Pharmaco-economic assessment of the HMG-CoA reductase inhibitors

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Objective. To perform a comparative pharmaco-economic assessment of two HMG-CoA reductase inhibitors.

Design. A cost-effectiveness analysis was employed using comparative efficacy data from selected clinical trials. A comprehensive international literature search formed the basis for this selection. Criteria for inclusion of clinical trial results in the analysis were set *a priori*. Acquisition costs used were the recommended reimbursement prices as at September 1994.

Main outcome measures. Two outcome measures are reported: *(i)* the comparative cost-effectiveness in lowering blood lipid concentrations; and *(ii)* the comparative cost-effectiveness of the medicines when used to achieve a predetermined therapeutic goal.

Results. The average cost per 1% decrease in total cholesterol is 21,9% higher on 10 mg pravastatin daily than on 10 mg simvastatin daily. Similarly the average cost per 1% decrease in low-density lipoprotein (LDL) cholesterol is 23,1% higher on 10 mg pravastatin than on 10 mg simvastatin daily. This difference is consistent throughout the dosage range. The use of incremental doses of simvastatin monotherapy in order to reach a predetermined therapeutic goal (LDL $\leq$ 4,14 mmol/l) is more cost-effective than an equivalent pravastatin dosage regimen. Total treatment costs for simvastatin-treated patients are 3,5% less than for pravastatin-treated patients. More patients on simvastatin are successfully treated; the difference in overall treatment costs per successfully treated patient is 27,9% in favour of simvastatin. Sensitivity analysis shows these results to be stable under extreme scenarios.

Conclusions. This analysis employed objective comparative efficacy data obtained from peer-reviewed sources to compare the economic and clinical outcomes of simvastatin and pravastatin in the treatment of hypercholesterolaemia. The acquisition cost of simvastatin is 10,3 - 22,8% higher than an equivalent milligram dose of pravastatin, depending on the dosage used. However, because of the greater milligram potency of simvastatin, it is a more cost-effective alternative. Simvastatin therefore provides better value for money than pravastatin in lowering lipid levels in clinical practice.

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Coronary heart disease (CHD) is one of the major causes of morbidity and mortality in the Western world. Primary hypercholesterolaemia is an established risk factor for CHD and elevated plasma cholesterol levels have been shown to impose a graded and continuous risk for CHD.[1] It has been firmly established that a reduction of total and low-density lipoprotein (LDL) cholesterol concentrations is accompanied by a decrease in the incidence of CHD morbidity and mortality.[1-3]

In the pharmacological treatment of primary hypercholesterolaemia, the HMG-CoA reductase inhibitors are emerging as the preferred pharmacological therapy.[4] The two agents in this class currently available in South Africa are simvastatin and pravastatin.

As a result of variations in efficacy and costs among the lipid-lowering agents, therapeutic decision-making regarding the use of these agents is complex.[5] Pharmaco-economic analysis can assist with the rational selection of therapeutic agents and help to ensure that each health care rand is spent in the most cost-effective manner.

This paper reports on the comparative cost-effectiveness of simvastatin and pravastatin. Two analyses are presented: *(i)* the cost-effectiveness of each drug in lowering blood lipid concentrations; and *(ii)* the cost-effectiveness of each drug when used to achieve a predetermined therapeutic goal.

Method

In order to conduct a reliable cost-effectiveness analysis, accurate data on the acquisition costs and comparative efficacy of the drugs across their accepted dosage range are required.

Data on the acquisition costs of simvastatin and pravastatin were obtained from the South African Pharmaceutical Ethical Price List of September 1994. Retail prices were used in all calculations and the cost of each unit dose strength was utilised, i.e. if a patient were taking a 10 mg dose, it was assumed that one 10 mg tablet was taken and not half a 20 mg tablet. Likewise if a patient were taking a 20 mg dose it was assumed that one 20 mg tablet was taken and not two 10 mg tablets. This is noteworthy as the cost of the 20 mg tablet is not twice that of the 10 mg tablet.

