Safety and tolerability of fluvastatin XL in the treatment of hypercholesterolemia : a postmarketing surveillance conducted in Indonesia

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Abstrak

Tablet fluvastatin XL 80 mg telah dipasarkan di Indonesia sejak Desember 2002. Survei pasca pemasaran ini dilaksanakan antara Mei 2004 dan April 2005 dengan melibatkan 98 dokter umum untuk melihat keamanan dan tolerabilitas fluvastatin XL 80 mg sekali sehari sebelum tidur selama 8 minggu untuk pengobatan pasien rawat jalan dengan hiperkolesterolemia. Efikasi obat dalam menurunkan kolesterol LDL dan parameter lipid lainnya juga dilihat dalam praktek klinik sehari-hari pada survei ini. Seluruhnya ada 740 pasien yang dapat dievaluasi keamanannya. Sebanyak 32 pasien (4,32%) melaporkan 39 efek samping yang dianggap berhubungan dengan terapi fluvastatin XL. Efek samping yang paling sering adalah pusing kepala (2,03%), nausea (1,22%), dan mialgia (0,68%). Tidak ditemukan efek samping serius pada survei ini dan tidak ada pasien yang menghentikan pengobatan akibat efek samping. Menurut penilaian global dokter, keamanan dan tolerabilitas pengobatan baik pada 91,9% pasien. Evaluasi efikasi hanya dapat dilakukan pada 566 pasien. Pada minggu 8, fluvastatin XL menurunkan kadar kolesterol LDL (LDL-C), kolesterol total (TC) dan trigliserida (TG) berturut-turut sebanyak 28,6%, 30,2%, dan 24,5%, dan meningkatkan kadar kolesterol HDL (HDL-C) sebanyak 14,3%. Pada 74 pasien dengan TG awal ≥ 300 mg/dL, penurunan TG 38,1% dan peningkatan HDL-C 18,1%. Penurunan LDL-C sebanyak ≥ 40% terjadi pada 19,6% pasien. Sebagai kesimpulan, survei pasca pemasaran ini menunjukkan bahwa pengobatan dengan fluvastatin XL 80 mg sekali sehari selama 8 minggu aman dan dapat ditoleransi dengan baik, dan juga efektif dalam menurunkan LDL-C, TC dan TG, dan menaikkan HDL-C dalam praktek klinik sehari-hari. ***(Med J Indones 2008; 17:88-95)***

Abstract

Fluvastatin XL 80 mg tablet has been marketed in Indonesia since December 2002. This post-marketing surveillance (PMS) was conducted between May 2004 and April 2005 involving 98 general physicians to observe the safety and tolerability of fluvastatin XL 80 mg once daily at bedtime for 8 weeks in the treatment of outpatients with hypercholesterolemia. The efficacy of the drug in lowering LDL-cholesterol and other lipid parameters was also observed in daily clinical practice in this PMS. A total of 740 patients were eligible for safety analyses. There were 32 patients (4.32%) with 39 adverse events that were considered related to fluvastatin XL therapy. The most common adverse reactions were dizziness (2.03%), nausea (1.22%), and myalgia (0.68%). No serious adverse event (SAE) was found in this PMS, and no patient discontinued due to adverse event. According to physician's global evaluation, the safety and tolerability of treatment was good in 91.9% of patients. For efficacy analyses, only 566 patients were eligible. At week 8, fluvastatin XL caused decreases in LDL-cholesterol (LDL-C), total cholesterol (TC) and triglyceride (TG) levels by 28.6%, 30.2% and 24.5%, respectively, and an increase in HDL-cholesterol (HDL-C) by 14.3%. In 74 patients with baseline TG ≥ 300 mg/dL, the decrease in TG was 38.1% and the increase in HDL-C was 18.1%. Reduction in LDL-C of ≥ 40% occurred in 19.6% of the patients. In conclusion, treatment with fluvastatin XL 80 mg once daily for 8 weeks in this PMS was shown to be safe and well tolerated, and also effective in reducing LDL-C, TC and TG, and raising HDL-C in daily clinical practice. ***(Med J Indones 2008; 17:88-95)***

Keywords: post-marketing surveillance (PMS), fluvastatin XL, hypercholesterolemia

