A randomized comparative trial of two low-dose oral isotretinoin regimens in moderate to severe acne vulgaris

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ABSTRACT

Background: Oral isotretinoin is highly effective in all forms and grades of acne, even in lower dosages (<0.5 mg/kg/day). There is a paucity of comparative data on the various low-dose regimens of oral isotretinoin in the Indian literature. **Objectives:** To assess and compare the efficacy and tolerability of two low-dose oral isotretinoin treatment regimens (20 mg daily and 20 mg alternate days) in moderate to severe acne vulgaris. **Materials and Methods:** A total of 240 patients with moderate to severe acne vulgaris were selected and randomized into two groups and treated with a fixed dose of 20 mg of isotretinoin (Group A - daily and Group B - alternate days) for 24 weeks and followed up for 12 weeks post therapy. **Results:** A total of 234 patients completed the study. At the end of therapy, decrease in the total acne loads up to 98.99% (Group A) and 97.69% (Group B) was achieved from the baseline ($P < 0.01$), excellent response was observed in 98.3% (Group A) and 93.96% (Group B) patients ($P = 0.166$). In the severe acne, Group A performed significantly better than Group B until the end of 36 weeks. While in the moderate acne, significant difference in the response between both groups was observed only up to 12 weeks. No serious side effect was observed. **Conclusion:** Both isotretinoin regimens were well tolerated and found to be an effective treatment for moderate to severe acne vulgaris. However, in moderate acne 20 mg alternate day regimen may be preferred. A 20 mg daily regimen is a better choice for severe acne in terms of response. **Limitation:** Small sample size and short follow-up period.

Key words: Acne vulgaris, fixed dose, low-dose isotretinoin

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INTRODUCTION

Acne vulgaris is a common inflammatory disease of the pilosebaceous unit,[1] which affects up to 87% adolescence and 54% of adults with varying degrees of severity.[2,3] Left untreated or inadequately treated, acne vulgaris can lead to psychological and physical scarring.[4,5] Treatment improves the QOL of patients with acne and can prevent scarring.[6] According to severity of acne, there are various topical and systemic treatment modalities. In systemic therapy, the commonly used drugs are oral antibiotics, isotretinoin, and hormones.

The multiple modes of action of isotretinoin (13-*cis*-retinoic acid) makes this compound the major pharmacological breakthrough in acne therapeutics.[7] Over the time, oral isotretinoin has proven to be a "wonder drug" that is highly effective in the treatment of all forms and grades of acne vulgaris, even in lower dosages.[8]

Oral isotretinoin in the standard regimen of 0.5–1.0 mg/kg/day for 16–32 weeks causes many dose-dependent mucocutaneous and systemic adverse effects. Various studies have reinforced the view that lower doses of isotretinoin are also effective in terms of response, adverse effects, and cost; therefore, other regimens should be used instead of the daily standard regimen. There are few randomized comparative studies of low-dose regimens of oral isotretinoin in the Indian literature. Thus, the present study was undertaken to compare the efficacy and tolerability of two

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different fixed low-dose oral isotretinoin regimens in moderate to severe acne vulgaris with a lager sample size and a longer follow-up period.

Aims and objectives

To assess and compare the efficacy and tolerability of two fixed low-dose (20 mg daily and alternate day) oral isotretinoin regimens in moderate to severe acne vulgaris.

MATERIALS AND METHODS

This prospective randomized comparative study included 240 patients with moderate to severe acne vulgaris attending the outpatient clinic in the dermatology department. Patients with a personal or family history of hyperlipidemia or diabetes, and those having drug-induced acne were excluded. Pregnant women, women desiring pregnancy, and women using temporary methods of contraception were also excluded. Acne involving all body sites was studied. A written consent was taken from the patients or their parents. After recording detailed demographic data, the patients were examined under good illumination. Patients were finally graded into mild, moderate, and severe acne based on severity as described by Pochi [Table 1].[9] To enable analysis of improvement in lesion count, total acne load (TAL) was calculated with the help of Definition Severity index [Table 2].[10] The patients were randomly assigned into two groups (A and B); each group consisted of 120 patients. Groups A and B were treated with a fixed dose of 20 mg of oral isotretinoin daily and alternate days, respectively, for a total period of 24 weeks and followed up for 12 weeks post-therapy. Patients were also advised to apply topical 1% clindamycin gel twice daily and white petroleum jelly on lips when required. All patients visited at an interval of two weeks for 24 weeks then six weekly interval for 12 weeks after completion of treatment. The adverse effects and response according to the number and types of lesions were recorded at every visit. TAL was also calculated at each visit. Complete blood cell counts, liver function tests, and serum lipid profile were done initially and repeated at four and eight weeks thereafter. Emergence of near pretreatment severity of acne in the treated patient within 12 weeks of follow-up was considered as relapse. Greater than twofold increase in baseline laboratory values of liver function tests and serum lipid profile was considered a criterion for discontinuation of therapy. Treatment response was evaluated according to mean percentage decrease in TAL. Treatment response was also evaluated according to response criteria, which is as follows:

1+ = Poor response (<30% reduction in the lesion counts)
2+ = Fair response (30%–60% reduction in the lesion counts)
3+ = Good response (60%–90% reduction in the lesion counts)
4+ = Excellent response (>90% reduction in the lesion counts).

Statistical analyses were done using computer software (SPSS version 20 and primer). All the findings were analyzed by using Chi-square test, Student's *t*-test and one-way analysis of variance (ANOVA), Mann–Whitney *U*-test, repeated ANOVA, and Wilcoxon-statistical test wherever required. Significance level for tests was determined as 95% ($P < 0.05$). The study protocol was approved by the research review board of the institution and had no financial support from any outside agency.

Table 1: Pochi *et al.* criteria for grading of acne vulgaris

Severity	Papules/pustules	Nodules
Mild	Few to several	None
Moderate	Several to many	Few to several
Severe	Numerous and/or extensive	Many

Number of lesions <5 = few, 5-15 = many and >15 lesions is taken as several

Table 2: Definition severity index

Type of acne lesions	Severity index
Non-inflamed comedones, open and closed (no erythema)	0.5
Comedones/papules with surrounding erythema	1
Superficial pustules <2 mm with no or little erythema	
Pustules with a diameter >2 mm	2
Pustules with a significant erythema	
Deep infiltrates with or without pustules, nodules, and isolated cysts	3

Total acne load = [(number of severity index 0.5 lesions) × 0.5] + [(number of severity index 1 lesions) × 1] + [(number of severity index 2 lesions) × 2] + [(number of severity index 3 lesions) × 3]

RESULTS

In the present study, a total of 240 patients with a mean age of 18.88 ± 2.46 years (range 15–30; median 18.51) were selected prospectively and randomly assigned into two groups. Out of 240 patients, six patients were lost to follow up during the study period. For final result analysis, there were 234 patients (Group A, 118 and Group B, 116). No statistically significant difference was observed in age, gender, and disease characteristics between the two groups [Table 3]. A statistically significant difference was observed in the family history of acne among both groups.

The initial mean TAL in both groups was comparable as per Mann–Whitney tests for independent samples (Group A = 113.38 ± 53.3; Group B = 108.7 ± 57.5; *P* value > 0.5). During follow-up, a statistically significant decrease in TAL in both groups was observed as per Wilcoxon paired two-tailed probability test (*P* value < 0.001 at each follow up) [Table 4].

Response rates according to mean percentage decrease in TAL in both the groups are summarized in Table 5 and

Table 3: Patient characteristics

Number of patients	Total (234)	Group A (118)	Group B (116)	*P* value
Age (mean±SD years)	18.88±2.46	18.96±2.71	18.79±2.20	0.611
Age of onset (15-20/20-25/>25 years)	151/78/5	78/36/4	73/42/1	0.868
Disease duration (<1/1-3/>3 years)	66/113/55	32/59/27	34/54/28	0.86
Gender (male/female)	189/45	98/20	91/25	0.467
Grade of acne (moderate/severe)	118/116	59/59	59/57	0.99
Family history of acne (present/absent)	117/117	69/49	48/68	0.013
Regional distribution of patients (rural/urban)	84/150	46/72	38/78	0.999
Site involved (face/face + trunk)	181/53	91/27	90/26	0.944
Type of skin (dry/normal/oily)	9/37/188	3/17/98	6/20/90	0.457

