

Isotretinoin Use in Acne: Prospective Evaluation of Adverse Events

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Abstract

Background: Isotretinoin is an effective treatment for severe acne. Although the spectrum of side effects has been well documented, the changing incidence of such side effects over the course of treatment has not been studied in detail.

Objectives: The purpose of our study was to examine a group of patients monthly over their course of treatment and prospectively document the side effects experienced.

Methods: Over the period between January 1991 and July 1996, 124 courses of treatment with isotretinoin for severe acne were followed. The patients were treated for 4 months at a dose of 1 mg per kg body weight. A questionnaire was administered monthly, inquiring specifically about side effects known to be associated with isotretinoin. Any additional side effects were also noted.

Results: The majority of patients experienced persistent dryness of lips. Dry eyes affected 40% of patients; this continued throughout treatment in 25%. Contact lens wearers were more likely to develop conjunctivitis. Lower back pain was reported early in about 30% of patients and fewer than 10% of patients would develop it later in the course of treatment. Arthralgia was noted in 16.5% of patients at the first visit and there was little change with ongoing treatment. Hair loss was experienced in a small percentage but was rarely noted on more than one occasion. Headaches occurred in less than 10% and were occasionally severe, but most often intermittent and recorded at a single visit. Depression occurred in 4% of patients and tended to persist throughout the treatment. All these patients completed the full course of treatment.

Conclusion: This prospective analysis has shown that patients treated with isotretinoin experienced a predictable series of side effects. Some occurred fleetingly, but several persisted for the duration of treatment.

Sommaire

Antécédents: L'isotrétinoïne traite efficacement les cas graves d'acné. Mais si la gamme des effets secondaires est bien documentée, l'incidence variable de ces effets en cours de traitement n'a toutefois jamais été étudiée en détail.

Objectif: Examiner tous les mois un groupe de patients en traitement et documenter les effets secondaires de manière prospective.

Méthodes: De janvier 1991 à juillet 1996, 124 cas graves d'acné traités par l'isotrétinoïne ont été suivis. Les patients ont été traités pendant quatre mois à raison de 1 mg par kg de poids corporel. Ils ont été priés de répondre chaque mois à un questionnaire portant spécifiquement sur les effets secondaires connus de l'isotrétinoïne. Tous les autres effets secondaires ont aussi été notés.

Résultats: La majorité des patients ont présenté une sécheresse labiale; 40 % ont présenté une sécheresse oculaire qui est demeurée pendant toute la durée du traitement chez 25 % des patients touchés. Les personnes portant des lentilles cornéennes ont semblé plus sensibles à la conjonctivite. Environ 30 % des patients ont signalé des douleurs lombaires peu de temps après le début du traitement et moins de 10 % en ont éprouvé plus tard. Une arthralgie a été notée pour 16,5 % des patients dès la première visite, sans grande évolution par la suite. Un petit pourcentage a éprouvé une perte de cheveux, mais rarement en plus d'une occasion. Moins de 10 % des patients ont signalé des maux de tête (une seule fois), parfois graves mais la plupart du temps intermittents. Quatre pour cent des patients ont souffert d'une dépression qui a généralement persisté pendant toute la durée du traitement. Tous les patients ont suivi le traitement au complet.

Conclusion: Cette analyse prospective de l'état de patients traités par l'isotrétinoïne montre une gamme prévisible d'effets secondaires, dont certains ont été fugaces mais dont plusieurs ont persisté pendant tout le traitement.

Isotretinoin (Acutane™) is an effective treatment usually indicated for severe acne unresponsive to conventional treatment. It is now regularly used for patients with less severe acne not responding adequately to systemic antibiotics and for patients with long-standing acne. The great

advantage of isotretinoin is that it regularly induces a long-term remission in most patients and, in some, may be curative. A significant number of patients may require repeated courses of isotretinoin to maintain suppression of their acne.

The side effect profile of isotretinoin has been extensively documented.¹⁻⁷ The most significant of these is its teratogenicity. Although the spectrum of side effects has been well documented, the changing incidence of such side effects over the course of treatment has not been surveyed in detail. Such an examination would allow a more realistic evaluation of the impact of side effects and would be more meaningful to patients contemplating this treatment. In this study, a group of patients were followed and side effects were prospectively documented throughout the treatment.

