Review

The use of isotretinoin in acne

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Key words: acne, isotretinoin, teratogenicity, relapse, European Directive

Systemic isotretinoin remains the most efficacious treatment for severe acne as well as many cases of more moderate disease that are unresponsive to other treatment modalities. The current chapter outlines the mechanisms behind the excellent efficacy, describes how to optimize treatment, reviews the recommended guidelines for monitoring and summarizes adverse effects.

Systemic Isotretinoin for the Treatment of Acne

Oral isotretinoin (13-*cis*-retinoic acid) was first approved as treatment for severe acne by the US Food and Drug Administration (FDA) in 1982. To date the efficacy of isotretinoin has not been superseded by any other treatment and over two decades later isotretinoin remains the most clinically effective anti-acne therapy, producing long-term remission and/or significant improvement in many patients.

Mechanism of Action

Isotretinoin is the only therapy that impacts on all of the major aetiological factors implicated in acne. It achieves this remarkable efficacy by influencing cell-cycle progression, cellular differentiation, cell survival and apoptosis.¹⁻⁷ It results in a significant reduction in sebum production, influences comedogenesis, lowers surface and ductal *P. acnes* and has anti-inflammatory properties. A dose of 0.5–1.0 mg/kg/day dramatically reduces sebum excretion by the order of 90% within 6 weeks. Unlike tretinoin (all-*trans* retinoic acid), isotretinoin has little or no ability to bind to cellular retinol-binding proteins or retinoic acid nuclear receptors (RARs and RXRs) but may act as a pro-drug that is converted intracellularly to metabolites that are agonists for RAR and RXR nuclear receptors.¹⁻⁴

Isotretinoin has at least five biologically important metabolites: 13-*cis*-4-*oxo*-retinoic acid (4-*oxo*-isotretinoin), all-*trans*-RA (tretinoin), all-*trans*-4-*oxo*-retinoic acid (4-*oxo*-tretinoin), 9-*cis*-retinoic acid and 9-*cis*-4-*oxo*-retinoic acid. Studies examining

sebum excretion rates in patients with severe acne have shown that, within 4 weeks, 4-*oxo*-isotretinoin (30–60 mg/day orally) only produces a 70% mean reduction compared with the same dose of oral isotretinoin over 4 weeks. Isotretinoin is also superior to 9-*cis*-retinoic acid and all-*trans*-retinoic acid in terms of sebum suppression.^{4,5} Only tretinoin and 4-*oxo*-tretinoin bind to RAR- γ , which is the receptor thought to be important in retinoid treatment of acne. Incubation of SZ 95 human sebocytes with isotretinoin leads to significantly higher intracellular concentrations of tretinoin than isotretinoin.⁶ The incubation with tretinoin generated very high intracellular concentrations of tretinoin and negligible concentrations of isotretinoin. These data suggest that tretinoin may be the active intracellular form of isotretinoin and prompted Tsukada et al.⁶ to conclude that isotretinoin should be considered as a pro-drug. Differences in the plasma concentrations of these metabolites could therefore explain the differences in the intensity of the therapeutic response and the severity and/or occurrence of side effects in individual patients. A recent study has demonstrated that isotretinoin induces apoptosis in sebocytes and these effects are independent of RAR receptor activation suggesting that it is sebaceous gland involution resulting from oral isotretinoin which leads to reduced sebum production.⁷

Isotretinoin produces a significant reduction in comedogenesis by decreasing hyperkeratinisation.⁸⁻¹⁰ The exact mechanism by which this is achieved remains uncertain, there is no evidence to suggest that isotretinoin affects the metabolic activity of the keratinocytes.¹⁰

Oral isotretinoin has no direct antimicrobial action, but by dramatically reducing SER and the size of the pilosebaceous duct it alters the microenvironment within the duct making it much less favorable to colonization with *P. acnes*. The result is a log₃ reduction in *P. acnes*—a suppression much greater than that seen with oral and topical antibiotics.¹¹⁻¹³ It has also been suggested that like all-*trans*-retinoic acid, isotretinoin might increase host defense mechanisms and modifies monocyte chemotaxis, which in part explains the anti-inflammatory effects of the drug.¹⁴ The significant reduction in the *P. acnes* population also contributes to the reduction in acne inflammation.¹⁵

