## CLINICAL PRACTICE

# The rational use of systemic isotretinoin in acne: A call for moderation

**Werner Sinclair**

Systemic isotretinoin effectively treats all forms of acne vulgaris. However, it has many side-effects, some potentially serious, that warrant limiting its use to serious cases of acne. Inappropriate use in large numbers of patients puts prescribers at risk of malpractice litigation should serious side-effects occur where safer alternative treatments were available. Doctors also risk losing access to the drug should authorities limit its use to reduce the occurrence of side-effects.

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Systemic isotretinoin can be considered to be a 'wonder drug' that has revolutionised the treatment of acne vulgaris, massively improving outcomes in nodulocystic acne. Isotretinoin can also 'cure' acne in 38% of cases[1] after a full course. It is highly effective in all forms and grades of acne vulgaris, even in lower dosages[2,3] though lower dosages rarely cure even minor degrees of the disease.[1] Even severe acne will usually be cleared or cured by high dosages. To a lesser degree, lower dosages usually effectively clear the skin, but this is merely symptomatic and may be required indefinitely to maintain the response and prevent relapse.

In South Africa, there is a massive trend towards the universal use of lower dosages of systemic isotretinoin for lesser degrees of acne vulgaris and it is prescribed by dermatologists and general practitioners alike. This custom is propagated by dermatologists in lectures and literature to general practitioners.[4] The efficacy of this approach is emphasised, but alternative recommended treatments are ignored, leaving the impression that indefinite low-dose isotretinoin is the treatment of choice for all acne cases.

Most countries subscribe and contribute to the Global Alliance for the Improvement of Outcomes in the Treatment of Acne Vulgaris (GA) who analyse all literature concerning acne and provide guidelines for its treatment. These were accepted by all dermatologists in South Africa and published in 2005.[5] The GA guidelines were published in 2003 and 2009.[6,7]

## Global guidelines on the use of systemic isotretinoin

The GA and South African official indications for the use of isotretinoin are:[5-7]

1. Grade IV (nodulocystic or conglobate acne)
2. Scarring acne
3. Lesser grades of acne not responsive to at least 3 months of oral antibiotics combined with a topical retinoid, or at least four cycles of hormonal therapy in females
4. Dysmorphophobic patients
5. Gram-negative folliculitis.

*Professor Werner Sinclair is Head of the Department of Dermatology, Faculty of Health Sciences, University of the Free State, Bloemfontein.*

***Corresponding author:*** *W Sinclair (sinclairw@ufs.ac.za)*

However, in Europe there are severe restrictions on the use of isotretinoin, as follows:[7] Systemic isotretinoin may not be used as first line of treatment for any grade of acne. For any form of acne, isotretinoin may only be prescribed after failure of a 3-month course of systemic antibiotics combined with topical treatment (retinoids or benzoyl peroxide). It may not be prescribed for acne in children under the age of 12 years. The minimum starting dose is 0.5 mg/kg/day, which may be increased to 1.0 mg/kg/day depending on side-effects. General practitioners may not initiate isotretinoin treatment. The pregnancy prevention programme (PPP) dictates that monthly pregnancy tests in females should be performed before, during and up to 5 weeks after completion of a course of isotretinoin. A supply of only 30 days of isotretinoin may be dispensed at one time and prescriptions are valid for only 7 days. Treatment may only start on the third day of a normal menstrual period. Where possible, patients should agree to at least one and preferably two complementary methods of effective contraception including a barrier method before initiating therapy. The clinician has the responsibility for assessing pregnancy tests before further prescriptions.

Not all experts agree on these harsh directives[8] and feel that in severe cases, systemic isotretinoin should be used earlier to limit the psychological impact of the disease and scarring.

