Original Article

Efficacy of Low Dose Isotretinoin (20 Mg) for the Treatment of Mild to Moderate Acne Vulgaris

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ABSTRACT

Objective: To determine the efficacy and safety of low dose (20 mg) isotretinoin for the treatment of mild to moderate acne for a duration of six to nine months.

Study Design: This was an observational, non-comparative, uncontrolled study.

Place and Duration of Study: This study was carried out at the Department of Dermatology, Shalamar Hospital Lahore from 01-1-2010 to 31-12-2013.

Materials and Methods: Six hundred adult patients of either sex with mild to moderate acne and, ages between 15 to 25 years were enrolled. They were treated with a fixed low dose of isotretinoin daily irrespective of weight, for six to nine months. Patients were evaluated clinically at baseline, then monthly during the treatment and follow-up.

Results: Of the 600 patients enrolled, 580 completed the study. 94% of patients were completely cured in six months with a cumulative dose of 62.37 mg/kg.Treatment was continuedfor 6 % of patients, who still had active acne lesions.The cure rate reached 98.96 % at the end of ninth months. Patients were followed for another six months and a relapse rate of 4.48% was observed. Mild cheilitis and xerosis were common. Laboratory abnormalities were mild and transient.

Conclusion: Six to nine months treatment with a daily dose of 20 mg/day isotretinoin was found to be effective in patients with mild to moderate acne. The drug was well-tolerated and showed almost negligible clinical and laboratory side effects.

Key Words: Acne, Low dose Isotretinoin, efficacy, side effects

INTRODUCTION

Acne Vulgaris is one of the most common skin disorder that involves pilosebaceous glands. It mainly affects adolescents, between 12 to 25 years of age, though may occur at any age[1]. Acne has a complex pathogenesis: increased seborrhoea, ductal cornification and colonization of pilosebaceous ducts by propioni bacterium acne with consequential inflammation. An elevation in gene markers such as Insulin like growth factor-1 (IGF-1), interleukin-1 beta(IL-1β) and tumor necrosis factor-alfa (TNF-α) is also a commonly observed [2].

Isotretinoin, an FDA approved drug for treatment of severe nodulo-cystic acne,has revolutionized the treatment of acne as it affects all the factors involved in the pathogenesis of acne[3]. Since its worldwide introduction, it has been accepted as the most effective mode of treatment for acne [4]. Its recommended dosage is relatively high, 0.5 mg/kg to 1.0 mg /kg per day for four to eight months until a cumulative dose of 120 mg/kg to 150 mg/kg is reached[5]. This regimen is widely used and produces good results, though a large number of dose dependent side effects are reported[6]. Due to these side effects, and high cost of the medicine, patients have difficulty in completing the treatment [7].

Common practice in some areas of the world is to administer low dose regimen, for the less severe cases of acne but this practice has not yet been well-established[8]. Recent studies have reinforced the view that low-dose isotretinoin is useful for mild to moderate acne, with less side effects (cutaneous, systemic and laboratory based) as compared to standard dosage [9]. As to date there is no data on use of fixed daily dose in mild to moderate acne,in population of Lahore, therefore, we planned to conduct this study.

The aim of this open label, observational study was:

1. To assess the efficacy of fixed daily low dose (20 mg/day) isotretinoin in the treatment of mild to moderate acne.
2. To determine the various side effects with oral isotretinoin in fixed low dose (20 mg/day).

To evaluate the incidence of relapse after treatment with low dose oral isotretinoin.

MATERIALS AND METHODS

Description of Participants: This was an observational, non-comparative, open label and, uncontrolled study. Six hundred patients from Lahore district and surrounding areas having mild to moderate acne were selected randomly from the outpatient of the department of dermatology at Shalamar Hospital Lahore. The study period was from 1st January 2010 to 31st December 2013.

Following criteriaswas used in selecting the study group:

Inclusion Criteria:

1. Patientsof age group 15 to 25 years irrespective of

sex or race.
2. Patients diagnosed as having mild to moderate acne (GAGS score of 10 to 38), no nodule or cystic lesion.

Exclusion Criteria:
1. Diabetes mellitus, hypercholesterolemia and hypertriglyceridemia.
2. Patients having acute or chronic liver disease.
3. Patients on oral contraceptive use or taking other drugs known to exacerbate acne.
4. Patients with severe nodulo-cystic acne.

All patients were advised to take isotretinoin 20 mg daily after a fatty meal for a period of six months and those not cured (GAGS score > 0) will continue for another three months. All other treatments except moisturizers were restricted for these patients.

Patients were examined clinically, were graded and recorded using the GAGS score at first visit and then every subsequent monthly visit. Information regarding age, sex, weight, duration of acne, and history of previous treatment was recorded (see Table-1). Non-inflammatory lesions (comedones) and inflammatory lesions (papules and pustules) were counted on first visit and then monthly for six to nine months, depending on how long the treatment was continued. Side effects caused by the treatment were also recorded at each visit.

