ORIGINAL ARTICLE

Low-cumulative dose isotretinoin treatment in mild-to-moderate acne: efficacy in achieving stable remission

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Abstract

Background Aimed at the reduction of post-treatment relapse of severe acne, the cumulative dose of oral isotretinoin should be ≥120 mg/kg. However, data on the appropriate oral isotretinoin treatment regimen in mild and moderate acne are lacking.

Objective The purpose of this study was to determine the efficacy of an isotretinoin-sparing protocol in inducing permanent remission of mild and moderate acne.

Methods In this open, prospective, non-comparative study, 150 patients affected with mild-to-moderate acne were treated with isotretinoin until complete recovery and for a further month of treatment, independent of the total cumulative dose reached. Patients then underwent a 1-year maintenance therapy with adapalene 0.1% cream. Patients were followed up for a further year, without any treatment.

Results A total of 139 patients completed the study. Overall, patients received a mean of 80.92 mg/kg cumulative dose of isotretinoin. In the 2-year follow-up, relapse only appeared in 13 patients (9.35%).

Conclusion Comparing our findings with published data, this isotretinoin-sparing regimen was shown to be effective in inducing stable remission and preventing acne relapses in patients with mild-to-moderate acne. Low-cumulative dose regimens may potentially lead to a lower incidence of side-effects and to lower costs than higher doses.

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Keywords

low-dose therapy, mild and moderate acne, oral isotretinoin, relapse

Conflict of interest

None declared.

Financial disclosure

None.

Oral isotretinoin (13-cis-retinoic acid) is indicated to treat severe acne unresponsive to other therapies. It is the only drug currently available that affects each of the pathogenic factors involved in acne, which explains its near universal efficacy during acne treatment. Moreover, oral isotretinoin leads to prolonged remission that may be permanent.

The recommended daily dose is 0.5–1 mg/kg of body weight.[1] In a previous observational study, we found that starting with daily doses ≤0.2 mg/kg may reduce the occurrence of acute acne flares during the first month of isotretinoin administration.[2]

Treatment of severe forms of acne should be continued until a cumulative dose of 120–150 mg/kg is achieved, as doses <120 mg/kg are associated with increased rates of post-treatment relapses.[3,4] Total doses >150 mg/kg are not of further therapeutic benefit.

Although it is remarkably effective, oral isotretinoin therapy is associated with numerous adverse effects, which are usually dose dependent.[5] Because of the side-effects and the necessity of long-term use of this drug, patients can have difficulty in complying with the treatment.

In clinical practice, oral isotretinoin is being increasingly prescribed in patients with less severe disease who have responded unsatisfactorily to conventional therapies, such as long-term antibiotics. In our experience, it is common to observe patients with mild-to-moderate acne who achieve a complete healing of the disease with a total cumulative dose of isotretinoin even much lower

than the classical recommended ones. In similar cases, one could doubt if reaching a cumulative dose of 120–150 mg/kg is really necessary in order to prevent relapse after isotretinoin discontinuation.

The aim of this observational study was to assess the effectiveness of an isotretinoin-sparing treatment protocol in inducing stable remission of mild-to-moderate acne. It was of particular interest to evaluate the incidence of acne relapse after a single course of oral isotretinoin followed by a maintenance therapy with a topical retinoid.

Material and methods

This was an open, prospective, non-comparative study consisting of 150 patients with mild or moderate acne treated with oral isotretinoin administered with a drug-sparing alternative treatment regimen. Only acne patients with a chronic clinical course who had not responded to previous conventional antibiotic therapy or who had relapsed after discontinuation of antibiotic treatment were included in the study. Leeds grading scale was used during dermatological assessment to grade acne severity.[6] Patients with a Leeds score <0.5 on the face, back or chest (corresponding to <10 comedones, <10 papules and pustules, no nodular or cystic lesions per each area)[7] were considered to have mild acne and those with scores between 0.5 and 3 (<20 comedones, 10–50 papules and pustules, no nodular or cystic lesions per each area)[7] moderate acne. Based on the number of anatomical sites involved by acne (face, back and chest), at the outset patients were divided in three groups: patients with one, two or three involved areas.

Liver function tests and lipid profiles were evaluated for all patients before treatment initiation and at 6 weeks after the beginning of treatment, and repeated again if needed. Pregnancy tests were carried out before treatment in female patients of child-bearing potential and oral contraception was started before and continued during the treatment period and 4 weeks' post-therapy.

Acne patients were treated with oral isotretinoin, receiving an initial daily dose ≤0.2 mg/kg, in order to reduce the potential for acne flare occurrence, as previously shown.[2] The dosage was subsequently increased by 5 mg every 2 weeks, until the highest dose tolerated was reached. All patients were treated until complete acne clearing, and for a further month of treatment. Decrease of the acne grade to 0.1 and disappearance of all lesions was regarded as complete healing. Then, oral isotretinoin was discontinued independently of the total cumulative dose reached. This protocol was formulated arbitrarily on the basis of our clinical experience. According to currently available guidelines, after isotretinoin withdrawal, patients were treated with a topical retinoid, adapalene 0.1% cream, once-daily for 12 months to maintain acne remission and prevent new lesions.[1] Patients were followed up for another 1-year period, without any treatment.

