Molecular findings

A total of 46 (42%) deletions were identified in 110 unrelated South African DMD patients. This deletion frequency is consistent with published values of 40 - 60% in other populations, where a similar methodology was used.[12-15] Of the 46 deletions detected in the present study, 65% had a breakpoint in the 3' mutation 'hotspot' whereas only 28% were detected in the 5' 'hotspot'. This distribution corroborates previous reports.[16,17] However, although the deletion frequency and distribution in South African patients are similar to those in patients reported elsewhere, considerable inter-ethnic variation is apparent. The low rate of deletions in black patients (less than 30%) might be due to other intragenic mutations lying outside the known deletion hotspots. The phenotype in those black patients in whom deletions were not detected is identical to that in other groups and non-allelic heterogeneity seems unlikely. It would therefore appear that intragenic deletions for DMD/BMD among blacks occur less frequently and may differ from those previously described in whites.

The low prevalence of DMD and BMD observed in black South Africans remains an enigma but is in keeping with findings elsewhere. It is probable, given the wide but mild spectrum of clinical manifestations of BMD, that many patients do not seek medical appraisal. Previously underscribed point mutations and deletions are likely to be discovered in some affected black patients. Studies to elucidate these anomalies at the molecular level are currently underway.

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Aspects of Roaccutane prescription in South Africa

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A nationwide postmarketing surveillance study on the use and outcomes of use of isotretinoin has been conducted in South Africa. A representative sample of prescribers of the drug was identified from drug utilisation data and the overall doctor response rate was 90,1%. A total of 766 patients was enrolled in the study, of which 728 were analysable for safety and efficacy. More than half the patients prescribed isotretinoin were women, of whom only 48,25% were practising some form of contraception. The mean overall dosage prescribed was 0,64 mg/kg/day and the mean overall duration of therapy prescribed was 15,5 weeks. The mean dose and duration of therapy prescribed by dermatologists was significantly higher than that prescribed by general practitioners. Potentially dangerous drug interactions involving the concomitant use of isotretinoin with tetracyclines, vitamin A and oral contraceptives together with antibiotics were noted. Mucocutaneous drying effects were the most common adverse events and the incidence of these effects decreased with continuation of therapy. The known effectiveness of the drug was confirmed by the results of the study.

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Isotretinoin is a highly effective drug used in the treatment of severe nodulocystic forms of acne which are resistant to therapy. It is an isomer of retinoic acid, a metabolite of vitamin A.

The exact mechanism of action of isotretinoin is not known; however, it reduces sebaceous gland size and inhibits sebaceous gland activity, thereby decreasing sebum secretion. A decrease in the number of *Propionibacterium acnes* organisms within the follicle has also been demonstrated with isotretinoin therapy. However, since the drug has no effect on *Propionibacterium acnes in vitro*, this action is probably a secondary effect caused by decreased sebum secretion.[1] Furthermore, isotretinoin has been shown to have anti-keratinising and anti-inflammatory actions.[2]

Isotretinoin has also demonstrated efficacy in numerous other disorders of keratinisation, such as keratosis follicularis (Darier-White disease), pityriasis rubra pilaris, lamellar ichthyosis, congenital ichthyosiform erythroderma, hyperkeratosis palmaris et plantaris and various other ichthyotic conditions.[3,4] It may also be useful in Gram-negative folliculitis and antibiotic-resistant rosacea.[5]

Although isotretinoin is accepted as the most effective treatment available for severe cystic acne, its use is complicated by its toxicity profile. It commonly causes reversible cutaneous and mucous membrane symptoms and, most problematic of all, it is a proven and potent teratogen. In addition, the efficacy of the drug is influenced by the dose and duration of therapy prescribed; the maintenance of clinical improvement is dose-related.[6]

The safety of isotretinoin is influenced by prescribing practices. Rigorous precautions are necessary to exclude pregnancy before treatment is instituted and to ensure that effective contraception is practised throughout treatment and for 1 month after its withdrawal. Concomitant use of vitamin A supplements and tetracycline antibiotics with isotretinoin pose additional safety hazards and should be avoided. Biochemical investigations are recommended before and during therapy.

