IAA Consensus Document

Oral retinoids

Isotretinoin (13-cis-retinoic acid) is a derivative of retinol (vitamin A). It is easily the most potent antiacne agent available today, and the only one that addresses all pathogenic mechanisms.[1] Isotretinoin represents the single most important advance in acne therapeutics. It was clinically evaluated in the 1970's and the first seminal papers were published in the USA in 1979[2] and in the UK the following year.[3] Isotretinoin is a potent sebosuppressive. During isotretinoin therapy sebum production is reduced by 90% or more (to prepubertal levels).[4] The mechanism of action is antiandrogenic through competitive inhibition of 3-alpha-hydroxysteroid oxidation by retinol dehydrogenase resulting in reduced formation of dihydrotestosterone and androstenedione.[5] Isotretinoin also normalizes ductal hypercornification, and generally thins the epidermis to produce increased light reflectance – retinoid glow – that is much cherished by patients. Isotretinoin is the most comedolytic of all antiacne agents.[6] It indirectly lowers *P. acnes* counts, and exerts an anti-inflammatory effect.[1] Isotretinoin-induced clinical improvement is associated with lowered levels of porphyrins in the sebaceous follicles[7] and reduced concentrations of MMPs in the sebum.[8]

Isotretinoin should only be used by experts – those who know acne well and are well versed with all aspects of the drug. It is the first choice therapy for severe forms of acne, especially nodulocystic acne. It is also indicated in difficult and refractory acne. The latter is defined as less than 50% improvement with conventional therapy consisting of oral antibiotics and topical combinations.[8] Difficult acne includes acne conglobata, acne corporis, adult acne, androgenic acne, severe infantile acne, acne fulminans, and SAPHO syndrome. Isotretinoin is the most dependable acne treatment and may be justified in mild to moderate acne where scarring is imminent. Isotretinoin is also an accepted treatment for acne associated with psychologic distress.[9]

ORAL ISOTRETINOIN: INDICATIONS

- Nodulocystic acne
- Fulminant acne
- Acne corporis
- Difficult/recalcitrant acne
- Moderate acne if scarring is imminent
- Acne associated with psychologic distress

Isotretinoin is available in India as 5, 10, 20, 30, and 40 mg sofgel capsules. Isotretinoin is now generic in USA and EU. In India, it was generic from the time of introduction (2001). The dose of isotretinoin is 0.5–1.0 mg/kg body weight, in two divided doses given after meals. Isotretinoin absorption is only 20% in fasted state versus 40% in the fed state.[10] In young children, sofgels can be dissolved in warm milk. The treatment is continued till a cumulative dose of 120–150 mg/kg has been achieved.[10] This typically may take 6–8 months.

The clinical response is generally quick but may vary from patient to patient [Figure 59–61]. Truncal acne is slow to respond. Initial flares are sometimes observed

