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# Roaccutane Treatment Guidelines: Results of an International Survey

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## Abstract

**Background:** Oral isotretinoin (Roaccutane®) revolutionized the treatment of acne when it was introduced in 1982. **Methods:** Twelve dermatologists from several countries with a special interest in acne treatment met to formally review the survey of their last 100 acne patients treated with oral isotretinoin. The primary purpose of the survey was to identify the types of acne patients who were prescribed oral isotretinoin and how the patients were managed. **Results:** Of the 1,000 patients reviewed, 55% of those who received oral isotretinoin had those indications treated historically, i.e. severe nodular cystic acne or severe inflammatory acne, not responding to conventional treatment. Forty-five percent of patients who were prescribed oral isotretinoin however had either moderate or mild acne. Most patients in this group had moderate acne (85%). However, 7.3% had mild acne on physical examination. The criteria for prescribing oral isotretinoin in this less severe group of patients included acne that improves <50% after 6 months of conventional oral antibiotic and topical combination therapy, acne that scars, acne that induces psychological distress and acne that significantly relapses during or quickly after conventional therapy. Treatment is usually initiated at daily doses of 0.5 mg/kg (but may be higher) and is increased to 1.0 mg/kg. Most of the physicians aimed to achieve a cumulative dose of >100–120 mg/kg. Mucocutaneous side-effects occur frequently but are manageable while severe systemic side-effects are rarely problematic (2%). The teratogenicity of oral isotretinoin demands responsible consideration by both female patients and their physicians. Significant cost savings when treating acne patients with oral isotretinoin as compared to other treatment modalities were further proven in this study. **Conclusions:** Our recommendation is that oral isotretinoin should be prescribed not only to patients with severe disease but also to patients with less severe acne, especially if there is scarring and significant psychological stress associated with their disease. Acne patients should, where appropriate, be prescribed isotretinoin sooner rather than later.

## Key Words

Acne treatment
Isotretinoin, oral

## Introduction

Oral isotretinoin (Roaccutane®) revolutionized the treatment of acne when it was introduced in 1982. More than a decade later, it remains the most effective anti-acne pharmacotherapy since it is the only treatment that affects all major aetiological factors implicated in acne. Sebum production [1–3], comedogenesis [2], surface and ductal colonization with *Propionibacterium acnes* [1, 2] and monocyte chemotaxis [2, 4] are all significantly reduced by

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**Table 1.** Roaccutane usage

Based on the last 100 patients you treated with Roaccutane:

(1) How were these patients categorized?

| | | |
|---|---|---|
| Severe acne | | _____ |
| Moderate acne | | _____ |
| With scarring | _____ | |
| With psychological complications | _____ | |
| With both | _____ | |
| With neither | _____ | |
| Mild acne | | _____ |
| With scarring | _____ | |
| With psychological complications | _____ | |
| With both | _____ | |
| With neither | _____ | |
| Other, e.g. pyoderma faciale, acne fulminans, gram-negative folliculitis, vasculitic acne | | _____ |

(2) What were your dosage recommendations?

| | |
|---|---|
| Daily dose, mg/kg | _____ |
| Therapy duration, weeks | _____ |
| Total course dose, mg/kg | _____ |
| Did you vary according to acne severity? | _____ |

(3) Do you recommend a total dose (cumulative) to minimize relapse? yes/no

If yes, please continue

| | |
|---|---|
| (3a) What cumulative dose do you prescribe? | _____ |
| (3b) In what proportion of patients (percent) do you administer a total cumulative dose? | _____ |

isotretinoin therapy. Oral isotretinoin is established as a uniquely successful therapy capable of long-term remission in up to 70–89% of patients [5–9].

When isotretinoin was first introduced in the early 1980s, its use was restricted predominantly to patients suffering with severe nodulocystic acne. With increasing clinical experience, however, its use has been expanded by many physicians to include patients with less severe disease who are responding unsatisfactorily to conventional therapies such as long-term antibiotics and appropriate topical therapies. Currently among some physicians, patients with nodular acne represent only a small proportion of their isotretinoin-treated patient population. Thus, if the prescribing of isotretinoin is limited by other physicians to patients with severe nodular acne, then many patients are not receiving appropriate therapy and many such patients will scar. Unfortunately, more and more patients are failing to respond to long-term antibiotics and appropriate topical therapies because of an increase in resistance of *P. acnes* to many antibiotics, in particular erythromycin and tetracycline [10–13]. Even patients with moderate acne can scar significantly, and currently there is not much successful treatment for the majority of patients who do scar [14–16].

