—Regular Articles—

Pharmacoeconomic Analysis of Hypertriglyceridemia Treatment at the Medical Institutions

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It has been demonstrated that HMG-CoA reductase inhibitors effectively decrease low density lipoprotein and total cholesterol levels, and presently, HMG-CoA reductase inhibitors are most widely used in hyperlipidemia treatment. On the other hand, it has been demonstrated that fibrate agents decrease triglyceride levels more effectively compared to HMG-CoA reductase inhibitors. A cost-effectiveness study comparing fenofibrate, a fibrate agent, and atorvastatin was therefore conducted in hypertriglyceridemia patients. Referring to an analytical method published in the UK, the percentage of patients received fenofibrate and atorvastatin treatments at each dose level was estimated from prescription records at the medical institutions investigated. Changes in the total cholesterol and triglyceride values after the drug administration were investigated examining published reports. Based on the said data, the treatment effectiveness was measured by the percentage of patients who achieved the target lipid levels. The treatment costs were estimated based on the number of patients investigated and reimbursement prices of the drugs. The incremental cost-effectiveness ratio of fenofibrate in decreasing triglyceride levels was dominant over atorvastatin. The incremental cost-effectiveness ratio of atorvastatin in decreasing low density lipoprotein cholesterol levels was JPY 69911. This provides a model for choosing drug treatments that reflects clinical practices at medical institutions by substituting figures for individual cases.

Key words——hypertriglyceridemia; fibrate; pharmacoeconomic; cost-effectiveness; HMG-CoA reductase; prescription record at the medical institution

INTRODUCTION

The interest level in choosing drug treatments from an economic perspective had been low in healthcare professionals and patients. This was largely attributable to a retrospective payment, or so-called ''fee for service'', system under the nation's health insurance scheme and low patient copayment. Nevertheless, cost containment measures were put forward also in Japan following other developed countries, and a prospective, or fixed-fee, payment system, including the Diagnosis Procedure Combination (DPC), is being introduced in medical institutions. There is a growing awareness of the need for healthcare professionals to increase their economic interest and provide healthcare services and medical treatment in consideration of cost effectiveness.[1)]

Arteriosclerotic diseases are considered to lead life-threatening disorders or conditions that significantly decrease patient quality of life (QOL), and many studies suggested the importance of preventing arteriosclerotic diseases.[2)] Prevention of arteriosclerosis to avoid coronary artery diseases is one such preventative measure, and the 2002 Japan Atherosclerosis Society Guidelines for Diagnosis and Treatment of Atherosclerotic Cardiovascular Diseases specify reference cholesterol levels for arteriosclerotic disease diagnosis and treatment.[2)]

It has been demonstrated that HMG-CoA reductase inhibitors (statins) effectively decrease LDL cholesterol (LDL-C) and total cholesterol (TC) levels,[3–9)] and presently, statins are most widely used in hypercholesterolemia treatment. On the other hand, it has been demonstrated that fibrate agents decrease triglyceride (TG) levels more effectively compared to statins.[10,11)] We therefore looked into determinants in choosing between statins and fenofibrate in hypertriglyceridemia treatment by taking the cost into consideration.

Among many pharmacoeconomic studies of hypercholesterolemia treatment, K. Wilson *et al.* made an analysis[12)] in which the number of patients who achieved target LDL-C and TC levels was set as the treatment outcome. According to their analytical

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method, we previously conducted a cost-effectiveness study comparing the average reduction rate and standard deviation of LDL-C and TC values in statin treatments, at each dose level, in practical use (prescribed) at medical institutions. The study demonstrated that atorvastatin was most cost-effective among pravastatin, simvastatin, fluvastatin and atorvastatin.[13] Using the same method, a comparison was made in reduction of TG and LDL-C levels.