Postmarketing surveillance evaluates the use and outcomes of use of drugs in the postmarketing or 'real world' environment. It is a discipline that employs epidemiological methods to identify prescribing trends, the target patient population, populations at risk, outcomes of treatment and important signals on safety and effectiveness.

In order to assess the nature and consequences of the prescription of isotretinoin in South Africa, a nationwide postmarketing surveillance study was conducted by the Drug Surveillance Research Centre (DSRC) at the University of Cape Town.

The study addressed both the quantitative and qualitative aspects of the utilisation of the drug and, in this article, aspects of the prescription and outcomes of the use of the drug are presented.

Methodology

A descriptive, uncontrolled cohort study was performed. A detailed description of the methodology used for sample identification and data verification is given elsewhere.[7]

Identification of prescribers

A sample frame representing doctors who prescribed the drug over a set period of time was compiled from two data sources — the pharmaceutical wholesalers and the pharmaceutical societies.

Pharmaceutical wholesalers purchasing isotretinoin from Roche Products (Pty) Ltd, SA, were identified. Selected wholesalers were requested to supply monthly isotretinoin sales data to the DSRC. A minimum of 3 months' data were collected from each wholesaler. This enabled doctors who are buying the drug, i.e. doctors dispensing isotretinoin, to be identified.

Isotretinoin prescription data were supplied to the DSRC by the prescription pricing units of the pharmaceutical societies. Prescription data covering a period of 2 months were collected from each unit. This enabled doctors prescribing (but not dispensing) isotretinoin to be identified. All data were kept strictly confidential.

Sampling

Doctors identified from the surveillance of drug sales and prescription data were stratified according to geographic area of practice and specialty. A random sample of 95, representing 25% of the prescribers identified, was chosen for enrolment in the intensive surveillance study. Sample sizes per area were determined by proportional allocation based on the numbers of prescribing doctors identified per area.

The composition of each subsample per area, i.e. the number of general practitioners (GPs) and dermatologists (DERMs), was determined by proportional allocation based on the amount of the drug prescribed by these groups in each area.

Doctor enrolment

The resulting sample of doctors was enrolled telephonically. Participants were posted a file containing a covering letter and questionnaires. DERMs were requested to enrol all patients (up to a maximum of 40) requiring isotretinoin during the 3-month study period. GPs were requested to enter all patients who required therapy seen over a 3-month period. Patient enrolment rates of each practitioner were assessed by comparing the number of patients enrolled with the number expected to be enrolled, based on the practitioner's previous drug utilisation; information was verified at a final interview.

Data collection

Data collection was facilitated by means of posted questionnaires designed to act as the complete patient record card. Each questionnaire consisted of three loose-leaf, carbonised sections attached to a cardboard base.

Common adverse medical events during therapy were reported by means of a prompted collection mechanism where events are reported simply by making a cross next to the appropriate event listed in the case report form. Any other adverse medical event was documented on a spontaneous reporting card. All adverse events were reported by the doctor, not the patient.

Patients' personal details were captured on the base card only and were therefore not received by the DSRC; this ensured total confidentiality. The loose-leaf sections of the questionnaire were collected by trained fieldworkers on completion of the study, checked for accuracy and completeness and returned to the DSRC.

Results

Doctor response rate

Ninety-one of the 95 doctors sampled participated in the study. Reasons for non-participation were not related to the study or the drug — the doctors in question were either due to retire, on vacation or state-employed.

Of the 91 participants, 5 doctors did not respond, citing time constraints and/or lack of financial incentive as the reason. Four additional doctors who enrolled between 1 and 28 patients in the study were classified as non-responders because the number of patients enrolled by them was less than 80% of the expected number (calculated from their previous drug use), and the final interview confirmed that fewer than 80% of patients seen were enrolled.

