Research Paper

Effect of Oral Isotretinoin on Anxiety and Depression in Patients with Acne

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Abstract

Objective: To study the side effect profile of systemic isotretinoin (ITT) and its association with anxiety and depression in the Indian population. **Materials and Methods:** In this prospective observational study, 300 patients of either gender, aged >12 years, taking oral ITT were evaluated for severity of acne by the visual analog scale (VAS) and psychiatric side effects with the Hamilton anxiety rating scale (HAM-A) and Montgomery Asberg Depression Rating scale (MADRS) at baseline up till the fourth visit. Software R version 3.6.0. was employed to analyze the data. **Results:** A significant improvement in VAS score was observed at baseline to final visit ($P = 0.001$). Significant increase in MADRS score was observed at baseline to final visit ($P < 0.05$) with mild and moderate depression in four (1.3%) and two patients (0.6%), respectively. On the contrary, a significant decrease in HAM-A score was observed over the visits ($P < 0.05$). Xerosis-Pruritus (79.7%) and cheilitis (82.7%) were the most common side effects observed. A trend from regular menstrual cycles to irregular menstrual cycles was found with ITT. With respect to lipid profile, a significant difference was observed at baseline values to the final visit ($P < 0.05$). **Conclusion:** ITT has proven its efficacy in reducing the severity of acne. Although it showed an improvement in anxiety, a negligible association was found with depression. Hence, ITT can be used safely as its benefits outweigh its side effects.

Keywords: Acne, anxiety, cheilitis, depression, retinoids

Introduction

Isotretinoin (ITT) a first-generation synthetic retinoid derived from Vitamin A has been approved by the Food and Drug Administration for the treatment of acne vulgaris. Apart from acne vulgaris, it is used in a wide array of, off-label indications with proven efficacy (viz., rosacea, condyloma acuminatum, psoriasis, pityriasis rubra pilaris, hidradenitis suppurativa, and granuloma annulare). It effectively treats acne vulgaris by acting on all its pathogenetic mechanisms, such as comedolytic effect, anti-inflammatory effects, sebostatic effect, and its inhibitory effect on proliferation of Propionibacterium acnes.[1] However, ITT also has a black box warning suggesting the risk of depression, aggression, psychosis, and suicidality.[2] Mucocutaneous side effects are the most encountered side effects although, most of them are transient and diminish once the drug is stopped.[3] The spectrum of side effects of ITT is extensively documented, but its changing trends have not been studied very well.[2,3]

Systemic ITT and the occurrence of psychiatric disorders such as anxiety, depression, and suicidal tendency have been a controversial topic of debate among investigators.[4-6] According to published literature, till date there is no study in the Indian scenario to assess the association between depression, anxiety and suicidal tendency with systemic ITT therapy. Hence, this study aimed to evaluate the side effect profile of systemic ITT and its association with anxiety and depression in the Indian population.

Materials and Methods

Post Ethics Committee Clearance (KIMSDU/IEC-307/043/06/12/2017), the prospective, observational study was carried out for 1 year, between June 2017 and July 2018 in

Access this article online

Quick Response Code:

Website: www.jpharmacol.com

DOI: 10.4103/jpp.JPP_17_20

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How to cite this article: Nikam B, Jamale V, Ravikumar ST. Effect of oral isotretinoin on anxiety and depression in patients with acne. J Pharmacol Pharmacother 2020;11:113-8.

Received: 19-02-2020 **Revised:** 03-09-2020
Accepted: 03-10-2020 **Web Publication:** 23-12-2020

the Department of Dermatology, Venereology, and Leprology of a tertiary care teaching hospital in Karad, Maharashtra, India. Based on the large, retrospective review conducted by Brzezinski *et al*., the estimated prevalence of psychiatric side effects among patients (n = 3,525) treated with oral ITT is about 25.16%.[7] Hence, the sample size was estimated by using formula . $\left[N = \frac{4PQ}{d^2}\right]$ Therefore, a minimum sample of 297 participants was required. We recruited 300 patients to maintain an adequate sample size in case of any dropouts.