MATERIALS AND METHODS

This is a virtual cohort study conducted in 1000 patients referring to an analytical method published in the UK.[12] The analysis was made from a payers' perspective. To measure the cost effectiveness, annual treatment costs were estimated on the premise that the patients continued the drug therapy irrespective of whether or not they achieved the treatment target. In the calculation, the reduction rate measured during the clinical study for response evaluation was used (that at 8 weeks for fenofibrate treated patients and at 12 weeks for atorvastatin treated patients).

Effectiveness In this analysis, the cost effectiveness of each drug treatment was measured through roughly four steps.

Step 1: The clinical effectiveness varies depending on the baseline TG and cholesterol levels before treatment. To specify the baseline TG and cholesterol level distribution in the patients subject to treatment, baseline TG and cholesterol levels were investigated in the patients who started and were receiving pravastatin or atorvastatin treatment in the period between April 2003 and March 2005 (continuously received statin treatment for at least about 100 days) at Surugadai Nihon University Hospital. The virtual cohort distribution of TG values was then stratified by every 20 mg/dl and that of LDL-C values by 10 mg/dl (Table 1).

Patients with a LDL-C value of 140 mg/dl or above and TG value of 150 mg/dl or above were selected as patients subject to treatment.

Step 2: The reduction rates of TG and LDL-C values in fenofibrate or atorvastatin treatments at each dose level were estimated based on the reports of dose finding studies[9–11] (Table 2).

Step 3: The reduction rate of TG and LDL-C values required to achieve the treatment target were calculated according to the following formula (Table 3).

Table 1. Patient Distribution Based on Baseline Sholesterol Levels

TG

TG level (mg/dl)	160	180	200	220	240	260	280	300	320
Actual no. of patients (n=83)	18	9	8	6	7	5	4	5	2
No. of patients per 1,000	217	108	96	72	84	60	48	60	24
Cumulative % of pts. from lowest TG level	21.7%	32.5%	42.2%	49.4%	57.8%	63.9%	68.7%	74.7%	77.1%

TG level (mg/dl)	340	360	380	400	420	440	460	480	>500
Actual no. of patients (n=83)	4	2	4	3	1	1	0	1	3
No. of patients per 1,000	48	24	48	36	12	12	0	12	36
Cumulative % of pts. from lowest TG level	81.9%	84.3%	89.2%	92.8%	94.0%	95.2%	95.2%	96.4%	100.0%

Target LDL-C level 140 mg/dl

LDL-C level (mg/dl)	140	150	160	170	180	190	200
Actual no. of patients (n=90)	12	9	20	18	13	8	4
No. of patients per 1,000	133	100	222	200	144	89	44
Cumulative % of pts. from lowest LDL-C level	13.3%	23.3%	45.6%	65.6%	80.0%	88.9%	93.3%

LDL-C level (mg/dl)	210	220	230	240	250	>260
Actual no. of patients (n=90)	4	0	0	1	0	1
No. of patients per 1,000	44	0	0	11	0	11
Cumulative % of pts. from lowest LDL-C level	97.8%	97.8%	97.8%	98.9%	98.9%	100.0%

TG: triglyceride, LDL-C: LDL-cholesterol.

Reduction rate required to achieve the treatment target (%)
= {1 − (Target lipid level/Cholesterol value at each stratum)} × 100

The target lipid levels indicated in the 2007 Japan Atherosclerosis Society Guidelines for Diagnosis and Treatment of Atherosclerotic Cardiovascular Diseases (TG: 150 mg/dl and LDL-C: 140 mg/dl) were used referring in the calculation.

Step 4: To estimate the proportion of patients who actually received fenofibrate and atorvastatin treatments (prescriptions) at each dose level, prescription records dated April 2003 to March 2005 were extracted from the prescription database at Surugadai Nihon University Hospital. Based on this, the number of patients at each dose level, when total 1000 patients received the treatments, was estimated (Table 4). If there were any changes in the dosage during the period, the analysis was made based on the new dosage.

