Clinical Pharmacology

Is it Cost-Effective to Change Brand-Name to Generic Simvastatin in Taiwan?

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Background: The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) have been well established to reduce the risk of cardiovascular diseases. Due to the increasingly high medical expenses in Taiwan, the government has tried several measures to combat this problem. One of the strategies is to promote the utilization of generic drug products. The purpose of this study was to clarify the lipid-lowering effect and cost-effectiveness during conversion of the brand-name simvastatin product (Zocor®) to its generic simvastatin product (Zolotin®) in Taiwanese patients.

Method: Electronic data in E-Da Hospital were collected from all patients actively converted from Zocor (20 mg/tablet, Merck Sharp & Dohme Pty. Ltd., Australia) to Zolotin® (20 mg/tablet, Genelabs Biotechnology Co., Ltd., Taiwan) between January 31, 2005, and July 31, 2006. The dosage of simvastatin remained the same when the Zocor® was converted to Zolotin®. The primary effectiveness end point was to compare the preconversion and postconversion low-density lipoprotein cholesterol (LDL-C) levels. The annual price per reduction of 1% of LDL-C with Zocor® and Zolotin® was also compared.

Result: A total of 83 patients were enrolled in this study. No significant difference was found in the LDL-C level before and after the conversion. The mean LDL-C- lowering efficacies with Zocor® and Zolotin® were -34.7 ± 15.7% and -36.3 ± 17.7%, respectively (P = NS). However, the HDL-C level after treatment was significantly higher with Zocor® (52.8 ± 12.0 mg/dL vs. 49.8 ± 11.9 mg/dL, P = 0.0045). There was no patient in this study with elevated transaminase > 3x upper limit of normal (ULN) value or CK > 10x ULN value under both statin treatments. The average annual cost for reduction of 1% of LDL-C with Zocor® and Zolotin® were 541.0 ± 910.0 New Taiwan dollar (TWD) and 557.0 ± 626.6 TWD, respectively (P = NS).

Conclusion: There was no significant difference of the LDL-C lowering efficacy after converting the brand-name simvastatin to the generic product in Taiwan. This study also implicated that it might not be more cost-effective to convert brand-name simvastatin to the generic product in Taiwan if the price of generic drug was not lowered significantly.

Key Words: Brand • Conversion • Cost-effective • Generic • Simvastatin

Received: February 25, 2008 Accepted: July 29, 2008

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INTRODUCTION

Dyslipidemia is highly prevalent in the developed countries worldwide. Many epidemiological studies have shown a clear link between dyslipidemia and increased risk of coronary heart disease (CHD).[1-3] The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) have been well established to reduce the risk of cardiovascular diseases. Results

from large, randomized clinical trials have established the safety and efficacy of statins, with demonstrated reductions in total and CHD mortality, acute coronary syndrome, revascularization procedure, and stroke.[4-7] Currently, the National Cholesterol Education Program's (NCEP) Adult Treatment Panel III (ATP III) recommends statins as the first-line agent to lower low-density lipoprotein cholesterol (LDL-C).[8,9]

Pharmaceutical expenditure (PE) of the Bureau of National Health Insurance (BNHI) program in Taiwan grew from 62.2 billion New Taiwan dollars (TWD) in 1996 to 94.5 billion TWD in 2003.[10] The government has been introducing many strategies to control PE since the inception of NHI, including price adjustment based on the prices of international products or existing products (inter-brands comparison), or market price and volume survey, delegation of financial responsibility to regional bureaus, co-payment for outpatient drugs, generic grouping (reference pricing scheme based on chemical equivalence), a global budget payment system for clinics and hospitals, and reduction in the flat daily payment rate of the drugs for clinics. One of these strategies is to promote the utilization of generic drug products, especially those contained in the National Insurance Drug List. Simvastatin, an HMG-CoA reductase inhibitor, has been listed as an essential drug for the treatment of dyslipidemia.

In the United States and Taiwan, generic products are usually determined to be the therapeutically equivalent by the Food and Drug Administration (FDA) in United States or Bureau of Pharmaceutical Affairs (BPA) in Taiwan, on the basis of pharmacokinetic (PK) measurements, rather than the use of clinical trials in patients or pharmacodynamic studies.[11,12] The manufacturer of a generic drug does not have to prove the clinical therapeutic equivalence, which would require further efficacy and safety studies; the drug must simply pass the test of bioequivalence. However, bioequivalence and clinical therapeutic effectiveness are not necessarily the same.[13]

Here, we reported the lipid-lowering efficacy during conversion of the brand-name simvastatin Zocor® (20 mg/tablet, Merck Sharp & Dohme Pty. Ltd., Australia) to its generic simvastatin product Zolotin® (20 mg/tablet, Genelabs Biotechnology Co., Ltd., Taiwan) in 83 Taiwanese subjects. We also compared the annual cost for reduction of 1% of LDL-C before and after the change of Zocor® to Zolotin® to evaluate the cost-effectiveness of this conversion.