The overall doctor response rate (percentage of doctors enrolling more than 80% of patients seen = compliant doctors) was therefore 90,1%.

Patient enrolment

A total of 766 patients was enrolled in the study, of which 728 (95%) were analysable for safety and efficacy. Of these patients, 87,6% were enrolled by DERMs and 12,4% by GPs.

The overall patient enrolment rate (number of patients enrolled in the study divided by the total number of patients seen by all the doctors sampled during the study period) was 82,7%.

Patient demographics

More than half (50,4%) of the patients enrolled in the study were female. Patients' ages ranged between 10 and 52 years (mean 21,42 years; SD 6,45 years), and weights ranged from 36 kg to 112 kg (mean 64,08 kg; SD 11,02 kg).

Severity of acne at start of treatment

Acne was graded according to the grading scale of Allen and Smith.[8] The majority of cases (41,7%) were grade 6, 34,6% were grade 4, while 14,3% and 9,1% of cases were grade 8 and grade 2 respectively.

Previous isotretinoin therapy

A total of 108 patients (14,8%) had previously been on isotretinoin therapy. The daily isotretinoin dose received by these patients during the previous course ranged from 4,3 mg to 80 mg, with a mean of 34,1 mg and a median of 35 mg. The duration of treatment previously received by these patients ranged between 4 and 104 weeks, with a mean of 17,7 weeks and a median of 16 weeks.

Prescribing characteristics

Dosage prescribed

The mean daily dosage prescribed at initiation of therapy was 0,64 mg/kg. Initial daily doses prescribed ranged from 0,12 mg/kg to 1,33 mg/kg; the median dosage prescribed was 0,63 mg/kg and the SD 0,24.

Marked differences were evident in the mean dosages prescribed by GPs and DERMs, with GPs prescribing a mean starting dose of 0,36 mg/kg/day and DERMs a mean starting dose of 0,68 mg/kg/day. Similar differences were evident in the dosages prescribed at follow-up visits.

Duration of therapy

The mean overall duration of therapy prescribed was 15,5 weeks (SD = 3,99; SEM = 0,15). Duration of therapy ranged between 3 weeks and 40 weeks; the median duration was 16 weeks. The mean duration of therapy prescribed by DERMs was 15,7 weeks, and that prescribed by GPs 13,6 weeks.

Contraception

Less than half (48,25%) of all female patients prescribed isotretinoin were practising some form of contraception. The injectable contraceptive and the intrauterine device were used by 0,81% and 2,96% of all female patients respectively. The oral contraceptive was used by 36,39% of women, and 8,09% practised other forms of contraception (e.g. sterilisation, condoms and vasectomy of partner).

In the remaining 51,75%, contraception was deemed unnecessary. This group included patients who were not sexually active, had given informed consent or had religious objections to contraception.

Potential drug-drug interactions

Isotretinoin and tetracyclines. Tetracycline antibiotics were prescribed concomitantly with isotretinoin to 5 patients. Minocycline was prescribed to 3 patients at a dose of 50 mg twice a day, and lymecycline was prescribed at a dose of 300 mg daily to 1 patient and at an unspecified dose to another. The duration of concomitant tetracycline therapy was 1 month in 2 patients, 2 months in 2 patients and 4 months in the 5th patient.

Isotretinoin and vitamin A. A multivitamin preparation containing vitamin A was taken concomitantly with isotretinoin by 1 patient.

Antibiotics and oral contraceptives. Five of the 135 female patients on oral contraceptives were prescribed antibiotics concomitantly. Three patients were using tetracyclines, 1 patient erythromycin and 1 a sulphonamide antibiotic.

Biochemical tests

Baseline cholesterol, triglyceride and liver function tests (LFTs) were performed in 60%, 47% and 53% of patients respectively. All biochemical investigations were performed less frequently at each follow-up visit thereafter, with cholesterol, triglyceride and LFTs being performed in 18%, 14% and 18% of patients respectively at the third follow-up visit.