In order to obtain unbiased comparative efficacy data on the two drugs, an extensive search of the Medline database from 1988 to 1993 was conducted. This search was supplemented with data from the Micromedix database and a review of standard reference texts.

Studies identified from the literature search were screened to ensure that: *(i)* the patients were on a lipid-lowering diet prior to initiation of drug therapy; *(ii)* results were reported in a dose-specific way; and *(iii)* efficacy was measured at least 4 weeks after initiation of therapy or change of dose.

From the studies that met these requirements, those which were randomised and compared the two drugs within the same study were selected.

Only the results of the randomised comparative studies were used in the cost-effectiveness analysis. The mean decrease in total and LDL cholesterol produced by each dose of the drugs used in these studies was weighted by the number of patients studied, and the weighted mean was

used in the calculations. The comparative cost-effectiveness of the drugs was calculated by dividing the cost of 1 month's supply of the drug by the average decrease in lipid levels produced by that drug.

In order to assess the comparative cost-effectiveness of the two drugs in achieving a predetermined therapeutic goal, the studies were screened to identify those which reported on treatment regimens after stepwise dosage increments and accepted treatment target levels. The results of these studies were costed out to account for the cost of the drugs, doctor visits and lipograms. The costing assumed that all patients would require an initial consultation and a follow-up consultation 6 weeks thereafter. It was also assumed that a lipogram would be required at both these visits, and that a patient not attaining target cholesterol levels would require a further consultation and lipogram until the target was reached, whereafter annual monitoring would be required. The total treatment costs were then divided by the proportion of successfully treated patients to calculate the cost per successfully treated patient.

A sensitivity analysis of the results was performed using the ranges of efficacy from all the relevant studies.

Results

Comparative costs

The acquisition costs of simvastatin are higher than the costs of an equivalent dose of pravastatin. A daily 10 mg dose of simvastatin costs 22,8% more, and a daily 20 mg dose 10,3% more than the same dose of pravastatin.

Comparative efficacy

Twenty-four clinical studies that met the criteria for inclusion in the study were identified.[4, 6-28] The weighted mean reduction in total and LDL cholesterol obtained from the results of the comparative studies on the 10 mg and 20 mg daily dose are shown in Table I.

Table I. Comparative costs, efficacy and cost-effectiveness of simvastatin versus pravastatin (10 mg and 20 mg daily)

	Simvastatin 10 mg	Pravastatin 10 mg	Simvastatin 20 mg	Pravastatin 20 mg
Costs				
Cost of drug per month	R221,06 (+22,8%)*	R179,96	R332,57 (+10,3%)*	R301,51
Efficacy				
Average decrease in:				
TC	23,2%	15,5%	31,0%	22,0%
LDLC	31,0%	20,5%	40,0%	26,0%
Cost effectiveness				
Cost per 1% decrease in:				
TC	R9,53	R11,61 (+21,9%)*	R10,73	R13,71 (+27,7%)*
LDLC	R7,13	R8,78 (+23,1%)*	R8,31	R11,60 (+39,5%)*

* Percentage difference between the drugs.
TC = total cholesterol; LDLC = low-density lipoprotein cholesterol.

Comparative cost-effectiveness

The comparative cost-effectiveness of equivalent milligram doses of the two drugs are shown in Table I. The results are presented as the comparative cost of lowering total and LDL cholesterol by 1 percentage point. The observed difference was consistent throughout the dosage range of the drugs.

Total treatment costs in clinical practice

The literature search identified one large double-blind, multicentre study[4] of 550 patients which best reflects the appropriate use of these drugs in clinical practice. This study employed dose titration, followed international guidelines on treatment endpoints, studied men and women aged 18 - 71 years and had reasonable entry criteria, including a LDL cholesterol requirement greater than 4,14 mmol/l.

The results of this study were applied to calculate the mean annual costs of treating a patient with incremental doses of simvastatin or pravastatin. These data are shown in Table II.

