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Original Article

# Efficacy and adverse effects of systemic isotretinoin therapy

**Ch. Muhammad Tahir**

Department of Dermatology, WAPDA Teaching Hospital Complex, Lahore.

**Abstract**

***Objective*** To determine the efficacy and frequency of adverse effects of systemic isotretinoin therapy in patients of acne vulgaris.

***Patients and methods*** All acne patients attending OPD from January, 2007 to December, 2009 at WAPDA Hospital Complex, Lahore fulfilling the inclusion criteria were enrolled and treated with isotretinoin 1mg/kg after baseline investigations. Patients were followed up fortnightly for clinical improvement and side effects.

***Results*** Out of 250 patients, there were 112 (44-8%) males and 138 (55.2%) females; age range 18-30 years. Two patients discontinued therapy due to drug-related side effects so that 248 patients were evaluable. Clinical improvement was 100% at end of 16 weeks. Similarly, all patients (100%) had suffered from some adverse effects.

***Conclusion*** Isotretinoin is a very effective therapy for moderate to severe acne; however, treated patients suffer from bearable side effects.

***Key words***
Isotretinoin, acne vulgaris, efficacy, adverse effects.

## Introduction

Acne is a chronic inflammatory disease of pilosebaceous unit, clinically characterized by comedones, papules, pustules, nodules, cysts and in some cases scarring.[1] It is the most common dermatological disorder affecting approximately 85% of individuals between 12-24 year of age.[2] There is no mortality associated with this disease but often there is significant psychological morbidity.[3] *Propionibacterium acnes* is now believed to contribute to inflammatory stages of the condition.

Treatment of acne depends on the type and severity of disease and includes topical and oral medications. Topical compounds are retinoids, benzoyl peroxide and antibiotics while antibiotics, isotretinoin and cyproterone acetate are commonly used oral compounds.[4]

Effective treatment in acne is important to prevent scarring and psychological distresses. Conventional topical and systemic anti-acne medicines in use are not much effective in relapsing and nodulocystic acne (with consequent complications like scarring and pigmentation). Modalities like anti-androgens play a role but there use is gender limited.[5]

Isotretinoin, 13-cis-retinoic acid, is a retinoid which produces miraculous response in a short period and can prevent complications.[6] It counteracts the pathogenic factors that contribute to development of acne.[7,8] Studies

**Address for correspondence**
Dr. Ch. Muhammad Tahir
Head Department of Dermatology,
Wapda Teaching Hospital Complex,
210-Ferozepur Road Lahore.
E-mail: drtahirchskin@hotmail.com

show that it produces changes in surface skin lipids composition[9] due to marked inhibition of sebaceous gland activity.[10] It reduces sebaceous gland size up to 90% by decreasing proliferation of basal sebocytes, suppressing sebum production and inhibiting sebocytes differentiation *in vivo*. It also causes significant reduction in microbial flora which persists for sometime even after discontinuation of therapy.[11,12] All these effects make it an effective treatment for acne refractory to other therapies.

It is a far safer compound[13] but sometimes can cause serious side effects.[14] Adverse effects appear intermittently, are reversible and are dose related.[15,16] Some of the most common ones are dryness of skin, lips, mouth and nasal mucosa. Other side effects are facial or body rash, dryness of skin, itching, peeling of palms and soles, increased photosensitivity, epistaxis, cheilitis, bleeding and inflammation of gums, easily injured skin and increased fatigue. There may be some redness, dryness or irritation of eyes. There have been reports of depression, suicidal ideation, suicidal attempts and suicide in patients treated with isotretinoin.[9] Teratogenic potential necessitates cautious use in females of child bearing age.

The current study was aimed to determine the efficacy and frequency of adverse effects of isotretinoin in moderate to severe acne.

## Patients and methods

The current study was carried out in outpatient Department of WAPDA Teaching Hospital Complex Lahore (affiliated with Central Park Medical College, Lahore) from January, 2007 to December, 2009. All patients of both sexes having moderate to severe acne, according to Global acne grading system,[17] who were not on other medications for last three months were enrolled. Children were ruled out. Written consent was taken from married ladies regarding contraception and side effects were explained. A daily dose of 1 mg/kg body weight was started. Dose calculated nearest to multiple of 20s according to age and was continued for 16 weeks. All possible effects and side effects were explained.