Fluvastatin is a fully synthetic HMG-CoA reductase inhibitor (a statin) which is approved in more than 90 countries worldwide. In Indonesia, fluvastatin was first registered as an immediate release formulation (40 mg capsules) in 1995. The comparative dose efficacy study of all marketed statins (the Curves study) showed that the same mg dose of fluvastatin produced smaller reductions in LDL cholesterol compared to the same mg dose of other statins, and these effects were consistent with those seen in previous comparisons between statins.[1] However, 4 major clinical outcome studies (LIPS, the Lescol Intervention Prevention

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Study; FLARE, the Fluvastatin Angiographic Restenosis trial; LiSA, the Lescol in Severe Atherosclerosis; and LCAS, the Lipoprotein and Coronary Atherosclerosis Study) have demonstrated that fluvastatin significantly reduced the incidence of MACE (major adverse cardiac events : cardiac death, nonfatal MI and revascularization), and all-cause mortality in patients with coronary heart disease.[2]

As treatments with statin is life-long and patients often receive multiple concomitant medications, optimal statin therapy should be well tolerated and drug interactions should be avoided. Serious side-effects of statin therapy are very rare, and generally associated with concomitant medications affecting statin metabolism. It should be appreciated that fluvastatin is regarded less susceptible to drug interactions than other statins. An extended-release formulation of fluvastatin 80 mg (Lescol® XL) has been developed to provide efficacious lipid lowering with a once daily dosing regimen and allowing for low plasma levels of the drug.[3] This fluvastatin XL has been marketed in Indonesia since December 2002.

The primary objective of this post-marketing study was to observe the safety and tolerability of fluvastatin XL 80 mg once daily at bedtime in the treatment of outpatients with hypercholesterolemia from Indonesia. The secondary objectives were to assess the efficacy of the drug in lowering LDL-cholesterol and other lipid parameters in daily clinical practice.

METHODS

This postmarketing study was carried out at private clinics throughout Indonesia between 2 May 2004 and 4 April 2005 with 98 general physicians, who collected 803 patients. Male and female (non-childbearing potential) patients, aged above 18 years with elevated LDL cholesterol (≥ 160 mg/dL) were eligible for the study. Patients with hypersensitivity to any component of fluvastatin XL, or receiving therapy with agents known or likely to interact with fluvastatin, or with active liver disease or increase in liver transaminases (> 3 x ULN) were excluded from the study.

Lescol® (fluvastatin) XL 80 mg was given once daily at bedtime. No other lipid-lowering drugs were permitted. The observational period was intended to be 8 weeks, with an intermediate follow-up visit at 4 weeks, providing data for 3 examinations (baseline, 4 weeks and 8 weeks examination).

The patients' demographic data, medical history, previous duration of dyslipidemia, previous dyslipidemic agents, and concomitant medications were recorded in the case report forms (CRFs) for every patient. At each follow-up (4 weeks and 8 weeks), a physical examination was performed and adverse events were recorded from each patient, and the physician was asked to give a global evaluation of the fluvastatin treatment. Serum lipids were determined at baseline and at both follow-up visits. Determinations were performed at the routine laboratories of the individual sites.

All CRFs from individual physicians were collected by the sponsor (PT Novartis Indonesia) and then sent to the Clinical Trial Center, Faculty of Medicine, University of Indonesia, Jakarta for analysis.

Adverse events

All adverse events during the study period were recorded irrespective of causal relationship with fluvastatin XL. Any adverse event was described in detail, including the signs and symptoms, onset, nature and duration. The physicians also recorded the actions taken, the outcome, and the possible relationship with fluvastatin therapy.

A serious adverse event (SAE) was defined as one resulting in death, a life-threatening event, requiring inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability / incapacity, or any other adverse event which was considered serious by the respective physician. The physicians were requested to report any SAE occurring during the study period within 24 hours by fax, telephone or e-mail to PT Novartis Indonesia.

Data Management and Analyses

Prior to data entry and analyses, the CRFs were checked for completeness and plausibility. Any missing or implausible data on the CRFs were communicated with the respective physician by telephone or mail to be resolved.

Adverse events were analyzed using descriptive statistics. The adverse events were grouped according to the body system and listed with the number of patients and percentage of incidence for all adverse events and adverse events considered related to fluvastatin.

