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Oral isotretinoin: intermittent and low-dosage regimen in acne

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Evaluation of: Kaymak Y, Ilter N. The effectiveness of intermittent isotretinoin treatment in mild or moderate acne. *J. Eur. Acad. Dermatol. Venereol.* 20, 1256–1260 (2006).

Acne is a chronic disease of the pilosebaceous follicle that affects primarily adolescents. It can be safely treated today and the physician must be aware of the main possible therapies, avoiding the treatment of discrete acne with strong systemic drugs and of severe acne with only mild local medication. Oral isotretinoin is one drug that is used successfully for some forms of acne but its optimum dose and ideal therapeutic scheme are still under discussion. Kaymak and Ilter present an intermittent and low-dose regimen, which is very interesting since it may decrease the adverse reactions, while maintaining its high efficacy.

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Retinoids are endogenous substances with a vitamin A-like activity. Isotretinoin (13-cis-retinoic acid isomer of all-trans-retinoic acid) is a first-generation retinoid used in the last 30 years to treat a great variety of dermatological diseases, many – acne included – with great success [1]. These oral synthetic retinoids brought hope to individuals with all forms of acne, folliculitis and rosacea, as well as those with photoaging and several other dermatological problems [2,3]. This medication modifies keratin synthesis, keratinocytic proliferation, sebaceous secretion and extracellular matrix components [3,4].

Acne vulgaris is the most common skin disease among adolescents, affecting approximately 85% (peak at 12–18 years of age). In addition, it may affect all ages (~40–50 million individuals each year in the USA alone) but it has its highest prevalence during the second and third decades of life [5]. Although it is considered typically to be a disease of youth, 12% of women and 3% of men will continue to have clinical acne until into their forties [6]. White boys and men have been shown to have more severe nodulocystic acne than black boys and men.

Acne vulgaris is a multifactorial disorder of the pilosebaceous unit and presents several forms, varying from the simple comedonal and papulopustular to the more severe types, such as nodulocystic and fulminans [5]. Genetic control of sebum excretion with modification of the development of clinical lesions by environmental factors influences susceptibility. In the majority of cases, its intensity is mild to moderate and the lesions concentrate on the face, shoulders and anterior and posterior trunk. They vary from simple comedones to papules and pustules, less frequently, nodules and cysts, and even the fulminans form [2,3,5,6].

Many researchers have shown that the initial dose of isotretinoin for the treatment of acne should be 0.1–2 mg/kg/day for 5–6 months, up to a cumulative dose of 120–150 mg per kg of weight [7].

Material, methods & results

Kaymak and Ilter evaluated 60 patients, 34 women and 26 men, between 18 and 33 years of age [8]. These individuals had discrete-to-moderate acne located on the face. Their acne did not respond to or had recurrence with antibiotic therapy and

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topical medications for 6 months. The Leeds scale was used and the authors considered scores less than 1 as mild acne and scores between 1 and 1.5 as moderate acne, according to Burke and Cunliffe [9]. Inflammatory lesions were counted on the forehead, cheeks, chin and neck.

As a treatment regimen, Kaymak and Ilter used isotretinoin in the dosage of 0.5–0.75 mg/kg/day, administered 1 in every 4 weeks for a total of 6 months. Moderate cases received 0.6–0.75 mg/kg/day and mild cases received 0.5 mg/kg/day [8]. Some 41 (68.3%) of the 60 patients completed the treatment. Of these, 25 had moderate acne and 16 had mild acne. The cumulative dose received by the patients was 32.68 ± 5.04 mg/kg. The treatment was well tolerated by all 41 patients and the grade and number of inflammatory lesions decreased significantly at the end of 6 months. A total of 34 patients had complete cure at the end of treatment. The authors did not observe differences related to age and gender in the time to recover and level of response.

Discussion & significance

Kaymak and Ilter agree that oral isotretinoin is the most efficient sebosuppressor and that low doses and intermittent applications are more effective, present fewer side effects and have a better cost–benefit correlation [8]. Nevertheless, they suggest that patients should have a more rigid follow-up since the suggested cumulative dose will not be reached.

Expert commentary & five-year view

Retinoids are considered to be vitamins because they are not synthesized inside the body and can be originated from the diet, but they are also hormones with intracrine activity, in view of the fact that they can be transformed into molecules that bind to cell nuclear receptors where they exert their effect [10,11].

