Australasian Journal of Dermatology

Australasian Journal of Dermatology (2012) ••, ••–•• doi: 10.1111/j.1440-0960.2012.00947.x

REVIEW ARTICLE

Isotretinoin: dose, duration and relapse. What does 30 years of usage tell us?

Marius Rademaker

Dermatology Department, Waikato Hospital, Hamilton, New Zealand

ABSTRACT

With 30 years of clinical use, it is appropriate to review the use of isotretinoin. We now understand that retinoids influence cellular growth, differentiation, morphogenesis and apoptosis, inhibit tumour promotion and malignant cell growth, exert immunomodulatory actions and alter cellular cohesiveness. This has expanded the indications of isotretinoin from just acne and rosacea to a wide range of inflammatory and malignant skin disorders. While the standard dose of 0.5 to 1 mg/kg per day for 4 months to a cumulative dose of 120–140 mg/kg per day has served us well in the management of acne vulgaris, there is emerging evidence that much lower dosages (as low as 5 mg/day) are just as effective but have significantly fewer adverse effects. Relapse of acne vulgaris continues to be a problem but we are beginning to recognise that this is related less to the cumulative dose and more to the length of sebaceous gland suppression. Other factors important for relapse include a macrocomedonal pattern of acne, smoking and age, both younger (under 14 years) and older (over 25 years). After 30 years of use, we now understand why isotretinoin is such an effective drug. Not only does it clear acne in almost all patients, long-term remission can be achieved in 70–80% of patients with a single course. Important changes in the use of isotretinoin include using a lower daily dose for a longer period of time. New indications continue to emerge, particularly as a potential treatment for both intrinsic and extrinsic (photo) aging. Teratogenicity however, remains a very significant concern.

Key words: acne vulgaris, adverse effects, dose, isotretinoin, relapse, retinoid.

INTRODUCTION

Since achieving registration in the USA in 1982, isotretinoin has truly revolutionised the management of acne vulgaris,[1] as well as finding a place in the treatment of a number of other dermatological conditions. Peck and colleagues[2] published the first study of oral 13-cis-retinoic acid (isotretinoin) for acne vulgaris in 1979, although initial research had started a decade earlier in several Austrian and German dermatology departments.

Early dose ranging studies[3–8] showed there was no dose effect in the range of 0.1 to 1.0 mg/kg per day, with both the rate of improvement, and the total clearance of acne, being the same for 0.1 mg/kg per day as for 1.0 mg/kg per day. However, a number of subsequent studies suggested that relapse 1–2 years after a single 16-week course of isotretinoin was greater in those treated with 0.1 mg/kg per day than with 1.0 mg/kg per day.[9] This was interpreted to indicate that the best long-term response from isotretinoin was obtained if the patient achieved a cumulative dose of 120–140 mg/kg.[10,11]

Now 30 years on, it is timely to review what we have learned over this period. This includes re-evaluating the evidence for the daily dose, the duration of treatment, cumulative dose, relapse, non-responsiveness and indications for isotretinoin.

THE PATHOPHYSIOLOGY OF ACNE

First, though, it is opportune to review our understanding of the pathophysiology of acne. The current model of acne

Abbreviations:

a*t*RA	all-trans retinoic acid
IL	interleukin
RAR	retinoic acid receptors
RARE	retinoic acid response element

Correspondence: Dr Marius Rademaker, Dermatology Department, Waikato Hospital, Private Bag, Hamilton, New Zealand. Email: rademaker@xtra.co.nz

Marius Rademaker, DM.

Conflicts of interest: The author was the principal investigator for a pharmaceutical company (Douglas Pharmaceuticals, Auckland, New Zealand) sponsored trial of very low dose isotretinoin (5 mg/day) for persistent low-grade adult acne vulgaris.