METHODS

The study was designed as a retrospective study. Electronic data in E-Da Hospital were collected from all patients with statin treatment converted from Zocor® to Zolotin® between January 31, 2005, and July 31, 2006. Patient prescription records from one year before to and three months after this conversion were recorded. Laboratory monitoring consisted of baseline and post-treatment lipid levels [total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG)]. Serum alanine aminotransferase (ALT) and creatine kinase (CK) were recorded if ordered by the in-charge physician. The annual costs per reduction of 1% of LDL-C with Zocor® and Zolotin® were also calculated. The price of each drug referred to that registered by the Taiwanese BNHI in year of 2006.

Patients

All patients aged more than 18 years receiving Zocor® with doses 10 mg to 40 mg daily were potential candidates for the conversion. Inclusion criteria for this study were the patients having received Zocor® prescription for at least 3 consecutive months before conversion. After Zocor® was replaced by Zolotin® in E-Da Hospital because of economical consideration, the patient should have Zolotin® prescription with the same dosage for another 3 consecutive months, with at least 1 measurement of lipid profile after that.

Exclusion criteria included the following conditions: (1) no LDL-C level available within 3 months before the conversion; (2) the diagnosis of familial hypercholesterolemia or hypertriglyceridemia with TG > 500 mg/dL; (3) coexistence of hypothyroidism, renal insufficiency (creatinine > 3 mg/dL), liver cirrhosis or acute obstructive liver disease; (4) combination therapy with other lipid-lowering agents (ex. gemfibrozil, fenofibrate, acipimox, ezetimibe, cholestyramine, etc. or glitazone).

The patients were further divided into primary-prevention and secondary-prevention categories. Secondary-prevention patients were defined as those meeting

the criteria for diabetes mellitus or atherosclerotic vascular diseases at the time of conversion. Diabetes registry was based on the diagnosis coding (*International Classification of Diseases, Ninth Revision* [*ICD-9*] code 250 for diabetes) and prescription records (oral hypoglycemic agents and/or insulin). Atherosclerotic vascular diseases registry was based on the diagnosis coding (*ICD-9* codes 410, 411, 412 and 414 for ischemic heart disease, codes 433-438 for stroke, code 440 for atherosclerosis, code 443.9 for peripheral vascular disease), procedure codes (Current Procedural Terminology 36.0x for percutaneous transluminal coronary angioplasty, 36.1x for coronary artery bypass graft), and prescription records (oral and topical nitrates). Patients not meeting the criteria for any one of the above registries were categorized in the primary-prevention group.

Endpoint

The endpoint of this study was to determine the cost-effectiveness of converting Zocor® to Zolotin® by comparing the LDL-lowering efficacy and cost before and after the conversion. The therapeutic effectiveness was examined by comparing the baseline and post-treatment lipid levels. The pre-conversion LDL-C level had to be measured within 90 days before the conversion date while the patient was on Zocor®. If a patient had multiple LDL-C measurements within the 90-day period, the data closest to the conversion date was used for the analysis. Post-conversion LDL-C level needed to be checked at a minimum of 12 weeks after the conversion date. For patients with multiple LDL-C tests performed after the conversion, the last LDL-C test result on Zolotin® therapy was used for the analysis. Although T-C, HDL-C and TG laboratory tests were recommended for all converted patients, this was not a requirement for inclusion in the analysis. Baseline and post-treatment T-C, HDL-C and TG levels were chosen with the same timing criteria used for LDL-C.

The safety study was to compare whether there was any difference of the level of serum ALT and CK before and after the conversion to document the occurrence of hepatotoxicity or myopathy. All ALT and CK tests done within 90 days before the conversion date (baseline) were collected. Post-conversion ALT and CK tests were those done at any point after the conversion date. If a patient had multiple ALT or CK tests, the highest level was used for comparison.

Statistical analysis

Patients served as their own controls in the conversion design. Paired *t* test was used for lipid profile levels and cost analysis. A P value less than 0.05 was defined as the level necessary to achieve statistical significance.