Baseline investigations like complete blood count, liver function tests, lipid profile and renal function tests were done and were repeated on monthly basis. Patients were followed up every four weeks for sixteen weeks. Topical adjuvant therapy, adapalene was also given at night time.

Assessment of patients was done every four weeks till 16 weeks. Every patient continued using the drug and the dose was not reduced in case of early improvement. Clinical improvement was graded as: 1-excelent [100% clearance of lesions], 2-good [75% clearance of lesion], 3-moderate [50-75% clearance of lesions], 4-slight [< 50% clearance of lesions].

## Results

In total, 250 patients were enrolled. There were 138 females (55.2%) and 112 (44.8) males. Age range was from 18-30 years. Mean age for males was 21.46 years and for females was 21.13 years. There were two dropouts due to drug-induced adverse effects so the results were evaluated in 248 patients.

Efficacy of the treatment is shown in **Table 1**. A continuous improvement was noticed and by the end of study period 100% of patients were free of their disease. Side effects were seen in 248 patients (100%). The frequency of encountered adverse effects is shown in **Table 2**. The vast majority had mucocutaneous reactions.

**Table 1** Efficacy of isotretinoin therapy in 248 patients.

| *Week* | *Mean improvement in acne lesions* |
|---|---|
| 4 | 20% |
| 8 | 60% |
| 12 | 75% |
| 16 | 100% |

**Table 2** Frequency of side effects seen in the study population (n=248)

| *Side effects* | *N (%)* |
|---|---|
| *Cutaneous* | |
| Cheilitis | 248 (100) |
| Dryness face | 200 (80.64) |
| Erythema face | 98 (39.51) |
| Skin dryness | 84 (33.87) |
| Acne flare | 80 (32..25) |
| Thinning of hair | 52 (20.96) |
| Pruritus | 29 (11.69) |
| *Mucosal* | |
| Dry oral mucosa | 35 (14.11) |
| Visual disturbances including blurring and problems with contact lenses | 10 (4.03) |
| Epistaxis | 4 (1.6) |
| Red eyes | 2 (0.80) |
| *CNS* | |
| Headache | 18 (7.25) |
| Depression | 10 (4.03) |
| Dropouts due to head ache | 2 (0.80) |
| Insomnia | 2 (0.80) |
| *Miscellaneous* | |
| Thirst | 42 (16.93) |
| Musculoskeletal pains | 24 (9.67) |
| Impaired lipids | 4 (1.61) |
| Impaired LFTs | 3 (1.2) |
| Mild diarrhea | 1 (0.40) |

## Discussion

In our study, 100% of patients showed improvement of acne by 16 weeks of treatment. This testifies the notion that oral isotretinoin therapy remains the gold standard treatment for severe acne.[18] Many previous studies reported similar results. Ghaffarpour *et al*.[19] noted a cure rate of 96.7%, Nawaf-al-Mutairi *et al*.[20] had a cure rate of 95.5% while Md Abdul Wahab *et al*.[21] reported 100% cure rate in moderate to severe acne with isotretinoin. Our results confirm this, as cure rate was 100% in this study.

Isotretinoin induces a dramatic reduction in size and output of sebaceous glands, modulates keratinocyte maturation and adhesion and reduces the inflammatory component of acne as well.[22] It has been used safely and effectively to treat acneiform eruptions even in elderly patients.[23] There may be recurrences in one quarter of the patients which are responsive to repeat course of therapy.[24]

