Journal of Pakistan Association of Dermatologists. 2015;**25 (1)**:1-3.

Editorial

Isotretinoin in acne: how much and for how long?

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The discovery and approval of isotretinoin (ISO) by the US FDA in 1982 revolutionized the treatment of acne. Although, initially approved for the severe refractory nodulocystic acne, ISO is being increasingly off-label used in mild to moderate disease. ISO has been the mainstay of acne treatment for more than three decades, and the cumulative experience suggests that daily dose, duration of therapy and cumulative dose are the three factors important in ISO treatment for acne; but due to inconsistent study designs, classification of acne, follow-up periods and definitions of relapse in different studies, the opinion about the optimum dose of ISO and duration of treatment remains divided.

American, European, Asian, Australian, South African and Pediatrics guidelines for acne recommend ISO as primary or second-order treatment in a dose of 0.5-1 mg/kg per day (higher dose), for 16-32 weeks (cumulative dose of approximately 120-150 mg/kg).[1,2] However, the higher doses are associated with higher degree of mucocutaneous adverse effects.[2] At 1 mg/kg per day, 98% of patients report adverse events, such as eczema, impetigo and photosensitivity, while at doses below 0.25 mg/kg per day, 50% of patients report adverse effects, which are generally less severe.[3]

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To reduce the incidence of side effects and improve patients' compliance, many experts prefer to use lower doses (<0.5mg/kg) of ISO. A dose-ranging study of ISO showed that a low daily dose (0.1mg/kg/day), intermediate daily dose (0.5mg/kg/day), and high daily dose (1mg/kg/day) given over 20 weeks cleared the vast majority of patients by the end of the active treatment course or within 12 weeks post-therapy in all three daily dosage groups.[1,3] This demonstrates that clinical response to ISO is independent of dose (low, intermediate or high). Using 20 mg daily ISO, Plewig *et al.*[4] noted improvement in all pathological parameters of acne i.e. 35-58% reduction of the sebaceous gland size, 90-95% decrease in sebum production, 55-70% reduction of follicular keratinization and 33-73% decrease in *Propionibacterium acnes* growth. Similar effects were observed even at lower doses. The Bestpractice Decision Support Module, New Zealand for prescribing isotretinoin recommends to use ISO in a dose of 10-20mg/day.[5]

However, acne is a chronic disease, which tends to relapse. As evidenced by the clinical data, the duration of remission induced by ISO and need for retrial (need for retreatment), depends on many factors like age when the initial ISO course was given, target cumulative dose, endogenous androgen-excess (i.e. polycystic ovary syndrome), presence/persistence of macrocomedones, presence of sinus tracts, patient adherence.[1]

Long-term follow-up showed that within 18 months of initial course of ISO in three groups i.e. low-dose (0.1mg/kg/day), intermediate dose (0.5mg/kg/day) and high dose (1mg/kg/day), 42%, 20% and 10% patients, respectively required retreatment with ISO.[1] Similarly, 88% of patients treated with either 0.1mg/kg/day or 0.5mg/kg/day required >2 courses of ISO within five years in contrast to only 9.5% patients treated with 1mg/kg/day. This means that relapse rate is higher in those treated with lower doses of ISO.[1]

The clinical data also suggest that duration of remission correlates with the target cumulative dose. There are a few studies which describe successful treatment results with low-dose ISO therapy (mean cumulative total dose of 81 mg/kg) for recalcitrant inflammatory acne, much less than 120mg/kg cumulative total dose, the majority of available evidence suggests that use of low cumulative dose markedly increases the likelihood of acne relapse and need for retreatment.[6] About two-third (65.4%) of 179 patients, followed up for more than three years, experienced recurrence of acne. The risk of acne recurrence was eight-fold greater in patients treated with a cumulative total dose of ISO <100mg/kg as compared to those receiving >100mg/kg. 22.9% requiring at least one additional course of ISO.[1,6] Some researchers used even much higher cumulative dose. Blasiak *et al*.[7] used a cut-off value of 220mg/kg and reported the relapse rate of 47.4% in the lower-dose treatment group (<220mg/kg), compared with 26.9% in the high-dose group (>220mg/kg).

FDA generally recommends a cumulative dose of (>120-150mg). Patient is started ISO in a dose of 0.5mg/kg/day and after one month the dose is escalated to 1mg/kg/day. This dose is continued till the target of cumulative total dose is achieved in five-month period.[1] Completing the course within the maximum FDA-approved duration (20 weeks) offers advantage in women of child-bearing potential by lessening the period of time in which pregnancy exposure to ISO can occur. On the flipside, many practitioners do not follow the concept of cumulative dose; they continue ISO until clearance of acne i.e. no active acne lesions, and then for another three to four months to limit recurrence.[2,3,5] This approach tends to result in a shorter duration of ISO treatment than with most cumulative dosing regimens, while maximizing patient outcomes and minimizing adverse reactions. The Bestpractice Decision Support Module, New Zealand recommends that the dose of ISO should be based on the patient's response to treatment and not on a cumulative dose.[5] They prescribe 10-20mg/day of ISO until there is a resolution of active acne lesions. Treatment dosages can then be halved and continued for a further two to four months. Nevertheless studies with long-term follow-up will be required to authenticate this approach.

Absorption of ISO increases if taken with fatty meals. Isotretinoin-Lidose, a new formulation of ISO, approved by FDA in 2012, has higher bioavailability than that of standard ISO under fasting conditions.[8] FDA recommends twice daily dosing, especially when high dose of ISO is used, as it is associated with improved gastrointestinal absorption of drug and reduced side effects related with maximum plasma concentration.

Summarizing the present day evidence, it appears that the short-term treatment success is not highly dependent on the daily dose of ISO (based on mg/kg) with no significant differences in acne clearance between 0.1mg/kg/day, 0.5mg/kg/day, and 1mg/kg/day (over treatment duration of 20 weeks); however, long-term treatment success is highly dependent on achieving a specific threshold cumulative dose

of 120-150mg/kg. Both the daily dose (based on mg/kg) and the duration of the treatment course need to be coordinated in order to reach the target cumulative dose.[1,2,6]

It seems clinically prudent to start a lower daily dose of ISO e.g. 0.1mg/kg/day, and dose should be gradually (fortnightly) increased to the maximum tolerable limit, titrating the dose according to the clinical response and incidence of severe side effects i.e. xerophthalmia, severe xerosis and/or cheilitis, myalgias etc. If the daily dose is lowered (based on mg/kg), the duration of the treatment would need to be extended for reaching the target cumulative dose.

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