In light of these observations, a review of current isotretinoin usage policies and treatment recommendations was made among dermatologists with a particular interest in acne. The ultimate objective was to provide treatment guidelines based upon collective clinical experience.

## Methods

Based upon evaluation of the last 100 patients treated with oral isotretinoin, each participant completed a questionnaire (cf. table 1) which requested detailed information regarding acne indications treated, dosage used as well as particular safety and tolerability concerns. Since the safety profile of isotretinoin is predictable consisting predominantly of manageable mucocutaneous effects such as cheilitis, dry skin and, less frequently, headaches and arthralgias, the questionnaires focused primarily on indications and dosage.

Since acne classification schemes vary among dermatologists, reaching consensus with respect to which types of acne warrant isotretinoin treatment was greatly enhanced by using representative patient pictures. These pictures covered the whole spectrum of acne physical severity. Many patients with mild or moderate acne, let alone severe acne, scar, and this feature was captured by the questionnaire. The psychological trauma of acne is well documented [17–20] and was also covered by the questionnaire. Acne morbidity is determined by other influencing factors such as the chronic and/or relapsing nature of the disease and the limited benefit of previous conventional therapy.

Isotretinoin has been shown to be cost effective [21–24]. Two centres re-investigated this issue by comparing the actual total costs of isotretinoin therapy with the cost if patients had received other than