A greater percentage of patients receiving therapy from DERMs underwent biochemical investigations at each follow-up visit than patients receiving therapy from GPs.

Effectiveness

Effectiveness was graded subjectively into five categories rating improvement of acne as: *(i)* no improvement; *(ii)* <20% improvement; *(iii)* 20 - 50% improvement; *(iv)* 50 - 80% improvement; and *(v)* > 80% improvement.

Ninety-four per cent of patients had experienced some improvement at the first follow-up visit. By the third follow-up visit, all patients had experienced some improvement and 56% of patients had experienced a more than 80% improvement.

Safety

Adverse events

Adverse events were experienced by 87,1% of the 728 patients. Mucocutaneous drying effects were the most common events reported, with dry lips, dry skin, dry nose, facial dermatitis and dry eyes the most frequent manifestations. Headache, muscle pain, photosensitivity and appetite disturbances were reported by fewer than 10% of patients via the prompted reporting method.

Table I shows the percentage of patients experiencing common adverse events at each follow-up visit during isotretinoin therapy. Less common adverse events associated with isotretinoin were reported spontaneously. Table II lists the spontaneously reported adverse events and the results of a standardised computer causality assessment.

Table I. Percentage of patients experiencing common adverse events at each follow-up visit

	Follow-up visits		
Common adverse event	1st	2nd	3rd
Dry lips	85,9	79,0	74,4
Dry eyes	23,5	15,8	14,9
Dry nose	34,8	26,7	22,9
Appetite disturbance	2,9	2,6	2,6
Dry skin	61,7	54,1	52,5
Facial dermatitis	27,5	19,8	19,7
Headache	6,4	4,2	3,7
Muscle pain	8,7	8,4	9,3
Photosensitivity	10,4	8,8	9,9

Table II. Adverse events reported by means of the spontaneous reporting mechanism

Description of adverse event	No. of events	Standardised computer-aided causality assessment*
Hoarse voice	1	Probable
Staphylococcal skin infection	1	Possible
Flushing and influenza-like illness	1	Definite
Irregular menses	4	All possible
Mood changes	1	Possible
Severe headache	1	Probable
Paronychial infection	1	Possible
Acute inflammation of acne	1	Possible
Backache	1	Possible
Hair growth on chin and upper lip	1	Possible
Insomnia	1	Possible
Influenza/bronchitis	1	Unlikely

* Algorithm used: Venulet J, Giucci AG, Berneker G-C. Updating of a method for causality assessment of adverse drug reactions. *Int J Clin Pharmacol Ther Toxicol* 1986; **24:** 559-568.

Biochemical adverse events

LFTs. A total of 734 LFTs were performed on 466 patients during the study. Thirty-two of these patients experienced abnormal readings at least once.

Cholesterol. Two hundred patients had more than one cholesterol level assessment during the study. Changes in cholesterol readings ranged from a drop of 14% to a rise of 83,3%. The mean overall change in cholesterol readings was a rise of 10,5% (SD 19,5; SEM 1,4).

Discussion

Methodology

The methodology employed in this study represents a novel approach to sample identification and validation of results for postmarketing surveillance studies.

The unusually high doctor response rate (90,1%) may be attributed to the intensive surveillance method employed, regular contact between the investigators and the study management team, the feedback provided to the investigators and the nature and safety characteristics of the drug studied. There is no reason to believe that the 9,9% of doctors sampled who refused to take part in the study biased the results in any way as, among the responders, there were doctors with similar characteristics (size of practice, specialty, area of practice and institution at which he/she studied) to the non-responders. The patient enrolment rate of 82,7% indicates that the patients enrolled into the study were representative of all patients seen by the sample of doctors.

Patient demographics

The age distribution and mean age (21,42 yrs; SD 6,45) of patients enrolled in the study are characteristic of patients likely to have acne.

