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Original article

Prevalence of potential drug interactions in Thai patients receiving simvastatin: The causality assessment of musculoskeletal adverse events induced by statin interaction

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ABSTRACT

Drug-drug interactions are one of the major risk factors associated with statin-induced myopathy. Although simvastatin is widely used in Thailand, studies investigating the prevalence of potential simvastatin-drug interactions (SDIs) and its clinical relevance in Thai population are still limited. We aimed to investigate the prevalence of potential SDIs (phase 1 study) and musculoskeletal adverse effects (AEs) associated with those interactions (phase 2 study). A phase 1 study was retrospectively conducted with outpatients at a 60-bed hospital who received simvastatin between July 1, 2012 and June 30, 2013. In phase 2, study was cross-sectionally conducted in outpatients whose prescriptions contain potential SDIs. Musculoskeletal AEs were evaluated by using symptom checklist questionnaires and measuring plasma creatinine kinase (CK). The causal relationship between the AEs and the potential SDIs was assessed using a Drug Interaction Probability Scale.

Out of 3447 simvastatin users, potential SDIs were found in 314 patients (9.1%). The prevalence of prescriptions containing potential SDIs was in the range of 4.7–6.0%. Two-thirds of the potential SDIs were rated to be highly significant while more than 70% were in contraindication list. The most common precipitant drugs were gemfibrozil (382 prescriptions), colchicine (171 prescriptions) and amlodipine (152 prescriptions). Of 49 patients recruited into phase 2 study, we found that 31 patients (63.3%) had myopathy. Myalgia was the most frequently identified AEs (n = 18, 58.1%), followed by asymptomatic rising CK (n = 8, 25.8%), and myositis (n = 5, 16.1%). Musculoskeletal AEs associated with SDIs were found in 16 patients (51.6%). Of these, we found 50.0%, 31.3% and 18.8% had asymptomatic rising CK, myalgia, and myositis, respectively. Precipitant drugs associated with myopathy were amlodipine (2 possible cases), colchicine (3 possible cases), gemfibrozil (8 possible and 1 probable cases), nevirapine (1 possible case), and nicotinic acid (1 possible case).

Potential SDIs have been found in the Thai population with a prevalence that is consistent with previous reports. Half of the musculoskeletal AEs identified were associated with SDIs. Systematic screening and management with interdisciplinary co-operation are needed to increase awareness of potential SDIs.
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1. Introduction

3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), are the cornerstones of dyslipidemia treatment. There is strong evidence supporting statin use for primary and secondary prevention of cardiovascular diseases (Stone et al., 2013). Statin use is generally safe and well tolerated; however, musculoskeletal adverse effects (AEs) are important causes of statin intolerance and discontinuation (Kashani et al., 2006; Law and Rudnicka, 2006; Armitage, 2007). In 2001, cerivastatin was withdrawn from the

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market because of the high report of fatal rhabdomyolysis, which was found to be associated with the patients who concomitantly received gemfibrozil (Furberg and Pitt, 2001; Staffa et al., 2002). Although a low incidence of statin induced myopathy was identified in clinical trials (Pasternak et al., 2002; Kashani et al., 2006), higher rates have been reported in clinical setting (de Sauvage Nolting et al., 2002; Franc et al., 2003; Bruckert et al., 2005). Many risk factors, including statin-drug interactions, were associated with higher incidences reported in clinical practice. To date, the computerized screening program has been developed and implemented in several hospitals to increase awareness of potential drug interactions. However, the co-prescription of statin, in particular simvastatin, with potential interacting drugs has been reported in several studies (Piacentini et al., 2005; Ratz Bravo et al., 2005; Tirkkonen et al., 2008; Bakhai et al., 2012). In Thailand, Boonmuang et al. (2013) reported that 40% of patients with statin induced myopathy received at least one potential interacting drug.

