THE COST-EFFECTIVENESS OF ISOTRETINOIN IN THE TREATMENT OF ACNE

Part 1. A meta-analysis of effectiveness literature

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Objectives. This paper reports the results of a meta-analysis of isotretinoin treatment in moderate to severe acne. It forms part of a comprehensive investigation into the cost-effective treatment of acne in South Africa and as such establishes the clinical foundation for an economic model of acne management. This foundation includes an evaluation of the daily dosages, treatment durations, success rates, clinical effectiveness and relapse rates reported in published trials since 1981.

Methodology. A predetermined protocol for the study established the scope, appropriate inclusion and exclusion criteria for peer-reviewed data, and the statistical rigour that would be applied to the selected data. Following an extensive literature search, data reflecting the effectiveness of isotretinoin were extracted, statistically assessed, described and reported. The combinability of the data was confirmed using analyses of variance and chi-square tests, as applicable.

Results. Isotretinoin consistently proved to be a highly effective agent in the treatment of moderate to severe acne vulgaris. The response rate determined by the meta-analysis indicated a clinical cure in 84.22% to 86.71% of patients treated. From the data considered, the average treatment duration was calculated to be 17.9 weeks (4 months). The relapse rate was low (21.45%) and dose-dependent. Optimal results were achieved by treating patients with a daily dose of 1 mg/kg and treating to a target cumulative dose of 120 mg/kg over the treatment duration.

Conclusion. The results of this meta-analysis support the continued use of isotretinoin in the treatment of acne. The results are important in the field of pharmaceutical benefit management where they will assist in the optimal management of this health condition. The results will be used to develop a pharmaco-economic model to evaluate the various treatment regimens used for acne in South Africa.

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South African health care costs are spiralling out of proportion to the national inflation rate, with the funders of health care, namely the medical schemes and insurance companies, taking financial strain within a fee-for-service environment where patients and providers have little incentive to minimise health care expenditure. Better health care provision requires a system that will manage the cost, possibly making medical cover more accessible, while maintaining the quality of delivery. This move to a managed care environment, although driven primarily by costs, requires good information and evidence-based medicine if it is to be successful.

In 1997 the cost to health care funders in South Africa of pharmaceutical products for dermatological conditions ranked within the costs for the top eight disease states, following such conditions as hypertension, hypercholesterolaemia, depression and ulcer therapy (Dr J van Heerden, Clinical Director, Interpharm Data Systems — personal communication). Dermatological products made up 6 - 7% of the reimbursed pharmaceutical benefits bill in 1997, showing an increase over the 1996 percentage of 5 - 6%. While it is very difficult at present to get accurate data on diseases in South Africa, approximately 55% of the money reimbursed for dermatologicals is attributable to acne. In terms of specific drugs used in acne treatment, isotretinoin attracts the biggest reimbursement. It also ranks within the top ten products in terms of turnover in the South African private market (IMS. Pharmaceutical Market South Africa: Total Private Market, June 1997).

In the UK acne is the most common dermatological condition, reportedly affecting 85% of teenage boys and 80% of teenage girls.[1] There is evidence from hospital referral patterns in the UK that there is an extension in the incidence of this condition from school-aged children to older teenagers and individuals in their 20s and 30s.[2] This implies that patients suffering from acne will be making an ever-increasing demand on health care resources.

From the above it would appear that isotretinoin will continue to be a major expense to the funders of health care. However, the cost of isotretinoin should be put into perspective before assumptions are made to limit or curtail its usage. The cost-effectiveness of this therapy needs to be compared with that of other acne therapies, taking into account the therapeutic outcomes and, if possible, quality of life measures. Such comparisons would not only assist the funders of health care in deciding the appropriate levels of reimbursement required for acne, but would also provide those organisations that are developing therapeutic guidelines and formularies with evidence on which to base decisions.