The estimation was made as follows. Firstly, the percentage of patients who received fenofibrate or atorvastatin treatments (prescriptions) at each dose level was calculated. Secondly, based on the premise that small doses are administered to patients with low baseline TG and cholesterol levels and large doses to those with high baseline TG and cholesterol levels, doses administered to each stratum (patient arm) of baseline TG and cholesterol levels were determined by the cumulative percentage of patients from the lowest baseline TG and cholesterol levels (Table 1) and the cumulative percentage of patients from the smallest dose levels (Table 4). For example, as the cumulative percentage, from the smallest dose, of the patients received fenofibrate 200 mg was 65.4% (Table 4), it was assumed that fenofibrate 200 mg was administered to the patient arm (Table 1) in the strata from a TG value of 160 mg/dl (0.0%) to 260 mg/dl (63.9%). As the authorized dosage and administration of fenofibrate ranges from 200 mg to 300 mg, it was presumed that 200 mg was administered to the patients to whom 200 mg or less fenofibrate was prescribed. Thirdly, based on the premise that the reduction rate of TG and cholesterol values at each dose level is normally distributed centered around the average reduction rate for the dose level shown in clinical studies[10,11] (Table 2), the number of patients

Table 2. Reduction Rate of Triglycerides and Cholesterol Levels after Treatment

Treatment and dose	TG	LDL-C
Fenofibrate		
100 mg	39±4 (49)	12±2 (59)
150 mg	34±6 (19)	13±4 (28)
200 mg	41±5 (50)	17±2 (46)
300 mg	47±4 (59)	25±2 (54)
Atorvastatin		
5 mg	27±32 (30)	31±12 (47)
10 mg	38±27 (20)	39±16 (46)
20 mg	44±16 (12)	50±11 (50)

Reductions (%) are the Mean±S.D. (n). 8 weeks after fenofibrate treatment and 12 weeks after atorvastatin treatment. TG: triglyceride, LDL-C: LDL-cholesterol.

Table 4. Number and Proportion of Patients Received Treatment

Treatment and dose	No. of patients treated	Percentage	Cumulative % from the smallest dose	No. of patients per 1,000
Fenofibrate				
100 mg	2	7.7%	7.7%	77
150 mg	9	34.6%	42.3%	346
200 mg	6	23.1%	65.4%	231
300 mg	9	34.6%	100.0%	346
Atorvastatin				
5 mg	401	32.3%	32.3%	323
10 mg	749	60.3%	92.5%	603
20 mg	93	7.5%	100.0%	75

Table 3. Reduction Rate of Triglycerides and Cholesterol Levels Required to Achieve Treatment Target

TG level (mg/dl)	160	180	200	220	240	260	280	300	320	340	360	380	400	420	440	460	480	500
Target: 150 (mg/dl)	6.3	16.7	25.0	31.8	37.5	42.3	46.4	50.0	53.1	55.9	58.3	60.5	62.5	64.3	65.9	67.4	68.8	70.0

LDL-C level (mg/dl)	140	150	160	170	180	190	200	210	220	230	240	250	260
Target: 140 (mg/dl)	0.0	6.7	12.5	17.6	22.2	26.3	30.0	33.3	36.4	39.1	41.7	44.0	46.2

TG: triglyceride, LDL-C: LDL-cholesterol.

who achieved the target TG and cholesterol level was estimated for each stratum of TG and cholesterol levels. Lastly, summing up the number of patients estimated for each stratum of TG and cholesterol levels, we estimated the number of patients who achieved the target TG level for fenofibrate or atorvastatin (Fig. 1).

Costs Assuming that only the drug costs differ among all the treatment costs required per patient annually, a cost analysis was made only in consideration of drug costs. The annual drug costs for fenofibrate and atorvastatin at each dose level were estimated as the daily drug costs multiplied by 365 days, using the reimbursement prices set at the April 2008 revision (Table 5).

Sensitivity Analyses To confirm the robustness of this study model to a diversity of data, the following sensitivity analyses were made.

