

ORIGINAL ARTICLE

The effectiveness of intermittent isotretinoin treatment in mild or moderate acne

Y Kaymak, †* N İlter‡

University of Gazi †Health Center and ‡Department of Dermatology, Faculty of Medicine, Ankara, Turkey

Keywords

acne vulgaris, intermittent treatment, isotretinoin, low dose therapy

*Corresponding author, Hoşdere cad. Şair Baki Sok. 2/5 Y. Ayrancı, Ankara 06540, Turkey, tel. +90 3124421216; fax +90 3122120284; E-mail: yesimkaymak@yahoo.com

Received: 11 August 2005,
accepted 14 December 2005

DOI: 10.1111/j.1468-3083.2006.01784.x

Abstract

Background Isotretinoin is the only drug that affects almost all factors in acne pathogenesis. Recently, its use for the treatment of chronic mild or moderate acne unresponsive to long-term antibiotic therapy, and with a tendency to cause scarring and leading to negative psychological effects, has become popular. The aim of the study was to investigate the effectiveness of intermittent isotretinoin treatment in mild or moderate acne.

Methods Sixty patients with mild or moderate acne localized to the face were enrolled in the study. The treatment regimen consisted of isotretinoin, 0.5–0.75 mg/kg per day, applied for 1 week every 4 weeks for a total period of 6 months, according to the degree of acne and number of inflammatory lesions.

Results Forty-one (68.3%) of the 60 patients completed the 6-month therapy. At the end of the treatment complete improvement was observed in 34 patients (82.9%) out of 41. All adverse effects were mild and discontinuation of the treatment was not necessary.

Conclusion Intermittent isotretinoin treatment was found to be a safe and effective choice for patients with mild or moderate acne.

Introduction

Acne vulgaris is a chronic, inflammatory disease with a multifactorial aetiology affecting the pilosebaceous units of the skin. It is clinically seen more often on the face and sometimes on the shoulders, chest and back as open or closed comedones, papules, pustules, nodules and cysts.¹

Acne vulgaris is seen in adolescents at a rate of 70 to 87% and peaks between the ages of 15 and 18. Although there is spontaneous regression following puberty, the disease continues even after 25 years of age in 10% of patients. Increased sebum secretion, abnormal follicular keratinization, microbial colonization and inflammation are thought to play a role in acne pathogenesis.² Isotretinoin has been used more commonly in recent years, especially for treatment-resistant nodular and nodulocystic acne.^{3,4} Oral isotretinoin is the most effective sebosuppressive agent and has revolutionized the treatment of severe acne. It is the only drug currently available that affects all

four pathogenic factors of acne. Some authors favour isotretinoin 0.5 mg/kg/day while others advocate a higher dosage of 1 mg/kg/day, but both regimens result in the same degree of long-term clinical improvement. A 6-month treatment course is sufficient for 99% of patients. Currently, a 6- to 12-month course of 0.5–1 mg/kg/day isotretinoin to reach a total cumulative dose of 150 mg/kg is recommended for most cases of severe acne.⁴ With increasing clinical experience, however, its use has been expanded by many physicians to include patients with less severe disease who have responded unsatisfactorily to conventional therapies such as long-term antibiotics and appropriate topical therapies. Recently, its use in treatment of chronic mild and moderate acne unresponsive to long-term antibiotic therapy, with a tendency to cause scarring and leading to negative psychological effects, has become popular.⁵ The aim of our study was to investigate the effectiveness of intermittent isotretinoin treatment for mild or moderate acne.

Materials and methods

Sixty patients with mild or moderate acne localized on the face were enrolled in the study. Only acne patients with a chronic clinical course who had not responded to 6 months of antibiotics and topical treatment or who had responded but showed recurrence when the medication was discontinued were included in the study.

Before treatment was initiated, age, weight, duration of acne and previous treatment of patients were recorded. The Leeds grading scale was used during dermatological examination to grade the acne.⁶ Patients with a Leeds score of < 1 were considered to have mild acne and those with scores between 1 and 1.5, moderate acne. This technique was used according to the classification of Burke and Cunliffe. This grading system consists of scores of 0–9 and both the lesion type (comedone or inflammation) and the number of inflammatory lesions on the head (half of the neck and head) and in the front or back of the body in an area measuring 15 × 15 cm (225 cm²) are taken into account.⁶ The patients had an acne grade less than 1.5. The inflammatory lesions on the forehead, cheeks, chin and neck were counted.

