Successful Conversion of Patients With Hypercholesterolemia From a Brand Name to a Generic Cholesterol-Lowering Drug

T. Craig Cheetham, PharmD; James Chan, PharmD, PhD; Victor Benson, MD; Cathlene Richmond, PharmD; Eleanor Levin, MD; and David Campen, MD

Objective: To evaluate the safety and effectiveness of a simvastatin-to-lovastatin therapeutic conversion program.

Study Design: Observational database study of a therapeutic conversion in members of the Northern and Southern California regions of Kaiser Permanente, using a pretest/posttest design.

Methods: All patients actively converted from simvastatin to lovastatin between April 1, 2002, and March 31, 2003, were identified for inclusion in the analysis. The conversion from simvastatin to lovastatin was based on an equipotent dose ratio of 1 mg of simvastatin to 2 mg of lovastatin. Electronic prescription record and laboratory data were collected for converted patients beginning 365 days before changing therapy through June 30, 2003. The primary effectiveness end point was a comparison of the preconversion and postconversion low-density lipoprotein cholesterol (LDL-C) levels. Safety end points included an analysis of preconversion and postconversion alanine aminotransferase (ALT) tests and creatine kinase values.

Results: A total of 33 318 converted patients met criteria for inclusion in the analysis. The mean LDL-C was lowered from 110.9 to 108.4 mg/dL ($P < .001$) following the conversion to lovastatin. The percentage of patients with serum ALT levels greater than 3 times the upper limit of normal (ULN) was similar before (0.7%) and after (0.6%) conversion from simvastatin to lovastatin. Creatine kinase elevations greater then 10 times the ULN occurred at similar rates before and after the conversion.

Conclusions: Overall, patients had an improvement in their lipid profile without evidence of hepatic or muscle enzyme elevations. Appropriately selected patients can be safely and effectively converted from simvastatin to lovastatin.

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It is well established that the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) reduce the risks of cardiovascular disease. Results from large, randomized clinical trials have established the safety and efficacy of statins with demonstrated reductions in total and coronary heart disease (CHD) mortality, acute coronary syndromes, revascularization procedures, and stroke.[1-8] Currently, the National Cholesterol Education Program's Adult Treatment Panel III (ATP III) recommends statins as first-line agents when drugs that lower low-density lipoprotein cholesterol (LDL-C) are indicated to achieve treatment goals.[9,10]

Selection of a statin(s) for inclusion on a formulary is reasonably made on the basis of comparative efficacy, clinical benefit, safety, and relative cost. In December 2001, generic versions of lovastatin were approved by the Food and Drug Administration. With the availability of a generic formulation, lovastatin became the most cost-effective statin for patients requiring mild to moderate LDL-C reductions within Kaiser Permanente (KP).

As the first statin approved for clinical use, lovastatin has undergone extensive study evaluating safety and efficacy. Dose-ranging studies with lovastatin demonstrated LDL-C reductions of up to 41% with lovastatin 80 mg daily, along with favorable effects on high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) levels.[11-13] Lovastatin has been shown to reduce cardiovascular events in a large primary prevention study.[4] In this study lovastatin was shown to reduce the risk of a first coronary event in men and women with average or mildly elevated LDL-C and TG levels and below-average HDL-C.[4] Angiographic studies have demonstrated beneficial effects of lovastatin with a reduction in the progression of coronary atherosclerosis.[14-17] In 2 of these studies, lovastatin also demonstrated clinical benefit in a secondary-prevention population.[16,17]

At the time generic lovastatin was approved, branded simvastatin (Zocor) was commonly prescribed within KP. Compared with simvastatin, the LDL-C–lowering potency of lovastatin is approximately half on a milligram-to-milligram basis (10-40 mg of simvastatin being approximately equipotent to 20-80 mg of lovastatin).[11-13,18-21] Relative safety appears to be similar when equipotent doses of simvastatin and lovastatin are compared.[22,23]

From the Pharmacy Analytic Service, Kaiser Permanente Southern California, Downey, Calif (TCC); the Pharmacy Outcomes Research Group, Oakland, Calif (JC); the Southern California Permanente Medical Group, Harbor City, Calif (VB); the Drug Information Service, Oakland, Calif (CR); and the Permanente Medical Group, Santa Clara, Calif (EL, DC).

