Canixa Life Sciences

Derma Digest

Issue 4

Isotretinoin – Preventing physical and psychological scars due to acne since 3 decades

Acne – A condition with a 100% prevalence rate

Acne has been one of the most widespread diseases in dermatology.[1] Acne vulgaris is a condition that is experienced by nearly every individual at some point in life.[2] Majority of the adolescents (16 to 18 years of age) and about 50% of adults have acne during their lifetime. This condition can be quite severe in 60% of all teenagers. About 50% of the individuals who are between 12 and 20 years of age and suffering from acne will develop psychological or social problems.[3] The primary treatment of acne vulgaris has to consider the severity of the lesion, which has been classified into mild (papulopustular or comedonal), moderate (papulopustular or nodular) or severe (nodulocystic or conglobate).[4]

The multifactorial pathophysiology of acne vulgaris

The pathogenesis of acne vulgaris encompasses multiple pathways. Abnormal functioning of the pilosebaceous units leads to acne. The generation of the microcomedo, which is an important acne precursor, is associated with irregular follicular epithelial differentiation and is accountable for causation of acne. High sebum production, growth of *Propionibacterium acnes,* and inflammation also cause acne. Exposure to moisturizers, tars, halogenated hydrocarbons, and medical agents such as phenytoin, isoniazid, iodides, phenobarbital, lithium, ethionamide, and steroids can aggravate acne.[2]

Isotretinoin – Acts on all the pathogenic pathways of acne

Isotretinoin is the only therapy that alters all the major underlying factors associated with acne. The endogenous retinoids act by modifying DNA transcription with the aid of nuclear retinoic acid receptors. However, isotretinoin does not adhere directly to the retinoic acid receptors. It is a prodrug that is activated by sebocytes before binding to the retinoid receptors. It also causes a reduction in comedone formation, as it regulates keratinocyte maturation and adhesion. A reduction in sebocyte-mediated androgen synthesis, along with an 80% decline in sebum production within a month of treatment, has been reported with isotretinoin use. Isotretinoin not only reduces the total number of resistant bacteria on the skin, but also decreases neutrophil chemotaxis. This compound produces a long-term remission of acne in 70-89% of the patients, with the advantages continuing even after termination of its use. This is a feature that is in contrast to other treatment regimens.[2]

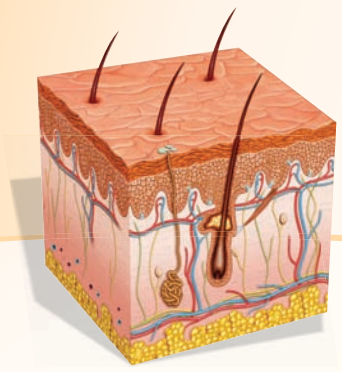
Isotretinoin – An efficacious agent in practically all patients[5]

Isotretinoin has been officially approved for the treatment of severe recalcitrant nodular acne that is not managed adequately with other available therapies like topical and oral antibiotics and oral contraceptive treatments. An international survey has confirmed that dermatologists all over the world prefer using isotretinoin for other indications such as acne that is not responding to other treatments, causing scarring, relapsing after discontinuation of medications, or leading to psychological stress. Thus, this medication can prove to be the drug of choice in cases ranging from severe-to-mild forms of acne. Additionally, this agent can be clinically favorable in patients with high sebum excretion levels, not responding adequately to an antibiotic regimen. Besides, antibiotic therapy can lead to resistance, which eventually restrains its efficacy and is also associated with a considerable number of side effects. Isotretinoin use has also proven to be a cost-effective modality in comparison with other acne therapies.[2]

Isotretinoin is useful for moderate-to-severe acne that is unresponsive to other available therapies. A study by Rao and colleagues proved that isotretinoin provided very good outcomes within 3 months in 90% of the patients with moderate-to-severe acne.[6] In a clinical trial by Sardana *et al*., a very good response was reported in 68.20% of the patients suffering from moderate acne, treated with both isotretinoin and an antibiotic.[7] An evaluation of the guidelines for the treatment of acne and the administration of isotretinoin has been provided in Table 1.[8]

