Increased Rosuvastatin Dose versus Concomitant Fenofibrate and Rosuvastatin Therapy to Achieve Lipid Goal in Patients with Diabetes or Atherosclerosis with Metabolic Syndrome

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Purpose: We aimed to ascertain whether increased rosuvastatin dose is non-inferior to concomitant fenofibrate and rosuvastatin therapy in patients with diabetes or atherosclerosis with metabolic syndrome.

Methods: After treatment with rosuvastatin 5 mg/day for 12 weeks, 112 patients were randomly assigned to receive either 10 mg/day rosuvastatin (group A) or 80 mg/day supra-film coated fenofibrate plus 5 mg/day rosuvastatin (group B). The therapy effects were evaluated by measuring the serum lipid profile, liver and muscle enzymes, and renal function after the treatment period.

Results: After the treatment, the total cholesterol, high-density-lipoprotein cholesterol (HDL-C), non HDL-C, low-density-lipoprotein cholesterol (LDL-C), and triglyceride were comparable between the 2 groups. The change in the non-HDL-C were -7.39 ± 26.58 (-6.62%) and -0.68 ± 24.49 (-1.19%) mg/dl (p = 0.28); and the change in the triglyceride were -36.61 ± 62.51 (-14.00%) and -44.77 ± 77.35 (-23.17%) mg/dl (p = 0.64), respectively. While 41.37% of group A and 38.69% of group B achieved their LDL-C goal (< 100 mg/dl) (p = 0.79), 37.26% of group A and 42.31% of group B achieved their triglyceride goal (< 150 mg/dl) (p = 0.53), respectively. The changes in the serum transaminase and creatinine phosphokinase were similar between the 2 groups.

Conclusions: After 5 mg/day of rosuvastatin, the lipid profile in patients with diabetes or atherosclerotic vascular diseases with metabolic syndrome could be improved by increasing rosuvastatin dose, and the resultant decrease of non-HDL and triglyceride were similar to those obtained with combination therapy. Both therapies were safe and feasible.

Key Words: Combination therapy • Diabetes • Fenofibrate • Metabolic syndrome • Monotherapy • Statin

INTRODUCTION

Patients with diabetes are at an increased risk of mortality due to cardiovascular diseases (CVDs) as compared to individuals without diabetes. The mortality rate of CVD has been reported to be increasing in several countries in Asia, including China, Malaysia, Korea and Taiwan. Recently, CVD and stroke have the second and third highest fatality rate in the Taiwanese population, respectively, and their treatment involves elevated cost in terms of medical resources.[1] Dyslipidemia is a major risk factor for CVD.[2] Since statin use reduces cardiovas-

Received: June 9, 2013 Accepted: July 24, 2013

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cular death, several large-scale trials have early reported that it can be used both in primary and secondary prevention of CVD.[3,4] The clinical benefits of statin in treating dyslipidemia in patients with type 2 diabetes mellitus (DM) should be at least equivalent to those observed in CVD.[5] A meta-analysis of 7 trials revealed that treatment with statins for approximately 5 years resulted in 25% reduction in the combined outcome of death from coronary heart disease and non-fatal myocardial infarction.[4,5] Fibrates are another group of hypolipidemic drugs that regulate lipid metabolism. They serve to reduce high triglyceride (TG) levels and increase low levels of high-density lipoprotein cholesterol (HDL-C), which are the characteristic lipid abnormalities commonly seen in patients with diabetes or metabolic syndrome; therefore, a daily dose of fibrate are prescribed for treating diabetic dyslipidemia.[6-8] However, in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial involving 9795 participants with type 2 DM, fenofibrate did not significantly reduce the risk of the primary outcome of coronary events.[9,10] The higher rate of starting statin therapy in patients who were administered the placebo might have masked the moderately larger benefit of the treatment. Furthermore, all the treatment trials to support the lipid treatment guideline were conducted in Caucasians individuals, and except for the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, no studies have investigated the effects of concomitant statin therapy with fibrate.[11,12] The findings of the ACCORD study do not support the concomitant use of fibrate and statin over statin therapy alone to reduce cardiovascular risk in patients with type 2 diabetes who are at high risk for CVD.