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Address correspondence to: Craig Cheetham, PharmD, MS, Pharmacy Analytic Service, Kaiser Permanente, 9521 Dalen Street, Downey, CA 90242. E-mail:craig.t.cheetham@kp.org.

Based on the evidence of comparable efficacy and safety, a conversion program to switch eligible patients from simvastatin to lovastatin was undertaken in the Northern and Southern California Regions of KP. In this paper, we report our experience in converting a large population of patients from branded simvastatin to generic lovastatin.

METHODS

KP is a large, national, not-for-profit, group-model HMO providing integrated healthcare services to its members. Between April 2002 and March 2003, a campaign was undertaken within KP California to convert patients taking simvastatin to an equipotent dose of lovastatin. The conversion from the formulary branded simvastatin product to generic lovastatin in selected patients (see criteria under "Patients") was deemed appropriate by medical staff committees involved with formulary decisions (regional pharmacy & therapeutics committees), cholesterol management, and specialist committees. Primary care providers were informed when their patients were potential candidates for the conversion. Providers either approved or disapproved the conversion for each patient.

Patients approved for conversion were informed by a letter from the prescribing physician/provider that the conversion was going to occur. Conversion occurred at the pharmacy when the patients came in to pick up their prescription. Patients were counseled by the pharmacist about the conversion and given written materials with their lovastatin prescription. Converted patients also were provided with instructions and a lab slip for a follow-up fasting LDL-C and serum alanine aminotransferase (ALT) test to be performed 6 to 8 weeks after starting lovastatin. This study (evaluating the conversion) was approved by the regional KP institutional review boards in both Northern and Southern California.

Design

The study was designed as a pre-post observational analysis of patients converted from simvastatin to lovastatin. The conversion from simvastatin to lovastatin was based on an equipotent dose ratio of 1 mg of simvastatin to 2 mg of lovastatin (eg, patients receiving simvastatin 10 mg/day were converted to lovastatin 20 mg/day). The patient's healthcare provider had discretion over the conversion dose of lovastatin, including reducing the amount a patient received based on clinical circumstances.

Electronic data were collected on all patients actively converted between April 1, 2002, and March 31, 2003. Patient prescription records for the year before conversion (simvastatin therapy) and the months after conversion (while on lovastatin therapy) were recorded. The daily doses of simvastatin and lovastatin were determined based on the tablet strength and the directions for use. Laboratory data were collected beginning 365 days before the conversion through June 30, 2003, for each patient. This allowed for a minimum of 3 months of follow-up for all patients. Laboratory monitoring consisted of baseline and postconversion lipid results (LDL-C, HDL-C, and TG) and all serum transaminase tests (ALT and aspartate aminotransferase [AST]). Creatine kinase (CK) tests were not required by the conversion protocol, but were captured if ordered by the patient's provider as part of usual care.

If a patient's baseline LDL-C was more than 10% above the identified goals for primary and secondary prevention, <130 mg/dL and <100 mg/dL, respectively, then a dosage adjustment was suggested as part of the conversion. A threshold of 10% above goal was based upon the prevailing opinion within the medical groups in early 2001 that slight elevations in LDL-C (eg, an LDL-C of 103 mg/dL for secondary prevention) did not necessarily warrant a dosage adjustment. Therefore, the thresholds for dose escalation recommendations were 143 mg/dL or greater for primary prevention and 110 mg/dL or greater for secondary prevention. For example, if a primary prevention patient had a baseline LDL-C of 150 mg/dL while taking simvastatin 10 mg/day, the recommended lovastatin conversion dose would be 40 mg/day instead of an equipotent lovastatin dose of 20 mg/day. The maximum lovastatin dose allowed on any conversion was 80 mg/day. If a patient was not at goal on simvastatin 40 mg daily, the recommendation was to adjust the dose to simvastatin 80 mg daily. In response to the postconversion LDL-C values, the decision to adjust a patient's lovastatin dosage was left up to the primary care provider. For purposes of this study we compared the final lovastatin dosage with the preconversion simvastatin dosage.