Among other statins, simvastatin has the highest potential for statin-drug interactions, in particular pharmacokinetic drug interactions. Simvastatin is a substrate of transporters including P-glycoprotein (P-gp) and organic anion transporting polypeptide (OATP) 1B1, and largely metabolized in the liver by CYP3A4 (Neuvonen et al., 2006; Shitara and Sugiyama, 2006; Chatzizisis et al., 2010; Bellosta and Corsini, 2012). Co-administration of simvastatin with interacting drugs that can inhibit these proteins may increase simvastatin exposure and potentiate its musculoskeletal AEs. In 2011, the US Food and Drug Administration (USFDA) changed the safety label of simvastatin (http://www.fda.gov/drugs/drugsafety/ucm256581.htm). Specifically, some changes include the addition of an interacting drug list for potential simvastatin-drug interactions. Simvastatin is mostly prescribed in Thailand, as it is in the Thai National List of Essential drugs and available in all hospitals. However, studies investigating the prevalence of potential simvastatin-drug interactions and their clinical relevance in Thailand are still limited. Thus, this study aims to investigate the prevalence of potential simvastatin-drug interactions in Piboonmungsaharn Hospital, a 60-bed secondary care setting, and to investigate the prevalence of musculoskeletal AEs associated with those interactions.

2. Methods

2.1. Study design

This study was divided into two phases. In phase 1, we retrospectively investigated the prevalence of potential simvastatin-drug interactions. Data were retrieved from hospital electronic medical records of outpatients who received simvastatin between July 1, 2012 and June 30, 2013. Potential simvastatin-drug interactions were screened based on the two references, Drug Interaction Facts 2011 (Tatro, 2011) and the USFDA safety communication 2011 (http://www.fda.gov/drugs/drugsafety/ucm256581.htm). According to Drug Interaction Fact 2011 reference, potential drug interactions were identified when the documentation level was in the level of possible or higher. In phase 2, we further investigated the prevalence and severity of the musculoskeletal AEs among the prescriptions containing potential simvastatin-drug interactions. Myopathy was evaluated by obtaining symptom checklist questionnaires and measuring plasma creatinine kinase (CK) levels. Myopathy was classified as asymptomatic rising CK, myalgia, myositis, and rhabdomyolysis (Pasternak et al., 2002). Causal relationships between musculoskeletal AEs and simvastatin-drug interactions were further evaluated with the Drug Interaction Probability Scale (DIPS).

2.2. Instruments

A musculoskeletal AEs questionnaire was used in this study to evaluate patient symptoms. The questionnaire is a symptom checklist that was modified from a previous study (Bruckert et al., 2005). The checklist consists of type, location, severity, duration, interruption of daily routine, onset of symptoms, other possible causes, management of the symptoms, and family history of myopathy. The questionnaire was tested for content validity in three health professionals containing one doctor and two pharmacists. The index of consistency was 0.95. The questionnaire was further tested in 10 patients to assure that they understand the questions. The causal relationship between a potential simvastatin-drug interaction and musculoskeletal AEs was performed with the Drug Interaction Probability Scale (DIPS), a tool that has been previously used to evaluate causation in potential drug interactions (Horn et al., 2007). The scale consists of 10 questions with the three answer options "yes", "no", or "unknown/not applicable". The total score is used to estimate the probability that the interaction is causally related to the AEs (Horn et al., 2007). In this study, we indicated that drug interaction is associated with AEs when the DIPS score is higher than or equal to 2. The probability can be classified as possible (2–4 scores), probable (5–8 scores) or highly probable (>8 scores) (Horn et al., 2007). The association is classified as doubtful if the total DIPS score is less than 2.

2.3. Data analysis

Data were evaluated with SPSS version 19 for Windows. The prevalence of potential simvastatin-drug interactions and musculoskeletal AEs associated with drug interactions was evaluated with descriptive statistics. The demographic data of patients in phase 2 with and without musculoskeletal AEs were compared with Mann-Whitney U tests and Chi-square tests for continuous and categorical variables, respectively.

2.4. Ethical approval

Both phases of study were approved by the Khon Kaen University Ethics Committee for human research (Institutional review board number: IRB00001189). Research was conducted in accordance with the principle of the Declaration of Helsinki and International Conference on Harmonization for Good Clinical Practice.

3. Results

3.1. Demographic data of patients in phase 1

All 3447 simvastatin users were screened for potential simvastatin-drug interactions. Demographic data are shown in Table 1. There were 2428 females (70.4%), and the average age was 60.8 ± 11.7 years old with the one-third of the patients being over 65 years old. Approximately 80% of the patients were agriculturists and used a universal coverage scheme for health payment. Most patients used 20 mg/day simvastatin (average dose 17.4 ± 6.5 mg/day); however, 122 patients used simvastatin at a dose of greater than 40 mg/day. More than half of the patients had underlying diabetes and/or hypertension.

