Research Article

Low-dose isotretinoin in acne vulgaris

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Abstract

Background: Oral isotretinoin is the only drug counteracting all the pathogenetic mechanisms causing acne. Its proper use can minimize scarring and induce long-term remission.

Objective: To assess the efficacy and safety of low-dose (0.5 mg/kg/day) isotretinoin in cases of acne vulgaris with the help of this prospective, single-arm, interventional study**.**

Materials and Methods: Cases with grades II (resistant cases), III, and IV acne vulgaris were enrolled. They were given oral isotretinoin for 4 months. After the completion of 4 months, those with complete clearance of lesions were switched to pulse therapy (1 week on, 3 weeks off), while those with new lesions were continued on isotretinoin for another 2 months. The total duration of therapy was for 6 months, and posttherapy cases were followed up for 6 months to check for relapse.

Result: A total of 96 patients were enrolled in the study. At 2-, 4-, and 6-months therapy, complete clearance was seen in 26.7%, 46.7%, and 93.3% in acne grade II (n = 15); 7.9%, 26.3%, and 60.5% in grade III (n = 38); 0%, 26.3%, and 52.6% in grade IV (n = 38) patients, respectively, and 7.4% and 14.1% cases on pulse and continuous therapies, respectively, showed recurrence 6 months after stoppage of therapy. The most common adverse drug reaction was cheilitis (89%). All mucocutaneous adverse events subsided with time, none warranting discontinuation of therapy.

Conclusion: Low-dose isotretinoin (0.5 mg/kg/day) therapy has a good efficacy and is associated with minimal side effects, improving patients' compliance and acceptability.

KEY WORDS: Acne vulgaris, isotretinoin, low-dose therapy

Introduction

Acne vulgaris and its consequent hyperpigmentation and scarring are a cause of great distress for almost all the adolescents. It is an inflammatory disease of pilosebaceous unit, and the four major pathophysiological mechanisms are increased sebum production, follicular hyperkeratinization, proliferation of *Propionibacterium acnes*, and inflammation.[1] Oral isotretinoin (13-*cis*-retinoic acid) is the only drug that counteracts all the pathogenetic mechanisms that contribute to the development of acne through its broad effects on cellular differentiation, apoptosis, inflammation, and sebaceous gland activity. It results in a significant reduction in sebum production, influences comedogenesis, lowers surface and ductal *P. acnes,* and exhibits anti-inflammatory properties.[2] Proper use of isotretinoin in acne can minimize the scarring and postacne hyperpigmentation and induce long-term remission.[3]

In 1982, US FDA-approved isotretinoin for use in severe recalcitrant nodular acne.[4] In recent days, isotretinoin is recommended in a dose of 1 mg/kg/day with a total cumulative dose of 120–150 mg/kg. The use of such a high dose (1–2 mg/kg/day) leads to a number of dose-dependent mucocutaneous, systemic, and biochemical side effects, which require regular monitoring and lead to a poor compliance.[3] One of the ways of reducing the dose-dependent adverse events and

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enhancing the compliance is to reduce the dose of isotretinoin used for the treatment of acne vulgaris.[5,6]

The aim of this study was to assess the efficacy and relapse rates with low-dose (0.5 mg/kg/day) isotretinoin in cases of acne vulgaris and study its mucocutaneous (cheilitis, dry skin, dry mouth, retinoid dermatitis, photosensitivity, etc.) and biochemical [altered liver function tests (LFTs) and lipid profile] adverse effects.

Materials and Methods

This single-arm, prospective, noncomparative, interventional study was conducted at the Department of Dermatology, Medical College and SSG Hospital, Vadodara, Gujarat, India, over a period of 2 years from September 2008 to August 2010. Patients with acne vulgaris grade III/IV and acne vulgaris with grade II, presenting severe psychological impact or not responding to oral antibiotics and topical therapy for 2 months were included in the study. Grading of acne was done as per the classification suggested by Tutakne and Chari.[7,8] Pregnant female subjects or women likely to become pregnant, nursing mothers, those noncompliant with contraception, cases with moderate to severe hypercholesterolemia or hypertriglyceridemia, those with significant hepatic/renal dysfunction, cases with leukopenia, hypothyroidism, and raised intracranial pressure, and cases with suicidal ideations were excluded from the study. Patient who took oral isotretinoin in the last 12 months were also excluded from the study.