Table II. Mean annual costs of treating a patient with incremental doses of simvastatin or pravastatin monotherapy to reach a predetermined therapeutic goal (LDL ≤ 4,14 mmol/l)[4]

Resource	Simvastatin	Pravastatin
Drug costs*	R5 367,77	R5 531,58
Lipogram costs†	R205,75	R227,74
Doctor visits‡	R125,61	R139,04
Total direct costs	R5 699,13	R5 898,36 (+3,5%)

*Retail price: Blue Book, September 1994.
†RAMS tariff 1994 (TC, LDL, HDL, TRIG).
‡RAMS tariff 1994 (general practitioner consultation).

Cost per successfully treated patient

The cost per successfully treated patient is shown in Table III. These data reflect the mean annual treatment costs of lowering a given patient's LDL cholesterol to a specified level.

Table III. Annual treatment costs and cost per successfully treated patient of incremental-dose monotherapy with simvastatin or pravastatin[4]

	Simvastatin	Pravastatin
A: Average overall treatment costs per year	R5 699,13	R5 898,36
B: Successfully treated patients (reached an LDL < 4,14 mmol/l)	84%	68%
C: Average cost per successfully treated patient (A ÷ B)	R6 784,68	R8 674,06 (+27,9%)*

*Indicates the pecentage difference between the two drugs.
LDL = low-density lipoprotein.

Discussion

The choice of appropriate and affordable pharmacotherapy inevitably involves the comparison of different drugs within a class.

It is essential to compare not only the cost of the drug, but also the clinical effects produced by that drug. Cheaper does not necessarily mean better value. This is clearly illustrated in this analysis of the HMG-CoA reductase inhibitors.

Cost containment versus cost-effectiveness

The retail price of simvastatin is 10,3 - 22,8% higher than an equivalent milligram dose of pravastatin. However, due to the greater effectiveness of simvastatin, the cost per 1% decrease in cholesterol levels produced by simvastatin is less than for pravastatin.

The average cost of lowering a patient's total and LDL cholesterol by 1%, respectively, is 21,9% and 23,1% higher on 10 mg pravastatin daily than it would be on the same dose of simvastatin. Simvastatin therefore provides better value for money in lowering cholesterol levels.

Cost-containment exercises tend to consider only the cost of a drug and ignore cost-effectiveness or value for money. Such exercises only lead to inefficiencies and greater overall long-term costs.

Drug costs versus total treatment costs

The actual cost of a drug should always be viewed in the context of its effect on the total costs of treating a patient. In this analysis, the more expensive drug (simvastatin) resulted in 3,5% lower overall treatment costs per patient.

The lower overall treatment costs with simvastatin were a result of its greater potency. The greater potency resulted in patients requiring a lower average dose to produce the intended effect which in turn lowered overall drug costs. The greater potency of simvastatin also resulted in more patients reaching their target cholesterol levels sooner, which in turn resulted in lower overall consultation and lipogram costs.

Not only were the overall treatment costs lower on simvastatin, but more patients were successfully treated with this drug. Eighty-four per cent of patients on simvastatin achieved the target of a LDL cholesterol level below 4,14 mmol/l compared with 68% of pravastatin-treated patients. The difference in overall treatment costs per successfully treated patient was 27,9% in favour of simvastatin.

These data clearly show that basing choice of drug on price alone may not only result in higher overall treatment costs, but can also result in poorer clinical outcomes.

Objectivity

Objectivity is essential to any pharmaco-economic assessment. The results depend firmly on the availability of unbiased data on the efficacy of the drugs being compared. An extensive literature search of international databases was therefore performed to ensure the objectivity of the efficacy data. Studies identified from the literature search were only used in the analysis if they met pre-defined criteria for design and protocol requirements.

This analysis used the lowest available input costs for non-drug expenditure. This was done to underestimate any potential differences between the drugs.

The costs of screening for and treating adverse events caused by the drugs and potential differences in patient compliance on these drugs were not included in this assessment as there is no convincing evidence to show that the drugs differ significantly in these respects.[9,29] Perceived differences in the safety profiles of the two drugs are not based on consistent scientific evidence.