3.2. Prevalence of potential simvastatin-drug interaction

Of 3447 simvastatin users, potential simvastatin-drug interactions were found in 314 patients (9.1%) (Table 2). We found potential simvastatin-drug interactions in 271 cases (7.9%) based on the information in Drug Interactions Facts 2011 and in 236 cases (6.8%)

Table 1
Demographic data of patients in phase 1.

Characteristics	
No. of patients; *n* (%)	3447 (100)
Female; *n* (%)	2428 (70.4)
Mean age (years); mean ± SD	60.8 ± 11.7
No. of patients with age > 65; *n* (%)	1116 (32.4)
Body weight (kg); mean ± SD	61.3 ± 11.5
GFR (ml/min); mean ± SD	70.4 ± 27.4
Baseline lipid profile; mean ± SD	
Total cholesterol (mg/dL)	235 ± 43.6
LDL-cholesterol (mg/dL)	125 ± 40.3
HDL-cholesterol (mg/dL)	45 ± 13.5
Triglyceride (mg/dL)	251 ± 157.3
Dose of statin (mg/day); mean ± SD	17.4 ± 6.5
No. of patients taking simvastatin > 40 mg/day; *n* (%)	122 (3.5)
Concomitant diseases; *n* (%)	
Hypertension	2243 (65.1)
Diabetes mellitus	1954 (56.7)
Chronic kidney disease	297 (8.6)
Cerebrovascular disease	151 (4.4)
Coronary heart disease	149 (4.3)
Gout	79 (2.3)

Table 2
Prevalence of potential statin-drug interaction.

	n (%)
Total no. of simvastatin users	3447 (100)
No. of patients with potential simvastatin-drug interactions	
Overall	314 (9.1)
Based on Drug Interaction Facts 2011	271 (7.9)
Based on USFDA drug safety communication 2011	236 (6.8)
Total no. of simvastatin prescriptions	13109 (100)
No. of prescriptions containing potential simvastatin-drug interactions	
Based on Drug Interaction Facts 2011	787 (6.0)
Based on USFDA drug safety communication 2011	611 (4.7)

based on the interactions listed in the USFDA drug safety communication 2011 (Table 2). Of 13,109 prescriptions we screened, we found 787 prescriptions (6.0%) and 611 prescriptions (4.7%) that contained potential simvastatin-drug interactions based on Drug Interactions Facts 2011 and USFDA drug safety communication 2011, respectively (Table 2).

3.3. List of precipitant drugs co-prescribed with simvastatin

Overall, most of the precipitant drugs co-prescribed with simvastatin were gemfibrozil (382 prescriptions), colchicine (171 prescriptions) and amlodipine (152 prescriptions). Based on Drug Interactions Facts 2011, gemfibrozil had the highest frequency of co-administration with simvastatin (48.5%), while colchicine (21.7%) and nicotinic acid (12.2%) were the second and third most frequently prescribed, respectively (Table 3). Additional precipitant drugs that were identified were ketoconazole (5.7%), nevirapine (4.6%), efavirenz (2.9%), erythromycin (1.5%), verapamil (1.5%), clarithromycin (0.6%), diltiazem (0.4%) and fluconazole (0.3%) (Table 3). According to data in USFDA drug safety communication 2011, gemfibrozil was most frequently co-administered with simvastatin (62.5%), while amlodipine (24.9%) and ketoconazole (7.4%) were the second and third most frequently prescribed, respectively (Table 3). Additional precipitant drugs that we identified were verapamil (2.0%), erythromycin (2.0%), clarithromycin (0.8%) and diltiazem (0.5%), as shown in Table 3.

Table 3
List of precipitant drugs that potentially cause simvastatin-drug interaction.

Precipitant medications	*n* (%)
Based on data in Drug Interaction Fact 2011[a]	787 (100)
Gemfibrozil (1)	382 (48.5)
Colchicine (4)	171 (21.7)
Niacin (4)	96 (12.2)
Ketoconazole (1)	45 (5.7)
Nevirapine (1)	36 (4.6)
Efavirenz (1)	23 (2.9)
Erythromycin (1)	12 (1.5)
Verapamil (2)	12 (1.5)
Clarithromycin (1)	5 (0.6)
Diltiazem (2)	3 (0.4)
Fluconazole (1)	2 (0.3)
Based on data in USFDA drug safety communication 2011	611 (100)
Gemfibrozil	382 (62.5)
Amlodipine	152 (24.9)
Ketoconazole	45 (7.4)
Erythromycin	12 (2.0)
Verapamil	12 (2.0)
Clarithromycin	5 (0.8)
Diltiazem	3 (0.5)

[a] Number in parenthesis indicates significant rating where a rating of 1 is major in severity with the effects of potentially life-threatening and with certain documented evidences, whereas a rating of 5 is unlikely evidenced or only limited data in resulting minor severity.