Similar restrictions apply in the USA concerning pregnancy prevention. All patients, male and female, must enrol in the iPledge programme, a national registry, failing which the patient would not receive the drug. Women of childbearing age must provide two negative pregnancy tests before their initial prescription, show proof of another negative pregnancy test before each monthly repeat prescription, and use two forms of contraception (that must be entered into the registry) throughout therapy and for 30 days after treatment. All patients sign confirmation that they are aware of potential adverse effects including depression and suicidal thoughts.[9] Male patients are also recommended not to engage in unprotected sexual intercourse while taking the drug as it is secreted in semen and could theoretically be absorbed by the female partner.[10,11]

These severe restrictive and controlling measures in Europe and the USA apply to all users of the drug, regardless of the dosage.

The accepted standard dosage of a full course of treatment is 0.5 - 1.0 mg/kg/day, as a single daily dose with a meal. This should continue until a total cumulative dosage of at least 120 mg/kg has been reached, but may be extended to a total of 150 mg/kg if the acne has not cleared up at 120 mg/kg.

These guidelines do not include low-dose oral isotretinoin in the management of acne, but the South African publication of 2005

allows for pulse therapy in recurrent acne after a full course of oral isotretinoin *and* if topical retinoids failed to prevent relapse or are impractical to use (e.g. truncal acne). Isotretinoin is then used at a maximum of 0.5 mg/kg/day for 1 week per month, with excellent results.[12]

Except for the pulse dosages, no guideline recommends long-term dosages below 0.5 mg/kg/day. None recommends systemic isotretinoin as first line for acne of moderate degree (i.e. other than nodulocystic acne), systemic isotretinoin as maintenance, or allows relaxation of precautionary measures where lower dosages are used.

## What is 'low-dose' systemic isotretinoin?

There is no consensus on what constitutes low-dose oral isotretinoin. European and American literature seem to regard a dose below 0.5 mg/kg/day as low, but this varies tremendously. A dosage of 10 mg/day three times per week for indefinite periods (even in young females!) may be seen, or sometimes it is taken in an 'as needed' fashion (recommended by a dermatologist! – personal communication). Although these regimens are effective in controlling mild acne,[2] using it as maintenance treatment mostly falls outside the accepted guidelines.

## The global guidelines on maintenance treatment for acne vulgaris

The only drugs recommended for maintenance treatment of acne, after initial clearance, are topical retinoids and hormonal treatment in females, which may be combined. Oral isotretinoin is not mentioned as an option but the South African guidelines allow for pulse therapy in selected cases. Two papers on the use of oral isotretinoin give excellent guidance on this issue, including its side-effects.[9,13]

### Adverse side-effects of systemic isotretinoin

Some pertinent or controversial points are dealt with here.

**Teratogenicity.**[14] Teratogenicity is the best known serious adverse effect; 'retinoid embryopathy' results in many cardiovascular, neurological and limb defects.[15] The risk is high (as for thalidomide), the effect is pharmacological and independent of dosage, and is thought to last up to 1 month after stopping the drug, after which pregnancy is safe. Topical retinoids seem to have no teratogenic effect when used in pregnancy,[16] but have not been cleared for use in pregnant women.

**Mucocutaneous side-effects.** Initial worsening of acne; xerosis and cheilitis; retinoid dermatitis; epistaxis; staphylococcal infections of the skin, often of the nail folds, to cause paronychia;[13] pyogenic granulomas of the nail folds are often seen on the toes;[17] hypertrophic scarring and keloids - dermabrasion should be delayed after isotretinoin because severe hypertrophic scarring may result;[18,19] hypertrophic scarring has been reported when isotretinoin was administered 2 months *after* dermabrasion[20] and also spontaneously, without prior surgery, on isotretinoin therapy.[21]

**Ocular complications.** Dry eyes that can persist indefinitely;[22] blepharoconjunctivitis; keratitis with corneal ulceration is rare;[13] recent use of isotretinoin is a contraindication to laser refractive eye surgery; decreased night vision is a common and potentially dangerous side-effect, making driving a vehicle at night hazardous and is the reason why aviation pilots may not use the drug. Night blindness can persist indefinitely.[22]