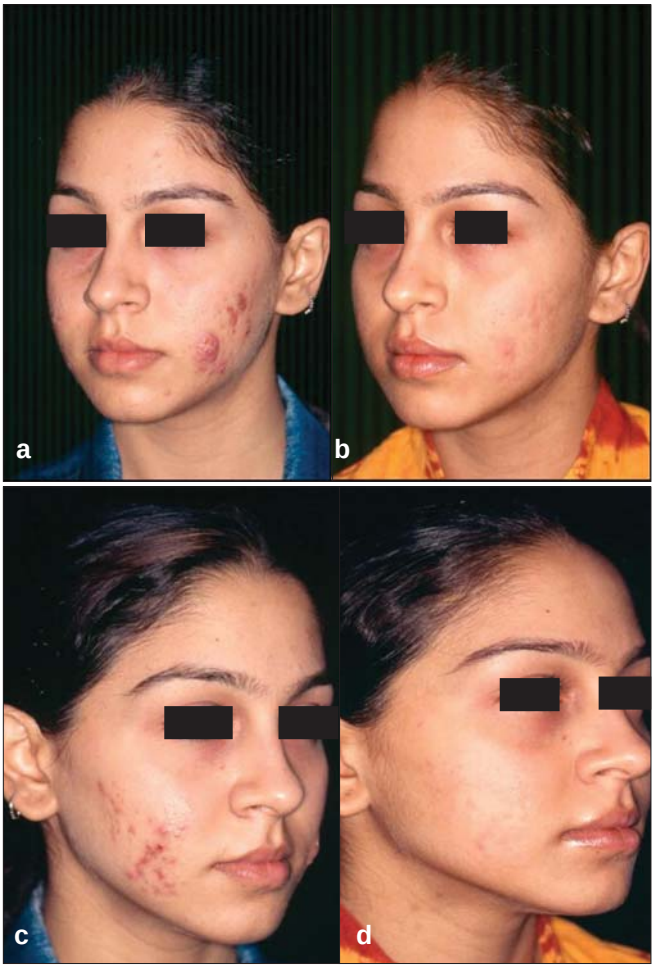

Figure 59: (a, b, c and d) Grade II acne with cysts, successfully treated with oral isotretinoin

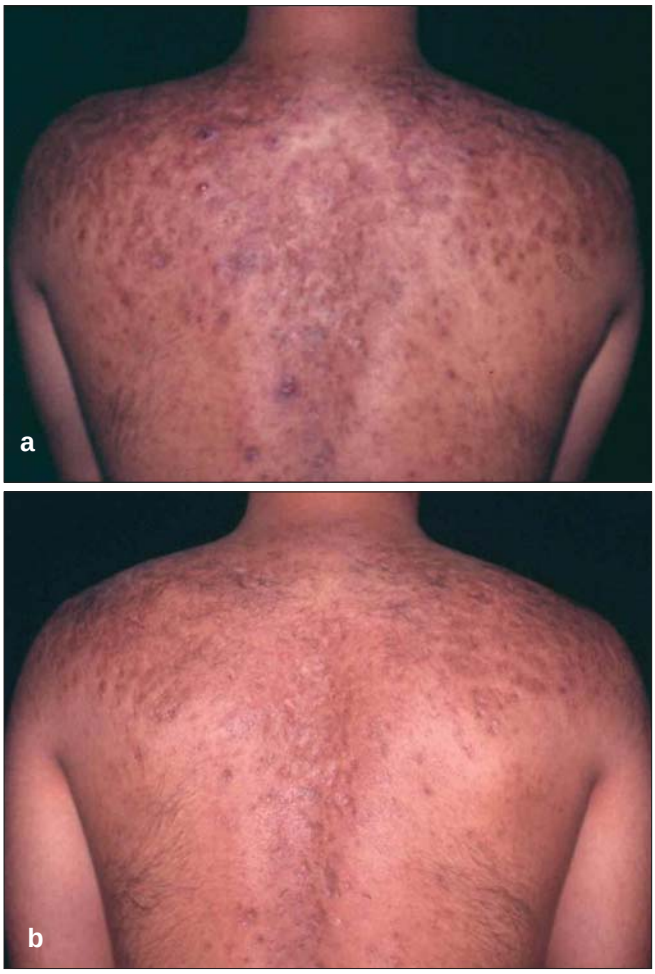

Figure 60: (a and b) Acne corporis (conglobata) before and after isotretinoin therapy

ORAL ISOTRETINOIN: DIFFERENT REGIMENS

Standard dosing	0.5–1.0 mg/kg daily in two divided doses
Pulse dosing	0.5 mg/kg/day for seven days each month
Low dosing	0.1–0.2 mg/kg daily for 6–12 months
Escalating dosing	20 mg o.d. x 1 month introductory dose increased in monthly steps to reach standard dosing
Intermittent dosing	Fifteen days treatment period alternating with 15 days of no treatment; not used in acne