Because isotretinoin is a vitamin A analogue, many of the side effects seen with this drug are similar to the clinical findings in hypervitaminosis A syndrome.[25] Adverse effects observed in this study were similar to those previously reported by Kapadia *et al*.[6] Mucocutaneous toxicity is the most common and frequent adverse reaction associated with isotretinoin. Monitoring is also required for liver function tests, lipid levels and other blood parameters. In two large clinical trials with isotretinoin, mainly mucocutaneous adverse events were observed. Other significant adverse events (psychiatric disorders, pseudotumour cerebri, decreased night vision, corneal opacities, inflammatory bowel disease, hyperostosis, hepatotoxicity and hypertriglyceridemia) have also been reported.[26]

Flare of the acne is a commonly reported side effect and was observed in 80 (32.25%) patients while it was observed in 87% of the patients by Ahmed *et al*.(32)[27], 94% by Goulden *et al*.[15] and 99% by Al-Khawajah.[28]

As regards cheilitis, chapped lips are expected to occur in every patient[26,27] as occurred in 100% of our patients. It is also comparable with that by Amichai *et al*.[16] where cheilitis was seen in 91% of cases. Dry skin and facial rash or irritation are

reported in 50% of patients[16,26,27] while in our study dry skin was seen in 33.9% and facial erythema in 39.5%. These findings correlate with study by Ahmed *et al*.[27]

Dry nose is a problem for 30-50% of cases[29] while in our study dry nasal mucosa was seen in 14% and epistaxis in 1.6% of patients. In the study by Amichai *et al*.[16] 2.5% of patients had epistaxis. Similarly, dry eyes were reported to be seen in one fifth of patient[26] but visual disturbances including blurring of vision and problem with contact lenses was seen in only 10 cases (4%).

Headaches were reported by 18 (7.25%) patients while 5.2% of the patients experienced headache in the study by Ahmed *et al*.[27] There were two dropouts due to persistent and severe headache in our study.

Musculoskeletal aches and pains were seen in 24 (9.7%) patients while it was reported in 15% of cases by Mclane.[26] Impotence has been reported previously[15,30] but none of our patient reported this adverse effect. Impaired LFTs and lipid levels were relatively rare and seen in 4 (1.6%) and 3 (1.2%) patients, respectively. This is comparable with Jacobs *et al*.[31]

Insomnia was reported in only two cases while depression was seen in 10 (4.03%) patients. Given the prevalence of depressive symptoms in dermatological population, it is important to be aware of the risk factor for suicide. There is no evidence to support a causal connection between isotretinoin and major depression or suicide.[30,31]

## Conclusion

Isotretinoin is a very effective therapy for nodulocystic acne; however, all patients suffer from some sort of side effects which usually do not warrant discontinuation of therapy.

## References


1. Thiboutot DM, Strauss JS. Diseases of the sebaceous glands. In: *Fitzpatrick's Dermatology in General Medicine.6th edn.* New York: McGraw-Hill; 2003. p. 672-87
2. Bergfeld WF. Topical retinoids in management of acne vulgaris. *J Drug Dev Clin Pract* 1996; **8**: 151-60.
3. Wilson BB. Acne vulgaris. *Prim Care* 1989; **16**: 695-712.
4. Leyden JJ. A review of the use of combination therapies for the treatment of acne vulgaris. *J Am Acad Dermatol* 2003; **49**: 211-7.
5. Farreli LN, Strauss JS, Strainer AM. The treatment of severe cystic acne with 13-cis retinoic acid. *J Am Acad Dermatol* 1980; **3**: 602-11.
6. Kapadia N, Khalid G, Burhany T. 13-cis retinoic acid (Ro acutance) a miracle drug in nodulocystic acne. *Ann Abbassi Shaheed Hospital, Karachi* 2003; **8**: 432-4.
7. Ward A, Brogden RN, Heel RC *et al*. Isotretinoin. A review of its pharmacological properties and therapeutic efficacy in acne and other skin disorders. *Drugs* 1984; **28**: 6-37.
8. Brelsford M, Beute TC. Preventing and managing the side effect of isotretinoin. *Semin Cutan Med Surg* 2008; **27**: 197-206.
9. Strauss JS, Peck GL, Oslon TG *et al*. Sebum composition during oral 13-cis-retinoic acid administration. *J Invest Dermatol* 1978; **70**: 228-31.
10. Strauss JS, Strainer AM, Farreli LN, Downing DT. The effects of marked inhibition of sebum production with 13-cis retinoic acid on skin surface lipid composition. *J Invest Dermatol* 1980; **74**: 66-7.
11. Leyden JJ, McCindey KJ, Foflea AN. Qualitative and quantitative changes in cutaneous bacteria associated with systemic isotretinoin therapy for acne conglobata. *J Invest Dermatol* 1986; **86**: 390-3.
12. Ganceviciene R, Zouboulis CC. Isotretinoin: state of the art treatment for acne vulgaris. *J Dtsch Dermatol Ges* 2010; **8**: S47-S59.
13. Alcalay J, Landau M, Zucker A. Analysis of laboratory data in patients treated with