Table 4: Mean total acne load at different time intervals in both groups

Weeks of treatment	Group A (*n*=118)			Group B (*n*=116)			*P* value
	Mean total acne load	SD	Median	Mean total acne load	SD	Median	
Initial	113.38	53.3	105.50	108.7	57.5	99.50	0.5
2	81.95	42.7	77.50	96.6	54.3	88.00	0.023
4	57.96	33.2	50.00	78.6	48.9	74.00	<.001
6	39.79	25.4	33.50	59.7	40.4	54.00	<.001
8	25.97	19.5	21.00	46.7	35.5	40.00	<.001
10	16.25	15.5	10.00	34.1	29.8	28.00	<.001
12	10.93	13.6	7.00	22.9	23.6	16.00	<.001
14	7.42	10.9	3.50	16.2	20.3	10.00	<.001
16	4.65	7.5	1.50	11.7	17.8	6.50	<.001
18	3.41	5.6	1.00	8.4	13.8	3.50	<.001
20	2.12	4.2	1.00	5.7	10.1	1.00	<.001
22	1.36	3.4	0.00	3.9	7.9	0.00	0.001
24	1.12	3.2	0.00	3.2	7.2	0.00	0.005
30	3.00	6.7	0.00	6.6	11.1	3.00	0.003
36	4.53	8.9	0.00	8.7	13	4.00	0.005

SD: Standard deviation

Table 5: Mean percentage decrease in total acne load at different time intervals in both groups

Weeks	Treatment group A (%) (*n*=118)	Treatment group B (%) (*n*=116)	*P* value
2	28.60	11.99	<0.001
4	49.46	29.74	<0.001
6	65.28	47.46	<0.001
8	77.04	59.99	<0.001
10	85.59	71.66	<0.001
12	90.39	81.40	<0.001
14	93.50	87.30	<0.001
16	95.92	91.38	<0.001
18	96.95	93.77	<0.001
20	98.11	95.77	0.001
22	98.76	97.08	0.004
24	98.99	97.69	<0.016
30	97.34	94.66	0.004
36	96.03	92.82	0.006

Figure 1. On application of ANOVA with repeated measures, Group A was found to perform significantly better in terms of mean percentage decrease in TAL as compared with Group B during the whole study period (*P* value < 0.01 at each follow up).

When the results were evaluated according to severity of acne, in cases of severe acne a statistically significant difference in response rate was noted between both groups (Group A better than Group B) during the whole study period (*P* value < 0.005 at each follow up) [Figure 2], whereas in cases of moderate acne statistically significant difference between both groups (Group A better than Group B) was observed only up to 12 weeks (*P* value < 0.02) [Figure 3].

According to response criteria, a statistically significant difference in the response was observed between both groups (Group A better than Group B) during the whole study period, whereas at the end of therapy (24 weeks) the response was same in both groups. At the end of 24 weeks,

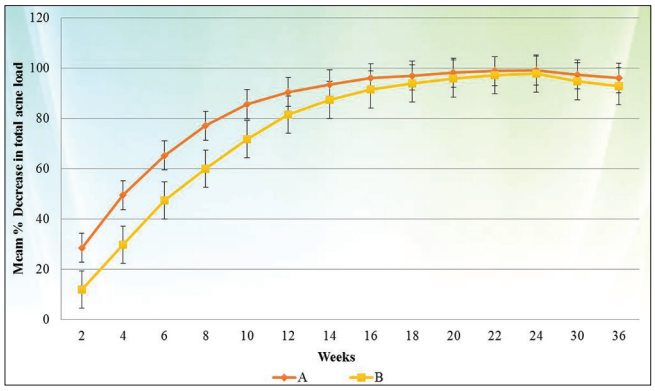

Figure 1: Response according to mean percentage decrease in total acne load at different time interval

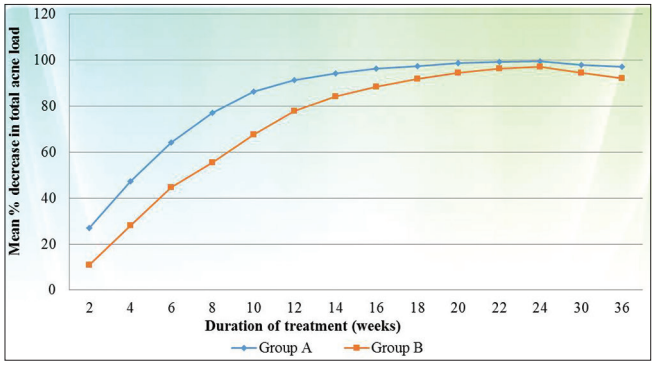

Figure 2: Comparison of mean percentage decrease in TAL between both groups in the cases of severe acne