Table 12: Isotetinoin adverse effects

Adverse effect	Comment
Cheilitis	May be severe, fissuring, bleeding, impetiginization
Dry nose	Occasional epistaxis
Dry eyes	Problematic for contact-lens wearers
Decreased night vision	Rare
Corneal ulcers/opacities	Very rare
Photosensitivity	Rare in Indians
Headaches	May indicate pseudotumor cerebri/overdose
Hair loss	Indicates overdose
Hyperostosis	Rare, dose-dependent
Elevated triglycerides	Common, reversible, occasionally precipitate pancreatitis
Elevated cholesterol	Uncommon, reversible
Hepatitis	Rare
Inflammatory bowel disease	Rare
Rhabdomyolysis	Rare, idiosyncratic, dose-independent
Teratogenicity	
Depression, suicidal ideation	Controversial

acne relapses in 20–40% of patients, typically 6–12 months after cessation of therapy.[11] There are other protocols. Isotretinoin has been successfully given as pulse dosing in adult acne.[12] Goulden *et al*. treated 80 patients with isotretinoin 0.5 mg/kg for one week every four weeks for six months; acne resolved in 68 patients; 26 patients relapsed after one year.[13] IAA members have used pulse dosing and found it effective. An escalating dose protocol is advised to prevent acne flares and a dose taper is employed to extend the course of isotretinoin with a view to minimize relapses.

A micronized version of isotretinoin has been introduced (not as yet available in India) which can be given in fasted conditions, as a single daily dose of 0.4 mg/kg which, reportedly, is equivalent to 1.0 mg/kg of standard isotretinoin.[10] Isotretinoin is viewed as adequate monotherapy in most forms of acne. However, many experts elect to coprescribe antibiotics.[4] Several of us in the IAA frequently do the same. We coprescribe antibiotics in the early part of the treatment for a speedier result. Some of us also coprescribe antiandrogens (EE-CPA, spironolactone) with isotretinoin to augment efficacy [Figure 62]. Such therapeutic maneuvers are justified in cases of under response. Often low dose isotretinoin (20 mg/day), or pulse dosing (vide supra) during the tablet-free periods of combination contraceptive pill (EE-CPA), does the trick. With isotretinoin–antibiotic coprescription, there is a higher risk of intracranial hypertension, and with