However, the treatment protocol is to include fibrates or placebo with high dose of statin. Because of limited medical resources in Taiwan, in case an initial statin dose is unable to control the lipid profile of the recipients, the quandary of whether to increase the statin dose or concomitantly administer fibrate usually occurs. In addition, one pill is more convenient and acceptable for patients than two or more pills. Therefore, we tested the hypothesis that increasing the rosuvastatin dose (monotherapy) is non-inferior to administration of fenofibrate with rosuvastatin (combination therapy) in patients with diabetes or atherosclerotic vascular diseases with metabolic syndrome.

METHODS

Study design

This was a multicenter, prospective, randomized, open-label, blinded end-point classification trial (PROBE design) carried out in Taiwan with the approval of the Institutional Review Board. From Jan. 2008 to Dec. 2010, we enrolled 112 patients into our study. The subjects were men and women from 20-79 years of age, with definite DM or atherosclerotic vascular diseases with metabolic syndrome who were first screened, and then asked to provide written informed consent. All patients who provided written informed consent underwent a 12-week rosuvastatin run-in treatment period during which the patients received rosuvastatin 5 mg once daily if they fulfilled the criteria for receiving lipid-lowering therapy according to Taiwanese lipid-lowering treatment guidelines. Of the 112 participants, 62 received 10 mg rosuvastatin (group A) and 50 received 5 mg rosuvastatin with 80 mg supra film coated (SFC) fenofibrate (group B). During the run-in period, all the patients adhered to the therapeutic lifestyle change (TLC). At the end of this rosuvastatin run-in period, the lipid profile [total cholesterol (TC), HDL-C, and TG], aspartate aminotransaminase (AST), alanine aminotransaminase (ALT), creatinine phosphokinase (CPK), serum creatinine levels, and estimated glomerular filtration rate (eGFR) were assessed. eGFR was calculated by the simplified Modification of Diet in Renal Disease (MDRD) formula. After the 12-week rosuvastatin run-in period, those patients who did not achieve TG levels of < 150 mg/dL were enrolled in the study and were randomized as follows: 10 mg rosuvastatin or 5 mg rosuvastatin plus 80 mg SFC fenofibrate once daily. At the end of 12 weeks of randomized treatment, the patients' lipid profile, AST, ALT, CPK, serum creatinine, and eGFR were re-measured, and their vital signs, adverse events, and concurrent medication information were obtained. The per day cost was USD $0.93 for 10 mg rosuvastatin, and USD $0.60 for 5 mg rosuvastatin (USD 0.47) plus 80 mg SFC fenofibrate (USD $0.13).

Eligibility

Patients were included in the clinical trial only if they met all of the following inclusion criteria: 20-79 years of age with type 2 diabetes or atherosclerotic vas-

cular diseases (coronary artery disease, cerebrovascular accident, or peripheral arterial occlusive disease) with metabolic syndrome and history of metabolic syndrome defined by the modified National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III panel as given below.