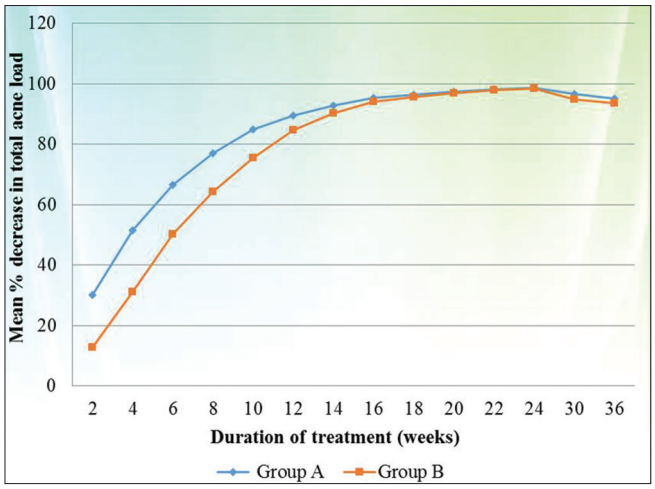

Figure 3: Comparison of mean percentage decrease in TAL between both groups in the cases of moderate acne

the excellent response in treatment groups A and B was seen in 98.3% and 93.96% patients, respectively (*P* 0.166), which at the end of 36 weeks decreased to 90.6% and 74.1% patients, respectively (*P* 0.004) (Figures 4–6: clinical photographs).

At 24 weeks 68.64% (Group A) and 56.03% (Group B) patients were acne free, which at the end of 36 weeks decreased to 50.84% and 39.65%, respectively (*P* 0.51) [Table 6].

Table 6: Percentage of the cases with various severities of acne at different time intervals

Weeks	0		4		8		12		16		20		24		36	
Treatment groups	A N-118	B N-116	A N-118	B N-116	A N-118	B N-116	A N-118	B N-116	A N-118	B N-116	A N-118	B N-116	A N-118	B N-116	A N-118	B N-116
Mild *n* (%)	0	0	16 (13.6)	11 (9.5)	51 (43.2)	47 (40.5)	71 (60.2)	74 (63.8)	53 (44.9)	67 (57.8)	42 (35.6)	49 (42.2)	33 (28)	44 (37.9)	50 (42.4)	58 (50)
Moderate *n* (%)	59 (50)	59 (50.9)	69 (58.5)	76 (65.5)	56 (47.5)	57 (49.1)	29 (24.6)	35 (30.2)	13 (11.0)	21 (18.1)	6 (5.1)	10 (8.6)	4 (3.4)	4 (3.4)	7 (5.9)	8 (6.9)
Severe *n* (%)	59 (50)	57 (49.1)	33 (28)	29 (25)	11 (9.3)	12 (10.3)	4 (3.4)	6 (5.2)	1 (0.8)	4 (3.4)	0 (0.0)	3 (2.6)	0 (0.0)	3 (2.6)	1 (0.8)	4 (3.4)
P value	0.999NS		0.471NS		0.906NS		0.789NS		0.49NS		0.246NS		0.300NS		0.51NS	

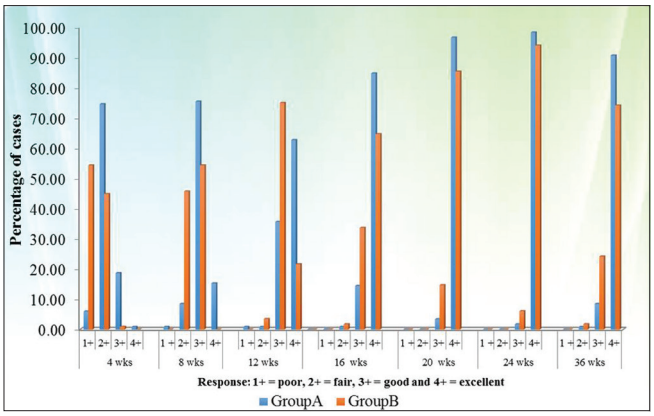

Figure 4: Comparison of response according to response criteria at different time intervals in both groups