On presentation, a detailed clinical history was elicited regarding duration and severity of acne, history of treatment received, and aggravating factors perceived by patients such as stress, cosmetics, sweating, etc. History was taken in all female patients for any menstrual irregularity and other associated features such as facial hair, thinning of scalp hair, and contraception practices. Family history of acne, metabolic syndromes such as diabetes mellitus and hyperlipidemia, and psychiatric disorders were asked. Patients were then thoroughly examined and acne lesions assessed according to a scoring system based on lesion count in four quadrants of face as shown in Table 1.

Laboratory investigations including complete blood count (CBC), LFT, lipid profile, and pregnancy test (for female subjects of reproductive age) were carried out at baseline. All the patients enrolled in the study were given oral isotretinoin in the dose of 0.5 mg/kg/day to be taken in two divided doses with meals. They were advised regarding photoprotection and asked to use a sunscreen. Patients with pustules were also given azithromycin (500 mg) orally on three consecutive days per week till the pustular lesions subsided. The female patients were counseled to use two methods of contraception including one barrier method.

The patients were followed up initially 2 weekly for 2 months and later 4 weekly. After 4 months, patients who were completely cleared of acne were given isotretinoin pulse therapy in a dose of 0.5 mg/kg/day for 1 week/month, and those with new lesions were given treatment (0.5 mg/kg/day daily) for another 2 months. Thus, all the patients were given isotretinoin for 6 months (in varying regimens based on the response) and were followed up for another 6 months thereafter (without isotretinoin) to assess the relapse rate. The total duration of follow-up was 12 months.

Table1: Clinical scoring of acne

Score	1	2	3	4	5
No. of comedones/ papules/pustules	<10	10–25	25–50	50–100	>100
No. of nodules/cysts	1–2	2–6	6–10	>10	—

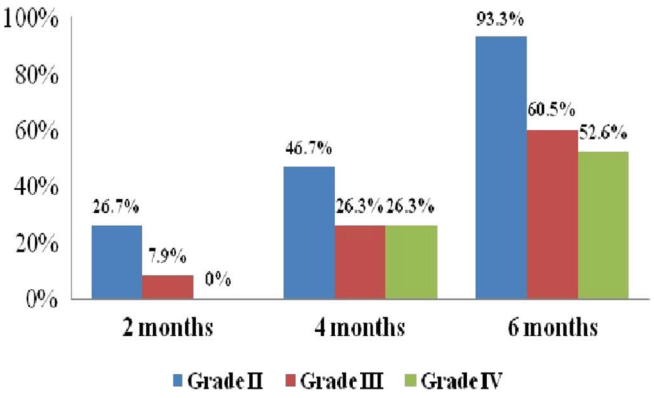

Figure 1: Patients with complete response to low-dose isotretinoin therapy.

On all the follow-up visits, the patients were evaluated clinically for response to therapy and adverse effects in terms of mucocutaneous and biochemical alterations. Response to therapy was noted by scoring acne lesions as—clear, 100% reduction in pretreatment score; excellent, 75%–99% reduction in pretreatment score; good, 50%–74% reduction in pretreatment score; moderate, 25%–49% reduction in pretreatment score; and poor, 0%–24% reduction in pretreatment score. Laboratory investigations including CBC, LFT, and lipid profile were conducted after 2, 4, and 6 months. Cheilitis and dryness were managed by giving emollients and dry eyes with lubricating eye drops and artificial tears.

Result

Demographics and Baseline Characteristics

A total of 96 patients were enrolled in the study, of which 67 (69.7%) were male patients and 29 (30.2%) were female patients. Most of the patients were adolescents and young adults; 51 (53.1%) patients belonged to the age group of 14–19 years, while 42 (43.8%) patients belonged to the age group of 20–30 years; only three (3.1%) patients were aged older than 30 years. Thirty-one (32.3%) patients revealed acne for >1 year and 27 (28.1%) patients for >3 years.