Despite the teratogenic potential of the drug more than half the patients (50,4%) receiving isotretinoin were female. This is in contrast to the results of a survey conducted recently in the USA[9] on the prescription of isotretinoin. This survey showed that more than half of 577 respondents reported that between 30% and 50% of their patients treated with isotretinoin were women, with a mean of 38,5%.

Prescribing characteristics

Dosage and duration of therapy prescribed

For the treatment of recalcitrant cystic acne, severe acne, conglobate acne, Gram-negative folliculitis and acne rosacea, the recommended initial dosage of isotretinoin is 0,5 - 1,0 mg/kg/day taken with meals.[10]

The overall mean daily dosage prescribed at initiation of therapy in patients enrolled in the study was well within this range, at 0,64 mg/kg. However, there was a wide range of dosages prescribed and a tendency was found for GPs to prescribe lower dosages than DERMs. The mean daily dosage prescribed by DERMs was 0,68 mg/kg and by GPs 0,36 mg/kg.

This difference in initial dosage may well reflect the difference in severity of acne treated by GPs and DERMs or may be due to the fact that DERMs prescribe isotretinoin

more commonly than GPs and may therefore have greater confidence in more aggressive therapy.

The prescription of low doses of isotretinoin does not make good clinical or economic sense. The initial dose of isotretinoin prescribed has an inverse relationship to the likelihood of relapse of the disease. A clinical study comparing 0,1, 0,5 and 1,0 mg/kg/day showed an initial clearing of disease at all dosages but there was a greater need for retreatment with decreasing dose, with 40% of patients on the 0,1 mg/kg/day dose requiring a second course of therapy, compared with 20% and 10% of patients on the 0,5 and 1,0 mg/kg/day doses respectively.[6]

The recommended duration of isotretinoin therapy is 15 - 20 weeks.[10] Therapy may, however, be discontinued sooner if the total number of cysts have been reduced by 70%.

The mean duration of therapy prescribed in the study was 15,5 weeks; the mean duration prescribed by DERMs was 15,7 weeks, and by GPs, 13,6 weeks.

The duration of therapy prescribed ranged between 3 weeks and 40 weeks. Prolonged therapy (> 6 months) with isotretinoin may, however, predispose the patient to serious adverse events, including skeletal abnormalities, lipid-related morbidity and hepatotoxicity.

It is generally recommended that a drug-free interval of 3 - 4 months (at least 8 weeks) be allowed after completion of one course of isotretinoin (15 - 20 weeks) before a repeat exposure is considered.[11]

Contraception

In 51,4% of female patients taking isotretinoin, contraception was deemed unnecessary. A shortfall of the study is that this group of patients could not be further stratified to determine the proportion that had given informed consent, had religious objections to contraception, were not sexually active or who had other reasons for not using contraceptive measures concomitantly with isotretinoin.

Nevertheless, the relatively large proportion of female patients of childbearing age exposed to isotretinoin and not practising some form of contraception is of concern. A separate study to determine the exact extent of isotretinoin exposure during pregnancy is currently underway.

No data were collected on the frequency with which pregnancy tests were performed before initiation and during isotretinoin therapy. A decision was made to exclude these data from the case report form as it was felt that the collection of data of this nature would result in a low participation rate.

An analysis of the prescription of contraception by DERMs and GPs showed no significant difference in frequency of prescription between the two groups.

Interactions

Twelve patients were taking concomitant medication that could predispose to unfavourable outcomes. Five patients received supplementary therapy with tetracycline antibiotics. This combination of therapy is contraindicated as it has been associated with rare cases of pseudotumour cerebri or papilloedema.[12]

The use of multivitamin preparations containing vitamin A was noted in 1 patient. This combination may result in additive toxic effects as isotretinoin is a vitamin A derivative.

The reported interaction that is potentially the most serious involves the concomitant use of antibiotics, isotretinoin and oral contraceptives. This combination was used in 5 patients enrolled in the study. It is well known that isotretinoin is a potent teratogen[13] and that female patients on the drug should be practising reliable contraception. The concomitant use of antibiotics and an oral contraceptive may lead to contraceptive failure due to the possible inhibition of enterohepatic recycling of oestrogen or due to a mechanism not well understood.[14] Special care should be taken in the choice of contraceptive for acne patients receiving long-term antibiotic therapy.