Clinical Benefit of Oral Isotretinoin

Most patients who receive oral isotretinoin will be free of acne by the end of 4–6 months of treatment depending on the dose

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Submitted: 01/15/09; Accepted: 06/26/09

Previously published online as a *Dermato-Endocrinology* E-publication: <http://www.landesbioscience.com/journals/dermatoendocrinology/article/9364>

Table 1 Recommendations in the European Directive

	Pre-Directive	Post-directive
Dosage	0.5-1.0 mg/kg/day	Start 0.5 mg/kg.day
Indications for use	Isotretinoin recommended as first line therapy for severe acne (nodular and conglobata) as well as acne not responding to 3 months systemic antibiotics in combination with topical	The new recommendations suggest isotretinoin should only be used in severe acne (nodular, conglobata) that has or is not responding to appropriate antibiotics and topical therapy. The inference of this being that it should now not be used at all as first-line therapy.
Age	Previously no age limit	Not indicated in children <12 years
Monitoring	Liver enzymes and lipids should be checked before treatment and 1 month after the maximum dosage has been used	Baseline investigations as before but at 1 month and 3 monthly through out the course of treatment
Physical treatments	It was recommended that chemical and physical peeling should be avoided during treatment and for 6 months afterwards and that wax depilation should be avoided during and 6 weeks post-therapy.	All forms of peeling and wax depilation should be avoided during therapy and 6 months afterwards.
Pregnancy prevention programme	See text on PPP	

administered. Recent clinical experience suggests that the long-term cure rate may be lower than was initially thought.¹⁶⁻¹⁹ One explanation for this might be that isotretinoin is now used to treat patients with less severe acne. These cases respond extremely well and then expect to remain clear, whereas the initial cohorts of patients had severe disease and were less concerned by the resurgence of a few spots. Furthermore, some of the early reported 'cures' may have been due to the fact that patients had eventually grown out of their acne as they may well have received initial treatments much later on in the course of their disease. There is evidence to suggest that younger patients relapse more readily than older ones.²⁰ Isotretinoin currently has a license to treat severe acne as a second line agent in cases unresponsive to other combination therapies including antibiotics.²¹ Over the years experienced clinicians have prescribed isotretinoin first line to treat severe cases of acne, those with poor prognostic features as well as some acne related conditions.

An European directive on prescribing of isotretinoin was recently introduced. The aims of the directive were to (1) ensure generic prescribing was harmonized and delivered appropriately throughout the European Union and (2) to minimize the risk of adverse effects including pregnancy. Table 1 summarizes the recommendations made in this directive and contrasts these with previous prescribing habits.

The regulatory authority in each country has approved a Pregnancy Prevention Program (PPP). This program includes advice on education, therapy management and control of distribution of the drug.

• Education suggests that both patients and prescribers must be fully aware of teratogenicity. The patient should acknowledge

the problem by signing a consent form and should accept detailed counseling by the clinician prior to and during treatment.

• Therapy management includes medically supervised pregnancy testing before, during and 5 weeks after a course of therapy and provides advice on contraception.

• Distribution control suggests that only 30 days of oral isotretinoin can be supplied at one time to a female patient and the prescription will only be valid for 7 days.

The scope of the PPP suggests that it should include all females of childbearing potential. In the EU, the clinician can impose clinical judgment as to whether a patient should receive contraception if they establish that the patient is not currently sexually active. However, it is mandatory that clinicians check carefully at each 4 follow-up visits and record as well as act on any change in circumstance. Pregnancy testing is mandatory pre- and 5 weeks post-therapy. It has been suggested that the initial test can be done up to 2 weeks prior to the start of treatment providing contraception is used in those who require it. In addition, monthly pregnancy testing is recommended throughout the treatment period. The treatment should ideally start on day 3 of the menstrual cycle. The program suggests that where possible patients should agree to at least one and preferably two complementary methods of effective contraception including a barrier method before therapy is initiated. The dispensing restrictions do not apply to males as the process is aimed at ensuring that females do not get extended periods of treatment without pregnancy tests being performed. The responsibility for the assessment of pregnancy tests and the administration of further prescriptions lies with the clinician. Clinical problems relating to the implementation of this approach include difficulties in females with irregular menses, potential