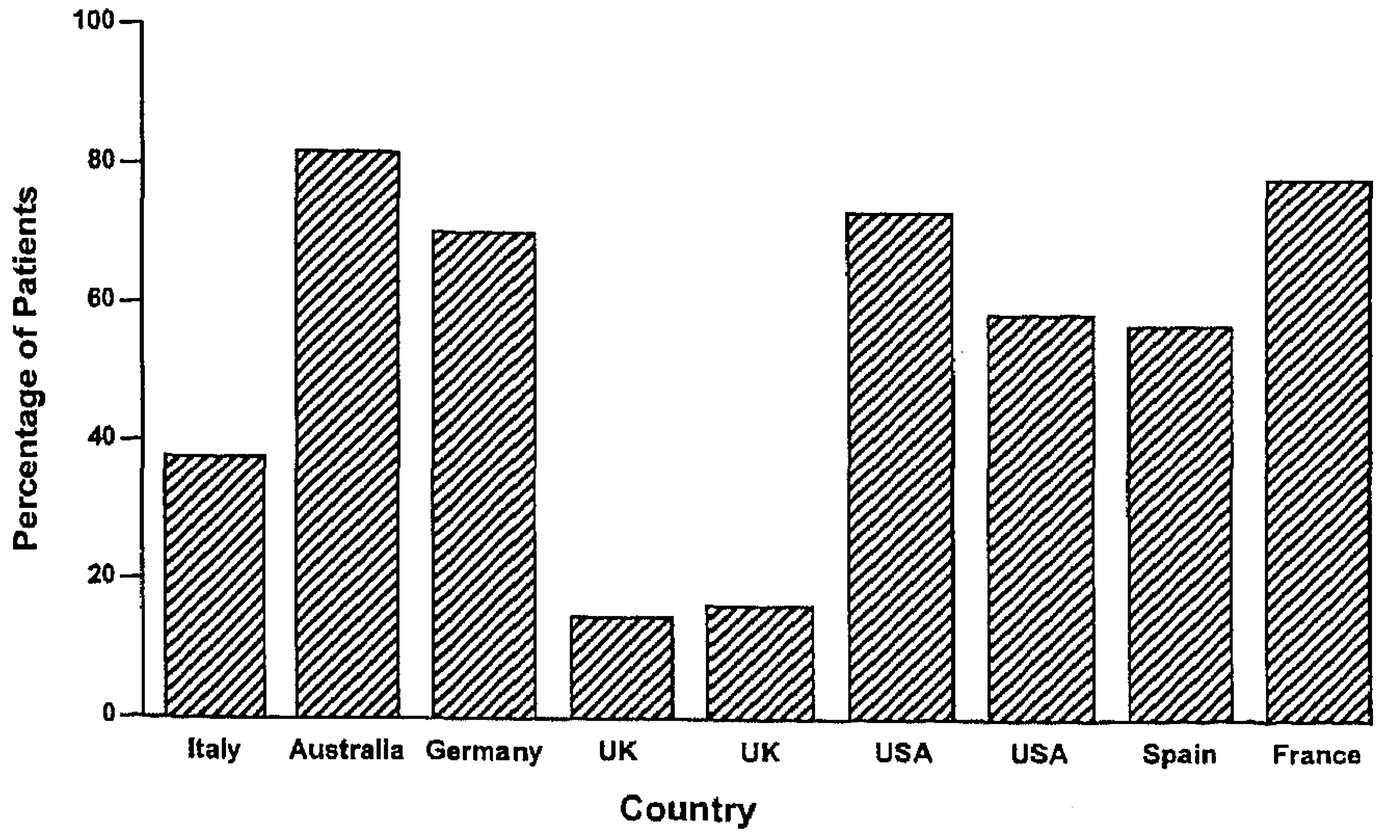


**Fig. 1.** Percentage of patients treated from 7 countries (10 centres: the Italian data from 2 centres were combined) with severe acne who were treated with oral isotretinoin.

oral isotretinoin therapy. The patients in the Australian cohort have been published elsewhere [22]. The UK data were based on 364 patients who were followed for 3 years from the start of the first course of isotretinoin. Two sets of cost data were calculated as described previously [21]. The data included all costs, i.e. drug, personnel time and overheads. The first set was based on the precise cost for the 364 patients. It included the initial cost of isotretinoin therapy plus any additional drug costs incurred for management of side-effects or acne therapy if the acne flared after the initial course of isotretinoin. The second set was calculated on a theoretical basis, assuming that isotretinoin was not available for these patients. These data assumed that the patient had requested therapy over this 3-year time period. Our approach in the pre-isotretinoin days would have been to prescribe rotational antibiotics, i.e. 6 months each of tetracycline, minocycline, trimethoprim and erythromycin (plus appropriate topical therapy). To both sets of data were added either the real or theoretical costs for all hospital overheads.

## Results

*Acne Indications*

*Severe Acne*

As shown in figure 1, all physicians prescribed oral isotretinoin in all patients with severe acne, but such patients represented varying proportions of the isotretinoin-treated population. Two physicians did not have accurate records of acne severity. Thus, such data from these two centres were not available. In Australia, 82% of the patients who received oral isotretinoin had severe acne; in France it was 80% and in Germany 70%. In the two USA clinics, the percentage was 60 and 75%. In the UK, only 14–16% of the patients receiving oral isotretinoin had severe acne; in Spain, the percentage was 58% and in the two Italian centres 38%.

*Moderate Acne*

All physicians used oral isotretinoin in patients with moderate acne that had failed to respond to long-term antibiotics or appropriate topical therapy (fig. 2). In the UK and Italy, such patients represented the greatest number of patients so treated (UK: 74–76% and Italy: 50%) whereas in Australia, France, Germany and Spain this subpopulation represented 16, 18, 20 and 32%, respectively. In the USA, 21–35% of isotretinoin-treated patients had moderate acne. In this subgroup of moderate acne, combined data from all countries revealed (fig. 3) that many had either scars (16.7%), psychological problems (18.7%) or both (64.2%). The percentage of patients with moderate acne who had scars and psychological problems was similar in most countries.

*Mild Acne*

All physicians used isotretinoin in patients with mild acne which was non-responsive to long-term antibiotics or appropriate topical therapies. All such patients, however, in this group had either scarring (15.5%) or psychological problems (19%) or both (65.5%). In most countries, this group of 'mild' acne represented less than 5% of oral isotretinoin usage except one centre, where 12% of all acne patients seen had physically mild acne with either scarring or psychological distress or both.

