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Report

Making sense of the effects of the cumulative dose of isotretinoin in acne vulgaris

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Abstract

Background The importance of the cumulative dose of isotretinoin with respect to relapse of acne vulgaris remains controversial. Although guidelines recommend 0.5–1.0 mg/kg/d to a minimum cumulative dose of 120 mg/kg, there has been a trend toward the use of lower daily dosages with no reference to cumulative dose.

Objectives This study aimed to determine the influence of daily and cumulative dosage on relapse in acne.

Methods Charts of patients with acne treated with isotretinoin were reviewed. Demographic details and daily cumulative doses and duration were compared between patients who received one course and two or more courses, respectively.

Results Of 1453 patients, 326 (22.4%) received a second course of treatment (study population). The remainder served as controls (n = 1127). Dosage varied from 10 mg/week to 1.1 mg/kg/d, cumulative dosage from 1 to >300 mg/kg, and duration of treatment from 8 weeks to 5 years. Compared with controls, patients who received a second course were more likely to be women (61 vs. 47%; $P < 0.001$) and received higher daily (0.71 vs. 0.58 mg/kg/d; $P < 0.001$) and cumulative (126 vs. 101 mg/kg; $P < 0.001$) doses. Patients treated with very low doses (e.g. 10 mg three times per week) and/or low cumulative doses (e.g. 25–50 mg/kg) did not relapse more often than controls.

Conclusions Neither daily nor cumulative dosages influenced relapse of acne vulgaris in patients treated with varying doses of isotretinoin as long as treatment was continued for ≥2 months after the acne had completely resolved.

Introduction

There is no doubt that isotretinoin (13-*cis*-retinoic acid) revolutionized the management of acne vulgaris when it was introduced in the 1980s as it was the first anti-acne drug to modify the disease, rather than to provide only symptom control.[1,2] In most medical jurisdictions, it is indicated for severe forms of acne vulgaris resistant to conventional therapy, particularly cystic acne and acne conglobata, and especially when the lesions involve the trunk. The recommended dose is 0.5–1.0 mg/kg/d over 12–16 weeks, with a suggested cumulative dose of 120 mg/kg, as this is stated to increase remission rates and prevent relapse.[3,4] Higher doses of up to 2 mg/kg/d are used in some countries.

The recommendation for cumulative dose has been derived from a number of small trials showing higher relapse rates in patients given a lower dosage and/or expert opinion.[5–9] Most of these studies used a fixed treatment period of 4–5 months and were not primarily designed to assess the role of cumulative dose in relapse.

There has been a trend toward individualizing doses of isotretinoin with the primary goal of completely clearing the patient's acne and keeping it clear for a number of months. This has led to lower daily doses of isotretinoin administered over longer periods.[10,11] However, it is not known how this change in dosaging affects relapse.

Materials and Methods

Patients

This study represents a retrospective chart review of clinical responses in patients started on isotretinoin over a 6-year period. All patients were seen in a private practice setting by a single specialist (consultant) dermatologist. Demographic details, medical history, body weight, and diagnosis were recorded. Details of the dose of isotretinoin used, concomitant medications, adverse effects, and outcome were prospectively collected at each visit. During the study period, isotretinoin was only available through a dermatologist prescription; follow-up data for patients who changed to another local dermatologist, or to the public health system, were obtained.

Patients who received two or more courses of isotretinoin were designated as the study population. Those who received only one course of isotretinoin were designated as the control group.

Isotretinoin dosage

Initially most patients received 1 mg/kg/d to a cumulative dose of 150 mg/kg over five months. However, at the mid-point of the review period, the dosing and duration of treatment with isotretinoin were increasingly tailored to the individual patient's needs and preferences, such that by the end of the review period, the most commonly prescribed dosage was 10–20 mg/d continued for 12 months, irrespective of body weight or cumulative dose. Other dosing regimens included 10–20 mg administered one to three times per week and a pulsed dosing of 20–60 mg/d for one week each month. All patients were seen at 2–3 months after the initiation of treatment; subsequent follow-ups were extended to 4–6 months, particularly for patients on lower dosages of isotretinoin. Treatment was generally continued until the patient had attended two consecutive follow-up appointments with no findings of active acne lesions; however, patients were allowed to discontinue treatment at any stage.