(1) The target lipid levels were set referring at 150 mg/dl for TG and 140 mg/dl for LDL-C[4] in the basic analysis. In the sensitivity analysis, however, the target lipid level was set at LDL-C: 160 mg/dl.

(2) The fenofibrate dose administered was estimated based on the actual prescriptions in the basic analysis. In the sensitivity analysis, however, the proportion of the fenofibrate 200 mg arm was altered.

RESULTS

The annual treatment costs, number of patients who achieved the treatment target and incremental cost-effectiveness ratio of fenofibrate to atorvastatin

Table 5. The Reimbursement Prices

Treatment and dose	the April 2008 revision	
	the daily drug costs	annual drug costs
Fenofibrate		
100 mg	¥38.40	¥14,016.00
150 mg	¥50.00	¥18,250.00
200 mg*	¥76.80	¥28,032.00
300 mg*	¥100.00	¥36,500.00
Atorvastatin		
5 mg	¥72.50	¥26,462.50
10 mg	¥138.40	¥50,516.00
20 mg*	¥276.80	¥101,032.00

annual drug costs=the daily drug costs×365 (day). * No release.

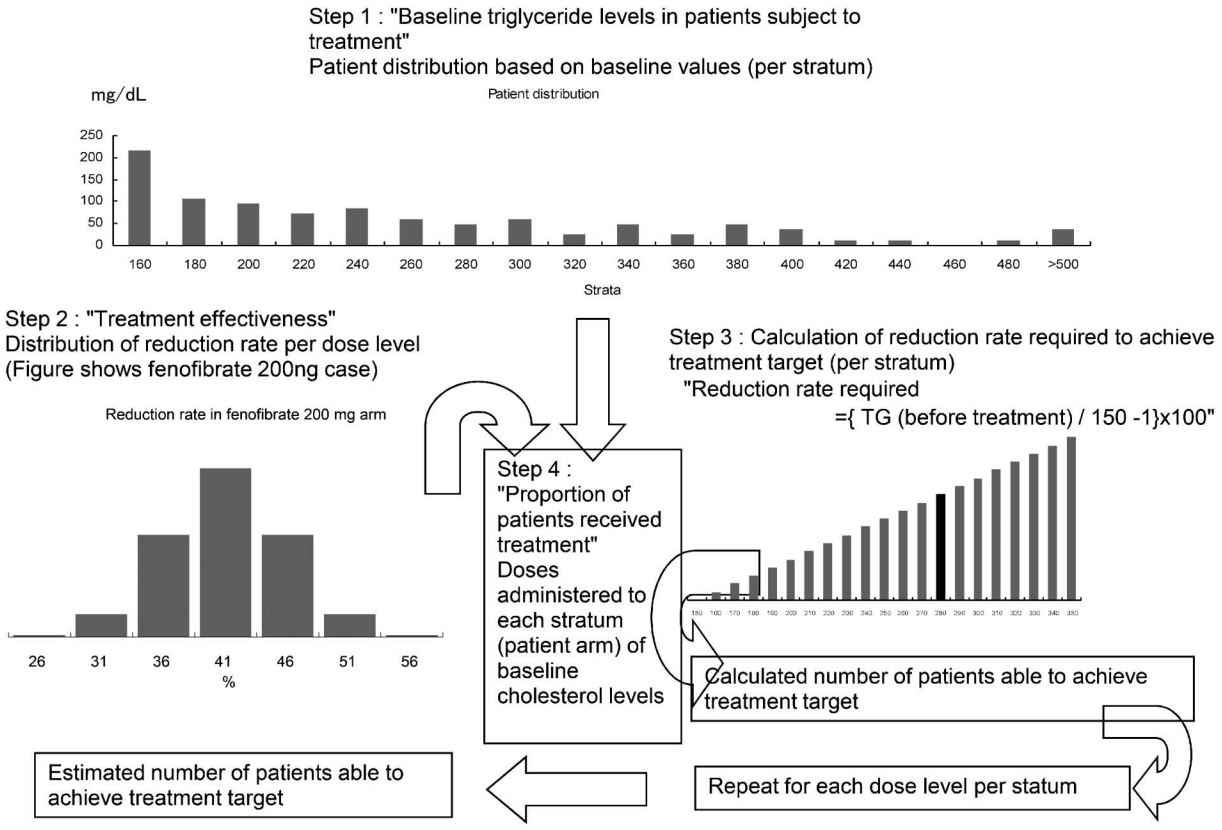

Fig. 1. Schematic Diagram

were estimated in a virtual cohort patient population of 1000.

The numbers of patients who achieved the target TG level were 622 for fenofibrate and 490 for atorvastatin. The numbers of patients who achieved the target LDL-C level were 683 for fenofibrate and 906 for atorvastatin. The annual costs per treatment were JPY 30963231 for fenofibrate and JPY 46535738 for atorvastatin. As a result, fenofibrate was dominant, higher in efficacy and lower in cost, over atorvastatin in decreasing TG levels, and the incremental cost-effectiveness ratio of atorvastatin to fenofibrate in decreasing LDL-C levels was JPY 69911 (Table 6).

Sensitivity Analyses With regard to TG values, fenofibrate was dominant over atorvastatin under all the conditions described (Table 6).

With regard to LDL-C values, the incremental cost-effectiveness ratios of atorvastatin to fenofibrate under Condition (1) increased to JPY 311525 (Table 7). Under Condition (2), as the number of patients in the fenofibrate 200 mg arm increased, the incremental cost-effectiveness ratio of atorvastatin to fenofibrate increased (Fig. 2).