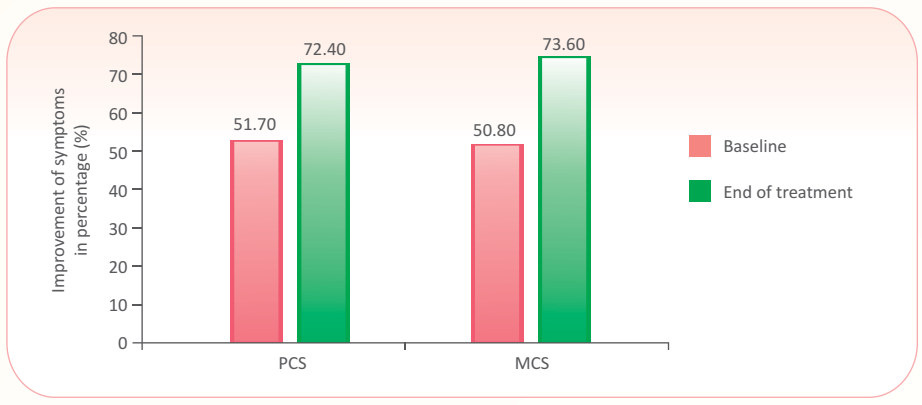
Table 1: Summary of guideline-based recommendations on use of isotretinoin in acne vulgaris

Source	Comments
Consensus on evidence-based practice in acne (Asian Working Group) [2011]	They recommend isotretinoin as a primary therapy for severe acne and second-tier treatment for moderate acne that is poorly responsive to other treatments; a target cumulative dose of 120-150 mg/kg must be reached over the treatment course
Evidence-based recommendations for pediatric acne (American Acne and Rosacea Society and American Academy of Pediatrics) [2013]	Isotretinoin at a starting dose of 0.5 mg/kg/day for the first 4 weeks, followed by an increase to 1 mg/kg/day is recommended. It is indicated for severe nodular acne, acne with scarring, and/or refractory inflammatory acne



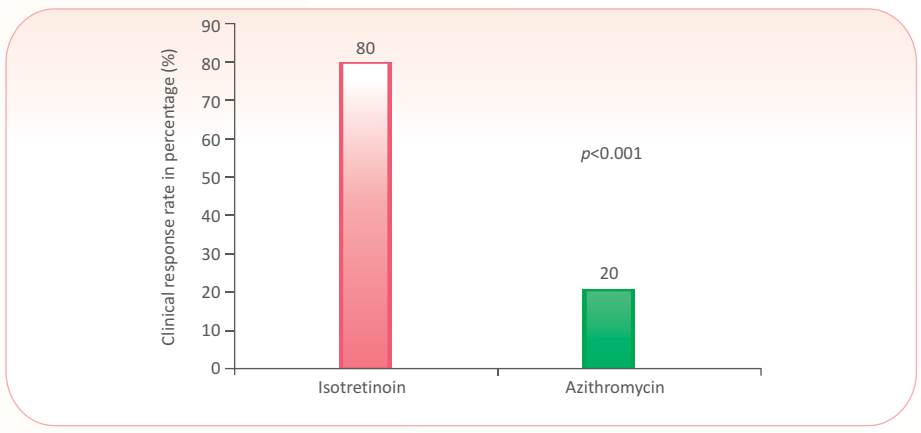
According to a study by Marron and colleagues, the negative impact of acne on the quality of life and the Hospital Anxiety and Depression Scale scores for anxiety and depression decreased significantly with the use of isotretinoin in patients with moderate acne. The mean level of patient satisfaction with improvement of symptoms attained in this study had been verified to be 84.4%. As per the Health Survey Short Form-36, both the physical component summary (PCS) and mental component summary (MCS) improved considerably with the treatment (Figure 1).[9]

Figure 1: Significant improvement in PCS and MCS with isotretinoin



In a study comparing isotretinoin with a weekly pulse dose of azithromycin in the treatment of moderate-to-severe acne, isotretinoin proved to be superior to the latter, since it acts on all the factors of acne. In addition, isotretinoin caused a decrease in the rate of relapse in comparison with azithromycin. An excellent clinical response was reported in 80% of isotretinoin patients as against only 20% of the patients treated with azithromycin (Figure 2).[10]

Figure 2: Comparison of the efficacy of isotretinoin and azithromycin in relieving acne



Micronized isotretinoin – A safe and effective formulation

Advantages of micronized[11] preparation:

- Decreasing the particle size of these drugs improves their rate of dissolution
- Fine grinding mills are used to micronize powders
- For each drug, micronization improved their digestive absorption, and consequently their bioavailability and clinical efficacy

The micronized formulation of isotretinoin, which possesses improved bioavailability, permits a 50% reduction in dosage without the requirement of simultaneous food consumption. The advantages of this form of isotretinoin include better compliance, reduction in mucocutaneous adverse reactions, and fewer alterations in lipid concentration, as compared to the standard isotretinoin treatment.[2] Isotretinoin has proved to be highly efficient in the management of the severe recalcitrant nodular acne. The use of micronized isotretinoin in these patients has been found to cause a decline in the risk of mucocutaneous events and hypertriglyceridemia.[12] A clinical trial by Strauss and colleagues studies the effects of micronized isotretinoin (n = 300) under fasted conditions or standard isotretinoin (n = 300) under fed conditions in the treatment of severe recalcitrant nodular acne.[13] The group A received single daily doses of 0.4 mg/kg of micronized isotretinoin without food, while the group B received 1.0 mg/kg per day of standard isotretinoin in two divided doses with food. Adverse events were monitored during 20 weeks of drug therapy. Researchers reported that adverse events in most body systems were generally lower in group A (patients receiving micronized isotretinoin).[13]

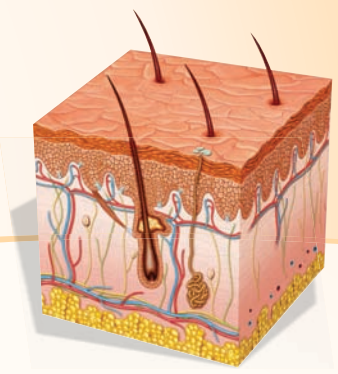
Conclusion

With over 30 years of experience in treating more than 5 million people with different forms of acne, isotretinoin has been validated as the best therapeutic agent for severe acne. The use of this agent has been expanded to include moderate forms of acne for averting the risk of physical and psychological scars.[2] Micronized isotretinoin has improved bioavailability, allows a 50% reduction in dose, thereby having better compliance and reduction in adverse events.[13]

References

1. Rigopoulos D, Larios G, Katsambas AD. The role of isotretinoin in acne therapy: Why not as first-line therapy? Facts and controversies. *Clin Dermatol.* 2010;28(1):24-30.
2. Lowenstein EJ. Isotretinoin made S.M.A.R.T. and simple. *Cutis.* 2002;70(2):115-20.
3. Acne, isotretinoin and depression. *Drug Ther Bull.* 2003;41(10):76-8.
4. Costa CS, Bagatin E. Evidence on acne therapy. *Sao Paulo Med J.* 2013;131(3): 193-7.
5. Rumsfield JA, West DP, Tse CS, Eaton ML, Robinson LA. Isotretinoin in severe, recalcitrant cystic acne: A review. *Drug Intell Clin Pharm.* 1983;17(5):329-33.
6. Rao PK, Bhat RM, Nandakishore B, Dandakeri S, Martis J, Kamath GH. Safety and efficacy of low-dose isotretinoin in the treatment of moderate to severe acne vulgaris. *Indian J Dermatol.* 2014;59(3):316.
7. Sardana K, Garg VK, Sehgal VN, Mahajan S, Bhushan P. Efficacy of fixed low-dose isotretinoin (20 mg, alternate days) with topical clindamycin gel in moderately severe acne vulgaris. *J Eur Acad Dermatol Venereol*. 2009;23(5):556-60.
8. Leyden JJ, Del Rosso JQ, Baum EW. The use of isotretinoin in the treatment of acne vulgaris: Clinical considerations and future directions. *J Clin Aesthet Dermatol.* 2014;7(2 Suppl): S3-S21.
9. Marron SE, Tomas-Aragones L, Boira S. Anxiety, depression, quality of life and patient satisfaction in acne patients treated with oral isotretinoin. *Acta Derm Venereol.* 2013;93(6):701-6.
10. Wahab MA, Rahman MH, Monamie NS, Jamaluddin M, Khondker L, Afroz W. Isotretinoin versus weekly pulse dose azithromycin in the treatment of acne – A comparative study. *Journal of Pakistan Association of Dermatologists.* 2008;18:9-14.
11. Chaumeil JC. Micronization: A method of improving the bioavailability of poorly soluble drugs. *Methods Find Exp Clin Pharmacol.* 1998;20(3):211-5.
12. Strauss JS, Leyden JJ, Lucky AW, Lookingbill DP, Drake LA, Hanifin JM, *et al*. Safety of a new micronized formulation of isotretinoin in patients with severe recalcitrant nodular acne: A randomized trial comparing micronized isotretinoin with standard isotretinoin. *J Am Acad Dermatol.* 2001;45(2):196-207.
13. Strauss JS, Leyden JJ, Lucky AW, Lookingbill DP, Drake LA, Hanifin JM, *et al*. A randomized trial of the efficacy of a new micronized formulation versus a standard formulation of isotretinoin in patients with severe recalcitrant nodular acne. *J Am Acad Dermatol.* 2001;45(2):187-95.