Table 2 Prognostic factors which should influence the early use of isotretinoin

- Family History
- Early onset
- Hyperseborrhoea
- Truncal acne
- Scarring
- Psychosocial difficulties
- Persistent or late onset acne

lack of continuity of treatment due to potential unavailability of patient and/or healthcare workers as well as forgotten tests. These factors may all contribute to early cessation and/or partial treatment resulting in ineffective management and associated financial burden on health care systems.²¹ Given potential side-effects of oral contraceptives, it may not always be appropriate to insist on all patients regardless of pregnancy risk using specific contraceptives.

The recommendations suggest that isotretinoin should not now be used as first-line therapy and/or should not be used below the age of 12 years. There are many publications advocating the use of isotretinoin for severe and scarring acne,²²⁻²⁴ hence delaying this effective therapy in certain cases may go against best and evidence-based practice. With increasing clinical experience, use of the drug has been expanded worldwide to include less severely affected patients who have responded unsatisfactorily to what have been called conventional treatments, including long-term antibiotics and/or appropriate topical antimicrobial or retinoid-like therapies.

Failure of conventional treatment may occur for many reasons, including resistance of *P. acnes* to antibiotics.^{25,26} A recent European review²¹ outlines when isotretinoin might be considered in light of the new European directive and identifies poor prognostic factors. These are outlined in Table 2 and should be taken into account when prescribing oral isotretinoin.

The recommendation to start at a dose of 0.5 mg/kg/day and to titrate the dose up as tolerated is well received when using isotretinoin for conventional acne. In some patients with persistent acne, especially in the mature age group, as well as cases where side-effects are not tolerated at these recommended doses low dose and/or intermittent treatment has been advocated in the literature.²⁷ The USA have adopted a more rigid program to pregnancy prevention and monitoring. In 2005 the FDA announced that both male and female users of 'Accutane' (oral isotretinoin) would have to enroll into the National Registry 'iPLEDGE'. If this is not achieved, patients will no longer be able to receive the drug. Women of childbearing age now have to 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 throughout therapy and for 30 days after treatment. They must enter these forms of contraception into the registry. All patients sign a document confirming that they are aware of potential adverse

effects including depression and suicidal thoughts. One unfortunate consequence of this strict regimen may be a reduction in the usage of isotretinoin, which could potentially disadvantage patients who require this effective treatment. In addition, the restriction of isotretinoin as a second-line therapy may have consequences on the evolution of acne scarring, and on the quality of life in many acne patients. Expert opinion supported by clinical data^{18,23,28} support the use of isotretinoin for patients with moderate acne who are failing to respond to conventional therapy, for whatever reason. Acne may produce scars in 30% of patients with moderate disease, and significant psychological morbidity in 12–13%.

The definition of poor response should be made against objective or semi-objective assessments where possible. The use of a clinical acne scoring system,²⁹ along with quality of life and psychosocial parameters should be used when evaluating acne. Physical and psychological severity of acne and local financial pressures will all play a role in the decision whether to prescribe isotretinoin. There is strong evidence to show that isotretinoin significantly reduces the psychological problems associated with acne.^{30,31}

A small number of patients with mild acne have psychological problems disproportionate to their degree of acne. These patients may have body dysmorphic syndrome. There is evidence to suggest these patients respond to isotretinoin but withdrawing the drug may be difficult.³²

Although the European directive suggests isotretinoin should not be used <12 years of age, up to 0.5 mg/kg/day has been used successfully in a number of neonates or juveniles with acne that have not responded to all appropriate topical or oral therapy.³³ Some pre-adolescent youngsters, even under 10 years of age, develop troublesome acne with scarring. Oral isotretinoin should be considered for pediatric acne patients if there are sufficient clinical indications.³⁴