The efficacy of fluvastatin XL on lipid parameters at 4 and 8 weeks of treatment from baseline were analyzed using paired ANOVA (Gaussian) if the distributions of the data per group were normal. If this prerequisite was not fulfilled, the statistical test used would be Friedman. The multiple comparisons would be Dunnett after paired ANOVA or Wilcoxon matched-pairs after Friedman. Responder rate was also classified by category of percent reduction in LDL-C as follows : < 15%, 15-29%, 30-34%, 35-39%, and ≥ 40%, at 8 weeks of treatment. Efficacy analyses were performed based on intent-to-treat principle, in which the last-observation-carried-forward (LOCF) principle was applied in all eligible (for efficacy) patients.

All statistical analyses were done using statistical software.

RESULTS

Of the 803 CRFs collected, 63 CRFs had only baseline visits and therefore were unevaluable. The remaining 740 CRFs had at least one post-baseline visit after receiving fluvastatin XL at baseline visit and therefore eligible for safety analyses.

Twelve patients did not have LDL-cholesterol values at baseline, while 137 patients had LDL-C values below 160 mg/dL at baseline, and therefore should be excluded from the study. Eleven patients did not have baseline HDL-C values, and 14 patients had baseline HDL-C > 85 mg/dL (very unlikely). The remaining 566 patients were then eligible for efficacy analyses.

Baseline characteristics

Of the 740 patients, 58.8% were males, and the mean age was 50.6 years, ranging from 19 to 81 years. Median duration of dyslipidemia was 5 years within the range of less than 1 month to 24 years. More than half of the patients (53.5%) did not receive any previous medication for dyslipidemia. Among those who previously treated, mostly with statins (29.1%), followed by fibrates (15.1%). These data are presented in Table 1.

Table 1. Baseline characteristics of patients

Total number of patients	740
Gender :	
Male	435 (58.8%)
Female	299 (40.4%)
Not specified	6 (0.8%)
Age (yrs) :	
Mean (SD)	50.6 (9.13)
Median	51
Range	19 → 81
Duration of dyslipidemia (months) :	
Mean (SD)	18.0 (28.59)
Median	60
Range	< 1 → 288
Previous medications for dyslipidemia :	
Statins	215 (29.1%)
Fibrates	112 (15.1%)
Others	17 (2.3%)
None	396 (53.5%)

Table 2. Baseline lipid levels (mg/dL)

	LDL-Chol.	Total Chol. (TC)	HDL-Chol.	Non-HDL-Chol.	Triglyceride (TG)
n	566	566	566	566	564*
Mean (SD)	202.9 (41.54)	291.7 (53.02)	42.8 (10.20)	248.9 (54.03)	224.5 (88.52)
Median	190.0	282.0	41.0	241.8	201.0
Range	160 → 480	173 → 584	21 → 85	127 → 546	70 → 998

*2 patients did not have baseline TG values
286 (50.7%) patients had baseline TG levels > 200 mg/dL

Concomitant diseases & medications

As expected from patients with hypercholesterolemia, the most common concomitant diseases were cardiovascular diseases (28.65% of total patients), with hypertension as the most prevalent disease (26.62%). The next most common concomitant diseases were endocrinologic diseases (22.3%), with diabetes mellitus as the most prevalent disease (16.62%). The number of patients without concomitant diseases were 382 (51.6%).

Similarly, the most common concomitant medications were antihypertensives (in 25.1% of all patients) consisting of ACE inhibitors, calcium channel blockers, beta-blockers, angiotensin receptor blockers, and diuretics. The next most common concomitant drugs were antidiabetics (in 19.6%), consisting mostly of metformin and sulfonylurea. There were also concomitant medications known or likely to interact with fluvastatin, i.e. simvastatin (in 3 patients), pravastatin (in 1 patient) and fenofibrate (in 4 patients). There were no adverse events found in these patients. In 56.9% of all patients, no concomitant medication was being taken.

Safety and Tolerability

A total of 39 patients (5.27% of 740 patients) reported 51 adverse events (AEs), of which 39 AEs (76% of 51 AEs) occurring in 32 patients (4.32%) were considered to have possible (35 AEs) or probable (4 AEs) relationship with fluvastatin XL therapy (Table 3). No serious adverse event (SAE) was found in this post-marketing study, and no patient discontinued due to adverse event.