**Laboratory abnormalities.** Liver enzyme disturbance; raised serum lipids (especially triglycerides).

**Central nervous system abnormalities.** Raised intracranial pressure – isotretinoin must not be combined with tetracyclines[23] or vitamin A. Mood disturbance, depression, inability to concentrate and study – this is controversial as large studies do not show an increase in depression and suicide ideation in isotretinoin users.[24] However, severe depression can occur as a rare, unpredictable, idiosyncratic event requiring prompt action.[25] The FDA recommends close monitoring of patients treated with isotretinoin for symptoms of depression or suicidal thoughts, sad mood, irritability, anger, loss of pleasure or interest in sports activities, sleeping too much or too little, changes in weight or appetite, decreased school or work performance, trouble concentrating, mood disturbance, psychosis or aggression. (FDA Alert for Healthcare Professional 07/2005). The British Association of Dermatologists recently reviewed psychiatric side-effects.[26]

**Musculoskeletal abnormalities.** *Myalgia and arthralgia* occur more frequently in patients who also engage in heavy exercise, seen in 2 - 5% of cases. CK-levels may become markedly raised. *Decreased bone density* does not occur in young people taking regular dosages of isotretinoin,[27] but it has been demonstrated where vitamin D deficiency co-existed.[28] Isotretinoin profoundly affects vitamin D metabolism,[29] but appears not to increase the risk for fractures.[30] No data are available for patients who have taken isotretinoin for prolonged periods, as is often the case when low dosages are used, especially in older patients. This has not been studied, probably because the rest of the world does not follow this practice. No data exist on bone density in 60-year-old patients who had previously taken low dosages of isotretinoin for 5 years. *Diffuse idiopathic skeletal hyperostosis (DISH)* can occur at higher dosages used for prolonged periods. The spinal ligaments are particularly prone to this complication. No data exist on this effect when low dosages are used for long periods. *Premature closure of epiphyses* is possible.

**Gastro-intestinal side-effects.** Ulcerative colitis is controversial; some studies[31] found that isotretinoin can cause ulcerative colitis, while others[32] deny it. The possible association of ulcerative colitis with isotretinoin, resulting in court cases, is a reason for an ethical company withdrawing their isotretinoin from the market in the USA.[33]

## When is acne cured?

The GA states that acne is cured when, after treatment is discontinued, no further treatment is required. A cure has been achieved if a recurrence is so mild that the patient does not deem treatment necessary. Problems in interpreting the literature mostly arise here. Differing definitions of a cure result in confusing conclusions from studies and the long-term effects of oral isotretinoin, e.g. a study[34] claiming a ridiculous 94% 'cure rate' for acne after using isotretinoin 20 mg per day for 6 months for moderate acne defined a relapse 'as the emergence of pretreatment severity of acne in a treated patient'; all others were seen as 'cured'. This is no cure by any standard and created a false impression of the results.

## The pitfalls of inappropriate use of oral isotretinoin

The pitfalls are largely medicolegal. For maintenance treatment of acne, the benefit/risk ratio of oral retinoids cannot compare with that of topical retinoids. The oral drug is slightly more effective, but topical retinoids have minimal risk and are therefore the maintenance drug of choice.

A hypothetical malpractice court case where a prescribing physician is litigated against for the trauma of any of the complications listed, would be *indefensible if the indications and dosing did not match the accepted, published guidelines at the time*. Lawyers would use evidence from the literature and any doubts will be applied in favour of the

complainant. That such action would not hold up in court means that the patient's best interests are not taken into account when using oral isotretinoin inappropriately. The fact that the patients often request, or force, doctors to prescribe it, does not relieve the responsibility to do the evidence-based correct thing.

## Why some dermatologists use isotretinoin in inappropriate dosing regimens and for the wrong indications

**Patient pressure** forcing doctors to comply to protect their client base. Teenage patients prefer to swallow a tablet to applying a daily messy cream. The drying effect of topical retinoids, although less than that of systemic retinoids, is often an excuse to use the systemic drug instead.

**Ignorance.** Many healthcare professionals are not aware of the published guidelines, especially those on topical retinoids and their excellent efficacy.