The treatment regimen consisted of isotretinoin, 0.5–0.75 mg/kg per day, applied for 1 week every 4 weeks for a total period of 6 months. Moderate cases received isotretinoin at a dose of 0.6–0.75 mg/kg/day while the dose was 0.5 mg/kg/day for mild cases. Clinical improvement, acne grade and number of inflammatory lesions and any side-effects due to drug administration were noted during monthly follow-ups.

Liver function tests (SGOT, SGPT, direct and total bilirubin) and lipid profiles (total cholesterol, LDL, HDL, triglyceride) were evaluated for all patients before treatment initiation and at monthly follow-ups. Female patients underwent pregnancy tests and were advised to use a contraceptive method during treatment and for 3 months after treatment.

Results

Sixty patients, 34 female and 26 male, aged between 18 and 33 (22.03 ± 3.05) with mild or moderate acne localized on the face were enrolled in the study. The acne

grade before treatment initiation, as determined by the Leeds grading scale, varied from 0.75 to 1.5 and number of inflammatory lesions varied from 4 to 18.

Forty-one (68.3%) of the 60 patients completed the therapy. Twenty-five had moderate (60.9%) and 16 (39%) had mild acne. The cumulative dose received by the patients was 32.68 ± 5.04 mg/kg. Six patients (14.6%) had no improvement at the end of 4 months although they received the full dosage. These six patients had moderate acne and the Leeds score was 1.5. Nine patients did not come to follow-ups after the treatment was initiated while three patients left the study after the first month, and one patient after the third month. The intermittent isotretinoin treatment was tolerated fairly well by 41 patients. The acne grade and number of inflammatory lesions had significantly decreased at the end of 6 months.

Thirty-four (82.9%) out of 41 patients who completed the study had complete healing at the end of the treatment. Decrease of the acne grade to 0.1 and disappearance of all lesions was regarded as complete healing. At the end of the treatment, three of the patients (7.3%) with partial healing had eight inflammatory lesions (Leeds score 1), two (4.8%) had four inflammatory lesions (Leeds score 0.5) and two (4.8%) had one inflammatory lesion with new lesions just starting to appear (Table 1).

There was no difference in the patients' time to recovery or level of recovery according to gender or age. The side-effects observed during the study are presented in Table 2. All side-effects were found to be mild and did not require discontinuation of the treatment.

Discussion

Isotretinoin is a synthetic isomer of all-trans retinoic acid with proven long-term effectiveness in treatment-resistant nodular and nodulocystic acne.²

Oral isotretinoin is the most effective sebostatic agent. It decreases sebaceous gland volume by 90%, and sebum production by 70–90%. It suppresses basal sebocyte proliferation and sebum production. Sebostatic activity is dose-dependent. Once treatment is discontinued, sebum content returns to normal but the sebum quantity stays at approximately 40% of the basal value.² It also modifies keratinocyte maturation and adhesion, thus

Table 1 Treatment regimen and results for our patients

Acne grade	Suggested dose	Starting treatment (n = 60)	Completing treatment (n = 41)	Total cure (n = 34)	Partial cure (n = 7)
Moderate (Leeds: 1.25–1.5)	0.75 mg/kg/day	35 (58.3%)	25 (60.9%)	19 (31.6%)	6 (10%)
Moderate (Leeds: 1)	0.6 mg/kg/day	16 (26.6%)	10 (25.4%)	9 (15%)	1 (1.6%)
Mild (Leeds: 0.75)	0.5 mg/kg/day	9 (15%)	6 (14.6%)	6 (10%)	–

Table 2 Side-effects during intermittent isotretinoin treatment

Side-effects	Number of patients	%
Cheilitis	41	100
Acne activation	38	92.6
Muscle and joint ache	6	14.6
Epistaxis	2	4.8
Hand dryness and dermatitis	7	17
Conjunctivitis	2	4.8
Headache	1	2.4
Fatigue	1	2.4
Nervousness	3	7.3
High triglyceride level	4	9.7
High cholesterol level	4	9.7
High SGPT level	1	2.4
High direct bilirubin level	1	2.4

decreasing comedone formation.⁷ Although it does not have a direct effect on *Propionibacterium acnes* (*P. acnes*), the suppression of sebum production leads to an indirect decrease in the number of *P. acnes*, causing changes at the follicular microsurfaces and producing an anti-inflammatory effect.⁸