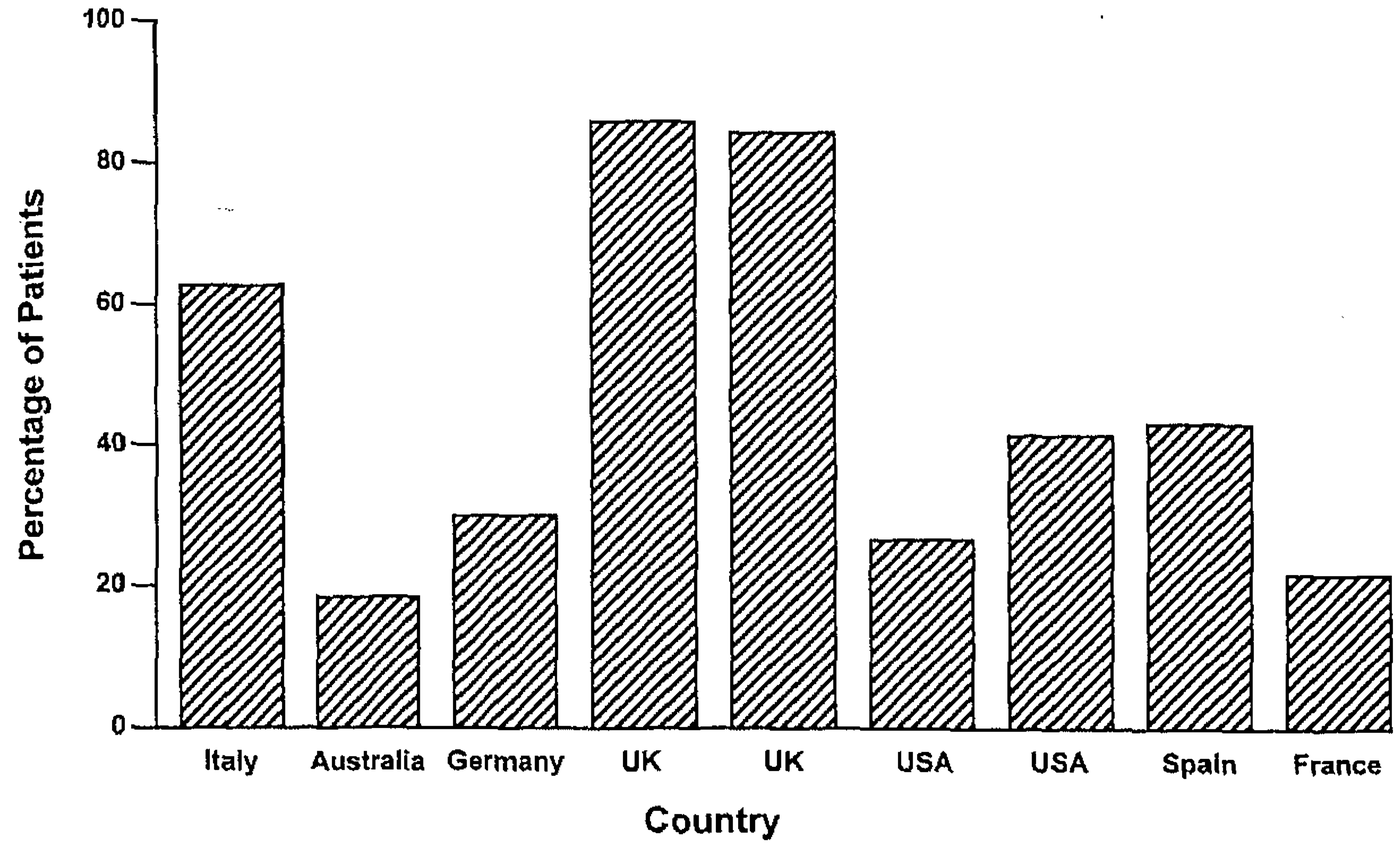


**Fig. 2.** Percentage of patients from 7 countries with **moderate and mild** acne who were treated with oral isotretinoin.

*Acne variants* such as acne fulminans, gram-negative folliculitis, rosacea fulminans and acne conglobata were rare causes for prescribing oral isotretinoin; this reflects the very uncommon nature of these diseases. Only 5 such patients were reported, all of whom required oral isotretinoin.