Table 3. List of adverse events, total and those considered related to fluvastatin XL treatment

	Total AEs No (% incidence)	AEs related to fluvastatin No (% incidence)
Gastrointestinal	15 (2.03)	11 (1.47)
▪ Nausea	12 (1.62)	9 (1.22)
▪ Diarrhea	1 (0.14)	-
▪ Flatulence	2 (0.27)	2 (0.27)
Nervous system	24 (3.24)	19 (2.57)
▪ Dizziness	19 (2.57)	15 (2.03)
▪ Headache	4 (0.54)	3 (0.41)
▪ Vertigo	1 (0.14)	1 (0.14)
Cardiovascular system	1 (0.14)	1 (0.14)
▪ Palpitation	1 (0.14)	1 (0.14)
Body as a Whole - General	2 (0.27)	2 (0.27)
▪ Malaise	2 (0.27)	2 (0.27)
Musculoskeletal system	6 (0.81)	2 (0.27)
▪ Myalgia	6 (0.81)	2 (0.27)
Respiratory	1 (0.14)	--
▪ Pharyngitis	1 (0.14)	--
Others	2 (0.27)	1 (0.14)
▪ Fever	1 (0.14)	--
▪ Hyperuricemia	1 (0.14)	1 (0.14)
Total	51 (6.89)	39 (5.27)

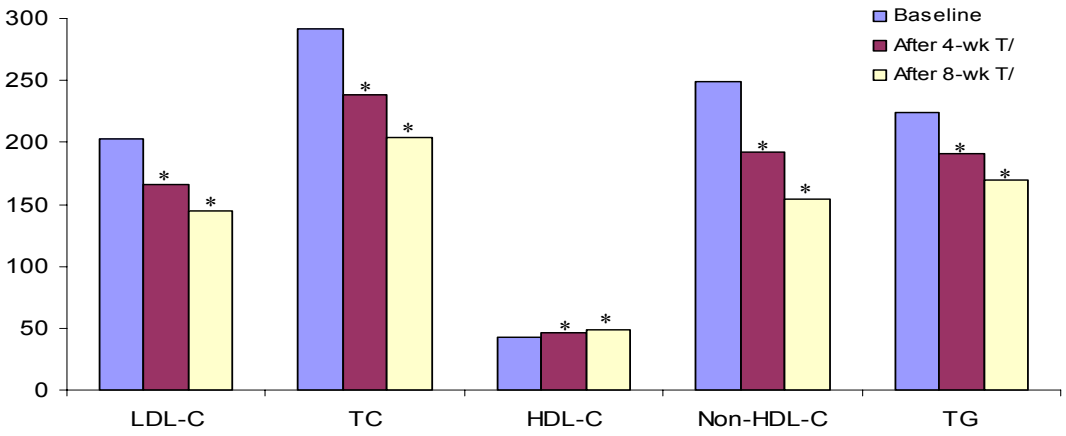
Efficacy of treatment

From 566 patients analyzed for efficacy, these patients were analyzed for LDL-C, TC, HDL-C and non-HDL-C, and 564 patients for TG (see Table 2). Table 4 and Figure 1 show the effects of fluvastatin XL on blood lipids after 4 weeks and 8 weeks. Data analyses were performed based on ITT (intent-to-treat) using paired ANOVA (Gaussian) because the distributions of the data per group were normal and the variances were homogen, followed by Dunnett multiple comparison because we were interested only in the differences from baseline. Table 4 and Figure 1 show that the decreases in LDL-C, TC, non-HDL-C and TG and the increase in HDL-C are all statistically significant, after both 4 weeks and 8 weeks of treatment with fluvastatin XL.