**Laziness, convenience.** It is less effort to prescribe low-dose systemic isotretinoin, with few obvious side-effects, than a complicated topical retinoid, for which the patient must be educated, and continually motivated to use it.

**Complacency about possible litigation.** Dermatologists naïvely believe that their 'loyal' patients will not litigate against them should complications arise.

**Defiance.** The 'I know best' attitude is rife in South Africa. 'I have been doing this for years, and never had any problems' is often heard.

## Why we must adhere to accepted global guidelines on the use of systemic isotretinoin

The main reason is to protect patients against the drug's adverse effects. Some are potentially serious and the more the drug is used, the more likely these events will be encountered.

Healthcare professionals must be protected against litigation for possible negligence when not prescribing the drug according to the guidelines and adverse events occur. Patients who 'force' the doctor to prescribe the drug are often the first to litigate if something goes wrong.

We cannot risk losing access to the drug, one of dermatology's most valuable assets, as a result of inappropriate use. The European restrictions prevent some deserving patients from accessing this drug. The American Gynecological Society lobbied for its ban for years, and such actions should not be given more ammunition through our carelessness.

## Recommendations on the rational use of systemic isotretinoin

Lower than standard doses of oral isotretinoin should only be prescribed in exceptional cases, after all safer alternatives have been considered and used but failed, or were impractical to use. It should never be used as primary therapy for moderate degrees of acne.

We should follow the world-wide accepted guidelines for which there are very good reasons.

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**Endorsement.** This paper has been endorsed by the academic heads of dermatology in South Africa.