Several well-researched, international studies are available (Brogan Consulting Inc. — data on file; Hoffman-La Roche Ltd), and have been published on the cost-effectiveness of isotretinoin[3-7] and on quality of life issues.[1,8] The objective of the

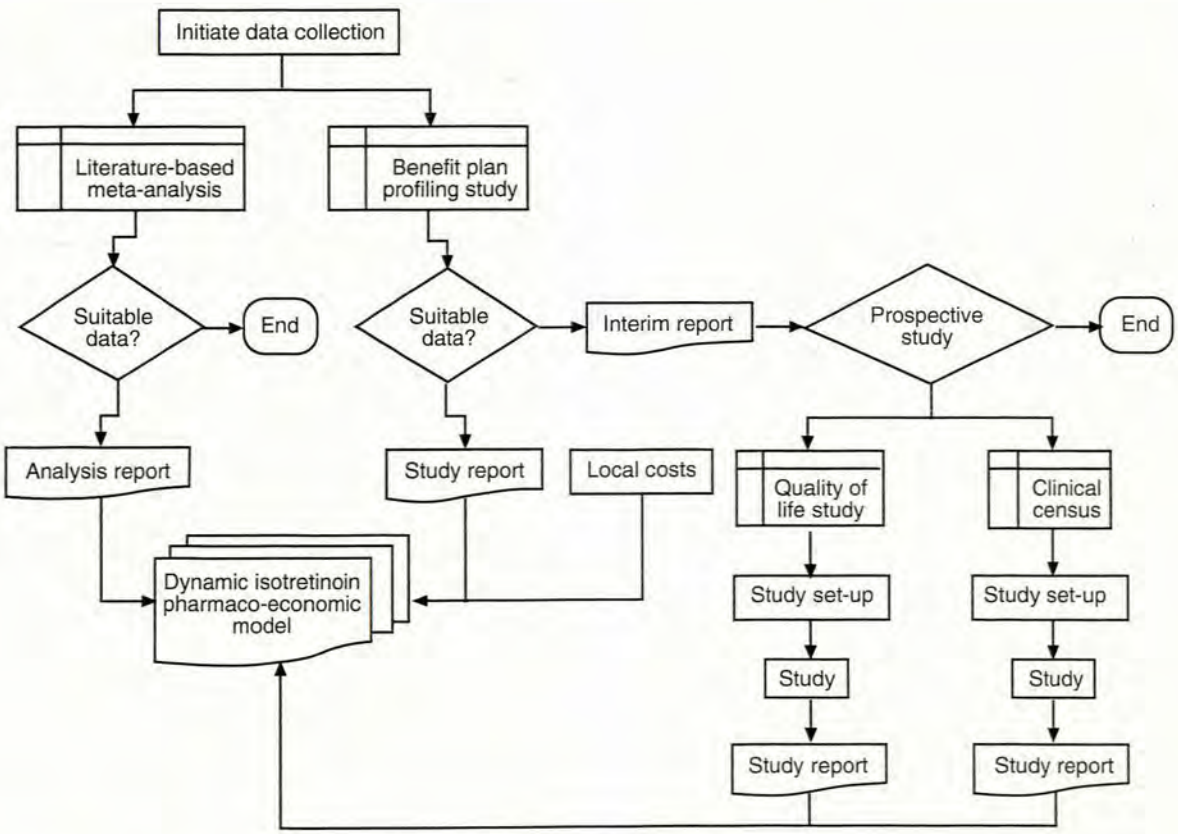

Fig. 1. Isotretinion pharmaco-economic strategy.

current research is to generate evidence on the cost-effective treatment of acne in South Africa. As shown in Fig. 1, the research strategy has been designed to be multifaceted, taking into account the availability and applicability of local data as well as various retrospective and prospective analytical techniques. The ultimate aim is to build a database of localised information on the treatment of acne to facilitate the above decisions.

Isotretinoin is well recognised as a successful therapy for acne vulgaris, nationally[9] (Pharmaceutical Benefit Management (Pty) Ltd. Acne minimum quality criteria, in-house publication, 1997), and internationally.[10-15] Published indications for its use include severe acne, failed or partial response to conventional treatment, frequent relapses, or acne associated with severe psychological disturbance. As part of a comprehensive investigation into the cost-effective treatment of acne in South Africa, the meta-analysis of the clinical effectiveness of isotretinoin reported here is designed to form the clinical foundation for an economic model of acne management. This foundation includes an evaluation of the daily doses, treatment durations, success rates, clinical effectiveness and relapse rates reported in published trials since 1981.