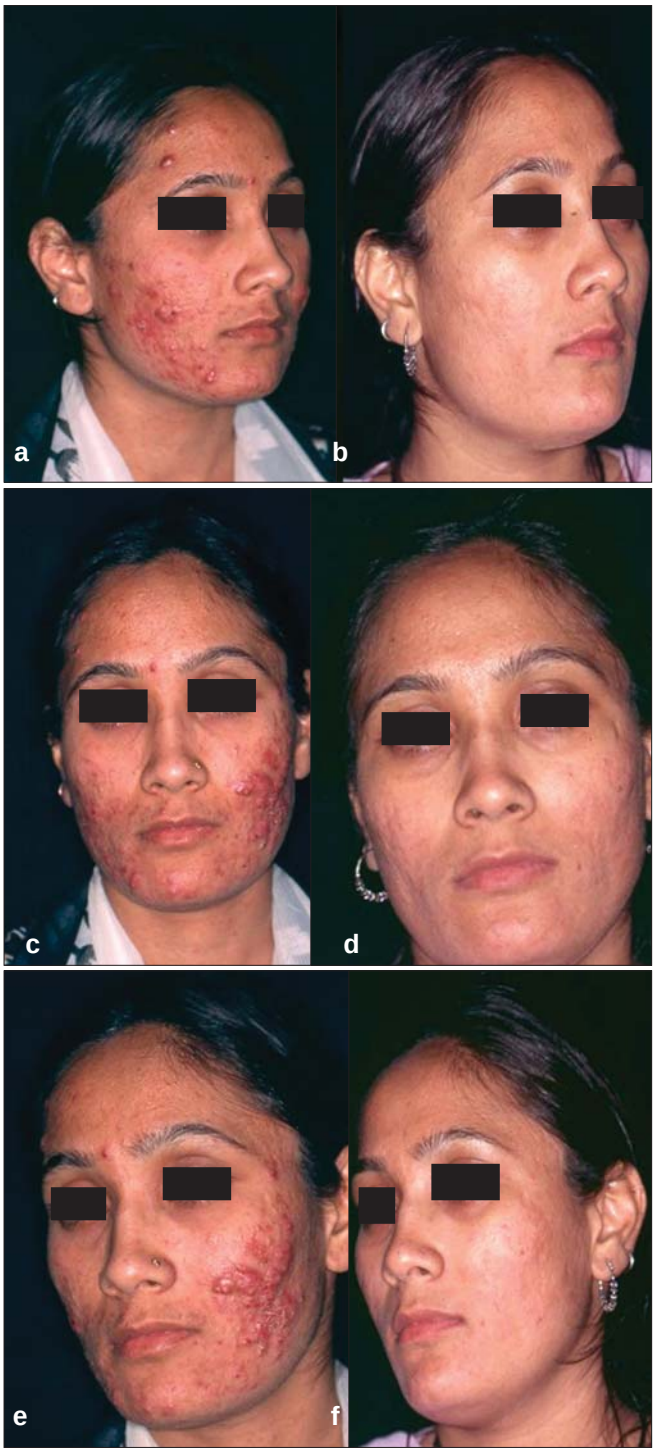

Figure 61: (a-f) Grade III acne treated successfully with isotretinoin and oral steroids

