

Isotretinoin was first manufactured in 1955 and has been used for the treatment of acne since the late 1970's. It is part of the retinoid family of compounds that have **biological** activity similar to that of vitamin A. Though most retinoids have been identified to act on the RAR or RXR receptors in the skin cells nucleus, the exact mechanism of action for isotretinoin has not yet been fully elucidated. Basically it binds to certain unknown receptors in the nucleus of skin cells to affect pathways involved in inflammation, cellular differentiation, apoptosis as well as sebaceous gland activity. This has proven beneficial to several other diseases that affect the skin (See table1).

In South Africa it is available in 10mg and 20mg capsules, however, 40mg capsules are also available overseas. Isotretinoin is taken orally, preferably with food, and is transported by plasma proteins to effect its action. Most patients take it as divided doses or single doses as per their convenience and the original guidelines aim at a total cumulative dose of 120-150mg/kg, to achieve a reasonable cure rate for acne. However, these guidelines are outdated as there is a relapse rate of more than one third over a one year period. Thus, many newer studies are advocating a much higher cumulative dose of 220mg/kg, which is said to have much lower relapse rates.

However, many physicians are afraid to write higher doses of this drug and end up giving very low doses, thus not achieving the required cumulative dose. This is despite the fact that American guidelines advocate a dose of 0.5-2mg/kg daily of this medication. Thus a 70kg patient can take up to 140mg of isotretinoin daily as per the American guidelines. Studies have also proven that the side-effects are not worse at a dose higher than 1mg/kg. . Therefore, this medication needs to be prescribed properly to those that will benefit, thereby decreasing relapse rates. It can be used in acne treatment of older patients, adolescents and preadolescents and may be used in younger patients with severe, refractory, and scarring acne (under dermatologist supervision).

Isotretinoin is prescribed for patients with recalcitrant nodular acne (inflammatory lesions > 5 mm) as well as to those who have not responded to conventional therapy. However, one should take into account the impact that the disease has on the person and not only the number of lesions, in defining severity. Thus treatment should be individualised and sometimes patients with even mild to moderate acne can be treated with it, depending on the burden that it is causing to them. Though proper doses are important to achieve a high cure rate, low doses and pulsed therapy can be used in peri-menopausal women and older patients. Patients with frequent relapses may also benefit from such therapy, to keep the disease under control. In these cases, the lowest possible doses are used on a long-term basis. Basically, this medication has very few absolute contraindications and this is summarised in table II.

There are many adverse effects of this medication and patients should be made aware of them, to improve compliance. Most can be easily managed with the use of sunscreens, moisturisers and lip balms, however, a few of them may warrant a discontinuation of the course or a decrease in the dose of the medication. Teratogenicity and spontaneous abortions are very well documented and therefore women must comply with strict birth prevention while on this medication (see table III). However, there is little, if any, risk of retinoid embryopathy in foetuses fathered by men taking systemic retinoid. Other side-effects are summarised in table IV.

Table I: Other uses of isotretinoin

Rosacea	It is very effective for all types of rosacea including phymatous type. Low dose isotretinoin can be used and once control is achieved, a maintenance dose of 10-20mg weekly may suffice
Seborrhoea	It is highly effective in the control of severe oiliness of the face. Low dose can be used.
Hidradenitis suppurativa	It can help with this disease, however, it does not offer full control. It is more effective when sinuses are absent and the anatomy is still intact.
Recurrent folliculitis of the scalp	Can be very effective in treating resistant folliculitis decalvans
Darier's disease	This rare disease has been controlled successfully with isotretinoin
Other diseases	Lichen planus (oral erosive, palmoplantar) lichen sclerosus, Lupus erythematosus, keratodermas, pityriasis rubra pilaris and sebaceous gland hyperplasia.