Submitted 28 June 2012; accepted 17 July 2012.

vulgaris includes a hormonally induced alteration in sebum production, abnormal growth and differentiation of epidermal cells leading to hypercornification of the pilosebaceous duct, abnormal growth of *Propionibacterium acnes* and a subsequent auto-immune response. This auto-immune response appears to be mediated via Toll-like receptor 2 and 4 and the release of pro-inflammatory mediators (interleukin [IL]-1α, IL-8 and tumor necrosis factor-α).[12] These result in neutrophil recruitment, the release of lysosomal enzymes and subsequent disruption of the follicular epithelium. In addition, there is upregulation of human beta defensin-1 and -2.[13]

RETINOIDS: HOW THEY WORK

Retinoids, including isotretinoin, can influence cellular growth, differentiation, morphogenesis and apoptosis, inhibit tumour promotion and malignant cell growth, exert immuno-modulatory actions and alter cellular cohesiveness.[14] They do so through a number of mechanisms, the most important being their ability to influence gene transcription. Retinoids exert some of their physiological effects by binding to two distinct families of nuclear receptors: RAR (retinoic acid receptors) and retinoid X receptors, which belong to the superfamily of nuclear receptors (that also include vitamin D3 receptors, thyroid hormone receptors and peroxisome proliferator-activated receptors).[14]

The direct effects of isotretinoin are mediated through binding to a specific retinoic acid response element (RARE) in the promoter region of target genes, whose transcription is then activated (this, for example, mediates the differentiation-inducing actions of isotretinoin). In contrast, the anti-proliferative and anti-inflammatory actions of isotretinoin are believed to be mediated by a negative, indirect regulatory mechanism. These indirect effects result from the downregulation of genes that do not contain RARE in their promoter region, by antagonising other transcription factors, such as activator protein-1 and nuclear factor-IL6 through competition for co-activator proteins. In addition all-trans retinoic acid or tretinoin (a*t*RA) has recently been shown to regulate the expression and activation of Toll-like receptors.

It is estimated that isotretinoin affects over 500 genes; 300 being upregulated and 200 downregulated, although only 27 of these seem to be mediated via the classic RAR/RARE pathway. Isotretinoin itself does not bind to retinoic acid receptors, but a*t*RA and 13-cis RA are geometric isomers and show reversible interconversion. Isotretinoin therefore acts largely as a pro-drug for a*t*RA, although its metabolites may also play a significant role.[15]

Of note, the pattern of gene expression induced by isotretinoin changes over time. Immediately following the commencement of isotretinoin there is upregulation of tumour suppressor genes, protein processors and genes involved in the transfer or binding of ions and small molecules.[16,17] After 8 weeks of treatment there is downregulation of the genes involved in the metabolism of steroids, cholesterol and fatty acids and upregulation of genes that encode structural proteins such as collagens and fibronectin. In other words, there is an initial induction of apoptosis and cell cycle arrest, particularly in the sebaceous gland, followed by the skin adopting a wound–healing-like pattern of gene expression, with subsequent repair and remodelling.[16,17] Clinical experience suggest this may be dose-dependent with reduced scarring at 0.1 mg/kg per day but hypertrophic scarring at 1–2 mg/kg per day.

DAILY DOSE OF ISOTRETINOIN

The dose of isotretinoin has been well established at 0.5–1.0 mg/kg per day for 16–20 weeks to a cumulative dose of 120–140 mg/kg.[15] We know this is effective, so why change? The main reason is that, while 1 mg/kg per day is as effective as 0.1 mg/kg per day in clearing acne, the adverse effects are very much greater. At 1 mg/kg per day, 98% of patients complain of adverse events, while at doses below 0.25 mg/kg per day, half the patients experience no adverse effects at all, and in those who do, the effects are significantly less severe.[18] While the evidence for an association between isotretinoin and psychiatric or gastrointestinal adverse effects remains controversial, a reduction in daily dose can only be regarded as being of potential benefit.

A further advantage of using a lower dose is the differential effect on acne scarring. At 1 mg/kg per day there is a well-established risk of excessive scarring, yet at doses of 0.1 mg/kg per day acne scarring is generally much less (see above).

The first published study of isotretinoin for acne used a dosage range of 1.0–3.3 mg/kg per day.[2] However, subsequent dose-ranging studies indicated that there was no dose effect in the 0.1–3.0 mg/kg per day range, in that all dosages cleared acne in equal measure and at the same rate.[3–8,19]

Plewig and colleagues[20] demonstrated that a single 10–20-mg daily dose of isotretinoin over 6 months reduced inflammatory lesions by 87–94% and non-inflammatory lesions by 81–88%. In addition, sebaceous gland size was reduced by 35–58%, sebum production by 90–95%, follicular keratinization by 55–70% and *Propionibacterium acnes* by 33–73%. Skin surface lipids, however, were reduced by only 6%. Geissler and colleagues[21] showed, albeit in patients with seborrhoea, that doses as low as 2.5 mg thrice weekly were effective in reducing sebum production, implying the minimal effective daily dose of isotretinoin is in the order of 2 mg/day, irrespective of bodyweight.