The most common aggravating factor reported by acne patients enrolled in the study was sun exposure/sweating (24%), followed by improper diet (15.6%). Twenty-six (27.1%) patients showed a family history of acne in their first-degree relatives. Among the 96 patients enrolled in the study, 33 (34.4%) patients had received treatment in the past. Oral antibiotics were the most commonly prescribed medications, and only three (32%) patients , presenting grade IV acne had received oral isotretinoin (more than 12 months back). Among the 96 patients enrolled in the study, 40 (41.7%), 40 (41.7%), and 16 (16.7%) patients presented with grades IV, III, and II acne, respectively. Seventy (72.9%) patients presented facial acne, while 26 (27.1%) patients experienced the involvement of both face and trunk.

Among the 96 patients (grade II: 16; grade III: 40; and grade IV: 40) enrolled in the study, five patients were lost to follow-up after enrollment in the study (before the first follow-up visit). All the other 91 patients (grade II: 15; grade III: 38; and grade IV: 38) completed the 12 months follow-up and thus, were, considered for efficacy and safety analysis.

Efficacy after 2 Months of Treatment

At the end of 2 months of therapy, four (26.7%) of 15 patients with grade II and three (7.9%) of 38 patients with grade III acne showed complete clearance of acne. None of the patients with grade IV acne showed a complete clearance at the end of 2 months of therapy. Four (26.6%) grade II, five (13.1%) grade III, and five (13.1%) grade IV patients showed an excellent response. Four (10.5%) patients with grade IV acne presented new lesions at the end of 2 months of follow-up.

Efficacy after 4 Months of Treatment

On completion of 4 months of treatment with low-dose isotretinoin, seven (46.7%) grade II, 10 (26.3%) grade III, and 10 (26.3%) grade IV patients showed complete clearance of lesions. Two (13.3%) grade II, 11 (28.9%) grade III, and 11 (28.9%) grade IV patients showed an excellent response to the therapy. The 27 (29.6%) cases who showed a complete clearance of lesions were started on pulse therapy, and the rest 64 (70.4%) cases presenting complaint of new lesions were given continuous therapy for another 2 months.

Efficacy after 6 months of treatment

At the end of 6 months of treatment with low-dose isotretinoin, 14 (93.3%) grade II, 23 (60.5%) grade III, and 20 (52.6%) grade IV patients showed a complete clearance of lesions. A total of 57 of the 91 (62.6 %) patients considered for efficacy analysis showed a complete clearance of acne at the end of 6 months, while 25 (27.5%) patients showed an excellent response to the therapy, and 42% of patients with truncal acne showed a complete clearance of lesions at the end of 6 months. O f the 91 patients, seven (18.4%) patients with grade IV acne, four (10.5%) patients with grade III acne, and none of the patients with grade II acne showed new lesions at the end of 6 months.

Table 2: Comparison of mucocutaneous adverse effects at 2, 4, and 6 months

Adverse effects	2 months, *?* (%)	4 months, *?* (%)	6 months, *?* (%)
Cheilitis	81 (89)	11 (12)	2 (2.1)
Dryness	21 (23)	7 (7.6)	—
Dry eyes	7 (7.6)	—	—
Hair fall	2 (2.1)	—	—
Folliculitis	1 (1.09)	—	—

Efficacy at 12 months of follow-up

Among the 91 patients followed up till the end of 12 months, 11 (12%) of them showed a recurrence of acne lesions. Among the 27 patients put on pulse isotretinoin therapy after 4 months of treatment, two (7.4%) of them showed a recurrence of acne lesions, while among the 64 patients continuing the low-dose isotretinoin for 6 months, the recurrence rate was 14.1%. There was no significant difference in the recurrence rates in the two groups (P = 0.61; χ^2-test) at the end of 12 months of follow-up. The recurrence of acne was the highest in patients with grades IV and III acne with seven patients (18.4%) and four (10.5%) patients, respectively, showing new lesions within 6 months of completion of therapy. In contrast, none of the grade II patients showed new lesions.