The NCEP ATP III panel defines metabolic syndrome as the presence of 3 or more of the following risk determinants: (1) increased waist circumference (> 90 cm for men and > 80 cm for women), (2) elevated TG (≧ 150 mg/dL), (3) low HDL-C levels (< 40 mg/dL in men and < 50 mg/dL in women), (4) hypertension (≧ 130/85 mmHg), (5) impaired fasting glucose (≧ 110 mg/dL), and (6) at least one of the following 2 laboratory values: (a) LDL-C level of 130-190 mg/dL and (b) elevated TG level of 200-500 mg/dL with either HDL-C < 40 mg/dL or TC/HDL-C > 5. All the patients provided written informed consent. In case of female patients of childbearing potential, the following inclusion criteria were applied: (1) adequate usage of contraception since the last menstruation, and continued usage of contraception throughout the observation period, (2) not lactating; (3) and negative urine pregnancy test when evaluate within 14 days before the initial dose of medication. Patients were excluded from the clinical trial if they met any of the following exclusion criteria: (1) any known contraindications to statin or fibrate therapy, previous intolerance to low or high dose of statin or fibrate, a history of hypersensitivity to statins or fibrates; (2) history of rhabdomyolysis or hereditary muscle disorders; (3) history or presence of pancreatitis, nephrotic syndrome, uncontrolled DM (hemoglobin A1c >9), or thyroid diseases; (4) serum creatinine level over 132.6 mmol/L (2 mg/dL) or bilirubin ≥ 1.5-fold the upper limit of the normal (ULN), AST or ALT ≥ 3 × ULN, or plasma LDL-C > 190 mg/dL or TG > 500 mg/dL; (5) coronary heart disease event or revascularization within a month, congestive heart failure (New York Heart Association classification III or IV), or hemodynamically important valvular heart disease; (6) gastrointestinal conditions affecting drug absorption or treatment with other drugs that seriously affect the pharmacokinetics of statins or fibrate; (7) life-threatening malignancy, treatment with immunosuppressive or other lipid-lowering agents (patients previously treated with statins or fibrates monotherapy were qualified if they had not had a dose higher than the equivalent of 5 mg of rosuvastatin or 80 mg of SFC fenofibrate); (8) blood biochemistry, hematology, or urinalysis abnormalities that, in the investigator's opinion, might confound trial results; (9) history of homozygous familial hypercholesterolemia or familial dysbetalipoproteinemia; (10) pregnancy or breastfeeding; (11) significant alcohol, drug or medication abuse as judged by the investigator; (12) serious or unstable medical or psychological conditions.

Statistical analysis

For continuous variables, the raw data were summarized as the number of observations, and the mean, median, standard deviation, minimum, and maximum values on an each-visit basis. Normally distributed data were analyzed using analysis of variance (ANOVA). Wilcoxon rank-sum test was used in the case of skewed distribution. For categorical variables, the raw data were summarized as the number of observations and frequency of each class on an each-visit basis. For nominal variables, the chi-square test, Fisher's exact test, or logistic regression was applied as needed. Ordinal variables were analyzed using the Cochran-Mantel-Haenszel (CMH) test. The demographic characteristics in both groups will be compared at baseline with Fisher's exact test for categorical variables, and *t* test was used for continuous variables. Analysis of covariance (ANCOVA) was used to account for any potential covariates such as baseline and demographic variables when investigating the difference in efficacy endpoints between the 2 groups.

RESULTS

At the end of the 5 mg/day rosuvastatin run-in period, the TC level in groups A and B were 182.96 ± 22.64 mg/dl and 181.77 ± 20.37 mg/dl, respectively (p = 0.79); the HDL-C levels were 44.24 ± 9.92 and 44.29 ± 13.66 mg/dl, respectively (p = 0.98); the LDL-C levels were 101.52 ± 18.33 and 97.28 ± 17.93 mg/dl, respectively (p = 0.27); the non HDL-C levels were 136.48 ± 21.52 and 135.72 ± 20.67 mg/dl, respectively (p = 0.76) and TG levels were 189.27 ± 70.31 and 205.95 ± 65.53 gm/dl, respectively (p = 0.24). The serum AST, ALT, and CPK levels were similar between the 2 groups; however, group B patients had higher creatinine (1.11 ± 0.34 vs.

1.29 ± 0.36 mg/dl; p = 0.05) and lower eGFR (69.47 ± 13.23 vs. 60.73 ± 18.20 ml/min/1.73 m^2; p = 0.04) (Table 1).