Table 4. Blood lipid levels after 4-week and 8-week treatment with fluvastatin XL

	Mean (SD)				
TG	LDL-C (n = 566)	TC (n = 566)	HDL-C (n = 566)	Non-HDL-C (n = 566)	(n = 564)
Baseline	202.9 (41.54)	291.7 (53.02)	42.8 (10.20)	248.9 (54.03)	224.5 (88.52)
After 4-wk T/	166.3 (34.82)	238.7 (40.31)	46.3 (11.58)	192.4 (41.71)	190.4 (63.01)
After 8-wk T/	144.9 (31.81)	203.5 (32.28)	48.9 (12.83)	154.7 (34.32)	169.6 (49.60)
Diff. from baseline					
▪ 4-wk	↓ 36.6 (18.0%)*	↓ 53.0 (18.2%)*	↑ 3.5 (8.2%)*	↓ 56.5 (22.7%)*	↓ 34.1 (15.2%)*
▪ 8-wk	↓ 58.0 (28.6%)*	↓ 88.2 (30.2%)*	↑ 6.1 (14.3%)*	↓ 94.3 (37.9%)*	↓ 54.9 (24.5%)*

* $p < 0.001$



* p , 0.001

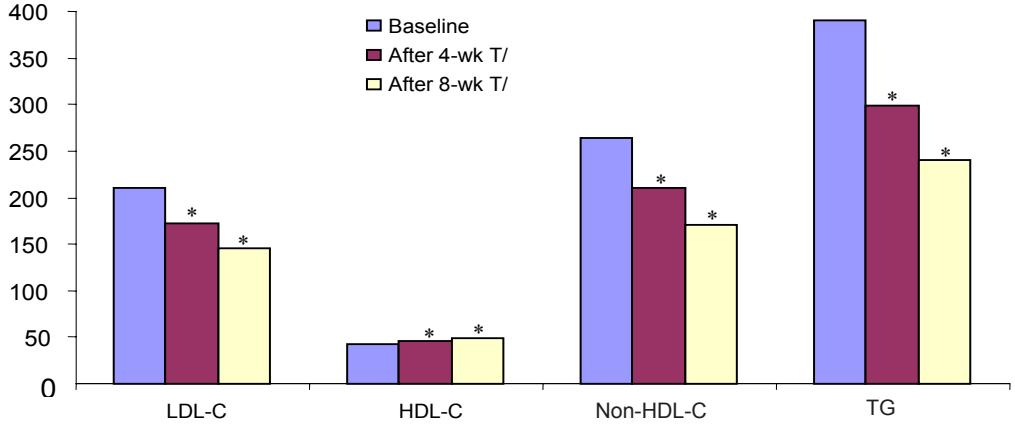
Figure 1. Lipid levels after 4-week and 8-week treatment with fluvastatin XL

In the subset of patients with baseline triglyceride levels ≥ 300 mg/dL, the changes in triglyceride, HDL-cholesterol and LDL-cholesterol levels are shown in Table 5 and Figure 2.

Table 5. Changes in LDL-cholesterol, HDL-cholesterol and triglyceride levels in patients with baseline triglyceride levels ≥ 300 mg/dL after treatment with fluvastatin XL

	Mean (SD)			
TG	LDL-C (n = 74)	HDL-C (n = 74)	Non-HDL-C (n = 74)	Triglyceride (n=74)
Baseline	210.4 (55.89)	42.0 (8.97)	264.2 (59.54)	389.8 (103.21)
After 4-wk T/	171.9 (47.23)	45.8 (14.77)	209.7 (51.97)	298.7 (76.37)
After 8-wk T/	145.3 (41.63)	49.6 (17.45)	170.7 (50.13)	241.1 (68.04)
Diff. from baseline				
▪ 4-wk	↓ 38.5 (18.3%)*	↑ 3.7 (8.8%)*	↓ 54.5 (20.6%)*	↓ 91.1 (23.4%)*
▪ 8-wk	↓ 65.1 (30.9%)*	↑ 7.6 (18.1%)*	↓ 93.5 (35.4%)*	↓ 148.7 (38.1%)*

* p < 0.001



* p < 0.001

Figure 2. LDL-C, HDL-C, Non-HDL-C and TG levels after 4-week and 8-week treatment with fluvastatin XL in patients with baseline TG levels ≥ 300 mg/dL

The efficacy of fluvastatin XL 80 mg in decreasing LDL-C levels by category of % reduction is shown in Table 6.

Table 6. Responder rates by category of % reduction in LDL-C at week 8

	n (%)
Responder < 15% from baseline	100 (17.7%)
15-29% from baseline	235 (41.5%)
30-34% from baseline	75 (13.3%)
35-39% from baseline	45 (8.0%)
≥ 40% from baseline	111 (19.6%)
Total	566 (100%)

Physicians' global evaluation of the fluvastatin XL treatment is shown in Table 7.

