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The Truth behind This Undeniable Efficacy – Recurrence Rates and Relapse Risk Factors of Acne Treatment with Oral Isotretinoin

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Since 1979 [1], oral isotretinoin has revolutionized the treatment of severe acne. It is the only drug available that directly suppresses abnormal desquamation of sebaceous follicle epithelium and sebum production, and diminishes the growth of *Propionibacterium acnes* and inflammation [2, 3]. However, despite its undeniable effectiveness isotretinoin is not a curative drug. Its discontinuation may be followed by relapses. Identifying the appropriate acne patient for isotretinoin treatment is nowadays important, since, being no longer patent protected, the compound has already drawn the attention of the European Committee on Proprietary Medicinal Products, which released a European directive to ensure harmonization of isotretinoin treatment throughout the European Union. In addition, both the European guidelines and the currently released iPLEDGE isotretinoin distribution program of the FDA are aimed at preventing the use of the drug in women during pregnancy.

Already in 1982, Goldstein et al. [4] described a partial recovery of sebaceous gland activity 16 weeks after a 16-week treatment of 7 men with severe acne with oral isotretinoin (1 mg/kg/day). In 1983, Jones et al. [5] reported recurrences after a successful treatment of previously unresponsive nodulocystic acne. An association of long-term effectiveness with the isotretinoin dose was first reported by Hennes et al. [6], whereas initial daily doses of 1.0, 0.5 and 0.2 mg/kg were followed by relapses in 4/19, 16/53 and 26/63% of patients 6 and 12 months, respectively, after discontinuation of treatment. On the other hand, Harms et al. [7] reported that younger patients relapsed more frequently than older patients, as also did male compared to female patients. Cunliffe and Norris [8] provided an association of duration of the disease prior to isotretinoin treatment and relapse rates. In addition, they reported that patients with truncal acne fared less well than those with predominantly facial acne. In a 12- to 41-month follow-up study of 172 patients treated with isotretinoin, Chivot and Midoun [9] reported 21% relapses. They added the severity of acne and Goulden et al. [10] the sebum excretion rate as additional factors that influence the percentage of relapses.

In first longitudinal retrospective studies, Lehucher-Ceyrac and Weber-Buisset [11] followed 188 acne patients and Layton et al. [12] 88 patients treated with isotretinoin in doses ranging from 0.5 to 1 mg/kg/day for an average of 9 years. In the first study, 29% of patients needed 2 or 3 courses of isotretinoin to achieve stable remission, whereas 12% of patients, mostly those with microcystic acne and women with endocrinological problems, only experienced partial remissions under treatment. In the second study, 39% of patients relapsed, and 23% of patients needed a second course of isotretinoin to

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achieve a long-term efficacy. Relapses mainly occured in the first 2 years after discontinuation of isotretinoin treatment. The cumulative isotretinoin dose was an important factor in determining the relapse rate. Those patients who received 0.5 mg/kg/day or a cumulative dose of <120 mg/kg had a significantly higher relapse rate than patients receiving a larger dose. In further longitudinal retrospective studies, Shahidullah et al. [13] reported a 5.6% relapse rate in excellent responders at the 6-month follow-up, and Lehucher-Ceyrac et al. [14] estimated rates of relapse at 1, 3 and 5 years of 14, 40 and 48%, respectively. Age and grade of facial acne were the only predictive factors for relapse. With their results Lehucher-Ceyrac et al. disputed the role of the mean daily dose and the cumulative dose of isotretinoin for acne relapses after discontinuation of treatment as reported by Layton et al. [12].

In this issue, Quereux et al. [15] report on a prospective study of efficacy and the first prospective 2-year follow-up study of isotretinoin treatment (0.3–1 mg/kg/day, cumulative dose 108–180 mg/kg/day) in 52 patients with previously unresponsive moderate to severe acne. All patients responded to treatment but only 46% presented complete remission at the end of the treatment. A decrease in seborrhoea occurred in 84% of patients, while sebaceous activity increased in 87% of patients after discontinuation of treatment. The adverse effect rates were similar to those previously reported. After termination of treatment, 52% of patients worsened or relapsed. Multivariate analysis confirmed important seborrhoea after treatment, a high number of superficial inflammatory lesions, young age at treatment initiation and acne on both the face and the body as risk factors for relapse. Additional new risk factors detected were family history, history of prepubertal acne and previous treatment with local tretinoin.

In conclusion, isotretinoin is still the most effective anti-acne drug available; nevertheless, it has lost a little bit of its magic.

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