Most dermatologists are treating increasing numbers of patients with acne that has persisted beyond the age of 25 years. The reasons for this change in the age/referral pattern are unclear, but may reflect increased expectations for cure based on the widely known clinical effectiveness of isotretinoin. Although the acne severity in these cases is not usually as great as when they were 15–25 years old, the persistence of the disease results in an increased risk of scarring and disproportionate psychological distress.³⁵ Isotretinoin can play an important role in the treatment of this age group. Adults with acne persisting at the age of 30 years are likely to have acne for at least a further 10 years. Small, intermittent-dose isotretinoin therapy may be appropriate for this subgroup of patients, but relapse often occurs quickly following a successful acne-free interval while on therapy.²⁷

Isotretinoin for patients with significant systemic disease. Patients with significant systemic disease have been successfully treated with oral isotretinoin. It has been suggested that these patients fall into three subgroups and therefore three appropriate protocols have been recommended (Table 3) aimed at minimizing adverse effects in the associated disorder. In all instances it is necessary that a careful check be made by the dermatologist and/or the relevant physician at monthly intervals to ensure that there

are no significant clinical or laboratory changes in the systemic disease.^{36,37}

1. Patients in Group 1 represent patients for whom there is evidence to show that the full dose of isotretinoin can be safely given.

2. Patients in Group 2 are those patients for whom there is limited information but, on balance, the drug probably does not cause any change in the associated disorder. These patients usually can start on a dose regimen of 0.25–0.5 mg/kg/day. If all is well, the dose can be increased at 2-month intervals to 0.5 mg/kg/day, and beyond if required, and therapy usually maintained for 24 weeks.

3. Group 3 includes patients who have rare diseases, or where not much information exists.

In these uncommon circumstances, it is recommended that therapy begins at 20 mg isotretinoin/week. The dose is increased by 20 mg each week so that at the end of 7 weeks patients are taking 20 mg/day. The cycle can then be repeated to achieve a higher dose, so that by the end of a further 7 weeks they are taking 20 mg twice a day. In this group of diseases, it is particularly important that the dermatologist links with the appropriate physician so that a very careful clinical and, where appropriate, laboratory measurement is made of the associated disease.

Isotretinoin in the treatment of acne variants. These diseases are rare and isotretinoin provides a useful treatment in many of these cases. This group includes patients with acne fulminans, rosacea fulminans, Gram-negative folliculitis, dissecting cellulitis of the scalp, hidradenitis suppurativa and acne conglobata.

Patients with acne fulminans and rosacea fulminans respond to oral isotretinoin.^{38,39} The best response in these conditions is obtained by starting with a course of prednisolone 0.5–1.0 mg/kg for 4–6 weeks. The steroids can usually be reduced gradually over the following 2 weeks, and isotretinoin can be introduced at a dosage of 0.5 mg/kg body weight/day and this can be increased gradually to 1 mg/kg/day according to the response.

Patients with acne conglobata and Gram-negative folliculitis usually do not require oral steroids, and can be started immediately on oral isotretinoin at a dose of 0.2 mg–10.5 mg/kg/day.⁴⁰ Hidradenitis suppurativa is a distressing disease that is difficult to treat. The response to isotretinoin is variable.^{41,42} However, oral isotretinoin may achieve some improvement in patients who have not responded to hormonal regimens or long-term high-dose antibiotics such as minocycline. Dissecting cellulitis of the scalp also responds variably to oral isotretinoin, but a 4-month course should be tried.⁴³

Steatocystoma multiplex does not respond well to isotretinoin and although the inflammatory component of this disease may improve, it may respond equally well to long-term oral antibiotics.⁴⁴

Recommended doses and duration of therapy. There have to date been variations in the way treatment is started. The European

Table 3 Isotretinoin dose schedules that may be most appropriate for patients with significant systemic disease

(1) Protocol A standard regimen	(2) Protocol B initially half the standard regimen	(3) Protocol C once-a-week regimen with gradual dose increase
Crohn's disease	Chronic renal failure	Behçet's syndrome
Diabetes mellitus	Renal dialysis	Cerebellar spongiform encephalopathy
Epilepsy	Hypertriglyceridaemia purpura	Idiopathic thrombocytopenic
Spina bifida	Immunosuppression	Leukaemia
Ulcerative colitis	Manic depressive psychosis	Mitochondrial degeneration
	Myalgic encephalopathy	Paroxysmal nocturnal haemoglobinuria
	Motor neurone disease	Polymyalgia rheumatica
	Multiple sclerosis	

Directive advocates a starting dose of 0.5 mg/kg/day with an increase to increase to 1.0 mg/kg/day according to tolerance and response. The half life is 22 hours and the bioavailability is 25%. Absorption of isotretinoin is markedly affected by the presence of fat and pharmacokinetic studies show that absorption can be doubled by taking isotretinoin with, or after, a meal compared with the fasting state.⁴⁵ It is therefore advisable to take the capsules with food at the same time of day. The dose can then be adjusted according to clinical response and presence or absence of side effects.