Patients were offered treatment with isotretinoin if they had severe acne, defined as acne of Leeds grade[12] 4 or greater, moderate acne (Leeds grades 1.5–4.0) that had not responded to six months of systemic antibiotics with or without hormonal therapy, or mild acne (Leeds grade < 1.5) that had not responded to 12 months of topical benzoyl peroxide/retinoid with or without systemic antibiotics or hormonal therapy.

Acne relapse

Relapse of acne was defined by the need to start a second course of isotretinoin for whatever reason. In most cases, this was at the patient's request. In the majority of patients requesting a subsequent course of isotretinoin, the acne grade was lower than the acne grade at the time of initiation of the first course of treatment.

Analysis

For the purpose of analysis, patients were categorized into four groups according to the dosage of isotretinoin administered: very low (<0.25 mg/kg/d); low (0.25–0.50 mg/kg/d); medium (0.51–0.75 mg/kg/d); and high (>0.75 mg/kg/d). The daily dosage in patients who took isotretinoin two or three times per week was calculated by dividing the cumulative weekly dose by seven days (i.e. a patient on a treatment regimen of 20 mg administered three times per week was calculated to be on a dose of 8.6 mg/d: [3 × 20 mg]/7 = 8.6 mg). In addition, the following cumulative dose groupings were used: 0–25; 26–50; 51–75; 76–100; 101–125; 126–150; and >150 mg/kg. Time to relapse was calculated from the planned end of treatment of the previous course to the start of the next course, rather than the time of recurrence of any acne. Data were analyzed using Student's paired *t*-test and/or Wilcoxon's signed-rank test. Data are presented as the mean ± standard deviation.

Ethics committee approval was not required because this was a non-identifiable review of clinical practice.

Results

Data for a minimum of 12 months follow-up (range: 12 months to 5 years) were available for 1453 patients started on isotretinoin. Daily dosages varied from 10 mg/week to 1.1 mg/kg/d, cumulative doses from 1 to >300 mg/kg, and duration of treatment from 8 weeks to 5 years. Of these 1453 patients, 326 (22.4%) received two or more courses of treatment and represent the study population. Those who received only one course of treatment serve as controls ($n = 1127$). A small number of patients may have moved out of the region and received a subsequent undocumented course of isotretinoin (estimated at no more than 1–2% of the control group).

Controls and study patients were well matched for age and initial severity of acne, as well as for duration of treatment. Table 1 summarizes basic demographics,

Table 1 Demographics, dose, daily dose/kg, duration of treatment and cumulative dose in all patients, control patients who received only one course, and in the first course of treatment in study patients who received two or more courses of isotretinoin for acne vulgaris

	Patients, *n*	Age, years Mean ± SD	Female *n* (%)	Duration, weeks Mean ± SD	Dose, mg Mean ± SD	Daily dose, mg/kg Mean ± SD	Cumulative dose, mg/kg Mean ± SD
All patients	1453	22.4 ± 9.0	732 (50.4)	30.0 ± 19.6	44.2 ± 19.8	0.66 ± 0.32	106.6 ± 57.5
Control group (one course only)	1127	22.5 ± 9.1	533 (47.3)	27.9 ± 21.1	42.7 ± 20.1	0.58 ± 0.32	100.7 ± 57.6
Study group (first course)	326	22.0 ± 8.9 NS	199 (61.0)[a]	28.3 ± 13.7 NS	49.2 ± 17.9[a]	0.71 ± 0.30[a]	125.7 ± 52.8[a]

[a] $P < 0.0001$.
NS, not significant; SD, standard deviation.

duration of treatment (in weeks), daily average dose, daily dose/kg body weight and cumulative dose in, respectively, all 1453 patients, the 1127 control patients, and for the first course of treatment in the 326 study patients who received more than one course.

Compared with control patients who received a single course of treatment, patients who received a second course of isotretinoin were more likely to be women ($P < 0.0001$) and to have received a larger daily dose (0.71 vs. 0.58 mg/kg/d; $P < 0.0001$) and greater cumulative dose (125.7 vs. 100.7 mg/kg; $P < 0.0001$) on their first course.

Table 2 describes the basic data for subsequent isotretinoin courses for recurrence. Patients tended to receive smaller daily doses for longer periods, reflecting less severe acne.

Table 3 shows the effect of gender. Men were younger, weighed more, and received a larger daily dose and cumulative dose. They were treated for shorter periods of time than women. Men were less likely to have received a second course of treatment (17.5 vs. 27.2%; $P < 0.001$).