During isotretinoin treatment, the following data were monthly assessed: (i) acne severity using the Leeds grading system; (ii) clinical side-effects; and (iii) patient satisfaction with the outcome of care. During the 2-year follow-up period, the patients were examined clinically for acne severity every 3 months. Adverse skin events due to adapalene were also recorded. Across the periods, all the patients were assessed by the same physician each time. Patients were required to contact our department in case of self-assessed acne deterioration. If this was the case, a visit was scheduled to calculate acne grade.

A 'relapse' was defined as the emergence of acne ≥0.5 grade severity and/or requiring a systemic treatment. Patients were followed up over a period of 2 years, as relapse is most common within the first year after isotretinoin therapy; relapse after 3 years is relatively uncommon.[8]

Results

Of the 150 patients enrolled, 11 dropped out as they did not come to follow-up after completing isotretinoin therapy, and 139 (60 male, 79 female patients, mean age 20.62 years) completed the study. Twenty-four (17.27%) had mild acne and 115 (82.73%) had moderate acne. Fifty-five (39.57%) patients had only one area involved by acne, 36 (25.90%) had two involved areas, and in 48 (34.53%) patients acne affected three body sites (face, back and chest). In no patient was the treatment discontinued due to drug-related side-effects or abnormality in laboratory values. Adapalene 0.1% cream was generally well tolerated and none of the subjects complained about significant local adverse events.

The mean cumulative dose received by the patients was 80.92 mg/kg (range 18–168, SD = 29.88). Demographics and clinical features of the patients who completed the study are reported in Table 1.

In the 2-year follow-up, relapse appeared in 13 patients (four male and nine female, mean age 18.77 years), which corresponds to 9.35% of the population who completed the study. Demographics

Table 1 Demographics and clinical data of acne patients

Patients (%)	Gender		Acne severity		Number of involved body areas			Total cumulative dose (mg/kg)		
	Male (%)	Female (%)	Mild (%)	Moderate (%)	1 (%)	2 (%)	3 (%)	Mean (min–max, SD)	<120 (%)	≥120 (%)
139 (100)	60 (43.17)	79 (56.83)	24 (17.27)	115 (82.73)	55 (39.57)	36 (25.9)	48 (34.53)	80,92 (18–168, 29.88)	124 (89.21)	15 (10.79)

SD, Standard deviation.

and clinical data of non-relapsing and relapsing patients are compared in Table 2. These data were analysed by means of the binary logistic regression test. Neither demographics, age ($P = 0.18$) and gender ($P = 0.99$), nor clinical features, acne grade ($P = 0.99$) and isotretinoin total cumulative dose ($P = 0.27$), were found to significantly relate to acne relapse in our population. Moreover, we divided the enrolled patients into four groups on the basis of total cumulative dose reached at the end of treatment: < 40 mg/kg (10 patients, two relapsing), 40–79 mg/kg (62 patients, seven relapsing), 80–119 mg/kg (52 patients, three relapsing), ≥120 mg/kg (15 patients, one relapsing). There was no statistically significant difference of acne relapse between the four groups according to the chi-squared test.

Fifteen patients (10.79%) reached a cumulative dose ≥120 mg/kg (Table 3). In 60% of these patients, acne affected the three body sites (face, back and chest). Among these subjects, one patient relapsed (6.67%). The rate of relapse in patients reaching a cumulative dose ≥120 mg/kg was compared with that in patients reaching a cumulative dose <120 mg/kg with a Fisher's exact test, and results showed no statistical significance ($P = 0.58$).

Discussion

It is well known that the severity of isotretinoin-induced side-effects is dose related.[5] In this respect, lower daily and cumulative doses represent a major therapeutic advance, as they reduce the risk and severity of side-effects and increase patient compliance. Duration of treatment may represent a further disadvantage for patients. Prolonged treatment could extend the window of opportunity for side-effects to appear or the development of pregnancy. In view of the potentially serious dose-dependent side-effects of conventional isotretinoin treatments, several low-dose regimens have been formulated.[9–15]

In our clinical experience, patients affected with mild-to-moderate acne treated with oral isotretinoin achieve complete healing at even much lower cumulative doses than those recommended for severe forms (≥120 mg/kg). In the light of this fact, we studied the efficacy of an isotretinoin-sparing protocol in inducing stable remission of mild and moderate acne. The chief aim of our study was to assess acne recurrence rate after an alternative application protocol, and to compare our findings with published data. The treatment regimen consisted of isotretinoin administered until complete acne recovery and for a further month of treatment. Afterwards, isotretinoin was discontinued independent of the cumulative dosage achieved. A maintenance therapy with adapalene 0.1% cream once a day was scheduled for 1 year; patients were followed-up for a further 12-month period, without any treatment. As most relapses occur within the first 18 months after discontinuing isotretinoin, we considered a 2-year follow-up to be adequate for an accurate detection of relapses. During this period, clinical evaluations and acne severity grading were regularly performed at three-monthly intervals, and at any additional time in case of need, in order to assess recurrences.