3.4. Documentation and significance of potential simvastatin-drug interactions

Documentation and significance levels of potential simvastatin-drug interaction were rated based on the data in Drug Interaction Facts 2011. According to the documentation, we found that potential simvastatin-drug interactions were rated as possible (267 prescriptions, 33.9%), suspected (441 prescriptions, 56.1%) and probable (79 prescriptions, 10.0%). These interactions had significance levels of level 1 (64.2%), level 2 (1.9%) and level 4 (33.9%). As classified by the USFDA prescribing recommendation 2011, 72.7% (444 prescriptions) of the prescriptions were in the contraindication list, while 2.5% (15 prescriptions) and 24.9% (152 prescriptions) were prescribed with simvastatin doses exceeding 10 and 20 mg, respectively.

3.5. Demographic data of patients in phase 2

Of 314 patients whose prescriptions contained potential simvastatin-drug interactions that were identified during phase 1, forty-nine patients were further investigated for musculoskeletal AEs during phase 2. Two hundred and fifty-one patients were excluded, as 53 patients used short course co-medication, 138 patients discontinued co-medication before starting phase 2, 38 patients were referred to primary care or other hospitals and 22 patients were lost during follow-up. When phase 2 was initiated, 14 patients were further excluded, as six patients discontinued co-medication by themselves and 8 patients were lost during follow-up throughout the study period. Demographic data of patients in phase 2 are shown in Table 4. Of 49 patients, there were 26 females (53.1%) and 23 males (46.9%) with average age of 63.9 ± 12.1 years old and average BMI of 24.6 ± 3.1 kg/m^2. Most patients (89.8%) had an education in primary school and were unemployed. All of the patients used a universal coverage scheme for health payment. Most patients had underlying hypertension and about half of the patients had diabetes. Most patients (75%) used 20 mg/day simvastatin (average dose 24.5 ± 10.0 mg/day) for primary prevention indications (87.8%). The respective average total cholesterol, LDL, HDL and triglyceride levels before simvastatin use were 257.0 ± 73.1 mg/dl, 150.4 ± 40.2 mg/dl,

Table 4
Demographic data of patients in phase 2.

Characteristics	With musculoskeletal AEs	Without musculoskeletal AEs	Total	*P*-value
No. of patients	31 (63.3)	18 (36.7)	49 (100)	
Gender; *n* (%)				0.790
Male	15 (65.2)	8 (34.8)	23 (100)	
Female	16 (61.5)	10 (38.5)	26 (100)	
Mean age (years); mean ± SD	64.3 ± 11.9	63.2 ± 12.6	63.9 ± 12.1	0.716
No. of patients with Age > 65; **n** (%)	15 (65.2)	8 (34.8)	23 (100)	
BMI (kg/m^2); mean ± SD	24.9 ± 3.2	24.0 ± 3.0	24.6 ± 3.1	0.340
Renal function; mean ± SD				
BUN (mg/dL)	22.5 ± 19.2	22.4 ± 18.1	21.7 ± 16.0	0.701
Cr (mg/dL)	1.5 ± 1.5	1.2 ± 0.4	1.4 ± 1.2	0.884
GFR (ml/min)	59.6 ± 22.5	60.5 ± 20.5	60.0 ± 22.0	0.694
Indication of statin; *n* (%)				0.854
Primary prevention	27 (62.8)	16 (37.2)	43 (100)	
Secondary prevention	4 (66.7)	2 (33.3)	6 (100)	
Baseline lipid profile; mean ± SD				
Total cholesterol (mg/dL)	241.9 ± 58.8	285.1 ± 89.9	257.0 ± 73.1	0.307
LDL (mg/dL)	154.1 ± 41.6	170.7 ± 35.8	150.4 ± 40.2	0.300
HDL (mg/dL)	46.5 ± 10.3	47.9 ± 16.9	46.9 ± 12.6	0.919
Triglyceride (mg/dL)	248.0 ± 136.4	246.5 ± 153.1	247.5 ± 140.8	0.860
Current lipid profile; mean ± SD				
Total cholesterol (mg/dL)	203.3 ± 60.4	231.2 ± 63.6	213.4 ± 62.4	0.232
LDL (mg/dL)	119.0 ± 36.5	137.7 ± 47.5	126.0 ± 41.5	0.237
HDL (mg/dL)	46.0 ± 11.8	51.4 ± 20.9	48.0 ± 15.6	0.169
Triglyceride (mg/dL)	234.3 ± 146.1	238.9 ± 154.8	235.8 ± 147.3	0.971
Dose of statin; *n* (%)				0.173
⩽10 mg/day	3 (60.0)	2 (40.0)	5 (100)	
11– 20 mg/day	22 (73.3)	8 (26.7)	30 (100)	
21–30 mg/day	0 (0.0)	1 (100)	1 (100)	
31–40 mg/day	6 (46.2)	7 (53.8)	13 (100)	
Duration of statin use (Days); mean ± SD	998.2 ± 600.4	1000.3 ± 658.7	1035.7 ± 611.3	0.611
Duration of coadministration simvastatin and precipitant drug (Days); mean ± SD	549.2 ± 455.7	530.6 ± 366.5	542.4 ± 412.3	0.500
Creatinine Kinase level (U/L); mean ± SD	180.8 ± 113.9	177.62 ± 115.5	176.7 ± 113.4	0.051