After the 12-week randomized treatment period, TC was 174.68 ± 32.76 mg/dl in group A and 180.46 ± 29.55 mg/dl in group B (p = 0.40), HDL-C was 45.14 ± 8.67 mg/dl in group A and 44.62 ± 11.15 mg/dl in group B (p = 0.80), LDL-C was 97.00 ± 31.85 mg/dl in group A and 104.63 ± 25.35 mg/dl in group B (p = 0.23), non HDL-C was 128.44 ± 29.58 mg/dl in group A and 134.76 ± 27.34 mg/dl in group B (p = 0.38) and TG was 162.77 ± 67.78 mg/dl in group A and 158.23 ± 62.05 mg/dl in group B (p = 0.75). The eGFR was 70.96 ± 14.02 ml/min/1.73 m^2 in group A and 58.34 ± 17.77 ml/min/1.73 m^2 in group B (p = 0.001) (Table 2). At the end of the 12-week treatment period, 93.6% of the patients in group A and 87.5% of patients in group B continued taking their assigned medication. According to the ATP-III treatment guidelines, 39.47% of group A and 36.11% of groups B achieved their TC treatment goal (< 160 mg/dl) (p = 0.70); 41.37% of group A and 38.69% of groups B achieved their LDL-C treatment goal (< 100 mg/dl) (p = 0.79); 57.89% of group A and 50.0% of groups B achieved their HDL-C treatment goal (≥ 40 mg/dl) (p = 0.45); 37.26% of group A and 42.31% of groups B achieved their TG treatment goal (< 150 mg/dl) (p = 0.53); 40.86% of group A and 36.45% of groups B achieved their non-HDL-C treatment goal (< 130 mg/dl) (p = 0.58).

The change in the TC level over 12-week treatment period was -7.53 ± 27.96 (-4.53%) and -0.06 ± 25.61 (-0.72%) mg/dl in groups A and B, respectively (p =

Table 1. Baseline characteristics of the patients after 12-week run-in period

Characteristics	Rosuvastatin 10 mg (Group A) (N = 62)	SFC Fenofibrate 80 mg + Rosuvastatin 5 mg (Group B) (N = 50)	p Value
Age (yr)	48.09 (8.86)	50.87 (10.86)	0.139
Waist circumference (cm)	93.37 (9.55)	92.87 (8.32)	0.855
Height (cm)	161.57 (9.43)	161.82 (7.91)	0.896
Weight (Kg)	72.60 (11.84)	72.38 (10.48)	0.927
Blood pressure (mmHg)			
Systolic	132.82 (15.09)	134.75 (18.20)	0.489
Diastolic	79.61 (10.20)	79.67 (8.74)	0.464
Heart rate (BPM)	72.58 (8.74)	72.73 (10.26)	0.937
Cholesterol (mg/dl)			
Total	182.96 (22.64)	181.77 (20.37)	0.794
High-density lipoprotein	44.24 (9.92)	44.29 (13.66)	0.984
Low-density lipoprotein	101.52 (18.33)	97.28 (17.93)	0.274
Non high-density lipoprotein	136.48 (21.52)	135.72 (20.67)	0.762
Triglyceride (mg/dl)	189.27 (70.31)	205.95 (65.53)	0.243
BUN (mg/dl)	11.33 (4.61)	19.38 (5.93)	0.081
Creatinine (mg/dl)	1.11 (0.34)	1.29 (0.36)	0.052
eGFR (ml/min/m^2)	69.47 (13.23)	60.73 (18.20)	0.043*
Fasting plasma glucose (mg/dl)	122.25 (35.33)	127.84 (45.88)	0.589
HbA1c (%)	6.57 (0.79)	6.84 (1.31)	0.363
Liver enzyme (IU/L)			
AST	31.10 (15.34)	33.00 (21.85)	0.690
ALT	38.10 (19.07)	37.32 (20.80)	0.863
Creatinine phosphokinase (IU/L)	119.97 (51.83)	138.94 (141.30)	0.451
Uric acid (mg/dl)	6.92 (1.96)	6.58 (1.47)	0.599

Value are presented as mean (SD) unless stated otherwise.