METHODOLOGY

Meta-analysis study design

The meta-analysis of published data on acne was conducted according to a predetermined protocol following the recommendations of Mulrow.[16] For the purpose of the analysis, 'effectiveness' was defined as 'the demonstration that a new health care intervention does more good than harm when used in usual circumstances', as proposed by Detsky and Naglie.[17]

Methods and assumptions

Literature search. A Medline search for published papers was conducted and supplemented by Internet searches. The key words used included 'acne', 'acne vulgaris', 'isotretinoin', 'effectiveness', 'cost-effectiveness', and 'quality of life'. Mainly English papers were assessed, although one French paper was considered but was judged to be inappropriate. In addition to these papers, publications were also sourced from commercial organisations, including Roche (SA), Pharmaceutical Benefit Management (SA) and Brogan Consulting Inc. (USA).

Inclusion criteria. Predetermined inclusion criteria were used to establish the suitability of the published papers for a meta-analysis. The criteria were: (*i*) studies stating a clear

diagnosis of acne vulgaris and including clinical success rate or treatment period; (*ii*) randomised, controlled clinical trials; (*iii*) clinical trials reporting the results of treatment with specified dosages of isotretinoin; (*iv*) studies reporting on the clinical effectiveness of isotretinoin; and (*v*) studies with a sample size of at least 50 patients in an isotretinoin treatment arm.

Exclusion criteria. Similarly, exclusion criteria were established and included: (*i*) any trial not stating the specific diagnosis of acne; (*ii*) those papers failing to satisfy the inclusion criteria; and (*iii*) studies dealing with patient cohorts in which the grade of acne being investigated was not moderate to severe.

Statistical methods. The validity of trial data for inclusion in the study was tested by means of chi-square (χ^2) tests and analyses of variance (ANOVAs). The significance level (alpha) was specified *a priori* as 5% (0.05). The treatment periods, success rates and relapse rates were calculated to be the weighted average of the results reported in the respective trials.

Criteria for combinability. Qualitatively, the inclusion and exclusion criteria were used to evaluate the combinability. In addition, the severity of the disease and the age of patients were considered. Apart from these parameters, the statistical methods described above were employed to test the homogeneity of the data. Chi-square tests and ANOVAs, as applicable, were performed on the data from all appropriate trials. Only once it was proved in this way that the results were not trial-dependent, were the trial data included in the meta-analysis and aggregated.

RESULTS AND DISCUSSION

A total of 37 published papers were collected and preliminarily evaluated. These papers all dealt with some aspect of acne treatment, however the focus of the studies varied significantly across the corpus of evidence. Initially only randomised, controlled trials were considered. However, most effectiveness studies reported in the literature were single-arm, retrospective studies and therefore did not meet this criterion. In addition, blinding was not included as a selection criterion. This was not considered to detract from the validity of the meta-analysis as this is not a comparative study. The minimum sample size of 50 patients was considered large enough to satisfy any assumptions of robustness for the statistical methods used.

The 37 papers were narrowed down to 18, including only those that reported on clinical effectiveness.[1,3-7,10,18-27] (and Brogan Consulting). Of these papers, Shahidullah *et al.*[3] and Lee and Cooper[7] reported on severe cases of acne; all the other papers reported on moderate and moderate to severe cases. Despite the potential bias that the inclusion of the results from the severe cases may introduce, it was decided to include these two papers as it was suggested that this would only make the results of the analysis more conservative.

From these selected papers, the relevant clinical evidence was extracted and is reported in Table I. Statistical tests were performed to determine the homogeneity of the data, which was defined as a consistency in the values of the research variables investigated. Where data were found to be homogeneous, it was concluded that the patient populations, treatments and clinical outcomes were comparable and therefore that the results could be combined. Heterogeneous data indicated, *inter alia*, that the study populations were not comparable, and a homogeneous subset of these data was then sought. Given the focus of the meta-analysis, the underlying causes of such heterogeneity were not explored.

