin through down regulation of inflammatory driving protein, S100a7a (8). In addition, isotretinoin targeting the Th17 pathway may offer an additional pathway for their therapeutic response (9).

Medical uses:
Isotretinoin is used for cystic acne and acne that has not responded to other treatments. It is not indicated for treatment of prepubertal acne and is not recommended in children less than 12 years of age (10).

A reduction in sebaceous secretion on the face and scalp was observed 3 months later with 10 mg every other day compared to antiseborrheic topical treatment. Cases of seborrhea and seborrheic dermatitis can be treated with therapeutic alternative by a low dose of isotretinoin (0.1 mg kg–1 day–1) as a (11 and 5).

Low-dose isotretinoin (0.3 mg/kg) for 12 weeks was similar to doxycycline for moderate-to-severe grades of rosacea (Gollnick et al., 2010). Low-dose isotretinoin may normalize the exaggerated toll-like receptors (TLR)-2-mediated innate immune response (12). In addition, rademaker observed that even isotretinoin in a very low dose (10 mg three times/week, or 5 mg/day) was a cost-effective therapy for refractory rosacea with significant improvement of ocular variant (13).

Recently, Kwon et al. studied the efficacy of combined therapy of pulsed dye laser and fractional microneedling radiofrequency with maintaining daily administration of low-dose isotretinoin (10 mg/day) for recalcitrant papulopustular rosacea. During administration of isotretinoin, only manageable skin dryness or cheilitis has been observed in 32% of the cases with pigmentation or scarring tendencies. That confirmed the safety of device-based treatments during intake of isotretinoin, and that a low-dose isotretinoin, compared to standard acne dose, is only required to improve papulopustular rosacea (14).

In other comparative study on the ocular changes in patients with moderate-to-severe papulopustular between doxycycline and low-dose isotretinoin, the authors noted that doxycycline was more effective in treating the ocular manifestations of rosacea. No patient experienced any serious ocular complications after administration of low-dose isotretinoin (15).

Olvera-Cortés and Pulido-Díaz (16) reported three patients with Morbihan’s disease, solid persistent facial erythema, and edema, who showed response to 40 mg of isotretinoin and maintained on long-term dose of 20 mg/day, for about 6–12 months with no recurrence. Furthermore, oral isotretinoin was found superior to topical form in treatment of plane warts (17).

Cases with recalcitrant warts at different sites with low-dose isotretinoin (0.1–0.2 mg/ kg/day) for a 3-month course and marked improvement after 1 month of therapy, with favorable improvement of pigmentation and scarring. Interestingly, duration of remission varied from 12 to 36 months (18).

By using a high-dose isotretinoin (1 mg/ kg) daily no significant difference in recurrence rate for treating human papilloma virus infections. However, a sever adverse effects in the form of dryness or cheilitis of the analyzed studies (19).

Oral isotretinoin used in dose of 20 mg (0.25 mg/kg) for the treatment of reticulated papillomatosis lesions daily. After 1 month later, with favorable response of the lesion and related pruritus control was achieved within 4 months (20).
Moreover, oral isotretinoin treatment used in a dose of 30 mg/day (0.46 mg/kg) for patients with lichen amyloidosis. Partial clearance of the rest of the lesions after 1 month and subsequent dyspigmentation obtained by the third month (21).

In addition, isotretinoin was effective in relieving of the fibrotic constriction bands at metacarpophalangeal joints and preventing amputation (22).

There was an improvement in patient with plantar keratoderma at 1-month follow-up; the dose was subsequently reduced by 5 mg every alternate day for a month (9).

Similarly, it has been used with significant response in other acquired in perforating folliculitis and reactive perforating collagenosis (23). Thus, isotretinoin may modulate sebum production, keratinocytes proliferation and differentiation, in addition to its immunomodulating activity, hence its efficacy in KD (13).

Also, patients with erythema dyschromicum perstans who was successfully tried low-dose isotretinoin (20 mg/day) with as response was noted; meanwhile, recurrence was seen when the drug was stopped. During the follow-up, the patient isotretinoin (10 mg/day) not observed any intolerable adverse effects (24).

Isotretinoin used with fractional CO2 laser for the treatment of exogenous ochronosis due to depigmenting cream containing hydroquinone (25). The therapy with retinoids in a low-dose isotretinoin, is suggested for the stabilization of cancerization in the skin field (26).

**Oral isotretinoin in acne:**

In moderate-to-severe papulopustular acne vulgaris treated with isotretinoin in a dose of (0.3 mg kg) in combination with oral azithromycin (500 mg/day) over 3 consecutive days weekly for 1 month, revealed a response to the combination with non-significant relapse post discontinuation (27).