Table 2 Comparison of demographics and clinical data between relapsing and non-relapsing patients

	Number of patients (%)	Gender		Acne severity		Number of involved body areas			Total cumulative dose (mg/kg)		
		Male (%)	Female (%)	Mild (%)	Moderate (%)	1 (%)	2 (%)	3 (%)	Mean (min–max, SD)	<120 (%)	≥120 (%)
Non-relapsing patients	126 (100)	56 (44.44)	70 (55.56)	23 (18.25)	103 (81.75)	50 (39.68)	32 (25.40)	44 (34.92)	81,87 (18–168, 29.56)	112 (88–89)	14 (11.11)
Relapsing patients	13 (100)	4 (30.77)	9 (69.23)	1 (7.69)	12 (92.31)	5 (38.46)	4 (30.77)	4 (30.77)	71,79 (22.1–145, 32.63)	12 (92.31)	1 (7.69)

SD, Standard deviation.

Table 3 Demographics and clinical data of patients reaching an oral isotretinoin cumulative dose ≥120 mg/kg

Patients (%)	Gender		Acne severity		Number of involved body areas			Total cumulative dose (mg/kg)
	Male (%)	Female (%)	Mild (%)	Moderate (%)	1 (%)	2 (%)	3 (%)	Mean (min–max, SD)
15 (100)	6 (40)	9 (60)	2 (13.33)	13 (86.67)	4 (26.67)	2 (13.33)	9 (60)	137.07 (120–168, 14.43)

SD, Standard deviation.

The mean cumulative dose in our study was 80.92 mg/kg (range 18–168, SD 29.88), which resulted much lower than the dosages recommended for severe acne. Among 139 mild and moderate acne patients who completed the study, only 13 (9.35%) relapsed over the 2-year follow-up.

In literature, patients treated with isotretinoin have shown a post-treatment recurrence rate ranging from 5.6% to 82%.[16–24] There are several possible explanations for this large discrepancy between published reports, such as small sample sizes and short follow-up periods, which might underestimate relapse rate. Moreover, relapse was not defined consistently across the different studies. In a recent population-based cohort of 17351 first-time isotretinoin users, 41% of the cohort experienced an acne relapse necessitating further treatment with an antiacne medication.[25] Among the variables that seem to have impact on the incidence of acne relapse, short-term treatments and low-cumulative doses have been found to predispose to post-treatment recurrence. Various reports have shown that a cumulative dose of greater than 120 mg/kg is associated with significantly better long-term remission than a lower dose.

In spite of these findings, although most of our population received a low-cumulative dose of oral isotretinoin, we found a recurrence rate that was no higher than previously reported. However, it must be borne in mind that our population was composed of subjects with mild or moderate acne, and all patients in our study underwent a 1-year maintenance treatment with topical retinoid.

We performed a statistical comparison between relapsing and non-relapsing patients on the basis of age, gender, acne severity and cumulative dose of isotretinoin. None of these variables resulted significantly related to acne recurrence. This means that in our population, patients who relapsed did not receive lower cumulative doses when compared with non-relapsing subjects. No difference in acne severity was found between the two groups of patients. Furthermore, according with these results, no significant differences of acne recurrence were found between groups of patients arbitrarily divided based on the total cumulative dose reached at the end of treatment (<40, 40–79, 80–119, ≥120 mg/kg respectively). This seems to suggest that in mild-to-moderate acne, administering oral isotretinoin for a further month of treatment after acne recovery could provide long-term remission, without significant association with the total cumulative dose reached.

Despite the isotretinoin-sparing intent of the protocol, 15 patients (10.79%) reached a cumulative dose ≥120 mg/kg, as long treatments were required to achieve complete acne healing in these cases. As in 60% of these patients acne affected three body sites (face, back and chest) (Table 3), it could be speculated that patients with larger body involvement respond less well than patients with localized acne. Among these 15 subjects, one patient relapsed (6.67%). No statistical difference was found between the rate of relapse in patients reaching a cumulative dose ≥120 mg/kg compared with that in patients reaching a cumulative dose <120 mg/kg. This finding seems to suggest that in our population reaching a cumulative dose of 120 mg/kg did not provide significant advantages in order to prevent acne relapse.

The main limitation of our study is the lack of an age-, sex- and acne severity-matched control group treated with a standard isotretinoin regimen. However, in comparison with published data of standard dose regimens, we found that the tested isotretinoin treatment could be effective to maintain a prolonged remission in mild-to-moderate acne patients. Therefore, it could be considered that reaching a cumulative dose of 120–150 mg/kg, as recommended for severe acne, is not necessary for less severe forms of the disease.

In conclusion, our findings seem to encourage low-cumulative dose courses of isotretinoin administration in mild-to-moderate acne, as lower cumulative doses may have many advantages for patients and lower costs than standard regimen. Use of topical retinoid as a maintenance treatment is advised to prevent acne relapses and consequent need for further systemic treatments.

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