1. Layton AM, Knaggs H, Taylor J, Cunliffe WJ. Isotretinoin for acne vulgaris - 10 years later: a safe and successful treatment. Br J Dermatol 1993;129(3):292-296.
2. Plewig G, Dressel H, Pfleger M, Michelsen S, Kligman AM. Low dose isotretinoin combined with tretinoin is effective to correct abnormalities of acne. J Dtsch Dermatol Ges 2004;2(1):31-45.
3. Lee JW, Yoo KH, Park KY, Han TY, Li K, Seo SJ, Hong CK. Effectiveness of conventional, low-dose and intermittent oral isotretinoin in the treatment of acne: a randomized, controlled comparative study. Br J Dermatol 2011;164(6):1369-1375.
4. Schwartz S. Low dose isotretinoin – what does the literature say? SA Dermatology Review 2011;11(2):6-9.
5. Sinclair W, Jordaan HF. Acne Guidelines 2005 update. S Afr Med J 2005;95:883-892.
6. Gollnick H, Cunliffe W, Berson D, et al. Management of acne: a report from a global alliance to improve outcomes in acne. J Am Acad Dermatol 2003;49(1):S1-37.
7. Thiboutot D, Gollnick H, Bettoli V, et al. New insights into the management of acne: An update from the Global Alliance to Improve Outcomes in Acne Group. J Am Acad Dermatol 2009;60:S1-50.
8. Layton AM, Dreno B, Gollnick HP, Zouboulis CC. A review of the European Directive for prescribing systemic isotretinoin for acne vulgaris. J Eur Acad Dermatol 2006;20:773-776.
9. Layton A. The use of isotretinoin in acne. Dermatoendocrinology 2009;1(3):162-169.
10. Vallance P. Drugs and the fetus. BMJ 1996;312:1053.
11. Schmitt-Hoffmann AH, Roos B, Sauer J. et al. Low levels of alitretinoin in seminal fluids after repeated oral doses in healthy men. Clin Exp Dermatol 2011;36(s2):12-17.
12. Goulden V, Clark SM, McGeown C, Cunliffe WJ. Treatment of acne with intermittent isotretinoin. Br J Dermatol 1997;137:106-108.
13. Ganceviciene R, Zouboulis CC. Isotretinoin: state of the art treatment for acne vulgaris. Exp Rev Dermatol 2007;2:693-706.
14. Stern RS, Rosa F, Baum C. Isotretinoin and pregnancy. J Am Acad Dermatol 1984;10(5 Pt 1):851-854.
15. Kuenzli S, Saurat J-H. Retinoids. In: Bolognia JL, Jorizzo JL, Rapini RP, eds. Dermatology (Volume 2). London: Mosby, 1991-1996 (2003).
16. Loureiro KD, Kao KK, Jones KL, et al. Minor malformations characteristic of the retinoic acid embryopathy and other birth outcomes in children of women exposed to topical tretinoin during early pregnancy. Am J Med Genet 2005;136(2):117-121.
17. Piraccini BM, Bellavista S, Misciali C, Tosti A, De Berker D, Richert B. Periungual and subungual pyogenic granuloma. Br J Dermatol 2010;163(5):941-953.
18. Zachariae H. Delayed wound healing and keloid formation following argon laser treatment or dermabrasion during isotretinoin treatment. Br J Dermatol 1988;118(5):703-706.
19. Rubenstein R, Roenigk HH Jr., Stegman SJ, Hanke CW. Atypical keloids after dermabrasion of patients taking isotretinoin. J Am Acad Dermatol 1986;15(2):280-285.
20. Bruce E, Katz BE, MacFarlane DF. Atypical facial scarring after isotretinoin therapy in a patient with previous dermabrasion. J Am Acad Dermatol 1994;30(5 pt2):852-853.
21. Bernestein LJ, Geronemus R. Keloid formation with the 585-nm pulsed dye laser during isotretinoin treatment. Arch Dermatol 1997;133:111-112.
22. Szabo B. Antiandrogenic effect of isotretinoin: Is the retina involved in mechanism of action? Med Hypotheses 2007;69(6):1281-1283.
23. Lee AG. Pseudotumor cerebri after treatment with tetracycline and isotretinoin for acne. Cutis 1995;55:165-168.
24. Cohen J, Adams S, Patten S. No association found between patients receiving isotretinoin for acne and the development of depression in a Canadian prospective cohort. Can J Clin Pharmacol 2007;14:s227–e233.
25. Wysowski DK, Pitts M, Beitz J. An analysis of reports of depression and suicide in patients treated with isotretinoin. J Am Acad Dermatol 2001;45(4):515-519.
26. Goodfield MJD, Cox NH, Browser A, et al. Advice on the safe introduction and continued use of isotretinoin in acne in the UK, 2010. Br J Dermatol 2010;162:1172-1179.
27. Tekin NS, Ozdolap S, Sarikaya S, Isik S. Bone mineral density and bone turnover markers in patients receiving a single course of isotretinoin for nodulocystic acne. Int J Dermatol 2008;47(6):622-625.
28. Saadi H, Afandi B, Houssami L, Saleh N, Mohamadiyeh M, Benedict S. Effects of isotretinoin on bone turnover markers and bone mineral density in women with acne vulgaris and vitamin D deficiency: a preliminary study. Int J Diabetes Metab 2008;16:107-112.
29. Ertugrul DT, Karadag AS, Tutal E, Akin KO. Does isotretinoin have effect on vitamin D physiology and bone metabolism in acne patients? Dermatologic Therapy 2011;24(2):291-295.
30. Vestergaard P, Rejnmark L, Mosekilde L. Hypervitaminosis A and bone fractures. Arch Dermatol 2010;146:478-482.
31. Shale M, Kaplan GG, Panaccione R, Ghosh R. Isotretinoin and intestinal inflammation: what gastroenterologists need to know. Gut 2009;58:737-741.
32. Bernstein C, Nugent Z, Longobardi T, Blanchard JF. Isotretinoin is not associated with inflammatory bowel disease: a population-based case – control study. Am J Gastroenterol 2009;104:2774-2778.
33. Alonso PW. Accutane pulled from market amid lawsuits, increased generic competition. http://www.yourlawyer.com/articles/read/16685 (accessed 11 September 2011).
34. Amichai B, Shemer A, Grunwald MH. Low-dose isotretinoin in the treatment of acne vulgaris. J Am Acad Dermatol 2006;54(4):644-646.

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