Table 4 shows the effect of daily dose/kg on relapse rate. Table 5 illustrates the effect of cumulative dose. Patients who received a larger daily dose or greater cumulative dose were more likely to subsequently receive a second course of isotretinoin.

Most patients were treated until the skin was completely clear. Table 6 shows outcomes (clear, excellent, moderate improvement, stopped because of adverse events) by course of treatment. Patients who received more than one course were less likely to stop because of

Table 2 Patient demographics, dose, daily dose/kg, duration of treatment and cumulative dose in subsequent courses of isotretinoin in patients with acne vulgaris

	Patients, *n* (%)	Age, years Mean ± SD	Female *n* (%)	Duration, weeks Mean ± SD	Dose, mg Mean ± SD	Daily dose, mg/kg Mean ± SD	Cumulative dose, mg/kg Mean ± SD
Course 1	1453	22.4 ± 9.0	732 (50.4)	30.0 ± 19.6	44.2 ± 19.8	0.66 ± 0.32	106.6 ± 57.5
Course 2	326 (22.4)	23.6 ± 9.1	199 (61.0)	37.2 ± 37.3	39.2 ± 20.0	0.44 ± 0.34	87.8 ± 60.0
Course 3	89 (6.1)	23.4 ± 8.2	57 (64.0)	44.4 ± 25.7	36.4 ± 20.8	0.33 ± 0.29	82.9 ± 53.6
Courses 4 + 5	21 (1.4)	20.5 ± 3.9	10 (47.6)	49.0 ± 31.0	27.7 ± 16.0	0.35 ± 0.27	105.3 ± 92.0

SD, standard deviation.

Table 3 Dose, daily dose/kg, duration of treatment and cumulative dose by gender in patients ($n = 1453$) treated with isotretinoin for acne vulgaris

	Patients, *n*	Age, years Mean ± SD	Weight, kg Mean ± SD	More than one course *n* (%)	Duration, weeks	Dose, mg	Daily dose, mg/kg	Cumulative dose, mg/kg
Male	721	20.4 ± 8.1	72.0 ± 10.1	127 (17.6)	25.9	49.1	0.68	116.7
Female	732	24.4 ± 9.5	64.7 ± 7.8	199[a] (27.2)	30.0	39.6	0.54	96.7

[a] $P < 0.001$.
SD, standard deviation.

Table 4 Daily dose (mg/kg/d) in patients who received one course of treatment ($n = 1127$) and in the first course of treatment in patients who received two or more courses ($n = 326$) of isotretinoin for acne vulgaris

Dosage, mg/kg				
Very low (0–25)	Low (26–50)	Medium (51–75)	High (>75)	Patients, *n*
Control group (one course only), *n* (%)				
196 (17.4)	373 (33.1)	112 (9.9)	446 (39.6)	1127 (100)
Study group (first course), *n* (%)				
38 (11.7)	72 (22.1)	21 (6.4)	195 (59.8)	326 (100)
All patients, *n*				
234	445	133	641	1453

Table 5 Cumulative dose (mg/kg) in patients who received one course of treatment ($n = 1127$) and in the first course of treatment in patients who received two or more courses ($n = 326$) of isotretinoin for acne vulgaris

Dosage, mg/kg							
<25	26–50	51–75	76–100	101–125	126–150	>150	Patients, *n*
Control group (one course only), *n* (%)							
103 (9.1)	165 (14.6)	167 (14.8)	163 (14.5)	97 (8.6)	149 (13.2)	283 (25.1)	1127 (100)
Study group (first course), *n* (%)							
5 (1.5)	22 (6.7)	39 (12.0)	48 (14.7)	25 (7.7)	61 (18.7)	126 (38.7)	326 (100)
All patients, *n*							
108	187	206	211	122	210	409	1453

adverse events but were also less likely to achieve the complete clearance of acne.

Table 7 shows the time (in weeks) between the end of the first course and start of the second course of isotretinoin, by cumulative dose (in 50-mg/kg groups). As the cumulative dose increased, so did the time to relapse.

Discussion

This study suffers from the methodological problems imposed by its status as a retrospective review of a dynamic clinical practice. Not only did the isotretinoin dosage and duration change over the study period, but the severity of disease and prerequisite treatments also changed; both decreased. However, the fact that the study includes a large number of patients and was conducted by a single clinician observer mitigates these issues to a certain extent.