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Table 1 Incidence of Side Effects Experienced during Course of Treatment

	Month 1 N = 121 F = 72 N (%)	Month 2 N = 96 F = 57 N (%)	Month 3 N = 91 F = 58 N (%)	Month 4 N = 50 F = 32 N (%)
Cheilitis	112 (92.6%)	82 (85.4%)	74 (81.3%)	38 (76.0%)
Xerosis	74 (61.1%)	59 (61.5%)	52 (58.2%)	27 (54.0%)
Dermatitis	60 (49.6%)	40 (41.7%)	34 (37.4%)	16 (32.0%)
Angular cheilitis	54 (44.6%)	38 (39.6%)	36 (39.6%)	22 (44.0%)
Nose bleeds	47 (38.8%)	36 (37.5%)	22 (24.2%)	7 (14.0%)
Dry eyes	44 (36.4%)	38 (39.6%)	35 (38.5%)	20 (40.0%)
Acne flare	42 (34.7%)	16 (16.7%)	8 (8.8%)	3 (6.0%)
Back pain	34 (28.1%)	20 (20.8%)	17 (18.7%)	10 (20.0%)
Tiredness	31 (25.6%)	22 (22.9%)	17 (18.7%)	9 (18.0%)
Conjunctivitis	26 (21.5%)	24 (25.0%)	25 (27.5%)	13 (26.0%)
Arthralgia	20 (16.5%)	14 (14.6%)	16 (17.6%)	7 (14.0%)
Myalgia	17 (14.1%)	9 (9.4%)	8 (8.8%)	5 (10.0%)
Visual acuity	12 (9.9%)	12 (12.5%)	8 (8.8%)	7 (14.0%)
Photosensitivity	12 (9.9%)	7 (7.3%)	13 (14.4%)	3 (6.0%)
Headache	9 (7.4%)	7 (7.3%)	10 (11.0%)	4 (8.0%)
Chest wall pain	8 (6.6%)	4 (4.2%)	5 (5.5%)	4 (8.0%)
Hair loss	9 (7.4%)	2 (2.1%)	3 (3.3%)	6 (12.0%)
Dry vulva	5 (6.9%)	7 (12.3%)	4 (6.9%)	3 (9.4%)
Depression	5 (4.1%)	3 (3.1%)	4 (4.4%)	2 (4%)
Night blindness	4 (3.3%)	4 (4.1%)	5 (5.5%)	3 (6%)
Weight loss	4 (3.3%)	0	1 (1.1%)	5 (10%)
Dysmenorrhea	4 (5.6%)	3 (5.3%)	5 (8.6%)	2 (6.3%)
Diarrhea	2 (1.7%)	0	1 (1.1%)	0
Change in moles	1 (0.8%)	4 (4.2%)	4 (4.4%)	1 (2%)
Paronychia	1 (0.8%)	1 (1.0%)	0	0
Pyogenic granuloma	0	0	1 (1.1)	1 (2.0)
Galactorrhea	0	0	0	0

Patients and Methods

Over the period from January 1991 to July 1996, 189 patients were started on isotretinoin for severe acne. Criteria for isotretinoin treatment included nodulocystic acne, acne with scarring, and acne not responsive to conventional treatment with systemic antibiotics. The patients were generally healthy, but one patient had insulin-dependent diabetes, another was treated with barbiturates for epilepsy, and a further patient with a history of spondyloarthropathy was taking tolmetin. The mean age was 26 years with a range of 16 to 60 years. There were 79 males and 110 females. Where possible, these patients were seen at monthly intervals and adverse events evaluated. A questionnaire was administered by the dermatologist inquiring specifically about cheilitis, angular cheilitis, photosensitivity, xerosis, dermatitis, dryness of the vulva and/or vagina, headaches, muscle pain, back pain, joint pain, chest wall pain, dysmenorrhea, nipple tenderness, galactorrhea, dry eyes, night blindness, changes in visual acuity, depression, hair loss, paronychia, diarrhea, weight loss, tiredness, change in moles or skin tags, exacerbation of the acne, and exuberant granulation tissue or pyogenic granulomas. Any additional side effects were also noted. When patients experienced headaches, a funduscopy was performed. In patients admitting to focusing problems no special ophthalmologic examinations were carried out. We did not perform objective psychometric testing in patients to establish depression. No specific treatment was given for musculoskeletal symptoms.

The patients were treated with isotretinoin for 4 months at a dose of 1 mg/kg. All the patients were advised to use sunscreens when in the sun and a prophylactic eye lubricant was also prescribed. A moisturizing cream (hydrous emulsifying ointment) was given when needed for xerosis and a noncomedogenic moisturizer was recommended for use on the face. All other topical acne medications, astringents, and soap cleansers were stopped.