RESULTS

A total of 106 patients were enrolled according to the inclusion criteria, and 23 of them were with no baseline LDL-C level available. Therefore, a total of 83 patients were included in the final analysis. The demographic data are listed in Table 1. The patients had a

Table 1. Demographic data

	Male		Female		Total (n = 83)	
Age (years) Mean ± SD	59.3 ± 12.1		61.6 ± 11.9		60.5 ± 12.1	
Number (%)	40	(48.2)	43	(51.8)	83	(100)
Indication (n, %)						
Primary prevention	18	(21.7)	19	(22.9)	37	(44.6)
Secondary prevention	22	(26.5)	24	(28.9)	46	(55.4)
Department (n, %)						
Cardiology	27	(32.5)	31	(37.4)	58	(69.9)
Neurology	8	(9.6)	7	(8.5)	15	(18.1)
Metabolism	5	(6.0)	5	(6.0)	10	(12.0)
Simvastatin daily dosage (n, %)						
10 mg	7	(8.4)	5	(6.0)	12	(14.4)
20 mg	28	(33.7)	37	(44.6)	65	(78.3)
40 mg	5	(6.0)	1	(1.3)	6	(7.3)

mean age of 60.5 ± 12.1 years, and 48% were men. Within this population, more patients were treated for secondary prevention (55%) than those for primary prevention (45%). About 70% of the patients were followed up at the cardiovascular department; the remaining patients were followed at the neurological and metabolic departments. The percentages of the patients under daily dosage of 10 mg, 20 mg and 40 mg of simvastatin were 15%, 78% and 7%, respectively.

The baseline LDL-C level before starting statin prescription was 165.9 ± 35.5 mg/dL, while the LDL-C levels under the treatment of Zocor® and Zolotin® were 106.4 ± 27.2 mg/dL and 104.2 ± 32.4 mg/dL (P = NS), respectively, as shown in Table 2. The HDL level after treatment was significantly higher with Zocor® (52.8 ± 12.0 mg/dL vs. 49.8 ± 11.9 mg/dL, P = 0.0045). There was no significant statistical difference in the TG levels under treatment with Zocor® or Zolotin®, however, the TC level was borderline lower with Zolotin® treatment (Zocor®: 190.3 ± 39.6 mg/dL vs. Zolotin®: 180.7 ± 43.6 mg/dL, P = 0.0318), as shown in Table 2. There was no significant difference in the LDL-C-lowering efficacy with Zocor® or Zolotin® (-34.7 ± 15.7% vs. -36.3 ± 17.7%, P = 0.NS, Table 2). However, Zocor® had stronger HDL-C-raising efficacy than Zolotin® (9.9 ± 24.5% vs. 2.9 ± 19.1%, P = 0.0013)

The annual expenses for reduction of 1% of LDL-C with Zocor® and Zolotin® were TWD 541.0 ± 910.0 and TWD 557.0 ± 626.6, respectively in year 2006 (P = NS). However, after the adjustment of BNHI price in September of 2007, the annual expenses became TWD 541.0 ± 910.0 and TWD 468.7 ± 527.2, respectively (P = NS) as shown in Table 3.

There were 47 subjects (56.6%) in Zocor® group

Table 2. Comparison of lipid profile before and after Zocor® and Zolotin® treatment

	Baseline	After statin prescription		Level of lipid level changed from baseline		
		Zocor®	Zolotin®	Zocor®	Zolotin®	*P* value*
		mg/dL ± SD			mg/dL ± SD (% ± SD)	
LDL-C (n = 83)	165.9 ± 35.5	106.4 ± 27.2	104.2 ± 32.4	-59.5 ± 31.3 (-34.7 ± 15.7)	-61.7 ± 33.9 (-36.3 ± 17.7)	0.448
HDL-C (n = 63)	49.1 ± 11.1	52.8 ± 12.0	49.8 ± 11.9	3.7 ± 10.2 (9.9 ± 24.5)	0.7 ± 8.3 (2.9 ± 19.1)	0.0046
TC (n = 74)	249.6 ± 51.2	190.3 ± 39.6	180.7 ± 43.6	-59.3 ± 43.9 (-22.5 ± 14.7)	-68.9 ± 43.9 (-26.8 ± 15.0)	0.0318
TG (n = 73)	168.5 ± 103.2	153.2 ± 104.1	145.3 ± 89.8	-14.9 ± 112.7 (-0.8 ± 62.0)	-25.9 ± 106.3 (-6.9 ± 48.4)	0.3598