*Dosing Regimen, Side-Effects and Blood Tests*

All physicians used a daily dose of 0.5–1.0 mg/kg and adjusted therapy duration to 16–30 weeks, depending upon the daily dose. They also adjusted the daily dose according to tolerability and all used a cumulative dose per course of 100 mg/kg or more. In 7 of the 10 centres, most patients reached a cumulative dose of 120 mg/kg.

Mucocutaneous side-effects were experienced by virtually all patients – as was to be expected. In only 4% (2–15%) were these troublesome and unresponsive to simple moisturizers. In such patients, topical steroids were frequently prescribed as were antibiotics to manage secondary infection. The most common systemic side-effects requiring specific therapy were arthralgias and headaches. Paracetamol or non-steroidal anti-inflammatory drugs were all that were required. In no patient were the side-effects a major problem.

Liver function tests and fasting lipids were performed at baseline by all authors, but the frequency of repeat blood tests varied from centre to centre. Laboratory tests were regularly performed by all but two authors. The time and frequency of blood tests varied. However, in none of the

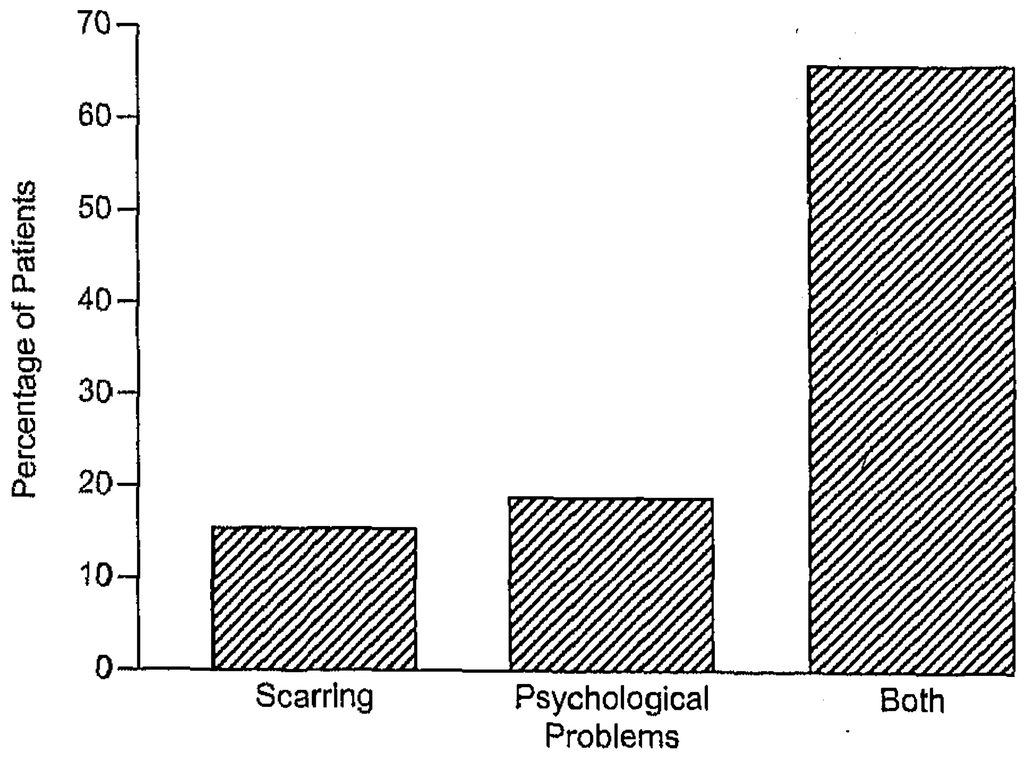


**Fig. 3.** Percentage of isotretinoin-treated patients with moderate acne who had significant scarring and psychological problems or both.

1,000 patients did any of the minor and expected laboratory changes (mild elevation of fasting lipids and liver enzymes) result in a change of dosage or cessation of therapy.