A total of 300 patients of either gender, aged >12 years, taking oral ITT for proven indications at standard recommended doses were included. A written informed consent was obtained from the patients (or parents if patients aged <18 years) prior to commencement of the study. Immunocompromised patients with a history of immunosuppressants, anticancer drugs, chronic infections such as tuberculosis and leprosy, chronic liver disorders, women of childbearing age group or those who were lactating, pregnant or planning to conceive were excluded. A follow-up was done for each patient regularly for a duration of 12 weeks; baseline, 1st visit (after 2 weeks), 2nd visit (after 4 weeks), 3rd visit (after 8 weeks), and 4th visit (after 12 weeks).

Before initiating the study, all patients were evaluated clinically and laboratory investigations were conducted for the diagnosis of any underlying disease (baseline). All patients were also advised not to go for blood donation and to stop all previous systemic or topical therapies (other than ITT) for similar indications. Changes in severity of acne was evaluated using visual analogue scale (VAS) on each visit.[8] At baseline, VAS for all patients was "0" as there was no improvement in acne severity. All patients were followed up throughout the course of the study to note development of side effects. Psychiatric side effects were evaluated using Hamilton anxiety rating scale (HAM-A; scale ranged from a total score of 0–56, where <17 indicates mild anxiety, 18–24 moderate, and 25–30 severe) and Montgomery Asberg Depression Rating scale (MADRS; scale ranged from a total score of 0–60, where 0–8 indicates no depressive symptoms, 9–17 mild depression, 18–34 moderate, and 35–60 severe).[9,10]

Statistical analysis

Data were analyzed using statistical software R version 3.6.0. Normality of the data was determined using the Shapiro–Wilk test. Continuous variables with normal distribution were presented as mean ± standard deviation. Categorical variables were presented as frequency and percentages. Continuous variables of both groups were compared using paired sample t-test and Wilcoxon-matched pairs test. A $P < 0.05$ was considered statistically significant at 95% confidence interval.

Results

Out of 300 patients, 166 (55.3%) were male and 134 (44.7%) were female with a mean age of 27.85 and 27.57 years, respectively. Majority of the patients (70.8%) were found in the 21–30 years of age group. The study sample consisted of 277 (92.3%) patients diagnosed with acne vulgaris and remaining 23 (7.7%) with lichen planus.

As the study progressed, a steady and continuous rise in VAS score was observed. After 15 days (viz., 1st visit), mean VAS increased to 20.40 with none of the patients at 1st visit showing 100% improvement in disease severity. There was consistent and steady improvement in VAS score at each visit with significant difference to the baseline score [Table 1].

During the study, the mean oral ITT dose was in the range of 10.24–26.84 mg/day (0.17–0.44 mg/kg/day). Systemic ITT therapy was associated with a wide array of side effects [Table 2]. Cheilitis was the major side effect observed, initially at 1st visit 190 (63.3%) and eventually the count raised to 248 (82.7%) patients by the 4th visit. Similarly, xerosis and pruritus showed an immediate rise in the number of affected patients (207; 69%), within 15 days (viz., 1st visit). The eye was the major organ prone to side effects namely ocular irritation reported by 62 (20.6%) patients at 1st visit followed by 104 (34.6%), at 2nd visit, 173 (57.6%), at 3rd visit, and 209 (69.7%) at 4th visit. Cutaneous infection with *Staphylococcus aureus* was seen in 20 (6.7%) patients on the 1st visit and the number gradually increased to 149 (49.7%) patients on the 4th visit. Epistaxis could be a consequence of nasal mucosal dryness as it was seen in 68 (22.6%) patients on the 1st visit to 149 (49.7%) patients on the 4th visit. Feeling of thirst caused by oral mucosa dryness was seen in 7 (2.3%) patients on the 1st visit to 84 (28%) patients on the 4th visit. Retinoid dermatitis was seen in 2 (0.7%) patients on the 3rd visit however, treatment was not discontinued. A trend from regular menstrual cycles to irregular menstrual cycles (skipped menses) was observed with systemic ITT [Table 3].

Statistically, a significant difference was observed between the mean baseline score (0.02) of MADRS and mean score at each visit. However, the mean score of MADRS at all visits individually was below the minimum range of depression scale (0–8; no depressive symptoms). However, at the 4th visit, four out of 300 patients had MADR score in the range of mild depression (16.7 ± 0.5) and two patients were in the range of moderate depression (19 ± 1.4). On the contrary, a significant decrease in anxiety was observed over the visits [Table 4].