A key concept to keep in mind whilst interpreting this study is that each patient's treatment was individualized and continued until his or her acne had cleared. Patients rarely received a fixed dose for a fixed period of time as would be expected in a clinical trial; dose adjustments were the norm and mostly entailed a reduction in daily dose, although some doses were increased. A small number of patients with very inflammatory or severe acne will have received adjuvant treatment of 1–2 months of systemic steroids and/or 2–4 months of trimethoprim with their first course of isotretinoin.

The second issue of bearing is that isotretinoin was usually restarted at the patient's request; this means that a patient's experience of the first course of treatment will have been a significant factor in his or her decision making, and therefore patients who had received a high daily dose (1 mg/kg/d), with significant mucocutaneous adverse effects, may have been reluctant to request a second course of treatment. It is also likely that female patients had a lower threshold for requesting a second course of isotretinoin, although this should not matter because it is the patient's perception that is most relevant.

A third issue to consider is the effect of time. Acne is a chronic skin disorder, and relapse rates increase with time from the last treatment.[13] Therefore, some of these results may be artefactual because patients treated in the earlier phase of the review period will have had a longer opportunity to relapse, irrespective of daily or cumulative dose. Therefore, although these earlier patients mostly received larger daily (and cumulative) dosages, their higher relapse rate may be more closely related to their length of follow-up than to the particulars of their treatment regimen.

These comments accepted, the results show that patients who received a second course of treatment were

Table 6 Acne clearance by number of courses of isotretinoin in patients treated for acne vulgaris

	Clear (%)	Excellent (%)	Moderate (%)	Stopped (%)
Control group (one course only)	96.3	1.8	0.5	1.3
Study group				
Course 1	95.5	2.6	1.3	0.6
Course 2	95.4	2.8	0.7	0.1
Course 3	96.2	3.8	0	0
Course 4	84.2	15.8	0	0
All patients	96.1	2.0	0.7	1.1

Table 7 Time from the end of the first course to the start of the second course of treatment in patients ($n = 326$) treated with isotretinoin for acne vulgaris (in 50-mg/kg cumulative dose increments)

Cumulative dose, mg/kg	Patients, *n*	Time to second course, weeks
0–50	29	41.4
51–100	91	46.3
101–150	83	74.8
151–200	96	70.2
>200	27	81.7

more likely to be women, and had received a larger daily dose (0.71 vs. 0.58 mg/kg/d) and a greater cumulative dose (126 vs. 101 mg/kg).

Although isotretinoin is a very effective drug for acne, both primary and secondary failure do occur. Primary failure refers to the incomplete clearance of acne during treatment. Although many consider daily dose important in rates of clearance of acne, most studies do not show a dose effect in the 0.1–1.0 mg/kg/d range.[2,14–17] Clinical experience also indicates that duration of treatment is more important than daily dose. Essentially, treatment should be continued until the acne has totally cleared, which in macro-comedonal disease may take as long as 12–18 months.

The secondary failure of isotretinoin is marked by the relapse of acne that had initially cleared completely. Unfortunately there is no clear definition of what constitutes relapse: recurrence of any acne, return to pre-isotretinoin acne grade, or a patient's request for a second course of isotretinoin have all been used. In addition, no timeframe for relapse has been established: should a recurrence of acne at 2–3 years after a course of isotretinoin be considered equal to a recurrence within 2–3 months?

The decision to use isotretinoin a second time is complex and is affected by a number of factors, including national regulations, patient expectation, the severity of acne, and the adverse effects suffered during the first course of treatment, as well as financial considerations.

One of the first reports of relapse after isotretinoin was published as a letter by Jones and Cunliffe in the *British Journal of Dermatology*.[5] In this letter, the authors document that doses of 0.1, 0.5, and 1.0 mg/kg/day for 16 weeks were equally effective in clearing acne, but that the rate of relapse at 88 weeks post-treatment was higher in the lower dose groups (77, 50, and 42%, respectively).[5]