During the course of the treatment, physician-directed management of side effects was limited to encouraging compliance with the use of the eye lubricant, moisturizers, and sunscreens. Specific treatment or advice for managing musculoskeletal complaints, depression, and headaches was not given, and behavioural modification by patients was not controlled. Patients with severe conjunctivitis were referred to an ophthalmologist.

The following tests were performed prior to initiating treatment and at each subsequent visit: complete blood count, concentrations of fasting cholesterol and triglycerides, total bilirubin, AST and ALP. A pregnancy test was also performed on all female patients.

Results

The overall monthly incidence of side effects is shown in Table 1, whereas Figure 1 shows the monthly changes in selected side effects. These observations were analyzed to show when the side effect occurred for the first time, whether it continued during consecutive months, and when the side effect recurred later during the course of the treatment.

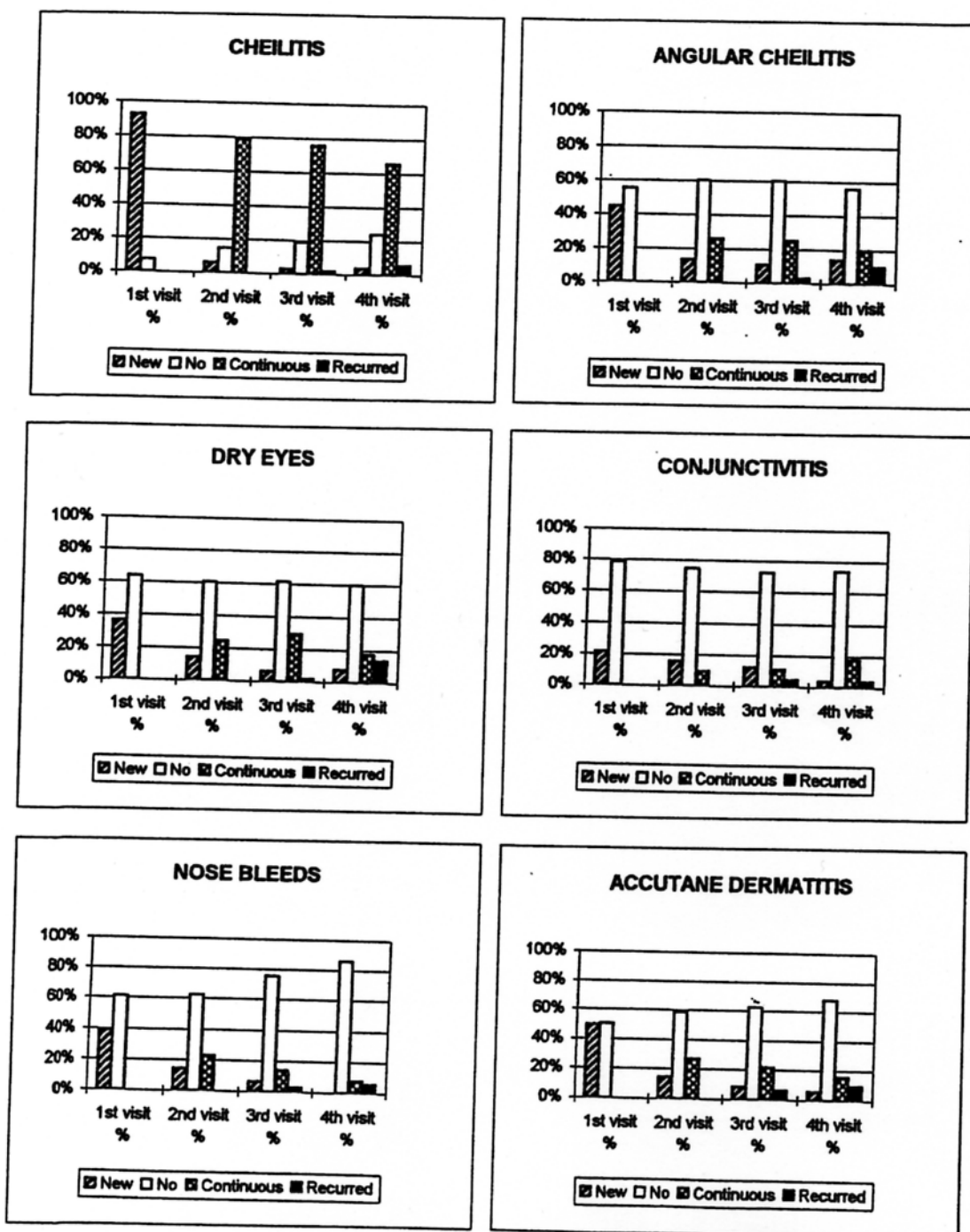


Figure 1 Side effects recorded each month for patients on isotretinoin.
 New : side effect occurring for first time
 No: side effect not experienced
 Continued: Side effect noted in previous month
 Recurred: Side effect recurred—first noted at least 2 months previously.