Table II: Contraindications

Absolute	Relative
Pregnancy and breast feeding	Moderate to severe cholesterol or triglyceride elevation
Non-compliance with contraceptives	Significant hepatic dysfunction
Hypersensitivity to parabens(in isotretinoin capsules)	Significant renal dysfunction

Table III Precautions in female patients of reproductive age

Guidelines:
<ol style="list-style-type: none"> 1. Female patients should not fall pregnant while taking isotretinoin and can try to conceive only one month after stopping the medication. This medication is completely eliminated from the body within 30 days. 2. Patients need to sign a disclaimer and must adhere to strict birth control. 3. It is safe to do a pregnancy test on sexually active patients and to ask them to start the medication after they have already started with their contraceptives. 4. Though 2 forms of contraceptives (e.g pills and condom) have been advocated by the FDA, it may not always be practical in our setting and compliance will be an issue. 5. The patient should undertake to inform the doctor immediately if the contraception fails and they end up falling pregnant. They will have to terminate the pregnancy. 6. This medication does not affect fertility.

Table IV: Side-effects of isotretinoin

Eyes	Reduced night vision, persistent dry eyes and repeated staph aureus infections. This is fairly common and is the reason why it is contraindicated in pilots
Bone	Diffuse skeletal hyperostosis, osteophyte formation and premature epiphyseal closure are fortunately uncommon
GIT	Can cause flare up of Inflammatory bowel disease and rarely cause pancreatitis. Rarely causes nausea, diarrhoea, abdominal pains, constipation and rarely rectal bleeding. Though mild elevation of transaminases is common, it rarely causes hepatitis
Endocrine effects	Hypothyroidism and diabetes mellitus are exceptionally rare with isotretinoin and may even be a co-incidence.
Neurologic	Pseudotumour cerebri: Transient headaches are relatively common early during the therapy, however, if it is accompanied by nausea, vomiting and visual changes, this should prompt further evaluation to exclude pseudotumour cerebri. The risk increases with the concomitant use of tetracycline, thus they should be avoided. Depression, suicidal ideation, mood changes: The exact link with the use of isotretinoin has not been fully elucidated. However, patients with a previous history of depression should be closely monitored and treatment should be stopped if their condition is aggravated. One should bear in mind that severe acne by itself can be the cause of depression and the use of isotretinoin can improve the mood of the patient. Very mild depression is common.
Cutaneous	Xerosis, palmoplantar and digital desquamation, photosensitivity (can lead to temporary darkening of skin colour), fine sensitive rash on sun-exposed areas, pyogenic granulomas as well as bacterial infections.
Hair	Telogen effluvium, abnormal hair texture and dryness
Nail	Fragility and nail softening, paronychia and onycholysis.
Mucous membranes	Cheilitis-esp lower lip, dry mouth, sore mouth and tongue. Dry nasal mucosa, decrease mucous secretion and epistaxis. Vaginal dryness is common.
Musculoskeletal	Arthralgias, neck and lower backaches, fatigue and muscle weakness. Rarely tendinitis

In our context, one has to offer a cost-effect and safe method of monitoring this medication. It is definitely not practical to perform all the blood tests and investigations set out by the FDA, as cost is a very big limiting factor. Though a very mild elevation of transaminases is common, it is very rare to have liver failure. Also, almost all patients will have a predictable elevation of lipids while on this medication. Therefore in a healthy young male, a good history and examination is sufficient to start the medication. The author tests for liver transaminases and lipid profile at one month, after the start of the medication. All the side-effects are dealt with at the same time. If everything is fine, the dose is maintained and the patient is reviewed once the medication is completed. Of course, this does not apply to patients with acne fulminans and those on very high doses. In female patients, pregnancy needs to be excluded and the absolute use of contraceptives needs to be reinforced during each visit.

Isotretinoin is a very effective medication and does change the life of many patients. It is however advisable that it be prescribed by Dermatologists who have a proper grasp of its side-effects as well

as ways to manage them. Not every patient reacts the same way to this medication and the dose can be tailored to specific requirements.

Dr Rakesh Newaj

MBBCh (Wits) FC Derm (SA)

Arwyp medical centre, Kempton park

www.dermatologistjohannesburg.com

dermatologistjhb@gmail.com