Topical antibiotics are first choice for the treatment of mild acne while antibiotics and anti-androgenic agents are effective in moderate forms. However, long-term usage of antibiotics leads to the proliferation of resistant bacteria in the skin of acne patients.⁹ There has been a decrease in the number of resistant bacteria following oral isotretinoin treatment. The reason for inadequate response to antibiotics without antibiotic resistance may be the dilution of the effective substance due to the high sebum secretion rate. The sebum secretion rate decreases by 90% following treatment with isotretinoin for a month.^{10–12}

Conventional treatments do not decrease inflammation rapidly because of the late onset of their effects and this can lead to permanent scarring.¹³ The late initiation of treatment, frequent recurrence of lesions and scar formation increase the psychological morbidity due to acne. Difficulty in relations with the opposite sex, social phobia, depression, anxiety, suicidal thoughts and suicide attempts have been reported in acne patients.^{14–16} Isotretinoin also decreases the severity of scarring due to the rapid onset of its action. Isotretinoin is therefore preferred for moderate and mild lesions and provides more than 90% decrease in inflammatory lesions.¹³ In diseases with decreased quality of life such as acne, effective treatment such as isotretinoin can provide the pre-disease quality of life. Isotretinoin has led to improvement in social functions, mental health and self-confidence in a study that used four different quality-of-life measures.¹⁷

There are different opinions about the dose of isotretinoin for treatment. The suggested standard dose is 0.5–

1 mg/kg/day for 20–24 weeks. Recurrence is seen more frequently following treatment with a low dosage.^{18,19} In a 10-year follow-up, patients treated using isotretinoin with a dosage of 1 mg/kg/day have shown a post-treatment recurrence rate of 22–30% while the rate was 39–82% for those treated with a dosage of 0.5 mg/kg/day.³ Cunliffe *et al.* treated 1000 patients with severe nodular cystic acne or moderate and mild acne resistant to conventional treatment and reported that isotretinoin may be used in moderate or mild cases with a tendency to scarring and causing psychological stress, and that this treatment would also be more cost-effective in the long run.³

New isotretinoin formulations and low-dose or intermittent application protocols have been tried in recent years. Low-dose protocols with doses such as 0.1 mg/kg/day and intermittent application protocols, especially for adult patients, those with oily skin, or with chronic moderate or mild acne have been reported.^{20,21}

Goulden *et al.* treated 80 patients over 25 years of age with chronic mild and moderate acne resistant to conventional treatment with 0.5 mg/kg/day of isotretinoin for 6 months to determine the efficacy of low-dose isotretinoin application. The treatment regimen consisted of isotretinoin, 0.5 mg/kg per day for 1 week every 4 weeks, for a total period of 6 months. It was reported that 75 patients completed the study. The treatment was found to be very well tolerated with mild cheilitis as the only side-effect by the authors. At the end of treatment, they indicated that acne had resolved in 68 (88%) patients and both total acne grade and lesion counts were significantly reduced ($P < 0.0001$). The intermittent application of low-dose isotretinoin was found to have less side-effects and to be more cost-effective than the full-dose protocol in patients with a total acne grade of less than 1, number of inflammatory lesions less than 20, and a sebum secretion rate of less than 1.25 $\mu\text{g}/\text{cm}^2/\text{min}$.⁵

We studied the effects of 6-month isotretinoin treatment with a dose of 0.5–0.75 mg/kg/day for 1 week every 4 weeks in 60 patients with moderate or mild acne. We detected complete healing in 34 patients (82.9%) out of 41 and partial healing in seven (11.6% of the 60 patients, 17% of the 41 patients). Six patients (14.6%) treated with the full-dosage protocol had no improvement at the end of 4 months. The observed side-effects were mild and did not require discontinuation of treatment. The rate of complete and partial healing was similar to that reported by Goulden *et al.* The increased rate of side-effects in our patients may be due to the high dose we used for the patients with moderate acne.