Patients

All patients age ≥18 years receiving simvastatin at doses up to 40 mg daily were potential candidates for the conversion. To be eligible for the analysis, patients were required to have a baseline and a postconversion LDL-C lab test.

Exclusions from the conversion were based on safety considerations and the presence of potentially interacting drugs. Therefore, patients at increased risk of muscle toxicity were not converted. These included patients with decreased renal function (women with a serum creatinine [SCr] concentration of ≥2.0 mg/dL and men

with a SCr concentration of ≥2.5 mg/dL), patients taking drugs known to interfere with lovastatin metabolism (cyclosporine, macrolide antibiotics, azole antifungals, verapamil, amiodarone, protease inhibitors, and nefazodone), patients currently taking niacin or fibrates, patients with known HIV infection, and patients receiving more than 40 mg of simvastatin per day.

Patients were divided into primary-prevention and secondary-prevention categories. Estimating a patient's 10-year CHD risk was not possible because family history of heart disease, tobacco use, and blood pressure measurements were not available in our electronic databases. Therefore, secondary-prevention patients were defined as those meeting criteria for inclusion into 1 of 2 KP disease management registries at the time of conversion (Diabetes Registry and/or Coronary Artery Disease [CAD] Registry). Inclusion in the Diabetes Registry is based on diagnosis coding (*International Classification of Diseases, Ninth Revision* [*ICD-9*] code 250 - diabetes) and prescription records (oral antidiabetic agents and/or insulin). Inclusion in the CAD Registry is based on diagnosis coding (*ICD-9* codes 410, 411, 412 and 414—ischemic heart disease, 440—atherosclerosis, 443.9—peripheral vascular disease), procedure codes (Current Procedural Terminology 36.0x—percutaneous transluminal coronary angioplasty, 36.1x—coronary artery bypass graft), and prescription records (oral and topical nitrates). Patients not meeting inclusion criteria for 1 of these registries were categorized in the primary-prevention group.

End Points

Conversion effectiveness was determined by comparing baseline and postconversion LDL-C results. Baseline LDL-C tests had to be done within 365 days of the conversion date while the patient was on simvastatin. If a patient had multiple LDL-C tests within the 365-day window, then the lab value closest to the conversion date was used for the analysis. Postconversion LDL-C lab tests needed to be done at a minimum of 4 weeks after the conversion date. For patients with multiple LDL-C tests performed postconversion, the last LDL-C test result on lovastatin therapy was the primary end point used in the analysis. This result reflected any dosage titrations done subsequent to the initial conversion. We also analyzed the first postconversion LDL-C test results.

Although HDL-C and TG laboratory tests were recommended for all converted patients, this was not a requirement for inclusion in the analysis. Baseline and postconversion HDL-C and TG laboratory tests used the same timing criteria established for LDL-C testing.

The primary safety end points were a comparison of ALT and CK elevations postconversion versus preconversion. All ALT and CK tests done within 365 days before the conversion date (baseline) were collected. Postconversion ALT and CK tests were those done at any point after the conversion date through the end of therapy or June 30, 2003. If a patient had multiple ALT or CK tests, then the highest (maximum) test result was used for comparison. Therefore, the maximum result was not necessarily the test done immediately before conversion. CK increases associated with a myocardial infarction were excluded from the safety analysis. For purposes of this analysis, a myocardial infarction was defined as a Troponin I result of ≥0.3 ng/mL, or a combination of a CK-MB percentage of ≥3 plus a total CK-MB of ≥8.1 mg/dL.

Statistical Analysis

Patients served as their own controls with the pre-post design. A chi-square test and McNemar's test were used for categorical outcome variables and frequency results. A paired *t* test and the Wilcoxon signed rank test were used for continuous variables, with a decision based on the distribution of the results (normal vs non-normal distribution). Multivariate logistic regression was used to evaluate patient risk factors associated with elevated CK laboratory results after conversion. Given the large population of patients converted from simvastatin to lovastatin, a 2-sided $P < .01$ was defined as the level necessary to achieve statistical significance.