The commonest problem encountered by patients is dryness, cracking and crusting of the lips which, in this study, occurred in 93% of patients at the first visit and tended to persist throughout the treatment, although, by the fourth visit, 24% of patients did not admit to dry lips. Patients who

licked or sucked their lips had more problems. Angular cheilitis was seen in about 40% and tended to persist throughout treatment in about a quarter of the patients. Dryness of the eyes affected, and persisted in, a similar percentage of patients. Mild redness of the conjunctiva was

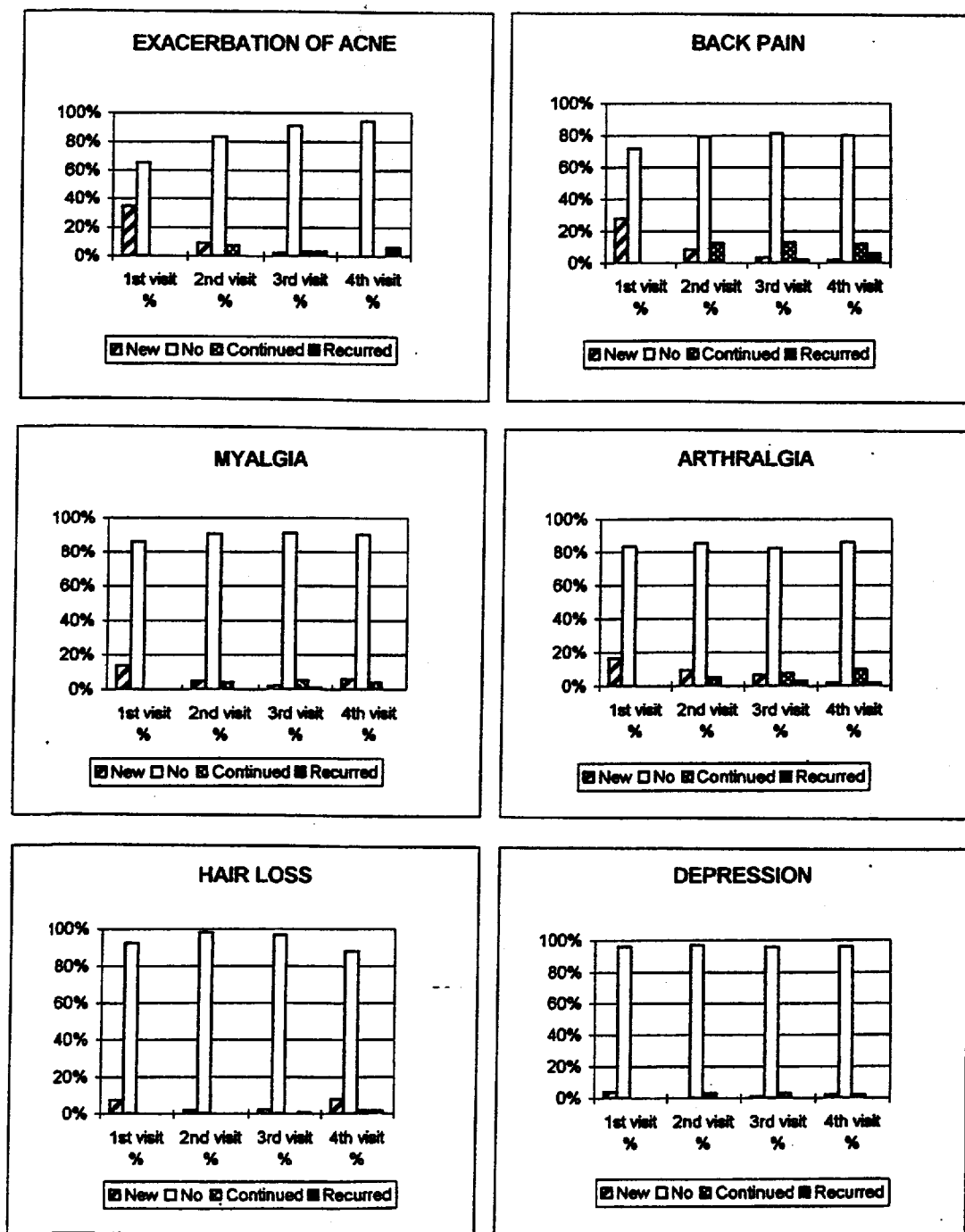


Figure 1 (Cont) Side effects recorded each month for patients on isotretinoin.