Plewig *et al.* used 0.05% tretinoin cream treatment together with 0.5 mg/kg/day isotretinoin for 5 months in 12 patients with papulopustular acne. There was an

Table 3 New and different approaches to isotretinoin treatment

Name of protocol	Recent studies	Number of patients	Treatment dose	Treatment duration	Degree of resolution (%)
Standard	Cunliffe <i>et al.</i> (1997)	1000	0.5–1 mg/kg/day	20–24 weeks	99
Intermittent	Goulden <i>et al.</i> (1997)	80	0.5 mg/kg/day (1 week every month)	24 weeks	88
Low dose	Strauss <i>et al.</i> (2001)	300	0.4 mg/kg/day	20 weeks	90
Low dose	Seukenan <i>et al.</i> (1998)	10	0.25 mg/kg/day	24 weeks	90
Low dose	Mandekov-Lefaki <i>et al.</i> (2003)	32	0.15–0.4 mg/kg/day	24 weeks	69
Low dose	Plewig <i>et al.</i> (2004)	12	0.5 mg/kg/day + 0.05% tretinoin	20 weeks	89–94
Mini dose	Amichai <i>et al.</i> (2003)	12	Standard treatment + 20 mg/day (1 day every week)	3 years	99

82–94% decrease in the number of inflammatory lesions at the end of treatment and low-dose isotretinoin was found to be effective in papulopustular acne.²² Authors of another study reported complete recovery in the nine patients who completed the treatment regime out of 10 patients treated with 0.25 mg/kg/day of isotretinoin for 6 months and that only one patient suffered a recurrence during 3 years of follow-up.²³

Palmer *et al.* studied the effects of low-dose isotretinoin administration for 1 or 2 days of each week in adult patients suffering from a relapse immediately after the standard dose of isotretinoin treatment was discontinued. They used 20 mg/day isotretinoin on eight adult patients with moderate acne who had showed signs of recurrence within a few weeks after the treatment was discontinued, and did not observe any relapses. The absence of recurrence was reported to have a positive psychological effect on patients and the treatment was found to be cost-efficient.²⁴ Amichai *et al.* similarly treated 12 female patients aged 23–42 with 20 mg of isotretinoin weekly for up to 3 years for relapses that developed between 6 months and 2 years after full-dose isotretinoin treatment. Side-effects were almost non-existent in these patients and there were no signs of any relapse during the treatment.²⁵

New developments and future trends are low-dose long-term isotretinoin regimens and new isotretinoin formulations (micronized isotretinoin)²⁶ (Table 3). Strauss *et al.* have tried a new formulation of isotretinoin and compared a single-dose 0.4 mg/kg/day micronized isotretinoin regime with 1 mg/kg/day treatment divided into two. They found no difference in the effectiveness at the end of 20 weeks. They also found that mucocutaneous side-effects and hypertriglyceridemia were rare with the new treatment.²⁷ Another study treated 32 patients with the standard dose of 0.5–1 mg/kg/day and another 32 patients with 0.15–0.4 mg/kg/day low-dose isotretinoin. The low-dose regime was recommended, as 69% of the patients treated with the low dose showed full recovery.²⁸

In conclusion, intermittent isotretinoin seems to be an effective and safe treatment option for patients with

moderate or mild acne. However, patients need close follow-up for recurrences, as the suggested cumulative dose is not reached in these patients.

References

- Dreno B, Poli F. Epidemiology of acne. *Dermatology* 2003; **43**: 1042–1048.
- Strauss JS, Thibautat DM. Diseases of the sebaceous glands. In: Freedberg I, Eisen AZ, Wolff K *et al.*, eds. *Dermatology in General Medicine*, 5th edn. McGraw-Hill, New York, 1999: 769–784.
- Cunliffe WJ, van de Kerkhof PCM, Caputo R *et al.* Roaccutane treatment guidelines: results of an international survey. *Dermatology* 1997; **194**: 351–357.
- Peck GL, Olsen TG, Batkus D *et al.* Isotretinoin versus placebo in the treatment of cystic acne. A randomized double-blind study. *J Am Acad Dermatol* 1982; **6**: 735–745.
- Goulden V, Clark SM, Mcgeown C, Cunliffe WJ. Treatment of acne with intermittent isotretinoin. *Br J Dermatol* 1997; **137**: 106–108.
- Burke BM, Cunliffe WJ. The assessment of acne vulgaris – the Leeds technique. *Br J Dermatol* 1984; **111**: 83–92.
- Ellis CN, Krach KJ. Uses and complications of isotretinoin therapy. *J Am Acad Dermatol* 2001; **45**: 150–157.
- Leyden JJ, McGinley KJ, Foglia AN. Qualitative and quantitative changes in cutaneous bacteria associated with systemic isotretinoin therapy for acne conglobata. *J Invest Dermatol* 1986; **86**: 390–393.
- Coates P, Adams CA, Cunliffe WJ *et al.* Does oral isotretinoin prevent *Propionibacterium acnes* resistance? *Dermatology* 1997; **195**: 4–9.
- Eady EA, Jones CE, Tipper JL, Cove JH, Cunliffe WJ, Layton AM. Antibiotic resistant propionibacteria in acne: need for policies to modify antibiotic usage. *Br Med J* 1993; **306**: 555–556.
- Layton AM, Knaggs H, Taylor J, Cunliffe WJ. Isotretinoin for acne vulgaris – 10 years later: a safe and successful treatment. *Br J Dermatol* 1993; **129**: 292–296.