A recent, as yet unpublished, study (Rademaker and colleagues) of persisting acne vulgaris in adults has shown that 5 mg/day clears acne very effectively compared to placebo, with minimal adverse effects.[22]

A further disadvantage of higher dosage isotretinoin is the well-recognised flare of acne after 3–6 weeks of treatment. This may relate to the degree of sebaceous cell apoptosis, which can largely be avoided by using doses of below 0.2 mg/kg per day.[23,24] The larger the dose of isotretinoin, the greater the apoptosis of sebocytes and thereby the greater antigen load to drive the auto-immune response.

While it is best to titrate the daily dose of isotretinoin to balance the patient's response and side effect acceptance,

the evidence is that 0.1 mg/kg per day is effective (i.e. 5–10 mg/day) and that increasing the dosage does not result in a better clearance of acne.

DURATION OF TREATMENT

The initial studies of isotretinoin for nodulocystic acne were at high daily doses and mostly continued for 16 weeks. Subsequent studies have slowly extended the treatment time, first to 20 weeks and now to 6 months. There are no studies that have specifically assessed the most appropriate duration of treatment to clear acne (as opposed to cumulative dose and relapse). In practice, dermatologists should continue isotretinoin until the patients' acne has cleared, and then for another 3 or 4 months: this may mean as little as 4 months of treatment for facial acne in some patients and over 18 months for significant acne on the trunk in others.

The benefit of this flexible dose approach is it maximises patient outcomes and minimises adverse reactions. Of note, though, isotretinoin is highly teratogenetic, so it would seem logical to limit the length of exposure of a female patient to this drug. However, many of the reports of isotretinoin-associated pregnancies suggest that these tend to occur early on in the course of isotretinoin.

CUMULATIVE DOSE

It was quickly noted that a significant percentage of patients relapsed after a single course of isotretinoin; relapse being defined as the need for a further course of isotretinoin, in the view of the treating physician. As this definition is quite subjective there has been significant variance in reported relapse rates among various studies. Some of the early studies suggested that the cumulative dose might be important in determining relapse, but this is not supported by most subsequent research.[25–28] This is not surprising as there is no physiological basis for using cumulative dose for any other medication or disease process.

Plewig and colleagues,[4] in a study of 64 patients using doses of 0.05, 0.1 and 0.2 mg/kg per day, showed a relapse rate of 45, 44 and 42%, respectively. Peck *at el.*,[6] in a follow up study of his original work showed a 43% relapse rate after a daily dose of 1.3 mg/kg per day in 33 patients.

Stainforth and colleagues,[29] in a study of 299 patients treated with isotretinoin for 16 weeks with a 5-year follow up, showed that 22.7% required further courses of isotretinoin (17% had two courses, 5% had three courses and 1% had 4–5 courses). Risk for relapse was determined to include lower dose regimens (0.1 and 0.5 mg/kg), the presence of severe acne, being a woman over the age of 25 and a prolonged history of acne.

Lehucher-Ceyrac and colleagues,[26] in another long-term follow up study of 219 patients treated with isotretinoin, showed the relapse of acne (not necessarily requiring further isotretinoin) was 14% at 1 year, 40% at 3 years and 49% at 5 years. Risk for relapse was determined to be age, severity of acne on the face, but not daily or cumulative dose.

A prospective study by Quereux and colleagues[27] of 52 patients showed a relapse rate of 52%, with 23% being treated with a further course of isotretinoin. Risk for a 2nd course included continued seborrhoea after treatment, severity of acne and young age, but not daily dose, treatment duration or cumulative dose.

So why the variance in these studies? It is now recognised that high-dose isotretinoin induces apoptosis, not only of sebocytes, but also of sebaceous gland stem cells. This results in the prolonged suppression of sebaceous gland activity, even after discontinuation of the drug. Smaller doses of 0.1 mg/kg per day are unlikely to induce the same degree of apoptosis of sebaceous gland stem cells. As a consequence, sebaceous gland recovery occurs more quickly with lower doses. What this means is that 0.1 mg/kg per day for 16 weeks effectively suppresses sebaceous glands for a shorter period of time than would 1.0 mg/kg per day, given for the same number of weeks of treatment. It is likely that you would need to continue 0.1 mg/kg per day isotretinoin for 4–6 months longer than 1 mg/kg per day to achieve the same length of sebaceous gland suppression.

The length of sebaceous gland suppression is a better explanation for the studies that showed increased relapse in lower daily dosage (given for the same periods of time) than cumulative dose, as there is no biological support for this concept. The early isotretinoin studies were largely in patients with severe nodulocystic acne treated with various daily doses, but all for a fixed period of time (mostly 16 weeks). More recent studies have been of 0.1–0.2 mg/kg per day, but for 8–12 months with no increase in relapse. The larger dose of isotretinoin does, however, mean that isotretinoin can be discontinued earlier, which has some theoretical advantages in the risk of becoming pregnant but has greater consequences for side effects, acceptance and perhaps attitude towards re-treatment.

RELAPSE

If cumulative dose is not important for relapse, which factors are? The significant factors for relapse include[28–33]

- stopping isotretinoin before acne has cleared completely
- macrocomedonal disease
- severity of acne
- excessive seborrhoea after finishing isotretinoin
- smoking
- younger age (under 14)
- older age (women over 25)
- polycystic ovarian syndrome.

These factors are also associated with slow response or apparent failure to respond to isotretinoin.[34] Another cause of apparent relapse is an alteration in the patient's perception of acne, where the patient becomes psychologically dependent on isotretinoin.

PERSISTENT ADULT ACNE

Acne vulgaris has generally been regarded as a self-limiting disorder affecting predominantly adolescents. However, a

significant and growing body of literature indicates that acne is a chronic disease that continues to afflict adults.[35,36] In a study of acne across a woman's life span, Perkins and colleagues[37] showed that among 2895 women aged 10 to 70 years, 55% had some form of acne, of which 27% was considered clinically significant. As expected, acne peaked in the teenage years but 45% of women aged 21–30 years, 26% aged 31–40 and 12% aged 41–50 still complained of clinical acne.[37] This is similar to a French study,[38] which showed the persistence of acne in 41% of older women (24% physiological acne, 17% clinical acne). In addition, 49% of the acne patients had acne sequelae, including scars and/or pigmented macules.[38] Despite this high prevalence of acne vulgaris in patients over 25 years of age, there are very few studies that specifically address treatment in this age group.

Seukeran and colleagues, in an open-label review, reported nine patients treated with 0.25 mg/kg isotretinoin per day for 6 months, with excellent clinical results.[39] Goulden and colleagues treated 80 older adults (of whom 58 were women) with persistent acne with intermittent moderate-dose isotretinoin (0.5 mg/kg per day for 1 week in every 4 weeks) for a total period of 6 months, with a similar excellent response.[32] Palmer and colleagues have described using microdoses of isotretinoin (20 mg once or twice a week) very successfully to manage eight adult patients who relapsed repeatedly after several standard courses of isotretinoin.[40] A review of persistent acne in women suggested lower dose isotretinoin (initially 0.5 mg/k per day according to the European directive for prescribing systemic isotretinoin), intermittent isotretinoin, or even very low dose isotretinoin (10–20 mg per day for 6–8 months).[41] Another review of retinoid therapy in acne suggested that good long-term control of seborrhoea in adult patients could be achieved in an off-label use, with doses as low as 20 mg of isotretinoin twice weekly.[42] A recently completed 42-week double-blind, placebo controlled study of isotretinoin 5 mg/day in persistent adult acne demonstrated that low-dose isotretinoin is very effective in this patient group with minimal adverse effects.[22]

Table 1 Clinical indications for isotretinoin

Acne	Nodulocystic acne
	Recalcitrant acne with tendency for scarring
	Persistent adult acne vulgaris
Other pilosebaceous disorders	Rosacea
	Periorificial dermatitis
	Hidradenitis suppurativa
	Eosinophilic pustular folliculitis
	Acquired immunodeficiency syndrome-associated eosinophilic folliculitis
	Pyoderma faciale
	Acne with solid facial oedema
	Scalp folliclitis
	Dissecting cellulitis of the scalp
Disorders of keratinization	Ichthyosis
	Darier disease
	Pityriasis rubra pilaris
	Keratoderma
	Papillon–Lefèvre syndrome
Chemoprophylaxis of neoplastic processes	Xeroderma pigmentosum
	Nevoid basal cell carcinoma syndrome
	Skin cancer in solid-organ transplant recipients
Treatment of neoplastic processes	Actinic keratosis and Bowen's disease
	Basal cell carcinoma
	Advanced squamous cell carcinoma
	Keratoacanthoma
	Kaposi sarcoma
	Sebaceous hyperplasia
	Muir–Torre syndrome
	Leukoplakia
	Langerhans cell histiocytosis
Miscellaneous conditions	Atrophoderma vermiculatum
	Bazex paraneoplastic acrokeratosis
	Confluent and reticulated papillomatosis of Gougerot and Carteaud
	Follicular mucinosis
	Granuloma annulare
	Lichen planus
	Lichen sclerosus
	Lupus erythematosus
	Sarcoidosis
	Subcorneal pustular dermatosis
	Ulerythema ophryogenes

NON-ACNE INDICATIONS

Isotretinoin has been used for an extensive range of other dermatological diseases (see Table 1).[45,44] These include acneiform conditions such as folliculitis, periorificial dermatitis, rosacea and malassezia (pityrosporum) folliculitis. It is beneficial in seborrhoeic conditions including seborrhoeic dermatitis and pityriasis versicolor. It has been used in a range of granulomatous disorders, including sarcoidosis and granuloma annulare, as well as in cutaneous discoid lupus erythematosus. Increasingly it is being used for chemoprophylaxis of skin cancer and the management of extensive actinic damage. However, perhaps the more intriguing new indication for isotretinoin is photoaging.[44–48]

SUMMARY

After 30 years of use we now understand why isotretinoin is such an effective drug. Not only does it clear acne in almost all patients, long-term remission can be achieved in 70–80% of patients with a single course. The cumulative dose story has been superseded by a focus on the length of actual sebaceous cell suppression.

Important changes in the use of isotretinoin include using a lower daily dose for the appropriate length of time. This usually means 10–20 mg/day for 3–12 months, depending on the severity of the acne and other patients' characteristics. These lower doses avoid most of the adverse effects of standard dose isotretinoin, including isotretinoin-induced flare of acne and excessive scarring and lower potential risks of developing psychiatric or gastrointestinal adverse effects. Teratogenicity however, remains a very significant concern, whatever the dose.

The use of isotretinoin in the management of acne vulgaris should be tailored to the patient response, rather than using a fixed dose/length of treatment. It is appropriate to

start with doses of 10 mg/day, and continue until all the active acne lesions have resolved. It is advisable to continue treatment for a further 2–4 months, perhaps at the lower dose of 5–10 mg/day (or 10 mg alternate day) to reduce the risk of relapse and help with resolution of acne scarring. Treatment may need to be continued for longer in smokers, patients with significant macrocomedonal disease and women with untreated hyperandrogenism. There remain, however, a very small number of patients who, for unexplained reasons, require larger doses (e.g. 1 mg/kg per day) to clear their acne.

New indications for isotretinoin continue to emerge, particularly as a potential treatment for both intrinsic and extrinsic (photo) aging.

REFERENCES

1. Layton AM, Cunliffe WJ. Guidelines for optimal use of isotretinoin in acne. *J. Am. Acad. Dermatol.* 1992; **27**: S2–7.
2. Peck GL, Olsen TG, Yoder FW *et al*. Prolonged remissions of cystic and conglobata acne with 13-cis-retinoic acid. *N. Engl. J. Med.* 1979; **300**: 329–33.
3. Farrell LN, Strauss JS, Stranieri AM. The treatment of severe cystic acne with 13-cis-retinoic acid. Evaluation of sebum production and the clinical response in a multiple-dose trial. *J. Am. Acad. Dermatol.* 1980; **3**: 602–11.
4. Plewig G, Gollnick H, Meigel W *et al*. 13-cis retinoic acid in the oral therapy of acne conglobata. Results of a multi-center study. *Hautarzt* 1981; **32**: 634–46.
5. Strauss JS, Stranieri AM. Changes in long-term sebum production from isotretinoin therapy. *J. Am. Acad. Dermatol.* 1982; **6**: 751–6.
6. Peck GL, Olsen TG, Butkus D *et al*. Isotretinoin versus placebo in the treatment of cystic acne. A randomized double-blind study. *J. Am. Acad. Dermatol.* 1982; **6**: 735–45.
7. Jones DH, King K, Miller AJ *et al*. A dose-response study of 13-cis-retinoic acid in acne vulgaris. *Br. J. Dermatol.* 1983; **108**: 333–43.
8. Marsden JR, Laker MF, Ford GP *et al*. Effect of low dose cyproterone acetate on the response of acne to isotretinoin. *Br. J. Dermatol.* 1984; **110**: 697–702.
9. Jones DH, Cunliffe WJ. Remission rates in acne patients treated with various doses of 13-cis-retinoic acid (isotretinoin). *Br. J. Dermatol.* 1984; **111**: 123–5.
10. Harms M, Duvanel T, Williamson C *et al*. Isotretinoin for acne: should we consider the total cumulative dose. In: Marks R, Plewig G (eds). *Acne and Related Disorders*. London: Martin Dunitz, 1989; 203–6.
11. Cunliffe WJ, van de Kerkhof PCM, Caputo R *et al*. Roaccutane treatment guidelines: results of an international survey. *Dermatology* 1997; **194**: 351–7.
12. Kim J, Ochoa MT, Krutzik SR *et al*. Activation of toll-like receptor 2 in acne triggers inflammatory cytokine responses. *J. Immunol.* 2002; **169**: 1535–41.
13. Chronnell CM, Ghali LR, Ali RS *et al*. Human beta defensin-1 and -2 expression in human pilosebaceous units: upregulation in acne vulgaris lesions. *J. Invest. Dermatol.* 2001; **117**: 1120–5.
14. Kuenzli S, Saurat J-H. Retinoids. In: Bolognia JL, Jorizzo JL, Rapini RP (eds). *Dermatology*, 2nd edn. Elsevier, 2008. Available from URL: http://www.expertconsult.com. (Accessed April 2012).
15. Layton A. The use of isotretinoin in acne. *Dermatoendocrinology* 2009; **1**: 162–9.
16. Nelson AM, Zhao W, Gilliland KL *et al*. Isotretinoin temporally regulates distinct sets of genes in patient skin. *J. Invest. Dermatol.* 2009; **129**: 1038–42.
17. Nelson AM, Zhao W, Gilliland KL *et al*. Temporal changes in gene expression in the skin of patients treated with isotretinoin provide insight into its mechanism of action. *Dermatoendocrinology* 2009; **1**: 177–87.
18. Rademaker M. Adverse effects of isotretinoin. A retrospective study of 1743 patients. *Australas. J. Dermatol.* 2010; **51**: 248–53.
19. Strauss JS, Rapini RP, Shalita AR *et al*. Isotretinoin therapy for acne: results of a multicenter dose-response study. *J. Am. Acad. Dermatol.* 1984; **10**: 490–6.
20. Plewig G, Dressel H, Pfleger M *et al*. Low dose isotretinoin combined with tretinoin is effective to correct abnormalities of acne. *J. Dtsch Dermatol. Ges.* 2004; **2**: 31–45.
21. Geissler SE, Michelsen S, Plewig G. Very low dose isotretinoin is effective in controlling seborrhea. *J. Dtsch Dermatol. Ges.* 2003; **1**: 952–8.
22. Rademaker M, Wishart J, Birchall N. Isotretinoin 5 mg daily for persistent low-grade adult acne vulgaris – a randomised double blind study. (in-press: abstract EADV Prague 2012).
23. Chivot M. Acne flares and deteriorations during oral isotretinoin therapy. *Ann. Dermatol. Venereol.* 2001; **128**: 224–8.
24. Borghi A, Mantovani L, Minghetti S *et al*. Acute acne flare following isotretinoin administration: potential protective role of low starting dose. *Dermatology* 2009; **218**: 178–80.
25. Chivot M, Midoun H. Isotretinoin and acne – a study of relapses. *Dermatologica* 1990; **180**: 240–3.
26. Lehucher-Ceyrac D, Weber-Buisset MJ. Isotretinoin and acne in practice: a prospective analysis of 188 cases over 9 years. *Dermatology* 1993; **186**: 123–8.
27. Quereux G, Volteau C, N'Guyen JM *et al*. Prospective study of risk factors of relapse after treatment of acne with oral isotretinoin. *Dermatology* 2006; **212**: 168–76.
28. Shahidullah M, Tham SN, Goh CL. Isotretinoin therapy in acne vulgaris: a 10-year retrospective study in Singapore. *Int. J. Dermatol.* 1994; **33**: 60–3.
29. Stainforth JM, Layton AM, Taylor JP *et al*. Isotretinoin for the treatment of acne vulgaris: which factors may predict the need for more than one course? *Br. J. Dermatol.* 1993; **129**: 297– 301.
30. Zouboulis CC. The truth behind this undeniable efficacy – recurrence rates and relapse risk factors of acne treatment with oral isotretinoin. *Dermatology* 2006; **212**: 99–100.
31. Bottomley WW, Cunliffe WJ. Severe flares of acne following isotretinoin: large closed comedones (macrocomedones) are a risk factor. *Acta Derm. Venereol.* 1993; **73**: 74.
32. Goulden V, Clark SM, McGeown C *et al*. Treatment of acne with intermittent isotretinoin. *Br. J. Dermatol.* 1997; **137**: 106–8.
33. Harms M, Masouye I, Radeff B. The relapses of cystic acne after isotretinoin treatment are age-related: a long-term follow-up study. *Dermatologica* 1986; **172**: 148–53.
34. Lehucher-Ceyrac D, de La SP, Chastang C *et al*. Predictive factors for failure of isotretinoin treatment in acne patients: results from a cohort of 237 patients. *Dermatology* 1999; **198**: 278–83.
35. Gollnick HP, Finlay AY, Shear N. Global alliance to improve outcomes in acne. Can we define acne as a chronic disease? If so, how and when? *Am. J. Clin. Dermatol.* 2008; **9**: 279–84.
36. Thiboutot DM, Lookingbill DP. Acne: acute or chronic disease? *J. Am. Acad. Dermatol.* 1995; **32** (5 Pt 3): S2–5.
37. Perkins AC, Maglione J, Hillebrand GG *et al*. Acne vulgaris in women: prevalence across the life span. *J. Womens Health (Larchmt)* 2012; **21**: 223–30.
38. Poli F, Dreno B, Verschoore M. An epidemiological study of acne in female adults: results of a survey conducted in France. *J. Eur. Acad. Dermatol. Venereol.* 2001; **15**: 541–5.
39. Seukeran DC, Cunliffe WJ. Acne vulgaris in the elderly: the response to low-dose isotretinoin. *Br. J. Dermatol.* 1998; **139**: 99–101.

40. Palmer RA, Sidhu S, Goodwin PG. 'Microdose' isotretinoin. *Br. J. Dermatol.* 2000; **143**: 205–6.
41. Williams C, Layton AM. Persistent acne in women: implications for the patient and for therapy. *Am. J. Clin. Dermatol.* 2006; **7**: 281–90.
42. Thielitz A, Krautheim A, Gollnick H. Update in retinoid therapy of acne. *Dermatol. Ther.* 2006; **19**: 272–9.
43. Fritsch P. Use of systemic retinoids in dermatology. *Wien. Klin. Wochenschr.* 1983; **95**: 817–22.
44. Bagatin E. Oral isotretinoin: the most promising dermatological off-label uses. *Expert Rev. Dermatol.* 2010; **5**: 617–26.
45. Hernandez-Perez E, Khawaja HA, Alvarez TY. Oral isotretinoin as part of the treatment of cutaneous aging. *Dermatol. Surg.* 2000; **26**: 649–52.
46. Kalil CL, Fachinello FZ, Lamb FM *et al*. Use of oral isotretinoin in photoaging therapy. *Skinmed* 2008; **7**: 10–14.
47. Rabello-Fonseca RM, Azulay DR, Luiz RR *et al*. Oral isotretinoin in photoaging: clinical and histopathological evidence of efficacy of an off-label indication. *J. Eur. Acad. Dermatol. Venereol.* 2009; **23**: 115–23.
48. Bagatin E, Parada MO, Miot HA *et al*. A randomized and controlled trial about the use of oral isotretinoin for photoaging. *Int. J. Dermatol.* 2010; **49**: 207–14.