Safety Analysis

The adverse reactions noted during the first2 months of the study were cheilitis (89%), facial dryness (23%), dry eyes (7%), altered LFTs (3%), altered lipid profile (2%), hair fall (2%), and folliculitis (1%) [Table 2]. At the end of 2 months, mild cheilitis was seen in 71 (78.0%) patients, whereas moderate and severe cheilitis was less common and presented in seven (7.7%) and three (3.3%) patients, respectively. Emollients were given to patients with cheilitis, and its incidence drooped down to 11 (12.1%) and two (2.2%) at the end of 4 and 6 months, respectively. Twenty-one (23%) patients showed dryness of skin at 2 months, which decreased to seven (7.6%) at 4 months and nil at 6 months. Incidence of dry eyes and hair fall was found only during the first 2 months and were mild and responded to supportive therapy.

In our study, two patients showed rise in bilirubin >2 times the normal levels (isotretinoin was stopped in both of them), three patients showed moderately raised liver enzymes (<2 times normal level), and two patients showed raised TGs (<2 times normal level).

Discussion

Isotretinoin is considered as the first-line therapy for grades III/IV acne.[9] However, 16 patients including 11 (16.67%) female patients of grade II acne needed isotretinoin in our study pointing toward the greater psychological impact of acne on female patients. Higher incidences of anxiety and depression were also found in studies conducted by