*Paired *t* test: comparison of LDL-C, HDL-C, TC and TG levels with baseline level after treatment with Zocor® and Zolotin®

Table 3. Comparison of annual price for lowering LDL-C with Zocor® and Zolotin®

	Zocor®	Zolotin®	*P* value*
Unit price of Zocor® and Zolotin®			
2006- BNHI price (20 mg)	36.8	37.2	
2007- BNHI price (20 mg)	36.8	31.3	
Price for lowering LDL-C (n = 83)		(TWD/year)	
†2006 Price for lowering 1 mg/dL LDL-C	366.1 ± 683.3	381.45 ± 507.4	0.8679
†2006 Price for lowering 1% of LDL-C	541.0 ± 910.0	557.0 ± 626.6	0.9019
‡2007 Price for lowering 1 mg/dL LDL-C	366.1.6 ± 683.3	321.0 ± 427.0	0.6057
‡2007 Price for lowering 1% of LDL-C	541.1 ± 910.0	468.7 ± 527.2	0.5568

*Paired *t* test: comparison of lipid profile change from baseline and price for lowering LDL-C with Zocor® and Zolotin®
†BNHI price Zocor® TWD 18.4 (10 mg/tab); TWD 36.8 (20 mg/tab); TWD 73.6 (40 mg/tab)
Zolotin® TWD 18.6 (10 mg/tab); TWD 37.2 (20 mg/tab); TWD 74.4 (40 mg/tab)
‡BNHI price Zocor® TWD 18.4 (10 mg/tab); TWD 36.8 (20 mg/tab); TWD 73.6 (40 mg/tab)
Zolotin® TWD 15.65 (10 mg/tab); TWD 31.3 (20 mg/tab); TWD 62.6 (40 mg/tab)
Reference: †BNHI http://www.nhi.gov.tw/inquire/query1.asp?menu=3&menu_id=58 (since 1st Nov., 2006)
‡BNHI http://www.nhi.gov.tw/inquire/query1.asp?menu=3&menu_id=58 (since 1st Sept., 2007)

and 53 subjects (63.9%) in Zolotin® group with ALT level follow-up. CK level was examined only in 6 subjects (7.2%) and 20 subjects (24.1%) receiving Zocor® and Zolotin® treatment, respectively. There was no patient in this study with elevated ALT > 3x upper limit of normal (ULN) value or CK > 10x ULN value under Zocor or Zolotin® treatment, as listed in Table 4.

DISCUSSION

The rationalization of health care expenditures is a high priority for the governments in many developed countries, and the introduction onto the market of generic drugs produces notable savings. To help alleviate the rising cost of imported drugs, many countries promote the usage of locally made generic products. However, most of the generic drugs were approved with only a small sample size of pharmacokinetic test at present. The actual clinical efficacy and safety have not been examined completely. The policy of many local hospitals and even medical centers in Taiwan tends to replace more and more brand-name drugs with generic products for the purpose of lowering financial budget. The clinical efficacy and safety of these generic drugs are usually monitored only by the in-charge clinical physicians. Our study offered a simple model to collect the data after conversion and to test the efficacy, safety and cost-effectiveness with larger samples but limited resources.

From the point of lowering LDL-C, our results supported the similar efficacy and safety for replacing the brand-name simvastatin (Zocor®) with a generic simvastatin product (Zolotin®) for Taiwanese as there was no significant difference in the LDL-C lowering effect before and after the conversion. The TC level was borderline lower when the patients took the generic drug. There was no patient in this study with elevated transaminase > 3x upper limit of normal (ULN) value or CK > 10x ULN value under both statins treatments. Both of them are quite safe for lowering LDL-C with dosage up to 40 mg/day.

Table 4. Comparison of safety under Zocor® and Zolotin® treatment

	Zocor®	Zolotin®
	Patient no. (%)	
ALT value	n = 47	n = 54
Normal (0-44 U/L)	41 (87.2)	39 (72.2)
Elevated (45-132 U/L)	6 (12.8)	15 (27.8)
> 3x elevated (> 132 U/L)	0 (0)	0 (0)
CK value	n = 6	n = 20
Normal (38-160 U/L)	5 (83.3)	15 (75.0)
Elevated (161-480 U/L)	1 (16.7)	5 (25.0)
> 3x elevated (> 480 U/L)	0 (0)	0 (0)

ALT: alanine transaminase; CK: creatine kinase.