As shown in Table I, not all papers reported on every variable listed. Only one of the papers reported on the reduction in acne grade achieved.[5] This study also reported a median disease-free period of 43 months. Most papers reported on success and relapse rates. Various definitions for clinical success were used; however, by defining this parameter as a greater than 50% clinical improvement, a comparison of rates for the combinability of the results was facilitated. This definition proved to be a very conservative approach as most of the success rates reported in Table I are for higher percentages of improvement. After treatment with isotretinoin, Shahidullah *et al.*[3] reported a success rate of 85.2% for clearing at least 50% of acne, Cunliffe *et al.*[4] reported greater than 60%

Table I. Clinical effectiveness data for isotretinoin

Author(s)	Sample size	Daily dosage (mg/kg)	Treatment duration (weeks)	Success rate (%)*	Relapse rate (%)	Reduction in acne grade	Disease-free period (months)
Shahidullah *et al.*[3]	250	0.5	16	85.20	5.6		
Cunliffe *et al.*[4]	100	0.5 - 1	19	88	56		
Simpson[5]	100	40†	18		29	96	43
Stainforth *et al.*[6]	299	0.1 - 1	16		22.7		
Lee and Cooper[7]	76	1	20	90	34		
Brogan Consulting	1 428			83.50			
Goulden[23]	720				19.9		

* > 50% improvement.
† Dosage in mg.

Table II. Meta-analysis of reported relapse rates

Paper	Non-relapse (%)	Relapse (%)	Total
Simpson[5]	71 (71)	29 (29)	100
Stainforth *et al.*[6]	231 (77.3)	68 (22.7)	299
Goulden *et al.*[23]	577 (80.1)	143 (19.9)	720
Aggregated rate	879 (78.6)	240 (21.5)	1 119
Standard error (%)	1.2		

improvement in 88% of patients, and Lee and Cooper[7] reported that 90% of patients responded with 70% improvement in acne severity.

There was not a consistent definition for relapse rate in the literature; however one definition that was widely used was 'the requirement for further systemic anti-acne therapy'.[5] The figures reported for the relapse rates in Table I are therefore clearly heterogeneous ($P < 0.0001$). If Shahidullah *et al.*[3] are excluded, the results still prove to be heterogeneous ($P = 1.72 \times 10^{-6}$); it is only when Cunliffe *et al.*[4] and Lee and Cooper[7] are also eliminated that the results become homogeneous. The meta-analysis of these homogeneous data, shown in Table II, indicates a relapse rate of 21.45% ($\chi^2 = 4.76$, df = 2, $P = 0.092$, standard error (SE) = 1.23%). Seventy-five per cent of those patients who relapse can be expected to do so during the first 12 months.[6]

Dosages reported in these studies were consistent and ranged from 0.1 to 1 mg/kg per day. Cunliffe *et al.*[10] reported an optimal daily dosage of 1 mg/kg and a cumulative dose of 120 mg/kg over the treatment course. As only one study[18] reported an 'average' daily dosage, this variable could not be evaluated statistically.

A comparison of the reported treatment effectiveness levels is presented in Table III. Shahidullah *et al.*[3] and Hogan *et al.*[18] graded the response to isotretinoin therapy in terms of a percentage clearance. Consequently categories of 'exceilent' (greater than 75% clearance), 'good' (50 - 75% clearance), 'fair' (25 - 50% clearance) and 'poor' (less than 25% clearance) were reported by Shahidullah *et al.*[3] Hogan *et al.*[18] reported grades of excellent, moderate and slight. A χ^2 test was used to assess the combinability of these responses. If the good and excellent categories from Shahidullah *et al.*[3] are collapsed into one category corresponding to the excellent grade of Hogan *et al.*,[18] and if the fair and poor categories are considered to be equivalent to the moderate and slight grades, respectively, then the χ^2 test seems to indicate homogeneity of results ($\chi^2 = 0.61$; $P = 0.894$). It is, therefore, reasonable to assume that by treating acne patients within the above-defined patient population with isotretinion, 84.8% will have an excellent response, 11.9% a fair response and 3.3% a poor response.