Derma Digest

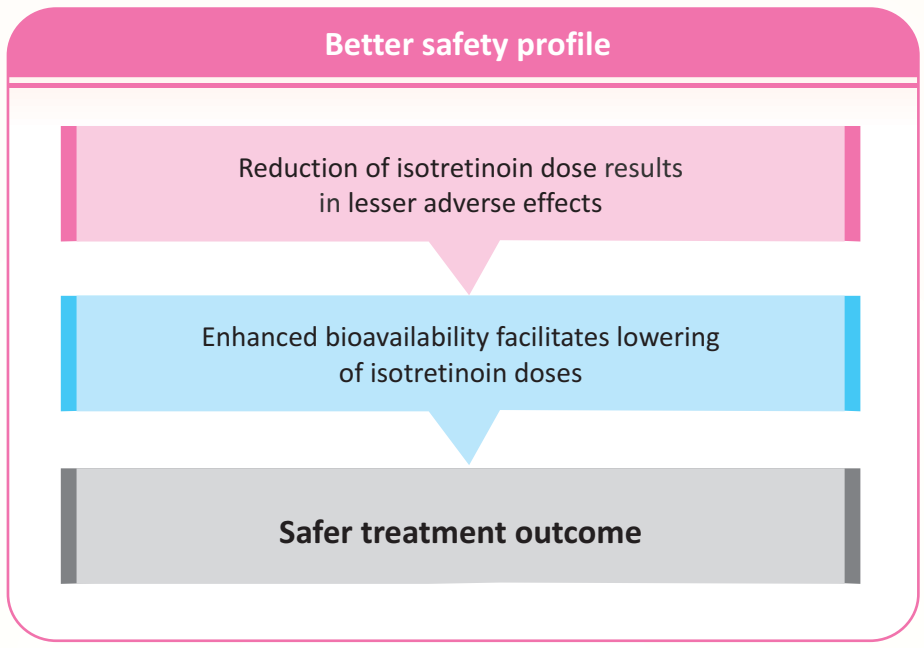


Derma trends

More towards improving clinical outcomes with micronized isotretinoin

- Oral isotretinoin revolutionized the treatment of acne, which is multifactorial in origin. This is the only drug that targets all the major etiologic factors implicated in acne
- A new micronized formulation of isotretinoin has enhanced bioavailability which allows for about a 50% lower dose to be taken once daily without the need for concomitant food ingestion
- Micronized isotretinoin increases compliance and offers a modest improvement in mucocutaneous side effects and lipid level changes compared with standard isotretinoin therapy

Figure 1: Advantages of micronized isotretinoin formulation



Source: Lowenstein EJ. Isotretinoin made S.M.A.R.T. and simple. *Cutis.* 2002;70(2):115-20.

Sardana K, Garg VK. Efficacy of low-dose isotretinoin in acne vulgaris. *Indian Journal of Dermatology, Venereology and Leprology.* 2010;76(1):7-13.

Case study

A case of severe acne

Dr. Anil Ganjoo
MD (Dermatology)
Senior Consultant Dermatovenereologist and Laser Surgeon at
Ganjoo Cosmetology and Skin Center, Delhi
Ex-president, Indian Association of Dermatologists, Venereologists and Leprologists (IADVL), Delhi
Recipient of the prestigious Dr Sardari Lal Memorial life time achievement award for meritorious contribution to the field of dermatology and lasers, awarded by the IADVL

Case presentation

A 23-year-old man reported to the doctor with complaints of painful and inflamed nodules along with pustules and comedones on his face and trunk. He had a history of acne for the past 4 years, and reported that it was affecting him socially, as it embarrassed him and lowered his self-esteem.