Table 7. Physicians' global evaluation at week 8

	Safety & tolerability	Efficacy
Good	680 (91.9%)	513 (90.6%)
Not satisfactory	8 (1.1%)	15 (2.7%)
No response	52 (7.0%)	38 (6.7%)
Total	740 (100%)	566 (100%)

DISCUSSION

According to the standard pharmacology book Goodman & Gilman, 80 mg fluvastatin reduces LDL-cholesterol around 31-35%, similar to pravastatin 40 mg, lovastatin 40 mg, simvastatin 20 mg and atorvastatin 10 mg.[4] However, fluvastatin together with pravastatin are less likely to interact with other drugs affecting statin metabolism, and therefore less likely to cause myopathy when used with one of these drugs.[5]

As mentioned in the prescribing information of Lescol® / Lescol® XL,[6] the most commonly reported adverse drug reactions are minor gastrointestinal symptoms, insomnia and headache. Previous drug surveillance study performed in Germany[7] showed that gastrointestinal symptoms were the most frequent adverse events after fluvastatin therapy, followed by central nervous system disorders, headaches, and muscle and joint symptoms. In the present post-marketing study, the most common adverse events were central nervous system problems (with dizziness as the most frequent event) followed by gastrointestinal symptoms (with nausea as the most prevalent), and musculoskeletal symptoms (myalgia) (see Table 3).

The number of all adverse events in the previous surveillance study[7] were 167 events in 5000 patients (3.34%) and these events occurred in 130 patients (2.6%). Almost all of the events were thought to be possibly related to fluvastatin. In the present study, the number of all adverse events were 51 events in 740 patients (6.89%), occurring in 39 patients (5.27%). Thirty-nine events (5.27%) were considered probably or possibly related to fluvastatin, and these occurred in 32 patients (4.32%). The lower incidence of AEs in the previous study may be caused by the lower doses of fluvastatin used in the previous study (20 mg and 40 mg),[7] however AE rates observed in individual PMS studies may be influenced by a variety of external factors which clearly limits any comparisons of findings across different PMS studies.

Among the concomitant medications, agents known or likely to interact with fluvastatin were simvastatin (3 patients), pravastatin (1 patient) and fenofibrate (4 patients). According to the protocol, these patients should be excluded from this study, but they were included. Fortunately, there was no adverse event reported by these 8 patients, which despite of the low number of patients (n = 8) may indicate the absence of interactions with fluvastatin.

In statin therapy, muscular side effects or musculoskeletal disorders (muscle cramp, myalgia, myopathy, rhabdomyolysis) are of particular interest. In the PRIMO (Prediction of Muscular Risk in Observational conditions) survey, muscular side effects were observed in an unselected population of 7924 hyperlipidemic patients receiving high-dosage statin therapy in a usual care, outpatient setting in France.[8] Multivariate analysis revealed the strongest predictors for muscular side effects were a personal history of muscle pain during lipid-lowering therapy (OR = 10.12), unexplained cramps (OR = 4.14) and a history of creatine kinase (CK) elevation (OR = 2.04).[8] Fluvastatin XL 80 mg was associated with the lowest rate of muscular side effects (5.1%) among individual statins.[8] The type of statin used was an independent predictor, and using high-dosage pravastatin as the reference, fluvastatin XL was associated with a significantly lower risk of muscular symptoms (OR = 0.33).[8] In the present study, the incidence of musculoskeletal disorders were 0.81%, while its predictors were not investigated.

In the present study, creatinine kinase (CK) level was not measured. From pooled Novartis-sponsored clinical trial data between 1987 and 2001, in 1724 hyper-

cholesterolemic patients treated with fluvastatin XL 80 mg, elevated CK levels ≥ 5 x upper limit of normal (ULN) was found in only 0.3% of patients, not more frequent than that found in placebo (0.9%), while elevation of CK levels ≥ 10 x ULN was not found.[9] In all of these studies, no cases of rhabdomyolysis were found with fluvastatin monotherapy.[9]