*Cost Savings*

The cost of treating patients with oral isotretinoin and any subsequent therapy with the theoretical cost of long-term antibiotics had isotretinoin not been available demonstrated a significant cost saving. This was documented very

**Table 2.** Mean cost of isotretinoin and any subsequent therapy compared with the theoretical cost if the patient had not been prescribed such therapy for 3 years

| Severity of acne | Percentage of patients | Mean cost if treated with isotretinoin, GBP | Mean cost without isotretinoin treatment, GBP | p value |
|---|---|---|---|---|
| Mild | 20 | 678±45 | 1,675±291 | <0.0001 |
| Moderate | 57 | 732±74 | 1,520±104.5 | <0.0001 |
| Severe | 23 | 803±117 | 1,856±204.5 | <0.0001 |

GBP = Calculated in British pounds. Means ±95% confidence limits.

impressively when treatment costs for acne patients in a country such as the UK were evaluated: comparing the precise treatment costs of 364 patients who were prescribed oral isotretinoin with the theoretical costs of antibiotic treatment revealed cost savings of approximately 60% over conventional 4-month rotational therapy with antibiotics plus topical agents (table 2). The savings were similar whether the patient had mild, moderate or severe acne. Since most of the patients with mild acne had psychological problems, an amount for additional counselling and reassurance was added to the theoretical cost. This explains why the theoretical costs of treating mild acne patients are greater than if the patient had moderate acne.

## Discussion

These data document for the first time worldwide experience on the overall use of isotretinoin. Isotretinoin should not be limited to patients with severe acne. Acne morbidity is determined by more than the apparent physical appearance. Influencing factors include the extent of the disease (trunk and extremities may be involved in addition to the face), the chronic and/or relapsing nature of the disease, the limited benefit of previous conventional therapy, the likelihood of permanent scarring and the degree of acne-induced psychological trauma.

Patients with severe acne should receive oral isotretinoin as first-line therapy. Patients responding poorly to conventional acne therapy after 6 months are too often prescribed more oral antibiotics before isotretinoin is considered. Many patients fail to respond to antibiotics since propionibacterial strains resistant to one or more antibiotics are increasingly detected [11–13]. Another reason for poor response to long-term antibiotics, in the absence of *P. acnes* resistance, is dilution of what could be otherwise effective therapy by high sebum excretion rates – a characteristic feature of acne [2]. Isotretinoin effectively cures acne, even in the presence of *P. acnes* resistance, and it markedly suppresses the sebum excretion rate by 90% within 1 month of initiating therapy [6, 25]. Thus, it is not surprising that oral isotretinoin is very effective in patients with moderate acne whatever their reasons for failure. All authors treated some such non-responding patients with isotretinoin. In one clinic, up to 74% of patients treated with oral isotretinoin had moderate and non-responsive acne, whereas at the other extreme it was only 16% so treated. In all clinics, a smaller percentage of patients with mild acne received oral isotretinoin. A high percentage of patients with moderate active acne as so defined had significant scarring and psychological problems. This was even more evident in those patients with mild acne who received oral isotretinoin.

Scarring from acne creates enduring physical and emotional ramifications; it should be a compelling rationale for isotretinoin treatment, since no other treatment is guaranteed to resolve inflammatory acne. Even when conventional antibiotic therapy is effective, its slower onset of action may be too late to preclude permanent scarring [15, 16].

The significant psychosocial impact of acne should not be underestimated and includes depression, anxiety, interpersonal and work-related difficulties, and attempted suicide [17–20]. Therefore, patients with acne-induced psychological distress such as severe depression or dysmorphophobia should be treated with isotretinoin [15] even when such patients display apparently 'mild' acne.

This unnecessary delay of therapeutic response is naturally frustrating for any acne patient seeking medical attention but may be permanently detrimental for those who scar or who suffer acne-iduced emotional distress [25, 26]. Although life quality is impaired in patients with acne as with many other diseases, few treatments are as effective at recovering predisease quality of life as is isotretinoin. A recent Oxford study, incorporating four different validated quality-of-life instruments, confirmed that isotretinoin treatment significantly improves social function, mental health and self-esteem among other indicators [27].

Additional indications where isotretinoin is used effectively represent but a small percentage of patients (<1%) and include severe acne variants such as gram-negative folliculitis, inflammatory rosacea (e.g. rhinophyma), acne fulminans, rosacea fulminans and hidradenitis suppurativa.