In a study by Layton *et al.*,[6] 88 patients treated with 0.5–1.0 mg/kg for an average of four months were followed for 10 years; 23% required a second course of isotretinoin. Relapse occurred within three years. Of patients who received 0.5 mg/kg/d, 39% relapsed, whereas only 22% of patients treated with 1.0 mg/kg/d did so.[6] In addition, 82% of those who received a cumulative dose of <120 mg/kg relapsed, whereas only 30% of patients who received a cumulative dose of >120 mg/kg did so.[6] In the same year, Stainforth *et al.*[7] reviewed 299 patients treated with isotretinoin 5–10 years previously. Of these, 23% required repeat courses of treatment; 17% had two courses, 5% had three courses, and 1% had four or five courses. Factors contributing to the need for further courses of treatment included lower dose regimens (0.1 and 0.5 mg/kg), the presence of severe acne, being a woman over the age of 25 years at the onset of therapy, and having a prolonged history of acne.[7]

A study by Lehucher-Ceyrac *et al.*,[8] conducted on 237 patients, suggested that, overall, the maximum effect was achieved with a cumulative dose of 110 mg/kg of isotretinoin, with a threshold dose of 150 mg/kg beyond which increased therapeutic benefit was not achieved. However, in one of the few prospective studies,[9] relapse after isotretinoin occurred in 27 of 52 patients, although all of them had received >120 mg/kg (mean cumulative dose: 137 mg/kg; range: 108–180 mg/kg). The mean daily dose was 0.73 mg/kg (0.36–1.00 mg/kg). In multivariate analysis, the factors significantly increasing the risk for relapse were severe seborrhea and a high score for inflammatory lesions at the end of treatment, young age, a family history of acne, prepubertal acne, and acne extending to the trunk.[9] Interestingly, in this cohort the daily dose expressed per unit of weight had no influence on therapeutic response or on the frequency of relapse.[9]

In a study assessing the importance of heredity,[18] a statistically significant difference was shown between patients with and without a family history of acne with respect to the likelihood of relapsing after a course of isotretinoin (50 vs. 23%; $P = 0.027$). Two or three courses of isotretinoin were usually necessary in patients with a strong family history of acne.

In one of the largest prospective studies, although open and non-comparative, 638 patients with moderate papulopustular acne treated with a fixed dose of isotretinoin (20 mg/d) were reviewed.[10] These patients were treated for six months and followed over periods of up to four years. Although patients received a mean cumulative dose of 70 mg/kg, relapse over a 4-year period was surprisingly low at 3.9 and 5.9% in patients aged <20 years and 21–35 years, respectively.[10]

These studies suggest that prepubertal acne, young age at the time of isotretinoin initiation, acne in women aged >25 years, a strong family history of acne, localization on the trunk, excessive seborrhea, and the presence of a high number of inflammatory lesions at the end of treatment are all independent prognostic factors for relapse, more so than cumulative dose.

A significant criticism of all of these studies refers to the fact that although they compared two or more dosages, they used the same fixed treatment period. Physiologically, cumulative dose does not really, in itself, explain the outcome, whereas the degree and length of suppression of sebaceous gland activity are of greater relevance. We now appreciate that isotretinoin causes apoptosis of sebaceous gland stem cells, probably in a dose-dependent fashion.[19] After treatment at a dose of 1 mg/kg/d, sebaceous glands may take many months to recover, whereas a dosage of 0.1 mg/kg/d may cause little apoptosis of stem cells, and therefore sebaceous gland recovery will be much quicker. Therefore, a 4-month

course at 1 mg/kg/d and an 8-month course at 0.1 mg/kg/d will have similar effects on sebaceous gland activity.

We need to recognize that acne is a chronic disease with a prolonged time-course.[20] To expect a cure is highly optimistic, particularly over a period of 4–5 months. This study, although subject to methodological criticism, indicates that individualized dosaging of isotretinoin obviates the need to target cumulative dose as an endpoint. Lower daily dosages of isotretinoin, over a longer period, result in significantly fewer adverse effects[21,22] but do not reduce the clinical effect. As most isotretinoin adverse effects are dose-dependent, a lower dose (e.g. 0.1 mg/kg/d) is much safer. However, the prolonging of treatment duration should be carefully balanced against the potential increase in risk for teratogenicity in women.

This study does not present definitive answers to questions of cumulative dose and relapse. This would require a very large study comparing outcomes of treatment at 1 mg/kg/d for a fixed period of 4–5 months against those of individualized dosaging (e.g. 5–10 mg/d) continued until the acne was clear and then for a further four months, with a 5-year follow-up. Unfortunately, this is unlikely now to occur. What this study does confirm is that tailoring patient dosage to the needs of the individual, with a consequently lower than recommended cumulative dose, does not result in an increase in relapse rate.

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