isotretinoin: Is there really a need to perform routine laboratory tests? *J Dermatol Treat* 2001; **12**: 9-12.
14. Wysowski DK, Swann J, Vega A. Use of isotretinoin (Accutane) in the United States: rapid increase from 1992 through 2000. *J Am Acad Dermatol* 2002; **46**: 505-9.
15. Goulden V, Layton AM, Cunliffe WJ. Long-term safety of isotretinoin as a treatment for acne vulgaris. *Br J Dermatol* 1994; **131**: 360-3.
16. Amichai B, Shemer A, Grunwald MH. Low dose isotretinoin in the treatment of acne vulgaris. *J Am Acad Dermatol* 2006; **54**: 644-6.
17. Doshi A, Zaheer A, Stiller MJ. A comparison of current acne grading system and proposal of a novel system. Int J Dermatol 1997;36:416-18.
18. Ingram JR, Grindlay DJC, Williams HC. Management of acne vulgaris: an evidence-based update. *Clin Exp Dermatol* 2010; **35**: 351-4.
19. Ghaffarpour G, Mazioomi S, Soltani-Arabshahi R, Seyed KS. Oral Isotretinoin for acne. *Drugs Dermatol* 2006; **5**; 878-82.
20. Al-Mutairi N, Manchanda Y, Nour-Eldin O, Sultan A. Isotretinoin in acne vulgaris: A prospective analysis of 160 cases from Kuwait. *J Drugs Dermatol* 2005; **27**: 34-40.
21. Wahab MA, Rahman MH, Monamie NS *et al*. Isotretinoin verses weekly pulse dose azithromycin in treatment of acne: a comparative study. *J Pak Assoc Dermatol* 2008; **18**: 8-13.
22. Goldfarb MT, Ellis CN, The uses of retinoids in dermatology. *Curr Opin Dermatol* 1997; **4**: 236-40.
23. Secukeran DC, Cunliffe WJ. Acne vulgaris in the elderly: the response to low-dose isotretinoin. *Br J Dermatol* 1998; **139**: 99-101.
24. White GM, Chen W, Wolde-Tsadik G. Recurrence rates after the first course of isotretinoin. *Arch Dermatol* 1998; **134**: 376-8.
25. Silverman AK, Ellis CN, Voorhees JJ. Hypervitaminosis A syndrome: a paradigm of retinoid side effects. *J Am Acad Dermatol* 1987; **16**: 1027-39.
26. Mclane J. Analysis of common side effects of isotretinoin. *J Am Acad Dermatol* 2001; **45**: S188-94.
27. Ahmed I, Wahid Z, Nasreen S. Adverse effects of systemic isotretinoin therapy: *J Pak Assoc Dermatol* 2005; **15**: 242-6.
28. Al-Khawajah MM. Isotretinoin for acne vulgaris. *Int J Dermatol* 1996; **35**: 212-5.
29. Cunliffe WJ. Management of adult acne and acne variants. *J Cutan Med Surg* 1998; **2** (Suppl): 7-13.
30. Bruno NP. Adverse effects of isotretinoin therapy. *Cutis* 1984; **33**:484-9.
31. Jacobs DG, Deutsch NL, Brewer M. Suicide, depression and isotretinoin: Is there a causal link? *J Am Acad Dermatol* 2001; **45**: S168-75.