Success rate was also assessed by means of a χ^2 analysis and is reported in Table IV. For the purpose of this analysis, the results from Shahidullah *et al.*,[3] Cunliffe *et al.*,[4] Lee and Cooper[7] and Brogan Consulting were considered. The χ^2 test appears to indicate homogeneity of results ($\chi^2 = 0.59$, $P = 0.899$). This may be interpreted to indicate an aggregated success rate of 84.22%, where clinical success is defined as above. However, there is some doubt about the inclusion of the Brogan Consulting study[10] in this analysis; the study population consisted of non-steroidal anti-inflammatory drug (NSAID) patients obtained from a US managed care organisation, and this may have biased the patient selection. In addition, the paper has not yet been published in a peer-reviewed journal and is considered to be an in-house technical publication. When this paper is excluded from the analysis, the results are strengthened ($\chi^2 =$

Table III. Comparative data of reported treatment effectiveness levels

Author(s)	Sample size (%)	Excellent (%)	Good (%)	Fair (%)	Poor (%)
Shahidullah *et al.*[3]	250 (100.0)	127 (50.8)	86 (34.4)	30 (12.0)	7 (2.8)
Hogan *et al.*[18]	86 (100.0)	72 (83.7)	—	10 (11.6)	4 (4.7)
Total	336 (100.0)	(84.8)*	—	40 (11.9)	11 (3.3)

*Excellent and Good combined.

Table IV. Chi-square analysis of success rate

Author(s)	Success rate (%)	Sample sizes	Observed frequency	Expected frequency	Chi-square scores	*P*-value
Shahidullah *et al.*[3]	85.2	250	213	210.56	0.03	
Cunliffe *et al.*[4]	88.0	100	88	84.22	0.17	0.8987
Lee and Cooper[7]	90.0	76	68	64.01	0.30	
Brogan Consulting	83.5	1 468	1 226	1 236.39	0.09	
Total	84.2	1 894	1 595	1 595	0.59	

Table V. Comparison of treatment periods

Author(s)	Treatment duration (weeks)	Range observed (weeks)	Sample size	Estimated standard deviation
Shahidullah *et al.*[3]	17.3	1.3 - 52	250	8.45
Cunliffe *et al.*[4]	19.0	8.0 - 59	100	8.50
Simpson[5]	18.0	8.0 - 43	100	5.83
Aggregate	17.9		450	

0.18; $P = 0.91$), resulting in an aggregated success rate of 86.71%. This is explained by the fact that the results from the eliminated paper represent the least favourable outcomes reported in the papers considered for this analysis. It is therefore reasonable to expect a success rate of between 84.22% and 86.71% to be observed for the moderate, moderate to severe and severe acne patient population under comparable conditions.

The papers were all reasonably consistent in the treatment period reported. This period was determined by local treatment guidelines, patient severity and total target dosage per patient body mass. To support this assessment of consistency, an ANOVA was conducted to confirm homogeneity of treatment duration evidence. The data sourced from the literature are given in Table V. A number of assumptions had to be made to satisfy the theoretical requirements for this test. An assumption of normality was made; the large sample sizes involved were thought to make this a fair assumption. The only statistics that could be obtained from the literature were averages or medians and data ranges. As some measure of variability is required for an ANOVA, the data ranges were assumed to represent six times the standard deviation inherent in the data. This is considered to be a rather robust assumption. Conditional on the assumptions reported above, the ANOVA seemed to indicate that the treatment periods reported in the literature were consistent ($P = 0.205$). From the data, an average treatment duration of 17.9 weeks was calculated.

Conclusion

The results reported above indicate consistent evidence of the effectiveness of isotretinoin in the treatment of acne vulgaris. Despite a very conservative methodology, high success rates were calculated (between 84.22% and 86.71%). These were obtained after an average treatment period of 17.9 weeks (4 months), with dosages of isotretinoin ranging from 0.33 to 1 mg/kg/day. Apart from the severity of the acne, the dosage proved to be a critical factor in predicting the need for repeat courses of isotretinoin.[6] For optimal therapy, a cumulative dosage of 120 mg/kg should be achieved,[10] administered at a daily dose level of 1 mg/kg depending on patient tolerance. Relapse rates proved to be relatively low (21.45%), although the rates reported in the literature are highly variable. However, there seems to be agreement that the relapse rate is reduced as the daily isotretinoin dosage approaches 1 mg/kg.[1,7,28]

The results of this meta-analysis are important in the field of pharmaceutical benefit management and should assist the managers of chronic medication plans in the optimal management of acne. The results form the clinical basis for an economic evaluation of the various treatment protocols used for acne. This basis will be used to develop a pharmaco-economic model for moderate to severe acne that is applicable to the South African health care environment.

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