46.9 ± 12.6 mg/dl and 247.5 ± 140.8 mg/dl, and the respective current total cholesterol, LDL, HDL and triglyceride levels were 213.4 ± 62.4 mg/dl, 126.0 ± 41.5 mg/dl, 48.0 ± 15.6 mg/dl and 235.8 ± 147.3 mg/dl. The average GFR for all patients was 60.0 ± 22.0 ml/min. Most patients did not consume alcohol and more than half of the patients had never smoked. The average duration of simvastatin use was 1035.7 ± 611.3 days and the average duration of co-administration of simvastatin and precipitant drugs was 542.4 ± 412.3 days. The average CK level for all patients was 176.7 ± 113.4 mg/dl. There were no significant differences in the demographic data between patients with and without musculoskeletal AEs (Table 4).

3.6. Prevalence and type of musculoskeletal adverse events

Of 49 patients recruited for phase 2, we identified 31 patients (63.3%) that had musculoskeletal AEs. Of these, 18 patients (58.1%) had myalgia, 8 patients (25.8%) had an asymptomatic increase in their CK levels, and 5 patients (16.1%) had myositis (Table 5). However, no patients had rhabdomyolysis. Gemfibrozil was the highest frequency of co-administration with simvastatin in patients with musculoskeletal adverse events ($n = 12$; 46.2%), while colchicine ($n = 11$; 35.5%) and amlodipine ($n = 5$; 16.1%) were the second and third most frequently used in those patients, respectively (Table 5). The type of actual musculoskeletal adverse events found in patients who received any interacting drugs is shown in Table 5. Using the DIPS to assess the association between simvastatin-drug interactions and AEs, we found that musculoskeletal AEs associated with simvastatin-drug interactions were found in 16 of 31 patients (51.6%) and could be divided into 5 patients (31.3%) with myalgia, 3 patients (18.8%) with myositis and 8 patients (50.0%) with asymptomatic increases in CK (Table 5). The precipitant drugs associated with simvastatin to induce myopathy were amlodipine (2 possible cases), colchicine (3 possible cases), gemfibrozil (8 possible cases and 1 probable case), nicotinic acid (1 possible case), and nevirapine (1 possible case).

4. Discussion

In phase 1 study, there were 3447 patients who used simvastatin between July 2012 and June 2013. Of these, we identified 314 users (9.1%) that had potential simvastatin-drug interactions. Two-thirds of the potential simvastatin-drug interactions were rated as highly significant, whereas more than 70% of the potential interactions were in the contraindication list as indicated in the USFDA drug safety communication 2011. The most common precipitant drugs we identified were gemfibrozil, colchicine and amlodipine.