We considered a six monthfollow-up to be adequate for detection of relapses. During this period, clinical evaluations and acne severity grading were regularly performed at monthly intervals. At the end of the study, the degree of satisfaction on a four-point scale was also documented by the participants where, 4-very satisfied; 3-satisfied; 2-slightly satisfied and 1-unsatisfied.

Serum lipid profile, Liver Function Tests (LFTs) and complete blood picture was done at the baseline before starting the treatment, after 1 month and thenevery three months during the treatment and during the six months follow-up period. Females with signs ofvirilization and hirsutism underwent ultrasonography to exclude Polycystic Ovarian Disease and adrenal hyperplasia.

Global Acne Grading System (GAGS)[10]: The GAGS global score was calculated by rating six different locations (forehead, right cheek, left cheek, nose, chin and chest/upper back) and then multiplying each rating by a factor that is specific to that area. Rating is based on the surface area and distribution /density of pilosebaceous units as follows:

Score of 0 = no lesion, Score of 1 = one or more comedo, Score of 2 = +one or more papule, Score of 3 = +one or more pustule, Score of 4 = +one or more nodule

Multiplication factor used for each location is as follows,

Forehead =2, right cheek =2, left cheek =2, nose =1, chin =1, chest and upper back =3.

The global score is the sum of all six-location scores, and the global acne grade according to the global score is defined as follows:

Nonefor global score = 0, Mild for global score = 1-18, Moderate for global score = 19-30, Severe for global score = 31-38, Very Severe for global score >38.

Statistical Analysis: Statistical analysis was done in R statistical computing software. T-tests and chi-squared were used where appropriate.

RESULTS

Of the 600 patients, enrolled in this study, 442 females and 138 males completed the study. Twenty patients dropped out of study for unknown reasons.Their ages ranged between 15 to 25 years (mean=17.69± 1.86 years), weight ranged from 45 kg to 75 kg (mean=57.8 ± 3.27 kg) and disease duration ranged between six months to three years (mean=6.4±10.7 months) (Table 1).

Table No.1: Study Details

Clinical Characteristics	
Gender	Male=144, Female=436
Age (Years)	17.69± 1.86
Weight (Kg)	57.8± 3.27
Previous history (Months)	6.42± 10.7
GAGS Score	
GAGS at Study Start	25.3± 6.27
GAGS at Month 1	15.74± 6.46
GAGS at Month 2	8.7± 5.81
GAGS at Month 3	3.67± 4.37
GAGS at Month 4	2.33± 3.59
GAGS at Month 5	1.36± 2.8
GAGS at Month 6	0.72± 2.05
Relapse	
Relapse (Percentage)	4.48

For the 580 patients whocompleted the study, the Isotretinoin dose was 20mg/day that according to weight ranged between 0.28 mg/kg to 0.49 mg/kg per day (mean=0.34 ± 0.017mg/kg/day). Patients received treatment for six to nine months. Total Isotretinoin dose range was 62.37mg/kg in six months to 93.55 mg/kg in nine months. Most patients started showing improvement at the end of first month and by the end of sixth months 94% (n=545) of the patients were free of any active acne lesions (GAGS score= 0) and the treatment was stopped (fig 1). Remaining 6% (n=35)

patients continued treatment for another three months, 3.96 %(n=23) patients were declared cured after nine months (GAGS score= 0). The total cure rate after nine months of treatment was 97.96%. Recurrence was observed in 4.48% (n=26) patients and was predominant in females.

About patient satisfaction, 94.6% of patients were very satisfied (4 points), 3.9% of patients were satisfied (3 points), 0.5% of patients were slightly satisfied (2 points) and 1 % of patients were not satisfied (1 point).The mean satisfaction rate was 3.92 points (±0.02).

Laboratory Abnormalities: Triglycerides and total cholesterol levels before and after completion of treatment were also compared. A slight increase in triglycerides and cholesterol (up to 15% higher than the upper limit of normal values) was detected in 4.28% (n=28) of patients. Slight elevation of alanine aminotransferase (ALT) was detected in 0.34% (n=2) of patients. Both the lipid profile and LFTs reverted to normal level within one month after stopping the treatment.

Side effects: The most common side effects reported were mild cheilitis in 91% of patients, mild xerosis in 42.93% of patients and Epistaxis in 2.5% of patients. No patient developed depression or any other psychological side effect.