Statistically, no significant difference ($P > 0.05$) was observed between mean baseline values of hemoglobin,

Table 1: Mean visual analog scale score from baseline to follow-up visits

Follow-ups	VAS (mean±SD)	*P**
Baseline	0.00	-
1st visit	20.4±4.79	0.00001
2nd visit	37.82±7.24	0.00001
3rd visit	64.28±7.25	0.00001
4th visit	89.58±6.47	0.00001

*Paired sample *t*-test. VAS=Visual analog scale; SD=Standard deviation

Table 2: Side effects may arise from isotretinoin use during the study

Side effects	1st visit	2nd visit	3rd visit	4th visit	Males	Females
	n=300, *n* (%)				*n*=166, *n* (%)	*n*=134, *n* (%)
Cutaneous side effects						
Exfoliation	58 (19.3)	125 (41.6)	161 (53.6)	169 (56.3)	91 (54.8)	78 (58.2)
Xerosis and pruritus	207 (69)	235 (78.3)	237 (79)	239 (79.7)	133 (80)	107 (79.8)
Pyogenic granuloma	0	1 (0.3)	2 (0.6)	4 (1.3)	2 (1.2)	2 (1.5)
Hyperpigmentation	1 (0.3)	3 (1)	9 (3)	10 (3.3)	6 (3.6)	4 (3)
Hyperhidrosis	10 (3.3)	14 (4.7)	19 (6.3)	25 (8.3)	13 (7.8)	12 (8.9)
Photosensitivity	143 (57.6)	186 (62)	198 (66)	200 (66.7)	108 (65)	92 (68.6)
Sticky skin	1 (0.3)	4 (1.3)	7 (2.3)	8 (2.7)	7 (4.2)	1 (0.7)
Retinoid dermatitis	0	0	2 (0.6)	2 (0.6)	0	2 (1.5)
Staph. aureus infection	20 (6.7)	51 (17)	113 (37.7)	149 (49.7)	81 (48.8)	68 (50.7)
Hair and nail side effects						
Thinning of hair	63 (21)	108 (36)	162 (54)	188 (62.7)	107 (64.4)	81 (60.4)
Dry hair	16 (5.3)	16 (5.3)	20 (6.7)	30 (10)	11 (6.6)	19 (14)
Onycholysis		1 (0.3)	1 (0.3)	1 (0.3)	1 (0.6)	0
Fragility of nails	134 (44.7)	187 (62.3)	211 (70.3)	213 (71)	117 (70.4)	96 (71.6)
Oral and mucosal side effects						
Cheilitis	190 (63.3)	230 (76.7)	245 (81.7)	248 (82.7)	137 (82.5)	111 (82.8)
Dryness of mouth	7 (2.3)	62 (20.7)	71 (23.7)	84 (28)	48 (28.9)	36 (26.9)
CNS related side effects						
Headache	90 (30)	149 (49.7)	188 (62.7)	211 (70.3)	114 (68.7)	97 (72.4)
Somnolence	0	0	0	1 (0.3)	1 (0.6)	0
Dizziness	0	0	1 (0.3)	3 (1)	2 (1.2)	1 (0.7)
Insomnia	0	1 (0.3)	8 (2.7)	20 (6.6)	12 (7.2)	8 (6)
Ophthalmic side effects						
Ocular irritation	62 (20.7)	104 (34.7)	173 (57.7)	209 (69.7)	114 (68.7)	95 (70.9)
Conjunctivitis	15 (5)	17 (5.7)	23 (7.7)	33 (11)	15 (9)	18 (13.4)
Reduced night vision	0	0	1 (0.3)	1 (0.3)	0	1 (0.7)
Persistent dry eyes	1 (0.3)	2 (0.6)	7 (2.3)	12 (4)	6 (3.6)	6 (4.4)
ENT related side effects						
Epistaxis	68 (22.7)	127 (42.3)	146 (48.6)	149 (49.7)	74 (44.5)	75 (56)
Nasal mucosa dryness	201 (67)	222 (74)	233 (77.7)	234 (78)	129 (77.7)	105 (78.3)
Musculoskeletal side effects						
Back pain	70 (23.3)	144 (48)	183 (61)	187 (62.3)	100 (60.2)	87 (64.9)
Gastrointestinal side effects						
Nausea, vomiting	109 (36.3)	168 (56)	201 (67)	206 (68.7)	109 (65.7)	97 (72.4)
Diarrhea	0	0	1 (0.3)	6 (2)	4 (2.4)	2 (1.7)
Miscellaneous						
Acne flare	56 (18.7)	75 (25)	96 (32)	112 (37.3)	58 (34.9)	54 (40.2)
Dry vulva	6 (2)	6 (2)	6 (2)	6 (2)	0	6 (4.5)