ALT, alanine aminotransaminase; AST, aspartate aminotransaminase; BPM, beat per minutes; eGFR, estimated glomerular filtration rate.

* p < 0.05.

Table 2. Randomized open-label treatment period for 12 weeks

Characteristics	Rosuvastatin 10 mg (Group A) (N = 62)	SFC Fenofibrate 80 mg + Rosuvastatin 5 mg (Group B) (N = 50)	p value
Waist circumference (cm)	92.14 (10.15)	94.57 (7.39)	0.252
Height (cm)	161.73 (9.77)	162.06 (8.77)	0.881
Weight (Kg)	72.24 (12.80)	71.13 (11.65)	0.694
Cholesterol (mg/dl)			
Total	174.68 (32.76)	180.46 (29.55)	0.404
High-density lipoprotein	45.14 (8.67)	44.62 (11.15)	0.802
Low-density lipoprotein	97.00 (31.85)	104.63 (25.35)	0.232
Non high-density lipoprotein	128.44 (29.58)	134.76 (27.34)	0.381
Triglyceride (mg/dl)	162.77 (67.78)	158.23 (62.05)	0.750
BUN (mg/dl)	15.19 (4.87)	19.95 (9.58)	0.097
Creatinine (mg/dl)	1.08 (0.27)	1.34 (0.54)	0.012*
eGFR (ml/min/m^2)	70.96 (14.02)	58.34 (17.77)	0.001*
Fasting plasma glucose (mg/dl)	112.54 (24.58)	117.27 (32.84)	0.502
HbA1c (%)	6.42 (1.23)	8.52 (1.55)	0.267
Liver enzyme (IU/L)			
AST	29.67 (11.29)	33.73 (20.10)	0.292
ALT	38.12 (21.86)	34.73 (25.20)	0.516
Creatinine phosphokinase (IU/L)	111.26 (63.67)	110.78 (52.60)	0.971
Uric acid (mg/dl)	6.61 (1.71)	6.06 (1.33)	0.301

Values are presented as mean (SD) unless stated otherwise.
ALT, alanine aminotransaminase; AST, aspartate aminotransaminase; eGFR, estimated glomerular filtration rate.
* $p < 0.05$.

0.26). The change in the HDL-C levels in groups A and B were +2.50 ± 4.27 (+2.03%) and +0.17 ± 12.70 (+0.75%) mg/dl, respectively (p = 0.31); the change in the LDL-C levels were -2.17 ± 23.17 (-4.45%) and +8.26 ± 21.67 (+7.56%) mg/dl, respectively (p = 0.07); the change in the non-HDL-C levels were -7.39 ± 26.58 (-6.62%) and -0.68 ± 24.49 (-1.19%) mg/dl, respectively (p = 0.28) and the change in the TG levels were -36.61 ± 62.51 (-14.00%) and -44.77 ± 77.35 (-23.17%) mg/dl, respectively (p = 0.64). The change in the serum AST level over the treatment period was +0.58 ± 11.62 and +1.28 ± 22.07 IU/L in groups A and B, respectively (p = 0.89); that in the ALT level was +2.04 ± 23.09 and -1.66 ± 25.89 IU/L, respectively (p = 0.58); that in the CPK level was -5.35 ± 38.89 and -12.67 ± 48.91 IU/L, respectively (p = 0.58) (Table 3). None of the patients in either group exhibited elevated creatine kinase level of more than 10× ULN or elevated AST or ALT level of more than 3 × ULN. There was a borderline significant difference in the change of serum creatinine level between the 2 groups (Group A: +0.01 ± 0.10 mg/dl and group B: +0.14 ± 0.28 mg/dl, respectively; p = 0.07), and the change in the eGFR was +2.43 ± 5.02 and -3.76 ± 8.08 ml/min/1.73 m^2 in groups A and B, respectively (p = 0.54). During the study period, one participant from each group was withdrawn because they complained of muscle pain. None of the participants were withdrawn from the trial due to significantly elevated liver or muscle enzyme or creatinine levels. No other adverse events were reported in any of the study groups.