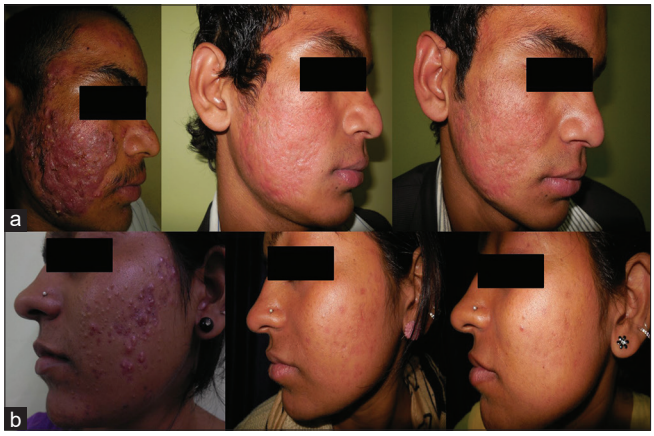

Figure 5: Clinical photographs of Group A patients: (a) Severe acne at 0, 24, and 36 weeks (b) Moderate acne at 0, 24, and 36 weeks

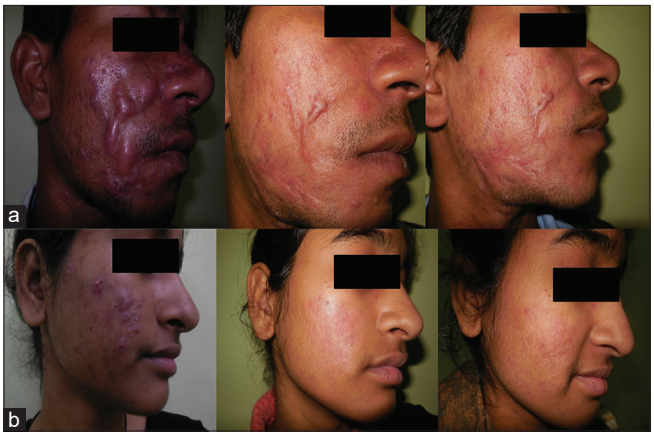

Figure 6: Clinical photographs of Group B patients: (a) Severe acne at 0, 24, and 36 weeks (b) Moderate acne at 0, 24, and 36 weeks

Most common adverse effects observed were cheilitis, dry skin, pruritus, dry eyes, hair fall, and other less-frequent adverse effects were also observed that are shown in Table 7. Although the frequency of adverse effects was slightly higher in Group A as compared with Group B, the difference was not statistically significant ($P > 0.05$).

DISCUSSION

In the era of smart phones with increasing popularity of social media and exchange of selfies between adolescents and young adults, the predominance of acne vulgaris in this psychologically labile age group coupled with its potentially lifelong sequelae makes it a matter of great financial and psychosocial concern. Oral isotertinoin continues to be the mainstay of therapy for acne, because of its efficacy, ability to target all the four pathophysiologic factors, high rates of permanent remission, and prevention of permanent scarring in acne.[11-14] Multiple studies have addressed that the duration of remission after initial course of isotretinoin is variable and appear to correlate with several potential contributory factors, for example, age of patient, male gender, cumulative dose administered, endogenous androgen-excess (ie, polycystic ovary syndrome), presence/persistence of macrocomedones, presence of sinus tracts, and patient adherence.[15] Recurrence of acne after an initial course of isotretinoin is not always of the same severity as before isotretinoin treatment.[16] Although isotretinoin was approved by the FDA for treatment of severe recalcitrant nodular acne, the appropriate use of isotretinoin also includes patients with moderate-to-severe acne or lesser degree of acne producing physical scarring or psychological distress and unresponsive to adequate conventional therapy.[17] It has been suggested that isotretinoin should be initiated early in the management of acne, even lower-dose isotretinoin (0.25–0.5 mg/kg/day for 24 weeks) offering a good balance between efficacy and dose-related adverse effects.[8,18] To decrease the incidence of adverse effects and to increase adherence of patients to therapy, the different low-dose isotretinoin regimens for different duration has been tried to treat acne in various studies (summarized in Table 8). The doses of isotretinoin that were used in these studies varied from 0.14 to 0.75 mg/kg/day. The cumulative dosage varied from 21 mg/kg to as high as 180 mg/kg with a mean dose of 49.71 mg/kg. On comparison of these studies, the efficacy of low-dose isotretinoin in the treatment of acne varied from 69% to 99.8% and the relapse rate varied from 0% to 39%.