Severity of acne

Isotretinoin is registered in South Africa for the treatment of severe cystic acne only. However, the results of the study indicate that there is marked variation in the severity of acne treated with isotretinoin. This observation is likely to reflect the inter-individual philosophies of prescribers with regard to acne therapy.

Biochemical tests

It is recommended that cholesterol and triglyceride levels, and LFTs, be monitored before commencement of and during isotretinoin therapy.

Maximum isotretinoin-induced rises in cholesterol concentrations usually occur after 4 weeks of therapy; however, they commonly remain within normal range.[15]

This phenomenon may be reflected in the management of patients. Cholesterol measurements were most commonly performed before initiation of therapy (60% of patients) and then at the first follow-up visit (30%). After the first follow-up visit, cholesterol measurements were infrequently performed (11% and 18% at third and fourth visits respectively).

A similar pattern of frequency of triglyceride and liver enzyme investigations was evident which reflects a greater degree of caution at initiation of therapy than at subsequent visits, possibly because of previous normal levels being reported.

Effectiveness

At the third follow-up visit 99% of patients had experienced an improvement in their acne of at least 20 - 50%. At this time, 90,4% had experienced an improvement in their acne of at least 50%, and 56,3% had experienced an improvement in excess of 80%. Improvement will generally continue after isotretinoin is discontinued; a patient with 80% improvement at the time of discontinuation of therapy will probably experience almost complete clearing.[16]

These results confirm the known efficacy of the drug when prescribed appropriately.

Safety

No reliable data on the use of isotretinoin in porphyria are available.11 One patient with porphyria variegata was prescribed isotretinoin in the study, and no untoward effects were reported.

Two methods of adverse event collection were used in the study, a prompted collection method and a spontaneous reporting system. It was hypothesised a *priori* that the prompted method would provide a more accurate measure

of the incidence of common adverse events, a known shortfall with the spontaneous reporting system. A comparison of the incidence of adverse events reported by means of the prompted reporting method with the incidence quoted in published texts is shown in Table III.

Table III. Comparison of the incidence of adverse events reported by means of the prompted reporting system with the incidence quoted in the literature (%)

Adverse event	Incidence in study using a prompted reporting system	Quoted incidence	
		AHFS[15]	USPDI[10]
Cheilitis	86,5	> 90	90
Dry eyes/conjunctivitis	29,5	± 40	± 40
Photosensitivity	13,8	5 - 10	± 5
Musculoskeletal effects	12,8	16	± 16
Dry skin	69,8	–	up to 80
Headache	8,9	–	± 5

These results indicate that the prompted method of adverse event reporting allowed for a relatively accurate incidence of adverse events to be identified, as well as the identification of trends in the occurrence of these effects with time. A definite downward trend in the frequency of mucocutaneous drying effects was evident with time. This downward trend was not as evident in other less common events such as appetite disturbances, and not evident in photosensitivity and muscle pain.

Conclusions

1. A reliable and verifiable method for postmarketing surveillance studies, employing drug utilisation data for sample identification and verification of patient enrolment, has been developed and implemented. The use and outcomes of the use of isotretinoin in South Africa were studied.

2. The method allowed for the accurate description of patient demographics, prescribing practices and outcomes of use.

3. The mean overall dose and duration of isotretinoin therapy were within the recommended ranges, although differences in prescribing practices were identified between subgroups of prescribers.

4. The majority of patients prescribed isotretinoin were female and problems in respect of the low incidence of use of contraception in these patients were identified.

5. The practice of prescribing concomitant medication, especially isotretinoin in combination with an oral contraceptive and antibiotics, was of concern.

6. The effectiveness and safety of isotretinoin as used in the community were assessed.

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