In the pooled Novartis-sponsored clinical trial data, fluvastatin was administered in combination with bezafibrate, fenofibrate or gemfibrozil, and the frequency of CK elevations was not statistically different from that of placebo or of each drug used as monotherapy.[10] In the present study, combination with fenofibrate (in 4 patients) caused no adverse event. Fluvastatin XL, with its sustained low plasma levels and slight potential for drug interactions, may represent a first choice statin for patients requiring combination lipid-lowering therapy.[11]

In the present study, fluvastatin XL 80 mg caused a 28.6% decrease in LDL-C at 8 weeks (Table 4), which was lower than 31-35% as mentioned in the standard book Goodman & Gilman[4] and 34% as mentioned in Lescol® / Lescol® XL prescribing information[6], and much lower than 38.1% found in the previous surveillance study,[7] but similar to that in some long-term studies with clinical endpoints (LISA 27% and LIPS 27%).[12] LISA, Lescol in Severe Atherosclerosis, recruited 365 patients with clinical CHD and treated with 40-80 mg fluvastatin od for 12 months, while LIPS, Lescol Intervention Prevention Study, recruited 1677 patients with post-PCI and treated with 80 mg fluvastatin od for 3.9 years.[12] In a pooled analysis of 3 clinical trial data, treatment with fluvastatin XL caused reductions in LDL-cholesterol of ≥ 40% in 40% of the patients[13] while in the present study, fluvastatin XL caused a reduction in LDL-cholesterol of ≥ 40% in only 19.6% of the patients (Table 6).

The decrease in total cholesterol in the present study was 30.2% after 8 weeks treatment with fluvastatin XL 80 mg (Table 4). This decrease was higher than 23% as mentioned in the in Lescol® / Lescol® XL prescribing information[6] and still higher than 27.2% found in the previous surveillance study.[7]

The increase in HDL-cholesterol in the present study was only 14.3% after 8 weeks treatment with fluvastatin XL 80 mg (Table 4). This increase was much lower than 27.3% found in the previous surveillance study,[7] but similar to 14% as mentioned in the in Lescol® / Lescol® XL prescribing information[6] and also to the pooled clinical trial data which ranged between 6.6% to 21.1%.[13] The higher the baseline triglyceride levels, the higher the increase of HDL-cholesterol. In the pooled clinical trial data,[13] the increase of HDL-cholesterol was 21.1% in the subset of patients with baseline triglyceride levels ≥ 300 mg/dL. In the same subset of patients in the present study, the HDL-cholesterol increased to 18.1%.

In the present study, treatment with fluvastatin XL led to a 24.5% reduction in triglyceride levels at 8 weeks (Table 4). This reduction was higher than 8.6% to 20.3% found in the previous surveillance study[7] which recruited patients with baseline triglyceride levels within normal to < 300 mg/dL. The decrease of triglyceride in the present study was higher than 19% as mentioned in the in Lescol® / Lescol® XL prescribing information[6] which recruited patients with baseline triglyceride levels ≤ 400 mg/dL. In the pooled clinical trial data,[13] the median decreases in triglyceride levels was 19%, increasing to 31% in the subset of patients with baseline triglyceride levels ≥ 300 mg/dL. In the present study, the decrease in triglyceride in the same subset of patients was even higher, 38.1% (Table 5).

The present study was a post-marketing study, and of course did not meet the criteria of a randomized controlled clinical trial. Therefore, the results were not quite the same as expected from controlled clinical trials. Although clinical trials provide the real efficacy with limited safety of the drug (because of the limited number of patients included), but the clinical situations are rather artificial. On the other hand, a drug surveillance study provide the safety and tolerability and effectiveness of the drug in a real life situation. A post-marketing study should recruit thousands of patients, therefore the present study with 740 patients was a small post-marketing study. Nevertheless, the results of this limited post-marketing study supported the results of the pooled clinical trial data that fluvastatin XL was well tolerated and effective. The physicians' global evaluation about treatment with fluvastatin XL at week 8 also came to the same conclusions (Table 7).

CONCLUSIONS

The results of this PMS study has demonstrated that treatment with fluvastatin XL 80 mg once daily for 8 weeks in 740 patients was safe and well tolerated. In around 560 patients with hypercholesterolemia (baseline LDL-cholesterol ≥ 160 mg/dL), fluvastatin

XL was also shown to be effective in reducing LDL-cholesterol, total cholesterol and triglyceride levels, and in raising HDL-cholesterol level in daily clinical practice.

Acknowledgement

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