RESULTS

A total of 33 318 patients met criteria for inclusion in the analysis. Patient demographics are listed in **Table 1.** Patients converted to lovastatin were elderly and predominantly male. Within our population, more women were being treated for primary prevention than for secondary prevention, while the split was more even with male patients. The average duration of lovastatin follow-up was 11 months, and the mean time between conversion and the last LDL-C laboratory test was more than 6 months. On initial conversion, the majority of patients (82.7%) received an equipotent dose of lovastatin, with a small percentage (5.6%) receiving a dose increase. We observed further dosage titration during the follow-up period, and an additional 5.1% of patients had their lovastatin dose increased.

The frequency of follow-up LDL-C testing varied, with 47.9% of patients having only a single test performed and 6.9% having 4 or more tests done. Based on each patient's last or only test result during follow-up (pri-

mary end point), LDL-C decreased by an average of 2.5 mg/dL, HDL-C increased by 2.2 mg/dL, and TG decreased by 1.6 mg/dL following the conversion ($P < .001$, **Table 2**). Results were slightly different when the first postconversion lab tests were analyzed: average LDL-C decreased by 1.8 mg/dL, HDL-C decreased by 1.0 mg/dL, and TG increased by 1.0 mg/dL. Improvements in lipid test results were seen in both primary-prevention and secondary-prevention patients. All lipid changes were highly significant ($P < .001$), except for TG changes in secondary-prevention patients. This level of statistical significance is likely due to the large size of the study population.

When grouped by postconversion dosage adjustment, all 3 groups of patients (dose increase, dose decrease, and equipotent dose) had lower LDL-C values after conversion, although differences were not always statistically significant. In patients who received an equipotent dose of lovastatin, the change in LDL-C was not statistically significant ($P = .78$).

The percentage of patients at target LDL-C values for secondary prevention (<100 mg/dL) changed from 55.7% preconversion to 56.4% postconversion ($P = .12$, not significant). For primary-prevention patients, the percentage of patients at goal postconversion was significantly higher than the percentage at goal preconversion ($P < .001$).

Only 72.6% of the patients who met inclusion criteria had both a baseline and a postconversion ALT measurement done (**Table 3**). An equal number of patients experienced mild elevations in ALT before and after converting to lovastatin. Marked elevations in ALT, greater than 3 times the upper limit of normal (ULN), occurred in 0.7% of the patients before and 0.6% of patients after the conversion. Compared with patients who had normal ALT values at baseline, patients with marked elevations in ALT before converting were more likely to have marked elevations after conversion (**Table 4**).

As CK tests were ordered at the discretion of the primary care providers, the total number of patients with CK tests at baseline and postconversion was different. Of those tested, marked CK increases (>10 ULN) occurred at the same rate before and after the conversion (Table 3). No patient with a marked elevation in CK before conversion experienced a similar increase on lovastatin. Male patients (odds ratio [OR] = 1.8, 95% confidence interval [CI] = 1.1, 3.0) and those with elevated CK results (>500 U/L) before conversion (OR = 16.1, 95% CI = 9.7, 26.3) were more likely to have elevated CK tests (>500 U/L) postconversion. Lovastatin dosage and age were not associated with increased odds of elevated CK test results postconversion.

DISCUSSION

Our results in 33 318 patients support the effectiveness and safety of converting patients from simvastatin to lovastatin. Postconversion lipid, ALT, and CK levels were similar to the preconversion levels. In a comparison of preconversion and postconversion average lipid test results, LDL-C decreased, HDL-C increased, and TG decreased. Rates of ALT and CK elevations were not significantly different before and after the conversion. These data confirm our a priori hypothesis that lovastatin is an effective and safe alternative for managing hypercholesterolemia.