The duration of therapy varies according to the dose administered over the course of the treatment period. The range is usually 16–30 weeks, with a mean between 16 and 20 weeks with patients receiving 0.5 mg/kg/day requiring a longer course of therapy to achieve appropriate results. Studies to derive a cumulative dose for maximum benefit and reduced relapse rate have confirmed that there is a definite effect of both dose and duration of therapy but that there is not a priori pharmacokinetic reason to support the concept of accumulation of drug or a cumulative dose effect. Post-therapy relapse is minimized by treatment courses that amount to a total of at least 120 mg/kg, but there is not necessarily any added benefit when 150 mg/kg is exceeded.^{46,47} Typically, this total dose can be achieved by 4–6 months at 0.5–1.0 mg/kg/day. The duration of therapy should be adjusted to give at least 90% clearance of acne based upon initial clinical acne grade scoring techniques followed by 4–8 weeks of consolidation.

Demographic factors, such as age, sex and duration of acne, may also govern the rate of response and relapse. Males with extensive truncal acne, more severe acne, and/or suffering from acne for less than 7 years, fail to respond as well as, and relapse more quickly than, female patients with predominantly facial acne of a less severe grade. Table 2 outlines poor prognostic factors.

Eighty-five percent of patients who receive a dose of 0.5–1.0 mg/kg/day are virtually clear of their acne by 16 weeks. Thirteen per cent require 5 or 6 months to clear, and 3% require a longer course. Less than 1% of patients may need up to 12 months of continuous therapy. Low-dose courses of isotretinoin

have been used successfully in mature adults with persistent and late-onset acne. A typical approach consists of 0.5 mg/kg/day taken 1 week out of 4 for a period of 6 months. Ninety-one percent will be clear of acne using this regimen^{46,47} but relapse is disappointingly frequent. Furthermore some patients will not accept even minimal disease and become very dependent on these small doses expecting to stay on the drug for many years at this lower dosage. It is not clear whether this approach will result in long term adverse effects and it is important to clarify with the patient that although nothing untoward has been reported to date this is clearly using the drug outside recommended guidelines and is not deemed appropriate for a female of reproductive potential.

What are the reasons for a slow response to isotretinoin?

Analysis of slow responders to isotretinoin shows that the cause is due to the presence of macrocomedones in the majority of cases 70%, although hyperandrogenism may also play a part in resistance to isotretinoin therapy.⁴⁸

An early post isotretinoin flare,⁴⁸ poor absorption, possibly differences in receptor sensitivity, colonization with *Staphylococcal aureus*, severe acne and unusual variants account for 25% of poor responders and the cause of poor response is unknown in about 5%.

Macrocomedones may be subtle and should be detected under a suitable lamp with the skin stretched. They should be identified before systemic isotretinoin is started as an acute flare of acne may ensue if left untreated before embarking on isotretinoin.⁴⁸ Treatment requires light cautery or hyfrecation. A local anaesthetic cream should be applied to the lesions for the requisite time beneath an occlusive dressing and then the lesions touched gently with light cautery⁴⁹ or hyfrecation. This procedure should initially be performed on a test area of 10 cm², to ensure that the patient does not develop scarring or hypo- or hyperpigmentation.