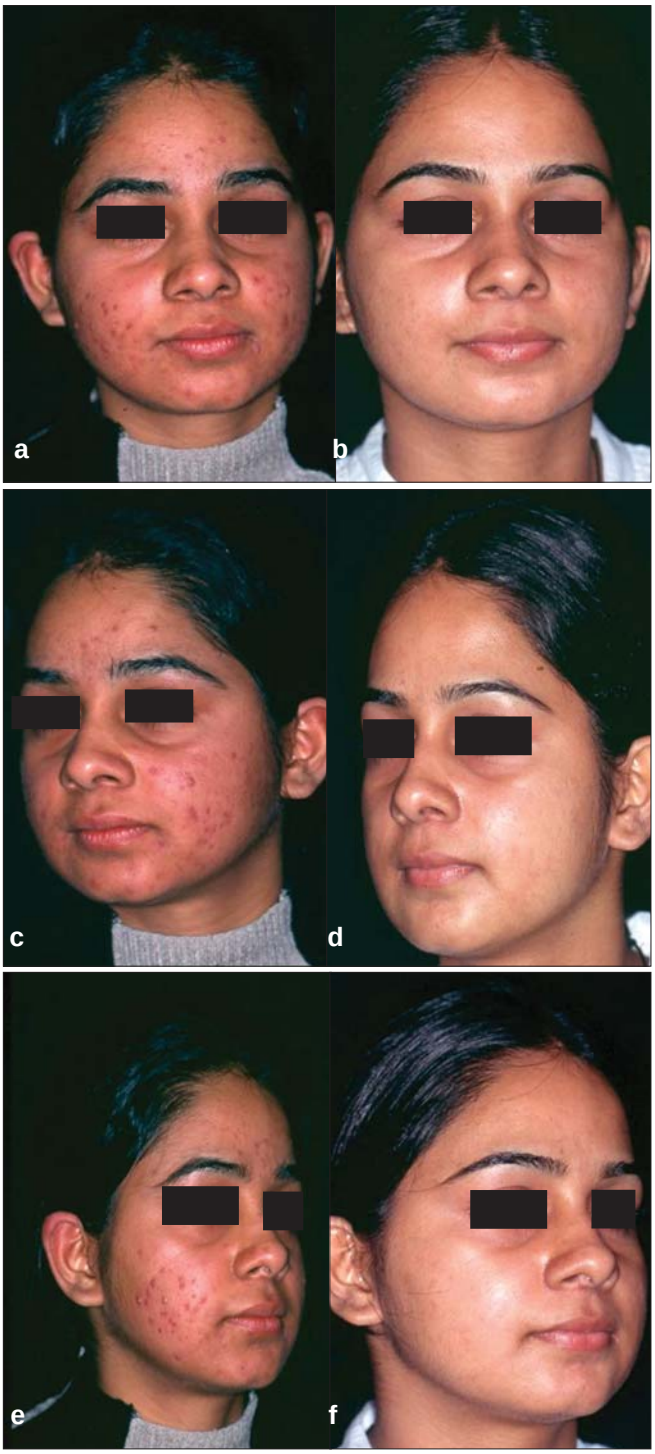

Figure 62: (a-f) Grade II acne treated successfully with combination of isotretinoin and Diane 35

isotretinoin–antiandrogen menstrual disturbances are more frequent. It is safe to repeat isotretinoin course in the event of relapse, especially when the interval between the courses is six months or greater. There is no limit on the number of courses given and the decision to do so is governed by clinical needs and safety issues that are individualized.

Isotretinoin should only be given to healthy individuals. It is absolutely contraindicated in sexually active women in the reproductive age group unless stringent contraception is secured and the need for treatment

is compelling. Many countries have strict pregnancy prevention programs. Accidental use of isotretinoin during pregnancy is associated with a high rate of spontaneous abortion and major, potentially life-threatening, congenital malformations.[13] Male acne patient on isotretinoin may father a child without risk of teratogenicity. Isotretinoin should be avoided in individuals with strong family history of coronary artery disease and dyslipidemias. Blood levels of apolipoproteins A are a better predictor than triglycerides for isotretinoin-related dyslipidemia (consensus of the IAA). Isotretinoin treatment in hypertriglyceridemia carries a risk of acute pancreatitis. Isotretinoin may be used for severe acne in the context of a chronic medical condition such as epilepsy but with due caution. Isotretinoin may be given for severe or difficult acne in preadolescents and adolescents; most experts agree that such a treatment in standard dosages and duration does not cause premature closure of epiphyses or growth retardation. On the rare occasion when adequate isotretinoin therapy fails, it is worthwhile excluding partial/incomplete congenital adrenal hyperplasia by testing for serum 17-α-hydroxyprogesterone (17-OHP).

ADVERSE EFFECTS

Isotretinoin comes packaged with warnings and a long list of possible/reported adverse effects [Table 12]. While this serves the purpose of discouraging self-medication, it makes the job of the dermatologist far more difficult in convincing the patient, the parents, and at times the extended family! It is very important to get the right perspective on this issue and to be able to perform sound risk-benefit analysis in each case. The only adverse effects that are frequently encountered are mucocutaneous, and they are dose dependent. Cheilitis (chapping of lips) occurs almost in 100% of cases although severity varies; it persists through the course of treatment and fortunately most patients adjust to it and make do with emollients. In severe cases, tacrolimus 0.3% and flucticasone-mupirocin ointments provide relief. Dry eyes, dry nose with nose bleeds sometimes, and general dryness, occur less commonly, often contributed to by environmental conditions, failure to adjust skin care, and concomitant use of drying and peeling agents. All this can be adjusted and it is permitted to use moisturizers in an unlimited way. Lubricating eye drops are helpful. Contact-lens wearers may have to switch to soft lenses. Rarely, dryness is severe and requires downward dose adjustment. Concomitant administration of vitamin E 800 IU/day was reported to be effective in diminishing mucocutaneous adverse effects but this was refuted by a subsequent study.[15]