Akman assessed the efficacy 0.5 mg/kg/day oral isotretinoin (10 days/month × six months or each day in first month then 10 days/month × five months or daily × six months) in moderate-to-severe acne and reported 90% resolution and relapse in 15% of cases.

Sardana *et al*. studied the efficacy of low-fixed dose isotretinoin (0.15–0.28 mg/kg/d × six months) plus topical 1% clindamycin gel in moderate grade of acne and observed clinically significant results in 87.54% of the patients, including 68.20% "very good" and 19.34% of "good" results.

In a recent study by Rao *et al*. (20 mg/d for a period of three months in moderate-to-severe acne), reported very

Table 7: Frequency of observed adverse effects

Adverse effects	Total (*n*=234)		Treatment group A (*n*=118)		Treatment group B (*n*=116)		*P* value
	No.	%	No.	%	No.	%	
Cheilitis	226	96.58	115	97.46	111	95.69	0.70
Dry skin	32	13.7	20	16.9	12	10.3	0.21
Dry mouth	5	2.1	3	2.5	2	1.7	0.98
Dry eyes	11	4.7	9	7.6	2	1.7	0.06
Dry nose	5	2.1	4	3.4	1	0.9	0.3
Facial erythema	6	2.6	3	2.5	3	2.6	0.69
Hair loss	10	4.3	7	5.9	3	2.6	0.34
Pruritus	16	6.8	11	9.3	5	4.3	0.20
Urticaria	7	3.0	4	3.4	3	2.6	0.9
Headache	3	1.3	2	1.7	1	0.9	0.98
Oral aphthous	1	0.4	1	0.8	0	0	0.99
Menstrual irregularities	**3 (*n*=45)**	**6.6**	**1 (*n*=20)**	**5**	**2 (*n*=25)**	**8**	**0.68**
Arthralgia	1	0.4	1	0.8	0	0	0.99
Myalgia	4	1.7	2	1.7	2	1.7	0.98
Abnormal lipid profile	5	2.13	4	3.38	1	0.86	0.37
Abnormal LFT	4	1.7	3	2.54	1	0.86	0.62
Forgetfulness	1	0.4	1	0.8	0	0	0.99
Pigmentation of face	1	0.4	0	0	1	0.8	0.99
Dermographism	1	0.4	0	0	1	0.8	0.99

Table 8: Comparison of different low-dose isotretinoin studies

Name of protocol	Authors	Number of patient	Treatment dose (mg/kg/d) and duration (weeks)	Degree of resolution (%)/relapse	Conclusion
Low dose	Hermes *et al.* (1998)[19]	94	0.43 (35)	99.8/33	Response was very good in 62.8% and good in 31.9% of patients
Low dose versus 0.5-1 mg/kg/d	Lefaki *et al.* (2003)[20]	32	0.15-0.4 (24)	69	Adverse effects low, beneficial effect on pre-existing scarring and relapse rate
Low dose	Amichai *et al.* (2006)[21]	638	0.3-0.4 (24)	93.7/5	Good efficacy, low incidence of severe adverse effects and lower cost than higher doses
Intermittent and daily	Akman *et al.* (2007)[22]	66	0.5 (24)	90/15	Effective in moderate acne, less adverse effects
Low dose, 20mg alternative day	Sardana *et al.* (2009)[23]	305	0.15-0.28 (24) + 1% Clindamycin	87.64/16.35	Almost equal efficacy, less adverse effects
Different regimens	Agarwal *et al.* (2011)[24]	120	0.4-1.0 (16)	93-96	Almost equal efficacy in mild-to-moderate acne
Low dose	De *et al.* (2011)[25]	70	0.3 (16) + pulse Oral Azithromycin	93.9/11.3	Therapy found to be effective in severe acne, acceptable side-effects
20 mg/d versus 20 mg bd × 7 days/month	El-Sherif NA *et al.* (2013)[26]	55	0.4-0.7 (16)	84.78/22-39	Equal efficacy in moderate acne, Intermittent regimen may be cost effective alternative
Low dose, 20 mg/day	Rao *et al.* (2014)[27]	50	0.4 (12)	90/4	Found to be effective in moderate-to-severe acne, low incidence of adverse effects

good results in 90% of participants and relapse in 4% of participants.