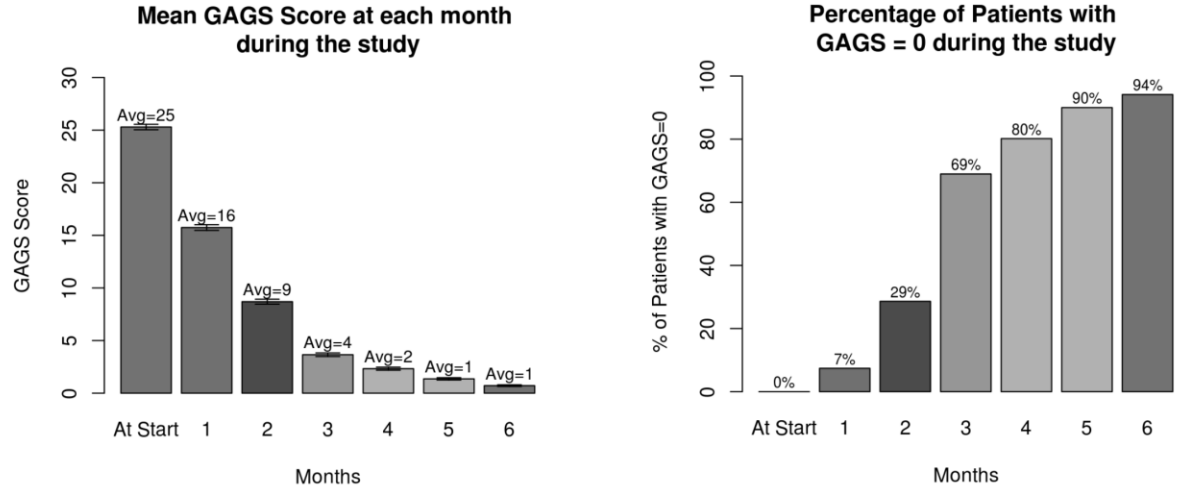

Figure 1: Improvement in patients observed by GAGS score assessment. **(A)** Barplot of the average GAGS score of patients (N=580) who completed the study over the period of six months. The error bars show the standard error for GAGS score. **(B)** Percentage of patients with GAGS Score=0 increases as the study progresses and indicates the improvement in patients' acne with this treatment.

DISCUSSION

The 20 mg fixed low-dose isotretinoin produced good results (GAGS=0) in 94% of patients after six months (Table 1). The cure rate increase to 97.96% after nine months of treatment. Our results were found to be similar to those reported in the literature in patients with moderate acne using the classical dosage of 0.5 mg/kg to 1.0 mg/kg per day[11]. A few studies like ourshave been carried out using low doseisotretinoin irrespective of patients' weight and have shown complete response in majority of patients. Gan et al [11] carried out low dosage treatment for seven to eight months and showed complete response in 93.9% of the patients. Similarly, Kubaisiet al[12] achieved excellent results in 93.5% of patients who also received a fixed dose of 20 mg/day of isotretinoin for a duration of four months. Our results are also supported by the findings of Beneret al[13], Sardana et al [14] and of Lee et al[15]who demonstrated the effectiveness of low-dose isotretinoin in the treatment of acne conglobate and moderate acne, respectively. A larger study (n=638) by Amichaiet al.[16], reported successful treatment of 94.8% of patients with moderate acne by a low-dose 20 mg/day for a total period of six months. Other reports have also supported the efficacy of the low-dose treatment[17].

The present study showed that lower dose of isotretinoinis well tolerated with milder side effects and is cost effective. Our patients showed muco-cutaneous changes like cheilitis, mild xerosis and/or epistaxis and the results are similar to that reported in previous studies with smaller dose[18]. Although no depression was reported in our patients throughout the study, one cannot postulate that low-dose isotretinoin would necessarily reduce the potential for this rarely reported idiosyncratic reaction [19]. In our study, triglycerides and total cholesterol level increased in 4.28% (n=28)of patients, liver enzymes increased in 0.34% (n=2) of patients. These increased levels were still lower when compared to other studies[20]. Laboratory abnormalities

reported in the literature include triglycerides (25% to 44%), total cholesterol (30% to 31%), and liver enzymes (10% to 20%) in patients treated with a standard dose of 0.5 mg/kg to 1.0 mg/kg per day for five to six months[21]. Abnormal laboratory findings in our study were of low grade and these effects were generally transient and reversible and did not alter the treatment course. Furthermore, no study patient discontinued isotretinoin therapy as a result of developing side effects or laboratory abnormalities.

We investigated the recurrence rate and long-term efficacy of our study, by carrying out a monthly follow-up evaluation for six months after the stopping the treatment. Majority of our patients were disease-free during the follow up period. The recurrence rate in our study was 4.48% (n=26), similar to the results shown by Amachi et al. [16]. The recurrence rate was higher in patients with six months of treatment than those with nine months of treatment which shows that the cumulative dose does affects the recurrence rate [21]. Factors shown to influence a relapse have included female gender, younger age (< 16 years of age), truncal acne, severity and, a prolonged history of acne [22].

We verified that the low-dose treatment had effects similar to the conventional treatment with same GAGS scores. The mean patient satisfaction score was 3.92±0.02. This result suggests that the low-dose regimen is superior to other regimens (conventional or intermittent) in terms of patient satisfaction and has similar effects, as compared with the conventional regimen for maintaining remission.

Limitations: The limitations of this study include study design, and the fact that it investigated outcomes of the treatment within a single institution. Our low incidence of reported side effects was based upon complaints documented. In addition, this study did not include patients with nodulo-cystic acne.

CONCLUSION

Our findings encourage 20 mg/day isotretinon as first-line therapy for mild-to-moderate acne. These results suggest that, when we consider tolerability, efficacy and patient satisfaction, the low-dose treatment regimen is the most suitable for patients with mild to moderate acne, with very little side effects.

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