When macrocomedones are not the cause of poor response, the dosage of isotretinoin should be carefully considered as some patients will suffer a deterioration in their acne at the start of a course of isotretinoin.⁵⁰ If the poor response or worsening acne is thought to be due to an early post isotretinoin flare which is well reported, an antibiotic can be used in combination with isotretinoin such as erythromycin 1 g daily or trimethoprim 200–300 mg b.d.⁵⁰ Tetracyclines should be avoided in combination with isotretinoin due to a possible increased risk of benign intracranial hypertension.⁵¹

If the acne is very inflammatory, then a significant reduction in the dose of isotretinoin and addition of oral steroids may be required (e.g. 0.5–1.0 mg/kg/day for 2–3 weeks). In other patients it may be appropriate to increase the dose of isotretinoin providing that the side effects are tolerated.

Some patients do not appear to metabolize isotretinoin as well as others and therefore may require higher doses. Adherence to therapy must also be considered. Mucocutaneous side effects particularly cheilitis are usually a good measure of absorption.

Unusual variants may lead to slow response and some female patients with hormonal dysfunction, due, for example, to polycystic ovarian syndrome, may need additional treatment with an hormonal preparation such as co-cyprindiol.

Persistent deep pustules in about 1% of patients may be due to *Staphylococcal aureus*, and bacterial swabs should always be examined and appropriate anti-staphylococcal therapy prescribed. Some patients have multiple reasons for the slow response.

Further courses of therapy are usually successful when required. There are no reports of cumulative toxicity from using repeat courses and tachyphylaxis has not been noted.

Side Effects

Isotretinoin has many side effects but most are predictable and rarely interfere with the patient management. The common mucocutaneous side effects are dose dependent and rendered tolerable by modification of the dose and/or additional symptomatic therapy.

Teratogenicity is well recognized and regarded as one of the most serious potential adverse effects.⁵² Fifty percent of pregnancies spontaneously abort, and of the remainder about half of the infants are born with cardiovascular or skeletal deformities. The European Directive and iPLEGDE in the USA have addressed the importance of pregnancy prevention as discussed previously. Discussion about the teratogenicity and recognized side effects should be recorded in the notes at each visit, and patients should be given appropriate written information.

Mood changes including depression are common among adolescents and have been reported in acne patients treated with isotretinoin. Two studies that looked at spontaneous reports of side effects for the FDA in the USA^{53,54} found little or no increase in psychiatric disease including depression and suicide over the background prevalence in the adolescent population. A further study of general practice databases in Canada and the UK showed similar findings as have subsequent studies.⁵⁵ A more recent controlled case cross-over study demonstrated a relative risk for depression of 2.68 (95% CI = 1.03 to 3.89) for acne patients exposed to oral isotretinoin.⁵⁶ This is the first controlled study to find a statistically significant association between isotretinoin and depression. Despite contradictory reports clinicians have been advised of a potential rare idiosyncratic reaction in some young vulnerable patients which could lead to mood changes and clinical depression during treatment with isotretinoin. It is therefore advisable to specifically enquire about related symptoms at each clinic visit.

If significant depression is identified, then a psychiatric referral may be indicated. Increased aggression has been identified in some male patients and the FDA in the USA has advised clinicians to warn potential patients about this side effect. If there is any doubt, the drug must be stopped.

The mucocutaneous side effects are dose dependent and can usually be controlled with regular use of moisturizers and lip salves. Occasionally retinoid dermatitis, a severe retinoid cheilitis or conjunctivitis occur, often complicated by secondary infection with *S. aureus*. These patients may need treatment with an intermediate-strength steroid ointment combined with an anti-septic. If there is impetiginization, oral anti-staphylococcal therapy such as flucloxacillin and/or topical mupirocin 2% ointment may be required.⁵⁷ A nasal preparation of mupirocin can be used

Table 4 Most common mucocutaneous problems that may arise from isotretinoin use

Adverse effect	Incidence up to
Cheilitis	98 %
Conjunctivitis/blepharitis	35%
Dermatitis	65%
Desquamation	20%
Facial erythema	65%
Epistaxis	35%
Epidermal atrophy	25%
Fragility of skin	20%
Hair loss	5%
Itching	25%
Mucositis	40%
Vestibulitis	50%
Xerosis	50%

to eradicate nasal carriage of staphylococci. Table 4 summarizes the most common mucocutaneous problems that may arise from isotretinoin use.