In this study, the variations in the indication for use of oral isotretinoin are, in part, explained by the variation in ways medicine is practised in different countries. In the UK, all patients with troublesome acne who may require oral isotretinoin are treated by a hospital dermatologist, simply because the drug is only available from hospitals. Thus, the physician is more likely to see a broader group of patients not responding to conventional therapy. In Europe, patients with less severe acne who ought to be prescribed oral isotretinoin are likely to visit a private practising dermatologist rather than a hospital dermatologist, whereas the European hospital/university specialist is more likely to see the more severe cases of acne.

Although there were variations in the doses prescribed, virtually all patients received 0.5–1.0 mg/kg/day. In 4 out of 9 clinics, the dose regimen usually started at 0.5 mg/kg daily and increased to 1.0 mg/kg/day, but in 2 centres most patients were started on therapy at 1.0 mg/kg/day. Published data indicate that optimal benefit is achieved with the higher dose [5, 6, 8, 18, 28, 29]. The term cumulative dose per course refers to the total amount of oral isotretinoin taken by the patient over the duration of therapy; in this study the duration of therapy varied from 16 to 30 weeks. Data on cumulative dose indicate that post-therapy relapse is minimized by a treatment course amounting to a total of at least 120 mg/kg [6–8, 25, 29] with no further therapeutic gain beyond about 150 mg/kg.

Most physicians in this study achieved such a cumulative treatment dose. Table 3 summarizes the relationship between daily dose, duration of therapy and cumulative dose.

Mucocutaneous side-effects such as dry lips, dry nasal passages and dry eyes are predictable and dose-dependent consequences of oral isotretinoin. They were evident in most patients in this series. Pretreatment counselling and the regular use of moisturizing agents and lip salves usually manage these adverse effects quite effectively. In this series, 4% of patients had troublesome mucocutaneous side-effects.

Severe systemic side-effects are rarely a problem. In this series, only 2% of patients suffered troublesome effects, in particular headaches, myalgia and arthralgia; all symptoms responded to oral paracetamol or non-steroidal anti-inflammatory drugs.

While oral isotretinoin is effective in treating acne, its teratogenic risk demands responsible consideration by both female patient and physician [30–32]. Women of childbearing potential must have a negative pregnancy test as well as practise effective contraception during and for 1 month after completing therapy [31–33]. Formalized educational campaigns by the manufacturer, including pregnancy prevention programmes, have been very successful [32, 33]. Furthermore, the required 1-month post-therapy contraceptive period affords a respectable safety margin since it has now been demonstrated that plasma concentrations of isotretinoin return to physiological levels within 10 days of therapy completion [34].

Significant cost savings over traditional acne therapies are well documented for isotretinoin [9, 35–37]. Rotational antibiotic therapy is not only less effective than isotretinoin, slower in onset of action and a potential public health hazard in terms of bacterial resistance, but substantially increases costs to patients or insurers. Even using an unrealistically short treatment period of 2 years for conventional therapy, French costs were estimated to be 15% lower with isotretinoin [36]. In Australia [22], conventional acne therapy costs for drugs, laboratory tests and physician consultations are 25% higher than for isotretinoin therapy. Considering costs in New Zealand of medicines, laboratory tests and consultation fees, even the highest dose of isotretinoin (1 mg/kg/day) is 50% less expensive than convential therapy [37]. Our data confirmed the cost effectiveness of isotretinoin in patients with mild, moderate or severe acne.

Professional and governmental health attitudes are focusing more and more on prevention and cost benefit. We therefore conclude that not only do acne patients gain immeasurable physical and psychological relief with almost 100% improvement within 4–6 months of therapy, but society gains by limiting bacterial resistance evolution and reducing health care costs. Thus acne patients should, where appropriate, be prescribed oral isotretinoin sooner rather than later.

**Table 3.** Relationship between the daily dose, the duration of therapy and the cumulative dose

| Daily dose mg/kg | Cumulative dose, mg/kg | | | |
|---|---|---|---|---|
| | 4 months (120 days) | 5 months (150 days) | 6 months (180 days) | 7 months (210 days) |
| 0.5 | 60 | 75 | 90 | 105 |
| 0.6 | 72 | 90 | 108 | *126* |
| 0.7 | 84 | 105 | *126* | *147* |
| 0.8 | 96 | *120* | *144* | *168* |
| 0.9 | 108 | *135* | *162* | 189 |
| 1.0 | *120* | *150* | 180 | 210 |

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