Table 3: Menstrual status during the treatment course with isotretinoin

Follow-ups	Regular menses	Irregular menses	Dysmenorrhea	Menopause
	n (females)=134, *n* (%)			
Baseline	106 (79)	1 (0.7)	0	0
2nd visit	98 (73)	9 (6.7)	32 (23.9)	5 (3.7)
4th visit	95 (70.9)	12 (8.9)	32 (23.9)	5 (3.7)

total leukocyte count, total bilirubin, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, serum urea, serum creatinine, serum amylase and the mean values on the 4th visit. However, alkaline phosphatase, total cholesterol, serum triglycerides, high-density lipoprotein, low-density lipoprotein (LDL), and very LDL showed significant differences ($P < 0.05$) [Table 5].

Discussion

In total, 300 patients taking oral ITT for various proven indications were enrolled in the study. Cutaneous disorders are themselves known to cause anxiety and depression in patients. A significant decrease in mean HAM-A score with each visit was observed. This is comparable to a study conducted by Ferahbas *et al*., in which a significant improvement in anxiety was found with ITT. The decrease in anxiety score is probably due to the role of ITT on improvement of disease severity.[11] A high percentage of dermatology research states that, there is no casual relation between ITT and depression by considering the postulate that acne causes depression and anxiety; treating acne with ITT is a way to manage these mood disorders (improved self-image).[12-18] Halvorsen *et al*. conducted a large cross-sectional study on Norwegian adolescents and supports an association between acne and social impairment, mental health problems, and suicidal ideation.[13] In contrast, Magin *et al*. established no association between presence of acne (or acne severity) and measures of anxiety and depression.[19] The present study findings were in concordance with recent studies, where depression occurs in a lesser proportion of ITT-treated acne patients.[20-22] Kaymak *et al*. reported the incidence of depression in one patient among 100 acne vulgaris patients who were treated with ITT.[14] On the contrary, Yesilova *et al*. reported significant improvement in clinical depression with systemic ITT therapy.[22] Hahm *et al*. discussed that improvement in depression is brought about majorly by quality of life in association with acne improvement (basis on the assessment of psychological and social effects of Acne) rather than by improvement in acne grade.[12] Kontaxakis *et al*. reported that patients with a family history of mental illness are more susceptible to depression during the course of treatment with ITT.[23] However, in our study, we could not correlate study findings with family history. As depression is a multifactorial disorder, there were no proven mechanisms of depression caused by systemic ITT. However, there are some hypothesis on association between ITT and depression, such as hypothalamic-pituitary-adrenal axis hyperactivity secondary to increased retinoic acid signaling, inhibition of biotinidase, and altered synthesis of neurotransmitters (viz., dopamine, norepinephrine, and serotonin) secondary to increased concentration of homocysteine.[24,25] Research indicates that these depressed patients may be highly susceptible to other central nervous system related side effects of ITT, such as headache. All of our patients who were in the clinical range of depression (as per MADRS) complained of severe headache.[26] Although ITT is constantly debated owing to its role in causing major depressive condition and suicidal ideation, none of the patients reported any suicidal tendencies. However, a cohort study by Anders Sundström *et al*. suggested that increased suicidal tendency was observed in patients only with a previous history of similar episodes and psychiatric disturbances.[27]

ITT is known to cause menstrual irregularities. Kwon *et al*. reported menstrual abnormalities such as skipped menses in 20% patients which returned to normal on discontinuation of ITT therapy.[28] In the current study, complaints of skipped menses and dysmenorrhea increased gradually over time. However, dysmenorrhea or pain during menstruation with

Table 4: Mean scores of Montgomery- Asberg Depression Rating Scale and Hamilton Anxiety Rating Scale-A during the treatment course with isotretinoin