A fixed dose of isotretinoin daily found to be safe in long duration and effective in the management of acne vulgaris in response of moderate-to-severe acne in daily or alternate daily in a dose of 20 mg of isotretinoin for 6 months. Both regimens were effective, but a daily as a fixed dose of 20 mg of isotretinoin was superior than the alternative doses in terms of response (28).

However, systemic therapy of isotretinoin, is not recommended for mild-to-moderate papulopustular acne due to increase the side effects (2).

The low-dose isotretinoin can significantly cause a decrease in the level of serum total testosterone, prolactin, and dihydrotestosterone, but cause an increase dehydroepiandrosterone (DHEA) level which is an important agent in the acne pathogenesis of hyperandrogenic patients. Sprinolactone decreases the level of DHEA increased by using of isotretinoin (29).

In patients with acne vulgaris were given either isotretinoin 20 mg/day or 0.5 mg kg daily for 6 months with no significant difference in relapse rate over a 12-month follow-up period was noted among the two isotretinoin regimens (30).

Using of isotretinoin with systemic corticosteroids due to initiation of lower dose of isotretinoin to minimize the risk of acne (31).

**Safety profile of isotretinoin:**

A good safety profile may persistent reluctance to prescribe the drug. Yet a delay in adequate treatment of acne can lead to physical scarring and affect quality of life – a balance must be struck to avoid undertreatment of this highly prevalent condition (33).

Administration of isotretinoin is commonly associated with hyperlipidemia and hypertriglyceridemia (34) and we can decrease this effect by giving 1 g/day omega-3 for lowering hypertriglyceridemia (35) and regular monitoring of patients with risk factors as obese patients and familial hyperlipidemia (36).

**Adverse effects:**
Isotretinoin may be given in conventional dose 0.5 mg/kg/day or low dose isotretinoin 0.25 mg/kg/day for 6 months (37). In some studies, intermittent fixed dose of 20 mg of isotretinoin is given on alternate day or 0.5–0.75 mg/kg per day, applied for 1 week every 4 weeks for a period of 4-6 months (28). However, this usually associated high incidence of mucocutaneous and systemic side effect including: persistent dryness of lips, lower back pain, headaches, arthralgia and hair loss (38).

Oral isotretinoin has been associated with nonspecific side effects involving various body systems. Side effects of isotretinoin may be categorized as: teratogenic, clinical (cutaneous or extracutaneous), and laboratory findings (39).

Isotretinoin has well known teratogenic effect in patients of childbearing age, skin dryness and erythema are the main factors that often limit the adherence to therapies (40).

Although effective for treating severe acne, isotretinoin is a potent human teratogen. There is an estimated 20%–35% risk for congenital defects in infants exposed to the drug in utero, including craniofacial, cardiovascular, neurological and thymic malformations. About 30%–60% of children exposed to isotretinoin prenatally have been reported to show neurocognitive impairment, even in the absence of physical defects (41).

Many women taking isotretinoin do not monitor for pregnancy before and during treatment. Only 44%–67% of women report taking a pregnancy test before starting isotretinoin therapy, and only about 1 in 5 reports taking a repeated pregnancy test (42).

The gold standard for preventing fetal exposure to isotretinoin relies on the following tenets: the woman’s awareness of the risks; ruling out pregnancy at the start of treatment; the use of 2 forms of contraception in parallel during treatment; monitoring for pregnancy throughout treatment; and avoiding pregnancy until the drug has been cleared from the body (43).

The US Food and Drug Administration (FDA) introduced the retinoid pregnancy prevention program. This program included explaining to women the risk to their unborn babies and obtaining their written agreement to use 2 methods of contraception in parallel, have monthly pregnancy tests and otherwise comply with the program. An evaluation of the program showed that despite 99% of patients recalling being told to avoid pregnancy, 36% failed to receive a pregnancy test before starting treatment (44).

In addition, the multimorphy of reported psychiatric adverse events (depression, suicide, psychosis) is associated with the multiplicity of isotretinoin’s effects on various neurotransmitter systems. Therefore, clinicians should be on the alert for potential psychiatric side effects following treatment with isotretinoin (45).

Long-standing consequences of isotretinoin use leading to development of dry eye symptoms and damaged meibomian glands; thus, treatment options for isotretinoin-associated meibomian gland dysfunction (46).

The association of isotretinoin exposure with prenatal developmental toxicity is well established. (47).

The other problem with oral isotretinoin is it is quite expensive. So, it is recommended in intermittent pulse therapy to make it more cost effective and reduce its side effects (48).

In a study included 150 patients, who were equally divided into group A and group B. Group A was given oral isotretinoin capsule 20 mg twice daily for one week after 3 weeks for 6 months as intermittent/pulse therapy. They included that the efficacy of oral isotretinoin for acne in intermediate/pulse therapy is same. So, we should prefer intermediate/pulse therapy as it is cost effective, there are reduced side effects of drug due to shorter duration and the patient is more complaint (49).

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REFERENCES:


