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ORIGINAL ARTICLE

Adverse effects of isotretinoin: A retrospective review of 1743 patients started on isotretinoin

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ABSTRACT

Background/Objectives: Isotretinoin has revolutionized the management of acne vulgaris. However, concerns continue regarding the adverse effect profile of isotretinoin. This study aims to review the adverse effects experienced by patients started on isotretinoin by a single dermatologist.

Methods: Retrospective chart review of 1743 patients started on isotretinoin for various dermatological conditions over a 6-year period. Details of the dose of isotretinoin used, concomitant medications, adverse effects and outcome were recorded.

Results: One-fifth (18.5%) of patients reported no adverse effects during the study period. Cheilitis was the most commonly reported adverse effect, affecting 78% of users, followed by eczema and tiredness, seen in 12% each. However, these were clearly dose-dependent, as the group treated with doses of isotretinoin under 0.25 mg/kg/day only reported cheilitis in 47%, eczema in 7% and tiredness in 5%, compared with 96%, 16% and 18%, respectively, in those treated with more than 0.75 mg/gm/day. Twenty-four patients (1.4%) stopped isotretinoin because of adverse effects; a further three patients complained of severe adverse effects on at least one occasion, but continued taking the medication. The adverse effect(s) that led to patients stopping isotretinoin were cheilitis (22 patients), mood change (13), tiredness (12), eczema (6) and pregnancy (2). There were no reported instances of suicidal ideation or attempted suicide.

Conclusions: Other than the two oral contraceptive failures, there were no serious adverse events recorded during this review period. Isotretinoin is a very effective medication with a low adverse-effect profile when used at lower doses.

Key words: acne vulgaris, depression, side-effect, teratogenicity.

INTRODUCTION

Isotretinoin (13-cis-retinoic acid) revolutionized the management of acne vulgaris and various other skin disorders when it was introduced in the 1980s.[1,2] Isotretinoin was the first medication to modify the disease, rather than provide symptom control. In the last decade, it is estimated that worldwide, in excess of 11.2 million courses of isotretinoin have been dispensed (81 million grams of isotretinoin were dispensed in 2000–2009, at 120 mg/kg × 60 kg = 7.2 g/course, or 11.2 million courses; source: IMS Health, MIDAS Database, MAT Dec 2000–MAT Dec 2009).

Isotretinoin was originally indicated for the management of severe nodulocystic acne vulgaris, at a dose of 1–2 mg/kg/day to a cumulative dose of 120–150 mg/kg, usually over 4–5 months.[3] Since then, isotretinoin has been used for an extensive array of other dermatological conditions including rosacea, periorificial dermatitis, seborrhoeic dermatitis, folliculitis, granuloma annulare, sarcoidosis and a variety of disorders of keratinization.[4] An exciting new use for isotretinoin under investigation is in the management of photoageing.[5]

The dose of isotretinoin has also changed significantly. Although it is still used at its original recommended dosages in some countries, the trend has been to use lower and more intermittent dosage regimens. Evidence is now accumulating that 10–20 mg per day is quite adequate for most individuals with acne vulgaris.[6,7]

The major limitation of isotretinoin has been the well-described adverse effects. With the exception of teratogenicity, most adverse effects appear to be dose-dependent. Controversy remains as to the association between isotretinoin and depression.[8,9]

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Conflict of interest: Dr Rademaker has been a recipient of various travel grants to attend the scientific meetings of several national dermatological societies as an invited speaker. These have included travel grants from Roche, Douglas, Taro and Darier Pharmaceuticals. Dr Rademaker is currently the Principal Investigator for a clinical trial on very low-dose isotretinoin for persisting adult acne, sponsored by Douglas Pharmaceuticals, New Zealand.

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This study reviews the adverse effects experienced by 1743 patients commenced on isotretinoin over a 6-year period of time.

MATERIALS AND METHODS

The clinical details of all patients started on isotretinoin for the first time, between the years 2000 and 2005, were analysed retrospectively. Patients were all seen in a private practice setting by a single specialist (consultant) dermatologist. Only patients in whom follow-up data were available were included.

Demographic details, medical history and diagnosis, were recorded. Details of the dose of isotretinoin used, concomitant medications, adverse effects and outcome were also recorded.

After lengthy counselling, all patients in whom isotretinoin was considered an appropriate treatment were offered this medication. Patients who agreed to start isotretinoin were given a pharmaceutical company-generated information pack, which included a comprehensive information booklet and several sample-size skin-care products (lip balm, moisturiser, sun block). Patients were given the telephone contact details for the practice nurse should they, or their guardians, have any questions/concerns while on treatment. Patients received written confirmation of the details/discussion of the consultation, 1–2 weeks after each visit, in the form of a copy of the letter to the patient's general practitioner. Investigations, other than pregnancy tests, were performed on a clinical needs basis only.

Most patients were followed up 3-monthly. At each follow-up visit, the patient/guardian was specifically asked a series of questions regarding common adverse effects of isotretinoin (see Appendix I). Although the patients were asked whether they had any other adverse effects (which were recorded), specific adverse effects such as night-blindness, sun sensitivity, inflammatory bowel disease, etc. were not specifically enquired for. If the patient admitted to an adverse event, they were then asked to grade the severity of any adverse effect(s) as: mild, moderate or severe; the highest grade of reported severity, from any visit, was used in the analysis. When possible, causality of the adverse effect was determined using World Health Organization accepted nomenclature.[10] Patients who complained of adverse effects were asked whether they wished to continue on isotretinoin. On completion of the course of isotretinoin, no further follow up was organized.

The dose of isotretinoin used evolved over the study period. Initially, most patients received 1 mg/kg/day to a cumulative dose of 150–160 mg/kg/day over 5 months. However, as the review period progressed, the starting dose of isotretinoin used was reduced, such that by the end of the review period, the most commonly prescribed dosage during the complete course of treatment was 10–20 mg/day continued for 6–9 months. Other dosage regimens included 10–20 mg × 1–3/week and a pulsed dosage of 20–60 mg daily for 1 week each month.

For the purposes of analysis, patients have been grouped into four dosage groups: very low (<0.25 mg/kg/day), low (0.26–0.50 mg/kg/day), medium (0.51–0.75 mg/kg/day) and high (0.76–1.0 mg/kg/day). Most patients will have been treated with the same dosage throughout the treatment period, although a minority started in one dosage group and moved to another (both up and down). For purposes of analysis, patients were included in the dosage group they spent more than 50% of the time in.

RESULTS

A search of the electronic patient records revealed 2008 patients were started on isotretinoin over the 6-year period. Two hundred and sixty-five patients (13%) were excluded from further analyses as 137 patients had not had a follow-up visit organized for practical reasons (the patient was moving to another town or country, or was under the care of another dermatologist), or there was no clinical need for review, or the follow-up appointment was outside the study period. The remaining 128 patients (6.4%), failed to attend any follow-up visit(s). Of these, approximately 20% were contacted by phone to enquire why they had failed to attend. Most stated their skin had improved sufficiently on isotretinoin such that they did not wish any further medication. A handful said they had changed their minds and had not started isotretinoin. None said they had failed to attend because of significant adverse effects.

A total of 1743 patients had one or more follow-up visits and were included in the study. The indications for using isotretinoin were acne vulgaris (1653 patients), folliculitis (38), rosacea or periorificial dermatitis (68), seborrhoeic dermatitis (50) and other conditions (55). Some patients had more than one skin disorder.

The demographics of the patients are summarized in Table 1. Isotretinoin was taken on a daily basis by 1344 patients (77.1%), three times per week (usually Monday/Wednesday/Friday) by 195 patients (11.1%), once or twice per week by 54 patients (3.1%) and daily for 1 week in every 4 weeks (i.e. pulsed dose) in 150 patients (8.6%). The response to isotretinoin is summarized in Table 2.

The frequency of adverse effects is summarized in Table 3. Of the patients, 18.5% reported no adverse effects during the study period; as one would expect, most of these were in the very low isotretinoin dose group. Twenty-four patients stopped isotretinoin because of adverse effects; a further three patients complained of severe adverse effects on at least one occasion, but continued on medication. The adverse effect(s) that led to patients stopping isotretinoin were cheilitis (22 patients), mood change (13), tiredness (12), eczema (6) and pregnancy (2). There were no reported instances of suicidal ideation or attempted suicide.

The more common adverse effects are summarized in Table 4, with cheilitis being reported in 96.4% of patients on high-dose isotretinoin, but in only 47.1% of patients on very low-dose isotretinoin. Tables 5 and 6 summarize less common adverse effects and infections.

Miscellaneous adverse events reported included alopecia (two reports), acanthosis nigricans (two), bed wetting (one), bone calcification (one), cardiomyopathy (one), chilblains (two), erythema nodosum (one), facial erythema (one), gall

Table 1 Demographics of patients by dosage group (very low to high) ($n = 1743$)

	Dosage (mg/kg/day)			
	Very low (0–0.25)	Low (0.26–0.50)	Medium (0.51–0.75)	High (0.76–1.0)
No. of patients	450	471	119	703
Age (years)				
Mean	31.9	20.9	20.5	19.7
Range	12–80	6–79	13–54	12–58
Weight (kg)				
Mean	67.1	69.8	63.8	66.2
Range	40–114	26–98	40–102	40–95
Sex				
Male	131	222	64	410
Female	319	249	55	293

Table 2 Response to isotretinoin by dosage group

	Dosage (mg/kg/day)				
	Very low (0–0.25)	Low (0.26–0.50)	Medium (0.51–0.75)	High (0.76–1.0)	Total
Skin clear	387 (86%)	448 (95.1%)	114 (95.8%)	675 (96%)	1624 (93.2%)
Excellent	30 (6.7%)	9 (1.9%)	1 (0.8%)	17 (2.4%)	57 (3.3%)
Controlled	26 (5.8%)	2 (0.4%)	1 (0.8%)	2 (0.3%)	31 (1.8%)
No change/moderate or poor	7 (1.6%)	12 (2.5%)	3 (2.5%)	9 (1.3%)	31 (1.8%)
Total	450	471	119	703	1743

Table 3 Reported adverse effects by dosage group

	Dosage (mg/kg/day)				
	Very low (0–0.25)	Low (0.26–0.50)	Medium (0.51–0.75)	High (0.76–1.0)	Total (%)
None reported	219 (48.7%)	91 (19.3%)	3 (2.5%)	10 (1.4%)	323 (18.5%)
Mild	203 (45.1%)	343 (72.8%)	93 (78.1%)	583 (82.9%)	1222 (70.1%)
Moderate	23 (5.1%)	27 (5.7%)	19 (16.0%)	102 (14.5%)	171 (9.8%)
Severe	1 (0.2%)	1 (0.2%)	0 (0%)	1 (0.1%)	3 (0.17%)
Stopped because of side-effects	4 (0.9%)	9 (1.9%)	4 (3.3%)	7 (1.0%)	24 (1.4%)
Total	450	471	119	703	1743

stones (two), insomnia (one), fainting (one), flare of inflammatory bowel disease (two), flare of psoriasis (one), gingival hyperplasia (two), haematuria (one), hyperthyroidism (one), home sickness (one), keratolysis exfoliativa (one), low platelets (one), mouth ulcers (one), polydipsia (one), pterygium formation (one), polycythaemia (one) and tonsillitis (one). Causality was considered probable for facial erythema, possible for alopecia (although androgenic alopecia was considered more likely), insomnia, homesickness and gingival hyperplasia. The rest were considered unlikely, including flare of inflammatory bowel disease.[11]

As patients were not seen after the completion of their isotretinoin course, no data on long-term adverse events were available.

DISCUSSION

Isotretinoin is now well established as a treatment for a variety of skin conditions including acne vulgaris, rosacea and seborrhoeic dermatitis. The traditional acne treatment paradigm is initial treatment with topical agents, moving on to short courses of anti-inflammatory antibiotics, hormonal treatment in women and then isotretinoin in more severe cases, particularly nodulocystic acne.[12] A systematic review of systemic monotherapy of acne has shown a 54 ± 3% improvement over baseline with tetracyclines, 65 ± 4% with cyproterone acetate plus ethinyloestradiol and 85 ± 10% with isotretinoin.[13] Moreover, studies suggest that isotretinoin reduces the risk of acne relapse in the few studies that included a follow-up period.

The major limiting factor for isotretinoin use has been the concern with, and the risks of, potential adverse effects. Teratogenicity is arguably the most significant, with estimates of 40% of exposed pregnancies associated with significant birth defects.[14] Both cases of pregnancy in this study had been prescribed oral contraceptives, and were considered oral contraceptive failures. Both had elective terminations.

Table 4 Prevalence of the more commonly reported adverse effects by dosage group (absolute numbers and percentage of patients by dosage group)

	Dosage (mg/kg/day)				Total
	Very low (0–0.25) $n = 450$ (%)	Low (0.26–0.50) $n = 471$ (%)	Medium (0.51–0.75) $n = 119$ (%)	High (0.76–1.0) $n = 703$ (%)	$n = 1743$ (%)
Cheilitis	212 (47.1)	365 (77.5)	112 (94.1)	678 (96.4)	1367 (78.4)
Eczema	33 (7.3)	45 (9.6)	22 (18.5)	111 (15.8)	211 (12.1)
Tiredness	25 (5.5)	36 (7.6)	24 (20.2)	126 (17.9)	211 (12.1)
Mood change	21 (4.7)	21 (4.5)	13 (10.9)	69 (9.8)	124 (7.1)
Skin fragility	15 (3.3)	17 (3.6)	7 (5.8)	67 (9.5)	106 (6.1)
Nose bleeds	9 (2.0)	17 (3.6)	6 (5.0)	58 (8.2)	90 (5.2)
Muscle aches	10 (2.2)	12 (2.5)	5 (4.2)	43 (26.1)	70 (4.0)
Eye problems	10 (2.2)	10 (2.1)	6 (5.0)	34 (4.8)	60 (3.4)

Table 5 Other adverse effects ($n = 1743$)

Adverse effect	No. of patients (%)
Infections	45 (2.6)
Abnormal serum lipids	43 (2.5)
Miscellaneous (see text)	43 (2.5)
Slow response to treatment	39 (2.2)
Periungal granulomas	37 (2.1)
Significantly abnormal liver function tests	20 (1.1)
Sun sensitivity	17 (1.0)
Headaches	13 (0.7)
Gastrointestinal upset	6 (0.3)
Pregnancy	2 (0.1)

Table 6 Infections reported/documented ($n = 45$)

Infection	No. of patients (%)
Non-specified viral infections	16 (0.92)
Staphylococcus infections	9 (0.52)
Glandular fever (Epstein–Barr virus)	7 (0.40)
Gram-negative folliculitis	3 (0.17)
Spa-pool folliculitis	2 (0.11)
Styes	2 (0.11)
Impetigo	2 (0.11)
Herpes simplex	2 (0.11)
Cytomegalovirus	1 (0.06)
Boils	1 (0.06)
Herpes zoster	1 (0.06)
Oral candidiasis	1 (0.06)

There is extensive literature and ongoing debate regards the possible association between mood change, depression and suicidality, and the use of isotretinoin.[8,9] To date, the majority of case–control and other epidemiological studies show no association, but they cannot exclude an individual idiosyncratic psychological adverse response to the drug.[15]

There is, however, little doubt that isotretinoin has a significant number of dose-dependent mucocutaneous and other adverse effects.[16,17] These are well established and generally well documented in patient information material and product data sheets.[18]

However, data on the frequency and severity of these adverse effects are less well-documented. This review of 1743 patients commenced on isotretinoin over a 6-year period shows that, for the majority of patients, the adverse effects were mild. Cheilitis was the most commonly reported adverse effect, affecting 78% of users, followed by eczema and tiredness, seen in 12% each. However, these were clearly dose-dependent, as the group treated with doses of isotretinoin under 0.25 mg/kg/day only reported cheilitis in 47%, eczema in 7% and tiredness in 5%, compared with 96%, 16% and 18%, respectively, in the high-dose treatment group (0.76–1.0 mg/kg/day).

Interestingly, the daily dosage did not seem to affect the percentage of patients stopping the drug because of adverse effects, being 0.9% for the very low-dose group and 1.0% for the high-dose group. The adverse effect that precipitated the patient to stop isotretinoin most frequently was cheilitis. Surprisingly, the cheilitis in these patients often appeared relatively mild, although often with a significant sun-sensitivity element, suggesting this was more the issue.

Mood change and tiredness was reported in 7.1% and 12.1%, respectively. These percentages halved when doses below 0.5 mg/kg/day were used. Most cases of mood change were preceded by symptoms of tiredness, although some patients had difficulty in distinguishing between the two; the self-reported severity was mild in most cases but mood change did contribute to stopping the medication in 13 patients. All 13 of these patients recovered; eight subsequently received isotretinoin at a later date, usually at a lower dosage, which was well-tolerated. Causality was initially assessed as probable in all 13 cases of mood change, but was later downgraded to possible in six of the eight patients who were re-challenged. No cases of suicidality were reported, although the author does have experience of two patients with suicidal ideation (including one suicide attempt) outside the review period.

A greater percentage of patients on the pulsed dosage regimen were aware of mood change; the pulsed dose was usually given at the time of the menstrual cycle, which may have confounded the association. When these patients were changed to a very low intermittent dose (e.g. 10 mg × 2–3/week), symptoms usually improved.

Of patients, 2.6% reported infections, mostly non-specific viral infections, followed by infections with *Staphylococcus*

aureus. Periungal granulomas were not categorized as an infection, although they would have been colonized with *S. aureus*. It is likely that patients only reported infections that had occurred in the 1–2 weeks before each follow-up visit, so that infections were significantly under-reported. The non-specific viral infections and cases of glandular fever were all associated with symptoms of tiredness.

Other than for regular pregnancy tests, investigations were generally only performed on a clinical need basis. The cases of abnormal liver function tests were mostly associated with intercurrent viral infections.

Slow response to isotretinoin was reported in 2.2% of patients. This generally meant limited improvement in inflammatory acne of the face after 6 months of treatment. A number of these patients had, in addition, extensive macro-comedonal pattern of acne vulgaris (submarine comedos), which is well recognized to respond very slowly to therapy (often taking 12 months). This slow response of inflammatory acne did not appear to be related to the dosage of isotretinoin used. Most slow responders were treated with the addition of trimethoprim, 300 mg/day for 2–3 months, with consequent improvement, although whether due to the addition of the antibiotic or the passage of time is undetermined.

Limitations

The study suffers from being a retrospective review, although the data were collected prospectively. The patient follow up finished with the completion of the course of isotretinoin, so the study does not address the question of long-term adverse effects. Of the patients, 6.4% of those started on isotretinoin did not attend for follow up, and were therefore not included in the analysis; some of these may have had serious adverse reactions that we may not have been aware of. Less common, but potentially serious, adverse effects such as night-blindness, benign intracranial pressure, etc. were not specifically asked for, so are likely to have been under-reported, even though patients were asked at each visit if they had any concerns. Although photosensitivity was common, this was not specifically recorded, except where it affected the lips. The division of the patients into the four dosage groups (high, medium, low and very low) was not clean, as there was some adjusting of dose during the study period, but this was in both directions. However, the strengths of the study include the large number of patients treated (1743), and that it reflects actual day-to-day clinical practice.

CONCLUSIONS

This study documents the adverse effect profile of isotretinoin in a large number of patients treated over a 6-year period of time. Most mucocutaneous adverse effects were dose-dependent, mild and easily managed by the patient. Isotretinoin was discontinued in 1.4% of patients, most often because of cheilitis, but also in association with mood change in 0.75% of patients. A number of these patients tolerated isotretinoin at a later date. No cases of suicidality or suicidal ideation were reported.

Other than the two oral contraceptive failures, there were no serious adverse events recorded during this review period. Isotretinoin is a very effective medication with a low adverse effect profile when used at lower doses.

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APPENDIX I

Questions asked at each and every follow-up visit

- Are you well?
- Have you had any dryness or cracking of your lips?
- Have you had any dryness or irritability of your eyes, or any problems with your vision?
- Have you had any nosebleeds?
- Have you had any problems with muscle aches or joint pains?
- Have you been more tired than normal?
- Have you been moody or depressed? (Note: If the patient came with a parent, they were asked the question independently.)
- Have your menstrual periods been normal, and is there any possibility of you being pregnant? (Female patients only.)
- Have you had any other problems or concerns with your treatment?
- Do you want to continue on isotretinoin?