Most of these studies have found that different low-dose regimens of isotretinoin are effective in moderate-to-severe acne with a low incidence and severity of adverse effects.

In the present study, we have tried to compare the response of two different fixed low-dose regimens of oral isotretinoin in moderate to severe acne vulgaris. We have tried to correlate treatment response on the basis of various scales such as mean percentage decrease in TAL, response criteria, and disease severity. A significant reduction in mean TAL from the initial

mean TAL was observed in the both groups. The initial mean TAL in groups A and B was 113.3 ± 53.3 and 108.7 ± 57.5, respectively, which at the end of therapy at 24 weeks decreased to 1.12 ± 3.2 and 3.2 ± 7.2, respectively. We observed that Group A performed significantly better as compared with Group B during the whole study period. The mean percentage decrease in TAL in Group A and Group B at 24 weeks was 98.99% and 97.69%, respectively ((*P* value < 0.01), which decreased to 96.03% and 92.82%, respectively, at 36 weeks ((*P* value < 0.01). When both the groups were compared according to severity of acne, in the cases of severe acne significant difference was observed in terms of response between groups A and B until the end of 36 weeks. While in the cases of moderate acne, significant difference in the response between both groups was observed only up to 12 weeks.

According to response criteria, at 24 weeks the excellent response in groups A and B was observed in 98.3% and 93.96% patients, respectively (*P* 0.166) which at 36 weeks decreased to 90.6% and 74.1% patients, respectively (*P* 0.004).

Although our study found that number of acne-free patients seen at the end of therapy was decreased at the end of follow up; however, the patients developing acne recurrence had mild-grade acne.

The doses of isotretinoin used in the present study were in the range of doses used in previous studies; however, the degree of improvement observed during our study was higher than most of the previous similar low-dose isotretinoin studies, this may be due to either the use of topical 1% clindamycin phosphate gel as adjuvant or because of the longer treatment period in our study.

In the present study, both treatment regimens were well tolerated. Most common adverse effects noted in both groups were cheilitis (Group A, 97.46% and Group B, 95.69%) and dry skin (Group A, -16.9% and Group B, 10.3%). Other less frequent adverse effects observed were pruritus, dry eyes, hair fall, urticaria, dry mouth, dry nose, facial redness on sun exposure, menstrual irregularities, head ache, myalgia, arthralgia, oral aphthous, moderately increased triglycerides level, abnormal liver function test, forgetfulness, dermographism, and pigmentation of face. All the adverse effects were managed successfully; none of the patients required discontinuation of therapy because of adverse effects. Various previous studies also showed that low-dose isotretinoin has lesser adverse effects as compared with the conventional high-dose regimen. None of our patients in either group reported initial flare of their acne. Borghi *et al*. reported that isotretinoin in the doses of < 0.2 mg/kg reduces the risk of acne flare upon initiation of therapy.[28]

Various studies have reported many neuropsychiatric adverse effects.[29] However, in our study one patient developed forgetfulness, which was reported in none of the previous low-dose studies. In 1983, in a series, 6/110 (5.5%) of isotretinoin-treated patients (1–2 mg/kg/day) developed symptoms of depressed mood, crying spells, malaise, and forgetfulness.[30] In contrast to various previous studies of low-dose isotretinoin, none of the patients in our study showed relapse, which may be due to the short follow-up period of 12 weeks.

CONCLUSION

We conclude that fixed low-dose regimen of oral isotretinoin should be encouraged because of excellent response in moderate-to-severe acne with the advantage of lesser adverse effects, patient compliance, and cost effectiveness. In moderate acne 20 mg alternate day regimen can be preferred, but for severe acne 20 mg daily regimen is a better choice in the terms of response. Limitations of the current study were a small sample size and short follow-up period. Prospective studies with larger sample sizes and longer durations of follow up are therefore required.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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