DISCUSSION

In this study, to compare cost effectiveness in clinical practice, incremental cost-effectiveness ratios of fenofibrate to atorvastatin were estimated based on actual doses prescribed at the medical institutions investigated and baseline TG and cholesterol levels in patients. As a result, fenofibrate was dominant, higher in efficacy and lower in cost, over atorvastatin in decreasing TG levels, and it was revealed that the cost effectiveness of fenofibrate was significantly higher compared to atorvastatin. Comparing atorvastatin with fenofibrate in reduction of LDL-C levels, the incremental costs required for a patient to achieve the target LDL-C level were JPY 69911.

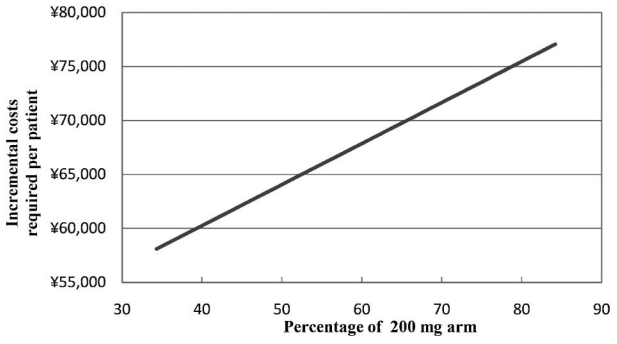

Fig. 2. Sensitivity Analysis (2)

In the sensitivity analyses, when the target LDL-C level was set at 160 mg/dl, the incremental cost-effectiveness ratios increased to JPY 311525. This indicated that the average reduction rate was larger in atorvastatin than fenofibrate. Furthermore, when the proportion of the fenofibrate 200 mg arm was altered, fenofibrate was dominant over atorvastatin in decreasing TG levels in any proportions. With regard to LDL-C values, compared to fenofibrate, the incremental cost-effectiveness ratio of atorvastatin increased as the proportion of the fenofibrate 200 mg arm rose.

Those results indicated that the cost effectiveness of fenofibrate was significantly higher compared to atorvastatin in achieving target TG levels. As the reduction rate of LDL-C was lower in fenofibrate compared to atorvastatin, a variance in the number of patients who achieved the treatment target was smaller in patients with a low baseline LDL-C level than those with a high baseline LDL-C level, and it was therefore expected that the effectiveness increased in fenofibrate.