Table 1. Demographic Information

Characteristic	Sex		All Patients
	Female	Male	
n (%)	14 852 (44.6)	18 466 (55.4)	33 318
Mean age, y (± SD)	65.7 (10.7)	64.0 (10.9)	64.8 (10.8)
Indication			
Primary prevention, %	59.4	48.8	53.5
Secondary prevention, %	40.6	51.2	46.5
CAD, %	11.6	22.5	17.7
DM, %	22.6	18.5	20.3
CAD and DM, %	6.4	10.2	8.5
Mean statin dosing			
Last simvastatin, mg (± SD)	25.5 (10.1)	25.7 (10.3)	25.6 (10.2)
Last lovastatin, mg (± SD)	50.7 (21.8)	51.4 (22.0)	51.1 (21.9)
Dose adjustment postconversion			
Dose decrease, %	12.1	10.7	11.3
Equal dose, %	76.9	78.8	77.9
Dose increase, %	11.0	10.5	10.7
Mean number of days			
Lovastatin treatment (± SD)	323 (109)	327 (106)	326 (107)
Between conversion and LDL-C test (± SD)	188 (98)	192 (98)	190 (98)

CAD indicates coronary artery disease; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol.

Table 2. Laboratory Results: Efficacy

Laboratory Test	Results: Baseline Value, mg/dL (± SD)	Results: Last Postconversion Value, mg/dL (± SD)	*P*
Mean LDL-C (n = 33 318)			
By indication			
All patients	110.9 (32.6)	108.4 (28.1)	<.001
Primary prevention	119.4 (33.1)	116.6 (28.2)	<.001
Secondary prevention	101.1 (28.9)	99.0 (24.9)	<.001
By dose adjustment			
Dose decrease	117.1 (45.6)	113.9 (33.9)	.04*
Equal dose	107.9 (29.4)	106.7 (26.9)	.78
Dose increase	125.9 (32.6)	115.1 (28.8)	<.01
Mean HDL-C (n = 33 173)			
All patients	48.5 (13.2)	50.7 (13.6)	<.001
Primary prevention	50.9 (13.4)	52.9 (13.8)	<.001
Secondary prevention	45.7 (12.4)	48.1 (12.9)	<.001
Mean TG (n = 32 116)			
All patients	171.1 (94.7)	169.5 (91.8)	<.001
Primary prevention	171.5 (91.1)	169.7 (89.5)	<.001
Secondary prevention	170.7 (98.8)	169.4 (94.4)	.05*

HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.
*Not significant based on a priori definition of significance (*P* <.01).

Table 3. Laboratory Results: Safety

Laboratory Test	% Patients: Baseline	% Patients: Postconversion
No. of Patients with ALT values	24 194	24 194
Normal (0-40 U/L)	84.9	86.5
Mild (41-120 U/L)	14.4	12.9
Marked (≥121 U/L)	0.7	0.6
No. of patients with CK values*	9771	7859
Normal (0-190 U/L)	82.8	81.1
Mild (191-500 U/L)	14.7	16.6
Moderate (501-2000 U/L)	2.3	2.2
Marked (≥2001 U/L)	0.2	0.2

ALT indicates alanine transaminase; CK, creatine kinase.
*The baseline and postconversion numbers are different because CK was not mandated by the conversion protocol; rather, it was ordered by the provider as part of clinical care.

Our results are consistent with previous statin conversion studies.[24-27] Three of these studies included relatively small numbers of patients (approximately 100) in their analysis.[24-26] The investigators in these studies found no difference in the preconversion and postconversion lipid levels and concluded that the conversion was safe and effective. Safety and effectiveness, however, are difficult to assess with sample sizes of only 100 patients. Ito et al conducted a large study involving 1032 Veterans Administration patients who completed a conversion from pravastatin to simvastatin.[27] Individual simvastatin doses were titrated to achieve predefined LDL-C results. In this study, LDL-C improved from 116 mg/dL to 99 mg/dL, and the percentage of patients at goal improved from 44% to 69% postconversion. Liver function tests and CK results were similar at baseline and postconversion. The authors concluded that conversion was effective and cost saving.