Susceptibility to impetigo and furunculosis increases,[4] and is quite common among our patients here in India. Impetigo is commonly seen in perioral location but also elsewhere [Figure 63]. Bacterial paronychias are documented. Pyogenic granulomas, reported in the literature, are rarely seen in our patients. Other adverse effects include: skin fragility, bone and joint pains, osteoporosis and osteophyte formation, and visual disturbances. Persistent headaches and excessive hair shedding may be signs of overdose. Depression and suicidal ideation have been reported and a causal association with isotretinoin has been debated.[15] It is advised that isotretinoin be avoided in acne patients with documented depression. It is also acknowledged that negative feelings associated with acne often ameliorate after treatment with isotretinoin.[16] Mild to moderate hypertriglyceridemia is noted in 25% of patients.[17] It is reversible. Biochemical monitoring occasionally throws up cytopenia or elevation of transaminases. While the former warrants discontinuing isotretinoin therapy, the latter if moderate (less than three times the upper limit) can be tolerated. Isotretinoin treatment of cystic acne in Greece was found to be associated with elevated levels of homocysteine at six weeks.[18] The explanation offered was possible suppression of enzyme cystathionine-beta-synthetase by the drug or because of the altered liver function.[18] High blood levels of homocysteine are a risk factor for premature occlusive vascular disease.[18]

Pretreatment pregnancy testing, and pre, intra, and post-treatment laboratory testing are handled

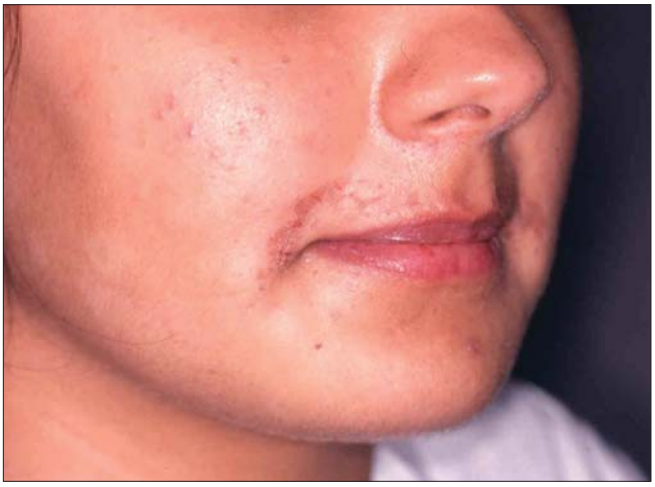

Figure 63: Impetigo following threading during isotretinoin treatment of acne

differently in our country. Unlike EU and USA, it is not mandatory for us to do two pretreatment pregnancy tests, and to have to repeat them every month. This will obviously not go down well with our patients. We limit ourselves to verbal enquiry to rule out pregnancy, and rely upon patient education to prevent pregnancy. It has worked well thus far and we are not aware of any instances of unwanted pregnancies, birth defects, or law-suits with isotretinoin in use now for over five years, thousands of female acne patients having taken it. It may be prudent to record in some way that pregnancy prevention was discussed with the patient. It can be done through consent forms (which are time consuming and evoke apprehension!), or imprinting stamps on prescriptions that say "Pregnancy alert", "Caution", or "Informed consent". The washout period for isotretinoin is 30 days and this is clearly conveyed during pretreatment discussions and reiterated during follow-up visits. Laboratory testing is also enveloped in disagreement. Many data have refuted the usefulness of routine and frequent laboratory testing in isotretinoin therapy of acne. Yet, from a medicolegal standpoint, and to identify the rare case of hypertriglyceridemia, it is advised that screening tests including blood counts, fasting lipids, and liver function be done, and repeated at 4 and 8 weeks, and if normal and unchanged, and if the dose of isotretinoin is not increased, no further tests need be done.[17,19]

ORAL ISOTRETINOIN: SOME DO'S AND DON'TS

- Isotretinoin should be taken after proper meals.
- Isotretinoin should not be shared with friends.
- Threading, waxing, strenuous work-outs, and contact sports should be avoided in the latter part of the treatment.
- Excessive alcohol consumption and fattening foods should be avoided.
- Blood donation should be avoided while on treatment and for one month after stopping therapy.

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