A sensitivity analysis was also performed to assess the stability of the results objectively.

Sensitivity analysis

A sensitivity (or 'what if') analysis was performed on the results, using the outer limits of efficacy data obtained from the non-comparative studies identified. The monthly cost range per percentage decrease in total cholesterol produced by simvastatin 10 mg was R9,61 - R10,53 and by simvastatin 20 mg, R11,88 - R12,79. The corresponding costs for pravastatin 10 mg and 20 mg were R10,59 - R13,84 and R12,56 - R17,74, respectively. These data show the results to be relatively stable under an extreme scenario.

As part of the sensitivity analysis, the costs of adding varying doses of cholestyramine to the treatment regimen of patients who have not reached their target cholesterol level were calculated. When it was assumed that all patients had reached the target cholesterol level on cholestyramine, the difference in overall treatment costs between drugs was 18,2 - 26,3% in favour of simvastatin, depending on the cholestyramine doses used.

Relevance of this analysis

Drummond *et al.*[30] have shown that the results obtained from cost-effectiveness analyses of lipid-lowering drugs depend on the unit of outcome measured. Different units of outcome have been proposed[30] and include CHD events avoided, CHD-free life years gained, life years gained and quality-adjusted life years gained. These clinical coronary outcomes have not been taken into account in this analysis as the measurement of these outcomes requires reliable data on CHD treatment costs, non-CHD mortality rates, reduction in CHD risk and/or quality-of-life data, which are not yet readily available in South Africa. We feel that the unit presented in this analysis (cost per percentage reduction in lipid level) is relevant for the practising clinician who is seeking to reduce cholesterol levels. Our analysis is based on objective, verifiable data and does not require sophisticated modelling or the use of ambitious assumptions.

The second analysis presented in this paper is of total treatment costs with incremental dose therapy. This analysis was based on the results of one large clinical study and assumes that treatment is initiated to achieve predetermined, accepted therapeutic goals. This approach is consistent with international guidelines on the treatment of hypercholesterolaemia. The results cannot account for individual differences that may occur in clinical practice. Furthermore the results can only be extrapolated to patients with baseline cholesterol profiles similar to those studied.

Conclusion

This analysis highlights the importance of pharmaco-economic analyses in promoting appropriate decision-making, eliminating inefficiencies and lowering overall health care costs.

Simvastatin, although currently more expensive than pravastatin, is more cost-effective in lowering lipid levels.

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Dokter en digter

Fantasia I: Die aand

Gee my die glorie van sonsondergang
As wolke dik lê aan die Westerkim
Dis goud en purper, pers en diepste rooi
Wat op die hemeltrans word uitgestrooi
Totdat die pragkleur breek, en stilletjies
Versag in teerste blou en karmosyn

Gee my die aandblom met haar heuning-geur
Om langsaam in die duisternis te vaar
En in die wêreld van my drome woon
Die vonkelende lig verdof
Omsluit deur newels wat sy glans verlei
O bleek verboeding van my groot verlange

Al swaarder word die voorbestemde vrag
Waarmee ek struikel deur die duisternis
en met loodswaar voete kruip die nag verby

Kan mens die lig vang na die daglik sterwe?
Met skemering, toe die vinke by die vlei
Die lug deurweef het met hul helder geel
Die weemoed wat met skemer daal
Die lag wat deurbreek deur die traan
Verlig die duister om ons heen.

Die see sy sagte aandgebed laat hoor
Kyk hoe die alwee kand'laars teen die hang
Aan brand gesteek word deur die Westerson!
Met mantels van skarlaken, goud-omsoom
Staan wolke in die weste saamgeskaar:
In die draaikolk van die duisternis
Wat nou die klere uit die weste suig
En soos 'n dief sluip die nag die bulte oor
Om hierdie laaste dromerige ligte
Met sterk swart vingers te vermoor.

Die wonder van die aandblom het eindelik gebeur
In laagtes wat soos wierookblomme oorloop van sy geur
En dit in heuningvlae oor die ganna sprei

'Ekuphumleni'