- 12 Layton AM, Cunliffe WJ. Guidelines for optimal use of isotretinoin in acne. *J Am Acad Dermatol* 2004; **27**: S2–S7.
- 13 Goulden V, Layton AM, Cunliffe WJ. Current indications for isotretinoin as a treatment for acne vulgaris. *Dermatology* 1995; **190**: 284–287.
- 14 Gupta MA, Gupta AK. Depression and suicidal ideation in dermatology patients with acne, alopecia areata, atopic dermatitis and psoriasis. *Br J Dermatol* 1998; **139**: 846–850.
- 15 Kellet SC, Gawkodger DJ. The psychological and emotional impact of acne and the effect of treatment with isotretinoin. *Br J Dermatol* 1999; **140**: 273–282.
- 16 Aktan S, Ozmen E, Sanli B. Anxiety, depression and nature of acne vulgaris in adolescents. *Int J Dermatol* 2000; **39**: 354–357.
- 17 Mallon E, Newton JN, Klassen A, Ryan TJ, Finlay A. Standard patient-assessed quality of life instruments can be used to measure the benefits of acne treatment. *Br J Dermatol* 1995; **133**: 45–35.
- 18 Chivot M, Midoun H. Isotretinoin and acne: a study of relapses. *Dermatologica* 1990; **180**: 240–243.
- 19 Stainforth JM, Layton AM, Taylor JP, Cunliffe WJ. Isotretinoin for the treatment of acne vulgaris: which factors may predict the need for more than one course? *Br J Dermatol* 1993; **129**: 297–301.
- 20 Piquero-Martin J, Misticone S, Piquero-Casals V, Piquero-Casals J. Topic therapy-mini isotretinoin doses vs. topic therapy-systemic antibiotics in the moderate acne patients. *Ann Dermatol Venereol* 2002; **129**: 382.
- 21 Marks R. Acne and its management beyond the age of 35 years. *Am J Clin Dermatol* 2004; **5**: 459–462.
- 22 Plewig G, Dressel H, Pflieger M, Michelsen S, Kligman A. Low dose isotretinoin combined with tretinoin is effective to correct abnormalities of acne. *JDDG* 2004; **2**: 31–45.
- 23 Seukeran DC, Cunliffe WJ. Acne vulgaris in the elderly: the response to low-dose isotretinoin. *Br J Dermatol* 1998; **139**: 99–101.
- 24 Palmer RA, Sidhu S, Goodwin PG. ‘Microdose’ isotretinoin. *Br J Dermatol* 2000; **143**: 205–206.
- 25 Amichai B. Long-term mini-doses of isotretinoin in the treatment of relapsing acne. *J Dermatol* 2003; **30**: 572.
- 26 Zoubolis CC, Piquero-Martin J. Update and future of systemic acne treatment. *Dermatology* 2003; **206**: 37–53.
- 27 Strauss JS, Leyden JJ, Lucky AW *et al*. A randomized trial of the efficacy of a new micronized formulation versus a standard formulation of isotretinoin in patients with severe recalcitrant nodular acne. *J Am Acad Dermatol* 2001; **45**: 187–195.
- 28 Mandekov-Lefaki I, Delli F, Teknetzis A, Euthimiadov R, Karakatsanis G. Low-dose schema of isotretinoin in acne vulgaris. *Int J Clin Pharmacol Res* 2003; **23**: 41–46.