New: side effect occurring for first time

No: side effect not experienced

Continued: Side effect noted in previous month

Recurred: Side effect recurred—first noted at least 2 months previously.

noted in about a quarter of the patients at each visit, but patients experiencing this for the first time constituted a considerable percentage of those affected at subsequent visits. Changes in visual acuity were noted in up to 14%, occurring early and tending to recur. Difficulties with night vision occurred in about 4% of patients and could occur

at any time during the treatment. In about half the patients affected, it was not persistent.

Dryness of the nasal vestibule was commonly associated with nose bleeds consisting usually of minor spotting. A mild dry, scaling, and at times eczematous dermatitis occurred mainly on the dorsa of the hands and/or on the

forearms and was noted particularly in the winter months; it affected half the patients on the first visit. The frequency of dermatitis decreased with further treatment. Topical steroid ointments were needed in some patients. Dryness of the mucosa of the vulva and anus did not worsen during ongoing treatment and most patients found that the use of moisturizing creams was beneficial.

An exacerbation of acne was most likely to occur in the first month, although a few patients noted a deterioration of the acne as late as the third month of treatment. Back pain was noted in nearly 30% of the patients and decreased only slightly during further treatment. This affected mainly the lower back and was more common in those with a history of previous backache. Physical activity aggravated the backache. In some patients this was also accompanied by arthralgia affecting mainly the larger joints. Arthralgia affected about 15% of all patients at each visit but there was a steady decline in the percentage of patients developing arthralgia for the first time. The patient with spondyloarthropathy did not notice a deterioration. Myalgia was less common. Both muscle pain and arthralgia were made worse by exercise.

Costochondral pain and tenderness were unusual, intermittent, and more likely to occur early. One patient developed this for the first time in the third month and another patient in the fourth.

Unusual tiredness occurred in about a quarter of the patients with a slight drop in the last two months of treatment. Photosensitivity was rare and, not surprisingly, was only seen in the summer. Headaches were intermittent, varying from mild to severe and were noted as a new adverse effect at each of the follow-up visits. For most patients, the reporting of such headaches did not persist for more than 2 months and in none were the headaches accompanied by nausea or vomiting. Fundoscopy was performed on all patients complaining of headaches. No cases of pseudotumour cerebri were encountered.

Increased hair shedding was mostly reported at the first visit but none of these patients complained of an ongoing problem at the second visit. At subsequent visits this complaint was new for most patients. All patients who complained of hair loss were asked to quantitate the loss. In none was the number of hairs shed greater than 100 hairs per day.

Depression was seen in about 4% of the patients and tended to persist throughout the treatment. Only one of these patients had a past history of depression. This patient as well as all the other patients with depression were able to complete the full course of treatment. Weight loss was not common and seldom a concern.

Discussion

Isotretinoin is presently being used more freely in the treatment of acne. In the past, its use was to a great extent restricted to severe cystic and scarring acne, but there is an increasing tendency for isotretinoin to be used early and for milder cases of acne. This use has been a natural consequence of its incomparable efficacy and a fuller understanding and better management of the many adverse effects of the treatment.

For patients, the listing of side effects, taken from the product monograph, prompts concern and may even result in the patients with severe acne rejecting treatment. Patients often perceive isotretinoin as being "strong" or a "last resort" treatment. Reported side effects, causing the patient the greatest pretreatment anxiety, include concerns about teratogenicity, the possibility of liver damage, fear of hair loss, dry cracked lips, excessive and observable dryness of the skin, a red face, and muscle and joint pains.

Previous studies and reviews of isotretinoin have described and established the overall prevalence of side effects,¹⁻⁵ but no other study has prospectively examined the changing frequency of such side effects throughout treatment.

This study shows that for the majority of patients treated with isotretinoin symptomatic, side effects are mostly predictable, usually minor, often temporary and easily managed.

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