Medical history

- The patient was suffering from acne for the past 4 years
- He reported that he had tried topical treatments, including over-the-counter 5% benzoyl peroxide (BP) gels and washes, as well as multiple facial cleansing products. However, these treatments were not found to be very effective
- Six months ago, he consulted a physician who prescribed him a topical cream containing clindamycin along with oral azithromycin 500 mg thrice weekly for 4 weeks. Even this therapeutic regimen failed to produce the desired effect[1]

Family history

- None of his family members were reportedly suffering from any major illnesses

Examination

- The patient was apparently healthy, and the physical examination detected no other abnormalities
- Height: 5 feet 5 inches
- Weight: 51 kg

Examination of the facial skin

- Inflamed nodular lesions on the cheeks and the neck
- Pustules ++
- Comedones ++

Laboratory investigations

- Complete blood count: No abnormality was detected
- Fasting blood sugar: Within normal range
- Renal profile: Suggestive of normal renal function
- Liver function tests: Within normal limits
- Lipid profile: No evidence of dyslipidemia
- Urine routine: Normal findings

Diagnosis

- Severe acne with nodular lesions

Treatment

- Treatment was initiated with oral micronized isotretinoin 10 mg PO bid for 4 months

Treatment outcome

- On follow-up after a month, he reported that he was tolerating the medications well and his lesions had started to improve
- At the end of 4 months, the complete resolution of the nodular lesions, pustules, and comedones was noted
- Treatment with micronized isotretinoin evoked a good therapeutic response, and no relapse of acne was reported

Discussion

Acne is a chronic inflammatory disease of the pilosebaceous units that is commonly reported in adolescents. It may have a significant impact on the psychological state and social status of the individual. Majority of the cases of acne present with pleomorphic forms of lesions, namely comedones, papules, pustules, and nodules; and in rare cases, the patient may also report scarring. In such cases of acne, retinoids may be considered as effective therapeutic agents.[1]

In dermatology, the introduction of isotretinoin – a first generation synthetic retinoid – has been advocated as a major therapeutic advance in treating moderate-to-severe cases of acne vulgaris. Furthermore, it is reported to be effective in the management of acne vulgaris that is unresponsive to conventional treatment.[1]

Oral retinoids were earlier reserved for severe disease, affecting the patients physically and psychologically, but now they are being used quite often for moderate disease as well. Also, low dose isotretinoin is being used by a lot of workers, as it gives good results with less side effects.[1]

Micronized isotretinoin: An effective and safe option for severe acne

Since severe forms of acne have been associated with embarrassment and anxiety, effective treatment mandates the prevention of significant psychological and social impairment in such patients. Therefore, oral isotretinoin is considered to be an effective therapeutic option for the management of patients with severe acne.[2]

A novel formulation of isotretinoin, i.e. its micronized formulation, is more effective for treating acne patients, as compared to its standard form. It has been shown that 0.4 mg/kg of micronized isotretinoin is equivalent to 1.0 mg/kg of standard isotretinoin.[3] Also, the micronized form is associated with a lower risk of mucocutaneous events and hypertriglyceridemia, as compared to the standard form in patients with severe recalcitrant nodular acne.[2] Therefore, it can be recommended as an effective monotherapy option in acne management.

Use of the micronized form can be combined with oral azithromycin initially. This not only adds to the efficacy but also reduces the likelihood of retinoid flares which are a distinct possibility during the initial weeks of retinoid therapy.

References

1. Rao PK, Bhat RM, Nandakishore B, Dandakeri S, Martis J, Kamath GH. Safety and efficacy of low-dose isotretinoin in the treatment of moderate to severe acne vulgaris. *Indian J Dermatol.* 2014;59(3):316.
2. Akman A, Durusoy C, Senturk M, Koc CK, Soyturk D, Alpsoy E. Treatment of acne with intermittent and conventional isotretinoin: A randomized, controlled multicenter study. *Arch Dermatol Res.* 2007;299(10):467-73.
3. Kubba R, Bajaj AK, Thappa DM, Sharma R, Vedamurthy M, Dhar S, *et al.* Oral retinoids. *Indian J Dermatol Venereol Leprol.* 2009;75(Suppl S1):39-43.