Significant systemic effects are uncommon (Table 5); headaches may uncommonly be an early feature of benign intracranial hyper-tension and arthralgia is seen most frequently in those patients participating in regular and heavy exercise. Tetracyclines, including doxycycline and minocycline, must not be prescribed with isotretinoin, as both drugs may produce benign intracranial hypertension.^{51,58} Systemic side effects are usually well controlled by dose reduction and concomitant the use of non-steroidal anti-inflammatory drugs or aspirin. There is a long list of very uncommon systemic side effects a detailed review of these is beyond the scope of this chapter.

An acute flare of acne early in a course of isotretinoin is a recognized problem in about 6% cases and is clinically significant in half of these.⁵⁰ The physician should inform patients accordingly and provide a fast track follow up should this problem occur as these flares can be very aggressive producing physical and psychological difficulties. Predisposing risk factors for a flare include the presence of macrocomedones and nodules.⁵⁰ If a severe flare occurs oral prednisolone should be given in a dose of 0.5–1.0 mg/kg/day over a period of 2–3 weeks, and the dose slowly decreased over the next 6 weeks. The isotretinoin should either be stopped or reduced to a dosage of 0.25 mg/kg/day depending on the severity of the problem. If stopped, the drug can be slowly reintroduced at a dose of 0.25 mg/kg/day, and then increased or decreased as response dictates.

There has been much debate as to whether liver function tests and lipids should be monitored while on therapy. Elevations in these tests occur in almost all patients and rapidly return to pretreatment levels after therapy has been stopped. It is, however, essential to carry out these tests before starting therapy. Published evidence suggests that the laboratory tests need not be repeated except in groups at risk, such as diabetics and patients with known familial hypertriglyceridaemia.⁵⁹ However, the EU directive is prescriptive in suggesting these investigations should be preformed at baseline, 1 month into therapy and 3 monthly

Table 5 Less common but recognized side effects of isotretinoin

<ul style="list-style-type: none"> • Achilles tendonitis • Acne fulminans • Depression • Diarrhoea/colitis • Headaches/benign intracranial hypertension • High-tone deafness • Mood changes • Night blindness • Paronychia • Pyogenic granulomas • Sticky palms • Urticaria • Vasculitis

throughout treatment. Amichai et al.⁶⁰ have published an excellent overview on the many side effects of oral isotretinoin.

Cost-effectiveness. Oral isotretinoin is clearly more effective than oral antibiotics in acne of all grades of severity. However, its relative expense and side effects have deterred some physicians from prescribing it. Cost-effectiveness comparisons prior to the EU directive and iPLEDGE in the UK,^{61,62} France,⁶³ New Zealand⁶⁴ and Australia⁶⁵ have shown that a 4–6-month course of isotretinoin is significantly cheaper than a 3-year therapeutic regimen of rotational courses of antibiotics and topical treatment. In fact, only patients treated with isotretinoin achieved complete clearance of acne when assessed 3–5 years post-treatment. Generic isotretinoin has made the cost effectiveness more apparent. However, the extra investigations, monitoring and prescription control introduced with the European Directive and iPLEDGE have negatively impacted on this cost effectiveness.

Drug interactions. Reduced efficacy has been noted when isotretinoin is taken with heavy alcohol intake.⁶⁶ Isotretinoin is metabolized by cytochrome P450 enzymes, these are inducible by ethanol and inhibited by some drugs e.g. ketoconazole. Hence, increased drug levels of isotretinoin may occur if combined with imidazole fungistatics. Salicylic acid and indomethacin represent acidic drugs with a high affinity for albumin. If present in the blood in high therapeutic concentrations they may displace isotretinoin from protein binding sites so resulting in an increase in the unbound concentration of the drug.⁶⁷ Carbamazepine plasma levels decrease when concurrent isotretinoin is taken, hence careful monitoring should be considered in epileptics on carbamazepine if requiring isotretinoin.⁶⁸ Oral tetracyclines and isotretinoin should be avoided as both can lead to benign intracranial hypertension. These are likely to be rare idiosyncratic reactions attributable to each drug in its own right but there are reports in the literature suggesting there could theoretically be an additive effect by combining the two.⁵¹ Vitamins supplements containing vitamin A should be avoided alongside isotretinoin as additive toxic effects could ensue.

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