Furthermore, in our earlier study, an analysis was made on the premise that the same dosage was given to all the patients. In this study, however, it was assumed that small doses were administered to patients with low baseline TG and LDL-C levels and large doses to those with high baseline TG and LDL-C levels. This enabled the study results to reflect actual drug treatment applied in clinical practice more closely.

In this study (model), the following must be taken into consideration. Firstly, in pharmacoeconomic analyses, the primary endpoint is usually set at survival related to the onset of arteriosclerotic diseases. The endpoint of this study is, however, set at achievement of the target lipid levels (treatment target). Nevertheless, this analysis can be more practical for the purpose of choosing drug treatments at medical institutions, as a treatment goal in clinical practice is set at achievement of the target lipid levels.

Secondly, since the doses of fenofibrate prescribed were small, the confidence level in the fenofibrate proportion was considered low. The sensitivity analysis was therefore made, and the proportion was altered based on the dosage and administration indicated in the package insert.

Table 6. Incremental Analysis Results

Treatment and dose	In virtual cohort of 1,000 patients				
	Annual costs per treatment (yen)	No. of patients achieved treatment target	Incremental cost-effectiveness ratio to atorvastatin (TG)		
			Annual costs (yen) (A)	Incremental no. of patients achieved treatment target (B)	Incremental costs required per patient (yen) (A/B)
		TG		TG	TG
Fenofibrate					
200 mg	18,328,615	579	—	—	—
300 mg	12,634,615	43	—	—	—
Total	30,963,231	622	−15,572,507	132	dominant
Atorvastatin					
5 mg	8,536,977	229	—	—	—
10 mg	30,439,649	257	—	—	—
20 mg	7,559,112	5	—	—	—
Total	46,535,738	490	—	—	—

Treatment and dose	In virtual cohort of 1,000 patients				
	Annual costs per treatment (yen)	No. of patients achieved treatment target	Incremental cost-effectiveness ratio to fenocibrate (LDL-C)		
			Annual costs (yen) (A)	Incremental no. of patients achieved treatment target (B)	Incremental costs required per patient (yen) (A/B)
		LDL-C		LDL-C	LDL-C
Fenofibrate					
200 mg	18,328,615	527	—	—	—
300 mg	12,634,615	156	—	—	—
Total	30,963,231	683	—	—	—
Atorvastatin					
5 mg	8,536,977	231	—	—	—
10 mg	30,439,649	618	—	—	—
20 mg	7,559,112	57	—	—	—
Total	46,535,738	906	15,572,507	223	69,911

TG: triglyceride, LDL-C: LDL-cholesterol. dominant: fenofibrate was dominant over atorvastatin in decreasing TG levels.

Table 7. Sensitivity Analysis Results

Treatment	In virtual cohort of 1,000 patients				
	Annual costs per treatment (yen)	No. of patients achieved treatment target	Incremental cost-effectiveness ratio to fenofibrate		
			Annual costs (yen) (A)	Incremental no. of patients achieved treatment target (B)	Incremental costs required per patient (yen) (A/B)
		LDL-C		LDL-C	LDL-C
Basic analysis Target LDL-C: 140 mg/dl TG: 150 mg/dl					
Fenofibrate	30,963,231	683	—	—	—
Atorvastatin	46,535,738	906	15,572,507	223	69,911
Sensitivity Analysis (1) Target LDL-C: 160 mg/dl (n=63)					
Fenofibrate	30,963,231	950	—	—	—
Atorvastatin	46,535,738	1,000	15,572,507	50	311,525

dominant: fenofibrate was dominant over atorvastatin in decreasing TG levels.

This provides a model for choosing drug treatments that reflect clinical practices at medical institutions by substituting figures for individual cases.

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