However, there was a statistically significant stronger HDL-C-raising effect noted with the brand-name Zocor®. There were several possible explanations for this finding. The first one, of course, is selection bias. The second one may be due to the difference in the patients' diet or lifestyle during these two treatment periods. The Zolotin® was always given after the Zocor® prescription, and there may be some change of the patients' behavior. However, this is one of the limitations of the study, because we did not record the patients' lifestyle or diet during the treatment. The third one may be due to a real significant difference of pharmacokinetic effect on the HDL-C metabolism existing in these 83 Taiwanese patients, which was not found during the relatively small preclinical PK study. Statins induce an increase in Apo A-I production of approximately 15%, primarily in the liver. In addition, as a result of an increase in the expression of LDL receptors, there is a dramatic reduction (up to approximately 50%) in the numbers of potentially atherogenic acceptors of cholesterol ester (CE) via the CE transfer protein (CETP) mechanism from HDL.[15,16] Clearly, the statin effects on the HDL-C metabolism are independently from the LDL-C-lowering mechanism. It was possible that although Zolotin® had similar LDL-C-lowering effect as Zocor®, there was significant difference in the PK effect on HDL-C metabolism between Zolotin® and Zocor®. The borderline difference of TC-lowering effect between Zolotin® and Zocor® in this study might be also explained by this significantly different HDL-C-raising effect.

Interestingly, although statistically insignificant, the annual expense for reduction of 1% of LDL-C with Zolotin® had a trend to be even higher than that for Zocor® (Zocor®: TWD 541 ± 910.0 vs. Zolotin®: TWD 557 ± 626.6) according to the unit price of BHI for year 2006 (Table 3). This indicated that the expense was not reduced after replacement with the generic drug. In fact,

it seemed to even have a trend toward increasing the expense after the conversion. Higher unit price of the generic Zolotin® in the Taiwan BNHI list might be the major reason. The Taiwan BNHI usually sets the price for the generic drug as 80-90% of that of the market price for the existing brand-name drug. Periodically, the drug price will be adjusted according to the average market price in the previous year. Because there was small market share of Zolotin®in 2005, its unit price was even a little higher than that of Zocor® in 2006. However, in 2006, Zolotin® had more market share in Taiwan and its average market price went down. Its BNHI unit price was adjusted lower accordingly and became cheaper than that of Zocor® in 2007. Therefore, after the adjustment of BNHI price in 2007, the calculated annual expense for reduction of 1% of LDL-C became TWD 468.7 ± 527.2 for Zolotin®. Although it had a trend to be lower than that for Zocor®, it was still statistically insignificant, not as we expected for using generic drugs (Table 3). There should be a big space for the price adjustment after the drug has been out-of-patent if our community really intends to combat the higher medical expences.

There were several limitations of this study. First, we did not record the patients' lifestyle, diet or drug compliance during the treatment because this study was designed as a retrospective registration. However, the data could reflect the real condition of daily clinical practice in Taiwan. Second, there was no wash out period between the conversions. Third, there was no marked hepatic or muscular enzyme elevation in both groups. A possible explanation for the low rate observed in this population was that patients were being successfully treated with brand-name Zocor® and were therefore self-selected. The small sample size of the enzyme examination might be another reason to explain the low adverse event rate. Fourth, the clinical outcomes were not measured and only the lipid laboratory results were used as surrogate efficacy markers for the analysis. Fifth, the timing of measuring lipid profile was not well defined, with an interval ranging from 3 months to 6 months; this might be a potential bias when comparing the lipid-lowering efficacy before and after the conversions. Further large-scaled prospective study with cross over and randomization design may be needed to test the real cost-effectiveness of the generic drug.

CONCLUSION

There was no significant difference of the LDL-C-lowering efficacy after converting the brand-name simvastatin to the generic product in Taiwan. This study also implicated that it might not be more cost-effective to convert brand-name simvastatin to the generic product in Taiwan if the price of generic drug was not lowered significantly. There should be a big space for price adjustment for the generic drug if our community really intends to combat the higher medical expenses. In addition, this study also provided a simple and available model for testing efficacy, safety and cost-effectiveness recarding the conversion from brand-name product to generic product in clinical practice and medical economics in Taiwan.

ACKNOWLEDGEMENT

This study was supported by a research grant from Wan-Lin Pharmosa., Ltd., Taiwan.

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