Follow-ups	MADRS	*P**	HAM-A	*P**
Baseline	0.02±0.17	-	12.13±3.58	-
1st visit	0.17±0.97	0.0173	9.76±2.94	0.00001
2nd visit	0.43±1.64	0.00001	7.08±3.0	0.00001
3rd visit	0.88±2.27	0.00001	4.23±2.92	0.00001
4th visit	1.39±2.65	0.00001	1.69±2.56	0.00001

*Wilcoxon-matched pairs test. HAM-A=Hamilton anxiety rating scale; MADRS= Montgomery- Asberg Depression Rating Scale

Table 5: Mean comparison of baseline clinical investigations with final visit

Investigations	Baseline	4th visit	*P**
Hb (grams/deciliter)	11.43±1.64	11.46±1.69	0.4914
TLC (cells/microliter)	8342.76±1781.87	8271.20±1740.14	0.2985
BUN (milligram/deciliter)	23.34±5.03	23.54±4.68	0.2559
Sr. creatinine (milligrams/deciliter)	0.99±0.75	0.98±0.75	0.2009
Total bilirubin (milligrams/deciliter)	0.66±0.15	0.64±0.18	0.0173
SGOT (units/liter)	23.35±4.71	23.72±3.53	0.1484
SGPT (units/liter)	25.37±7.14	25.29±4.93	0.8383
ALP (international units/liter)	84.132±16.87	87.132±17.67	0.999
Sr. amylase (units/liter)	74.21±23.78	74.30±2373	0.1045
Total cholesterol (milligrams/deciliter)	160.91±10.75	163.78±21.23	0.0251
Sr. triglycerides (milligrams/decilitre)	80.45±9.78	82.16±14.30	0.0096
HDL (milligrams/deciliter)	35.89±5.75	35.35±5.84	0.0090
LDL (milligrams/deciliter)	82.32±8.84	83.87±17.05	0.1148
VLDL (milligrams/deciliter)	22.52±2.61	22.84±3.1	0.0031

Hb=Hemoglobin; TLC=Total leukocyte count, SGOT=Serum glutamic oxaloacetic transaminase, SGPT=Serum glutamic pyruvic transaminase; ALP=Alkaline phosphatase; HDL=High-density lipoprotein; LD =Low-density lipoprotein; VLDL=Very low-density lipoprotein

ITT was reported for the first time and this might be due to excessive mucosal dryness caused by systemic ITT therapy.

Among cutaneous side effects, xerosis, and pruritus of skin were the most common side effect observed (79.7%). A study conducted by Rao *et al*. reported 84% incidence of xerosis in patients with ITT.[29] Pyogenic granuloma, also known as lobular capillary hemangioma, a rare condition associated with systemic ITT therapy. In the present study, four (1.3%) patients had pyogenic granuloma. Armstrong and Weinstein also reported four cases of pyogenic granuloma with systemic ITT therapy.[30] Fragility of nails was observed in 213 (71%) patients, one (0.3%) patient had onycholysis of toenail. Onder *et al*. also reported fragility of nails and onycholysis with systemic ITT therapy.[31] Fragility of nail can be correlated to the effect of systemic ITT. Nail side effects such as nail shedding, onychoschizia, and fragility are also reported as result of desquamative dermatitis induced by Etretinate therapy.[32] Cheilitis was observed as the commonest side effect (82.7%) in the present study, whereas Tahir CM reported that all the patients undergoing ITT therapy in their study showed cheilitis (100%).[33] The reason for this discrepancy might be the presence of other conditions like weather, sun exposure, the habit of frequent lip licking or nutrient and vitamin deficiency in their study population.

The present study has a few limitations. First, concomitant medications such as azithromycin (for acne vulgaris) and systemic corticosteroids (for lichen planus) that were taken by patients could interfere with the occurrence of side effects as well as disease severity. However, concomitant medications were taken by patients only for 2 months, while follow up was done for 3 months. Occurrence and persistence of side effects as a gradual increasing trend beyond 2 months, suggest that the effect of concomitant medications was very minimal. Second, the lack of a control group making interpretation of findings difficult.

Conclusion

ITT has proven its efficacy in reducing the severity of acne. Although it has shown improvement in anxiety, it causes depression in small number of patients. Hence, ITT can be used safely as its benefits outweigh its side effects.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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