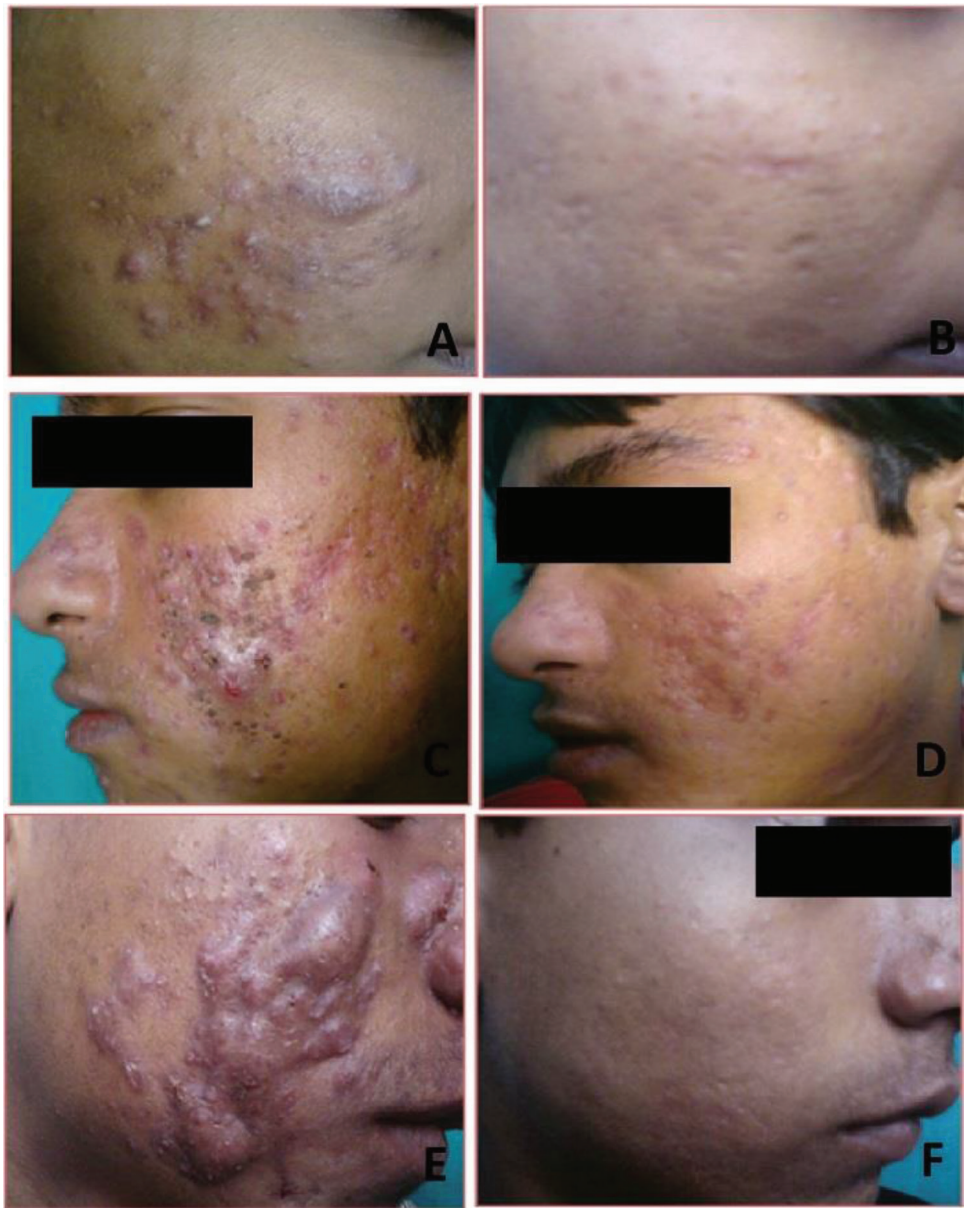

Figure 2: A, C, and E—Pretreatment photographs of patients with grades II, III, and IV acne vulgaris, respectively. B, D, and F—Posttreatment photographs of patients with grades II, III, and IV acne vulgaris, respectively.

Aktan et al.[10] and Yazici et al.[11] Aktan et al.[10] studied 2,657 high school students and found that acne results in higher anxiety in adolescent girls. The majority of patients in our study were male patients (69.7%), indicating a higher prevalence of severe acne in male patients. About 28.12% patients presented acne for greater than 3 years, which indicates the delay in initiation of isotretinoin, increasing the chances of scarring and economical burden.

After 2 months of therapy, none of the patients with grade IV acne showed a complete clearance in contrast to other grades, indicating a marked difference in response. However, responses at 4 and 6 months are comparable in grades III and IV acne. Only grade IV patients showed new lesions. At 6 months, there was a significant discrepancy between grade II and grade III/IV. All these indicate that grade IV acne need a longer duration of therapy or a higher dose for better response and 2 months of therapy is indeed suboptimal. The best results were seen with those with grade II acne, and, hence, in unresponsive cases or those with severe psychological impact, oral isotretinoin can be considered. Factors that determine recurrence are grade of acne at presentation, truncal acne, and duration of therapy.[12]

Cheilitis is the most frequent side effect observed and can be taken as a marker of patient compliance and drug action. This, however, is mild with low-dose isotretinoin and improves with application of emollients and usually does not need dose modification or drug withdrawal. Other mucocutaneous side effects were mild and responded well to supportive therapy. However, these should be explained to the patients to improve patient compliance. Considering the low incidence and mild nature of biochemical adverse effects in our study, cases with normal laboratory parameters at baseline need not be monitored frequently, and if found normal after 4–8 weeks of therapy, they need not be repeated. None of the cases in our study required drug discontinuation or dose modification owing to mucocutaneous adverse effects, and the incidence of these side effects were lower than the conventional doses of isotretinoin used in other studies.[9,13]

Conclusion

All the severe acne patients deserving systemic therapy may be offered isotretinoin early in the disease course to prevent a patient being "scarred for life." Use of isotretinoin in low doses should be considered in mild to moderate acne also. Low-dose isotretinoin (0.5 mg/kg/day) therapy has a high incidence of complete cure and prolonged remissions and is cost-effective in the long run. Pulse dosing of isotretinoin in the dose of 0.5mg/kg/day for 1 week every month can be introduced after complete clearance of acne, has comparable results, and is more acceptable by the patients. Low-dose isotretinoin has minimal side effects, improving patients' compliance and acceptability. Reducing the monitoring of biochemical tests keeping in mind the low-dose isotretinoin can further lower the economic burden.

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