One strength of our study is the large population of patients we were able to observe. This is important when evaluating both the effectiveness and the safety of a therapeutic conversion. In particular, our large sample provided the power necessary to evaluate rates of hepatic and muscle enzyme elevations associated with these 2 statins. Increases in ALT greater than 3 times the ULN and increases of CK greater than 10 times the ULN occurred at similar rates with simvastatin and lovastatin.

Our rate of marked hepatic enzyme elevation was comparatively low (0.6-0.7%).[28] A possible explanation for the low rate observed in our population was that patients were being successfully treated with simvastatin and were therefore self-selected. Patients intolerant to simvastatin and not taking the drug were not involved in the conversion. We also specifically excluded certain populations who were potentially at higher risk for toxicity based on coexisting conditions and potentially interacting drugs.

There was no difference in the rate of increased CK values between simvastatin (preconversion) and lovastatin (postconversion). However, the rate of marked CK elevations was higher in our population than is usually reported in the literature.[29] An explanation for the higher rates in our study is that our rates reflect only

those patients who had CK tests ordered; most of the published incidence rates report CK elevations as a percentage of the total number of patients on statin prescriptions.

The slightly improved lipid results we observed at equipotent doses may reflect external patient factors associated with the conversion. Patients may have become more compliant with their new regimen due to increased contact with providers. Patients also knew that laboratory follow-up was a necessary part of the conversion, and the fact that outreach efforts were made to those patients who failed to get laboratory tests done could also have affected the results.

Table 4. Alanine Transaminase Cross-tabulations

		Maximum ALT Before Conversion			
		Normal (0-40 U/L)	Mild Increase (41-120 U/L)	Marked Increase (≥121 U/L)	Total
Maximum ALT After Conversion	Normal (0-40 U/L)	19 067 (92.8%)	1763 (50.6%)	90 (53.9%)	20 920
	Mild Increase (41-120 U/L)	1391 (6.8%)	1681 (48.3%)	56 (33.5%)	3128
	Marked Increase (≥121 U/L)	87 (0.4%)	38 (1.1%)	21 (12.6%)	146
	Total	20 545	3482	167	24 194

ALT indicates alanine transaminase.

A limitation of this study is that it relied on electronic data capture and did not include direct patient contact or chart reviews by the investigators. This can lead to misclassification errors, especially when separating patients into primary-prevention and secondary-prevention categories based on registry data, or when evaluating postconversion dose-adjustment groupings. One anomalous finding was that patients with effective postconversion dosage reductions also achieved lower postconversion LDL-C values. Information not captured electronically but available to the provider may explain these results. For example, providers may have decided to reduce the dose based on clinical circumstances outside of LDL-C results and CK or ALT values.

Another limitation to this study is that clinical outcomes were not measured; lipid laboratory results were used as surrogate effectiveness markers and the primary end point for this analysis. The follow-up period also was short and variable, ranging from 3 to 15 months. Therefore, we were unable to assess patients' persistence (long-term adherence) with their new lovastatin regimen.

The relative cost of statins within managed care organizations is highly dependent on contracting, such that a cost analysis would have limited generalizability. Although generic lovastatin is the most cost-effective statin for mild to moderate LDL-C reductions within KP, this may not be the case in other organizations or outside of the managed care environment. From the patient's perspective, the availability of a generic statin may still be an advantage, especially for patients with tiered or generic-only drug coverage plans.

The results of our study revealed that just 56.4% and 72.2% of patients had reached the identified LDL-C goals of <100 and <130 mg/dL in the secondary-prevention and primary-prevention groups, respectively. Although this did represent an increase from preconversion values, significant opportunity for improvement remains. Although the original conversion program actively recommended consideration of dosage adjustment in patients with baseline LDL-C values at 10% above goal, it was not designed with an aggressive titration feature. Ongoing conversion programs now recommend a dosage or medication adjustment in patients whenever the baseline LDL-C value is greater than goal.

CONCLUSION

This study of more than 33 000 patients demonstrates that appropriately selected patients can be safely and effectively converted from branded simvastatin (Zocor) to generic lovastatin.

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