DISCUSSION

Our results demonstrated that these two treatment regimens made no significant difference on the TC, TG, non HDL-C and HDL-C levels. However, increasing the statin dose tended to further decrease the LDL-C levels from the initial levels as compared to combination therapy. There was no significant difference in the changes in CPK, AST, and ALT levels between the 2 groups. How-

Table 3. The difference between the end of run-in period and treatment after 12 weeks

Characteristics	Rosuvastatin 10 mg (Group A) (N = 62)	SFC Fenofibrate 80 mg + Rosuvastatin 5 mg (Group B) (N = 50)	p value
Waist circumference, cm	-0.49 (5.36)	0.95 (5.02)	0.27
Cholesterol, mg/dl			
Total	-7.53 (27.96) (-4.53%)	-0.06 (25.61) (-0.72%)	0.26
High-density lipoprotein	+2.50 (4.27) (+2.03%)	+0.17 (12.70) (+0.75%)	0.31
Low-density lipoprotein	-2.17 (23.17) (-9.45%)	+8.26 (21.67) (+7.56%)	0.07
Non high-density lipoprotein	-7.39 (26.58) (-6.62%)	-0.68 (24.49) (-1.19%)	0.28
Triglyceride, mg/dl	-36.61 (62.51) (-14.00%)	-44.77 (77.35) (-23.17%)	0.64
BUN, mg/dl	-0.35 (4.03)	-1.10 (3.55)	0.84
Creatinine, mg/dl	+0.01 (0.10)	+0.14 (0.28)	0.07
eGFR, ml/min/m^2	+2.43 (5.02)	-3.76 (8.08)	0.54
Fasting plasma glucose, mg/dl	-1.44 (10.39)	-0.39 (25.13)	0.87
HbA1c, %	-0.23 (0.51)	2.52 (1.55)	0.36
Liver enzyme, IU/L			
AST	+0.58 (11.62)	+1.28 (22.07)	0.89
ALT	+2.04 (23.09)	-1.66 (25.89)	0.58
Creatinine phosphokinase, IU/L	-5.35 (38.89)	-12.67 (48.91)	0.58
Uric acid, mg/dl	-0.38 (3.20)	-0.23 (0.55)	0.92

Value are presented as mean (SD) (% change) unless stated otherwise.
ALT, alanine aminotransaminase; AST, aspartate aminotransaminase; eGFR, estimated glomerular filtration rate.

ever, the serum creatinine level tended to be higher and correspondingly, eGFR tended to be lower after the 12-week period of the combination therapy.

Thus far, only 2 large-scale studies have assessed the efficacy of combination therapy with fibrate and statin. The first one is the LDS study carried out in UK, which was terminated prematurely due to the lethal toxicity induced by the drug cerivastatin, which has been withdrawn from the market. The second one is the ACCORD study by the National Heart, Lung, and Blood Institute (NHLBI) in the USA (published in April 2010) that compared the addition of fenofibrate or placebo to high doses of simvastatin. However, the ACCORD study treatment protocol is not practical for the medical system of Taiwan because fenofibrate was added only after the patients received high-dosed simvastatin therapy; this methodology would require more medical resources.

Rosuvastatin is the most potent of all the statins, and it has been reported that Asian patients require lower doses of statin than Caucasian patients.[13] These results indicate that initial therapy with a low dose of rosuvastatin is reasonable and practical in a country with limited medical resources. However, the TG level remains high after statin therapy in many patients with diabetes or metabolic syndrome. In such scenarios, many physicians prefer to add low-dosed fibrates in addition to the low dose of statin, in an attempt to lower the TG level. The results of our study showed that increasing the statin dose to improve the lipid profile in patients who have already received low dose (5 mg/day) rosuvastatin is non-inferior to the addition of low-dosed fenofibrate (80 mg/day) concomitantly with low-dosed rosuvastatin in our study population.