Isotretinoin was approved in the USA in 1982 for the treatment of severe nodulocystic acne and also for discrete-to-moderate acne that evolved with scarring or that was resistant to

other forms of election therapy [3]. The complete clearing of acne lesions is the desire of all patients and the best option for the treatment of moderate-to-severe acne is oral isotretinoin.

Despite the benefit of isotretinoin's therapeutic effects, its adverse reactions require adequate monitoring and an experienced physician. Dreno and colleagues agree that isotretinoin prescription must be made for all severe cases of acne [12], although they emphasize that many prognostic and psychosocial factors must be taken into consideration for the prescription of oral isotretinoin as first-line therapy for discrete and moderate acne. Spontaneous regression usually occurs after 20 years of age, but some patients continue to suffer with acne in the adult phase. The cutaneous lesions of acne are polymorphic and can sometimes leave very severe and disfiguring scars. In addition, periods of exacerbation and stability characterize the disease.

The most common adverse effects of isotretinoin involve the skin, mucus membranes and muscle–skeletal system and are dose dependent. Zane and colleagues found a high incidence of alteration of the blood levels of lipids and transaminases during the treatment of 13,772 patients aged between 13 and 50 years [13].

There is ongoing debate over the optimum dose of oral isotretinoin and the ideal therapeutic scheme and many different regimens have been proposed. Lower doses of 0.5 mg/kg/day present lower frequency of adverse effects and smaller incidence of initial flare-ups [14]. For rejuvenation, some researchers used oral isotretinoin in a dose of 10–20 mg, three-times a week, for 2 months [15,16].

In moderate-to-severe acne, Ghaffarpour and colleagues observed good patient compliance and low incidence of flares with a relatively high initial dose and considered isotretinoin to be beneficial for effective suppression of new lesions in a short time and for prevention of scars [17].

To establish the Brazilian algorithm, acne was divided into three major groups, according to the prevailing type of lesion – comedoneal, papulopustular and nodulocystic – with each one

Key issues

- Despite the benefit of isotretinoin's therapeutical effects, its adverse reactions require adequate monitoring and extensive physician experience.
- Isotretinoin must be prescribed for almost all severe cases of acne. It can also be used for mild and moderate forms but many prognostic and psychosocial factors must be considered for its use as a first-line therapy.
- Many different regimens for the use of oral isotretinoin have been proposed and there is considerable discussion regarding its optimum dose and its ideal therapeutic regimen.
- Kaymak and Ilter state that low doses and intermittent intakes are more effective, present fewer side effects and have a better cost–benefit correlation [9]. Their study presents the possibility of using an intermittent therapy with a smaller total cumulative dose.
- Isotretinoin certainly improves the life of acne patients who, without it, frequently develop physical scarring, psychosocial problems and low self esteem.
- Isotretinoin is an effective and safe drug in the hands of the experienced dermatologist.

subdivided according to intensity into mild, moderate and severe [18]. The Brazilian Acne Group suggested using oral isotretinoin in the severe forms of all three major groups, considering not only the severity of clinical aspects but also the psychological and emotional aspects, which adversely influence the quality of life [19].

Various factors are implicated in the onset of relapses, including age, severity of the disease and cumulative and daily dose of 120 mg/kg/day [14].

It is very important to highlight that isotretinoin is teratogenic and thus is totally contraindicated during pregnancy. Contraception for women of child-bearing age is obligatory 1 month before, during and 1 month after cessation of treatment [3].

This fabulous drug has made a wonderful improvement in the lives of acne patients, completely changing the prospective outcome, which frequently led to physical scarring,

psychosocial problems and low self esteem. It can be prescribed in many ways and dosages with a very good result. Kaymak and Ilter's study provides the possibility of using an intermittent therapy with a smaller total cumulative dose [9].

The physician who administers this drug to acne patients must know how and when to prescribe it, with regards to the quantity, frequency and duration of treatment. Isotretinoin cannot be prescribed by a general practitioner or other specialist who is not a dermatologist. This specialist in skin diseases must have experience with isotretinoin and, after Kaymak and Ilter's results [9], can now use intermittent prescriptions with smaller cumulative doses, which will produce fewer adverse reactions.

We hope that, in the next few years, besides these therapeutic schemes involving smaller but still effective dosages, we can have a safer oral retinoid available with fewer adverse reactions, especially in relation to teratogenesis.

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