In daily practice, it is generally acknowledged that fenofibrate reduces TG levels to a greater extent than statin. Therefore, it can be deduced that combination therapy with fenofibrate and statin should be more effective than statin alone in reducing TG. However, although the primary outcome of the ACCORD study did not differ significantly between the combined therapy group and the statin group throughout the 4.7 years of treatment and follow-up, the rate of decrease of TGs was not significantly different either (p = 0.64).[12] Our study result for TG control is similar to that of the ACCORD study. There are several possible reasons to explain this phenomenon. One possibility is that rosuvastatin is potent not only to reduce LDL-C but also TG levels.[14] In this study, the patients only received 5 mg rosuvastatin before the random-

ization. Increasing the statin dosage could significantly reduce the TG level. Second, the dosage of fenofibrate in this study was 80 mg, which may limit the efficiency for reducing TG. Third, group B patients had higher HbA1c levels before randomization, and this level increased further after the randomized treatment. Poorer control of diabetes could also have increased the TG level.[15-17] This is one of the limitations of this study.

In the ACCORD trial, the study drug was discontinued or its dose was reduced in some patients receiving fenofibrate, because of impaired renal function. Very few patients in this trial showed elevated CPK, AST, or ALT levels higher than the ULN. In this Taiwanese population, none of the patients withdrew from the study or received reduced dose of study drug due to impaired renal function. However, there was a borderline significant difference in the change of serum creatinine level between the 2 groups (A: 0.01 $\pm$ 0.10 mg/dl, B: 0.14 $\pm$ 0.28 mg/dl; p = 0.07). In contrast, the change in the eGFR was similar between the 2 groups. Previous studies have raised concerns about increased serum creatinine levels following fenofibrate treatment.[9,18] In the ACCORD study, the serum creatinine level increased in the fenofibrate group soon after the randomization, but remained constant thereafter as compared to the placebo group. In the FIELD study, the serum creatinine level returned to the baseline level by 8 weeks after the end of study. A similar phenomenon was observed in this study after the addition of fenofibrate, but this did not happened when increasing the dose of statin. The renal function in group B with a borderline significant deterioration needed longer follow-up to confirm, which is another limitation of this study.

With regard to the therapeutic cost/benefit, although a national health insurance (NHI) system has been well established, medical expenses are a considerable economic burden in Tawian. Based on the NHI payment system, monotherapy with 10 mg rosuvastatin would cost USD $0.93/day, whereas combination therapy with 5 mg rosuvastatin plus 80 mg SFC fenofibrate would cost USD $0.60/day. In other words, combination therapy could save USD $0.33/day for those patients with persistent hypertriglyceridemia after the low-dosed rosuvastatin therapy. However, 10 mg rosuvastatin might result in better lipid profile and lower creatinine level than the combination of the above mentioned drugs. Furthermore, it is more convenient for patients to take only one pill per day, i.e. better drug compliance. Because combination therapy has no further TG lowering effect, monotherapy with higher dose of rosuvastatin may be better for the patients with metabolic syndrome. Combination therapy may have only the benefit of lower medical cost.

CONCLUSIONS

In conclusion, after 5 mg/day of rosuvastatin, the lipid profile in patients with diabetes or atherosclerotic vascular diseases with metabolic syndrome could be improved by increasing rosuvastatin dose, and the resultant decrease of non-HDL and TG levels were similar to those obtained with combination therapy with fenofibrate and low-dose rosuvastatin. Both therapies were safe and feasible. While increasing dose of rosuvastatin tended to achieve more LDL-C and non-HDL-C goal and deteriorate less renal function, the combination therapy tended to achieve more TG goal and was more cost-effective in terms of medical resources.

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