The prevalence of potential simvastatin-drug interactions found in Thai patients is consistent with that of previous studies from other countries and is in the range of 6–13% (Ratz Bravo et al., 2005; Ming et al., 2008; Tirkkonen et al., 2008; Devold et al., 2009; Bakhai et al., 2012). However, the most common precipitant drugs for potential simvastatin-drug interactions were gemfibrozil, colchicine and amlodipine, while previous studies showed that verapamil, diltiazem and macrolide antibiotics were most frequently co-prescribed with statins (Ratz Bravo et al., 2005; Ming et al., 2008; Tirkkonen et al., 2008; Devold et al., 2009; Bakhai et al., 2012). These inconsistent results could be due to differences in research settings, criteria for selecting potential statin-drug interactions, availability of medication in hospital formularies,

Table 5
Prevalence and type of actual musculoskeletal adverse events and myopathy associated with simvastatin-drug interaction.

	n (%)
Patients without any musculoskeletal adverse events (*n* = 18; 36.7%)	
Patients with any musculoskeletal adverse events (n = 31; 63.3%)	
Myalgia	18 (58.1)
Myositis	5 (16.1)
Asymptomatic raising CK	8 (25.8)
List of interacting drugs and type of actual musculoskeletal adverse events	
Gemfibrozil (*n* = 12; 38.7%)	
Myalgia	7 (58.3%)
Myositis	1 (8.3%)
Asymptomatic raising creatinine kinase	4 (33.3)
Colchicine (*n* = 11; 35.5%)	
Myalgia	7 (63.6%)
Myositis	3 (27.3%)
Asymptomatic raising creatinine kinase	1 (9.1%)
Amlodipine (*n* = 5; 16.1%)	
Myalgia	2 (40%)
Myositis	1 (20%)
Asymptomatic raising creatinine kinase	2 (40%)
Nevirapine (*n* = 2; 6.5%)[a]	
Nicotinic acid (*n* = 1; 3.2%)[a]	
Patients with musculoskeletal adverse events associated with simvastatin-drug interaction[b] (*n* = 16; 51.6%)	
Myalgia	5 (31.3)
Myositis	3 (18.8)
Asymptomatic raising CK	8 (50.0)

[a] All cases presented myalgia.
[b] DIPS probability was at least possible level.

the reimbursement policy and the clinical practice guidelines during the study period.

There are limitations in the available medication in the setting we studied. For example, gemfibrozil is the only fibrate available in a community setting in Thailand, whereas tertiary care providers have fenofibrate as an alternative choice. Therefore, instead of gemfibrozil, they can use a combination of fenofibrate and statins, which have lower risks of myopathy than gemfibrozil (Stone et al., 2013). It should be noted that fenofibrate-simvastatin and gemfibrozil-simvastatin combinations are rated as 1 in the significance rating as indicated in Drug Interaction Facts 2011 (Tatro, 2011); however, according to the USFDA drug safety communication 2011, the combination of fenofibrate and simvastatin is not in the contraindication list (http://www.fda.gov/drugs/drugsafety/ucm256581.htm).

There is some variation in the precipitant drug selection criteria between studies. Some studies included both CYP3A4 inhibitors and inducers (Tirkkonen et al., 2008) while some studies used only CYP inhibitors and other drugs that have case reports and clinically relevant interactions (Ratz Bravo et al., 2005; Devold et al., 2009). In our study, we chose precipitant drugs that are listed in Drug Interaction Facts 2011 (Tatro, 2011) and the USFDA prescribing recommendation 2011 (http://www.fda.gov/drugs/drugsafety/ucm256581.htm). All of the drugs chosen are precipitant drugs that may potentiate musculoskeletal AEs from simvastatin use via pharmacokinetic and pharmacodynamic interactions. However, there are some differences in the precipitant drug lists between both references; for example, amlodipine is found in the USFDA prescribing recommendation 2011 but not in Drug Interaction Facts 2011.

The practice guidelines use in each country may also affect the list of common interacting drugs found between studies. For example colchicine use is recommended for the treatment of gout. In Thailand, guidelines recommend colchicine use for up to 12 months to prevent exacerbation of gout attacks (Personal communication). However, in European countries, colchicine is recommended for the treatment of acute gout attacks in short-term therapy that is limited to less than 6 months (Jordan et al., 2007). Use of colchicine over longer periods of time may enhance the risk of drug-drug interactions.

In phase 2 study, we found 63.3% of patients with potential simvastatin-drug interactions that had musculoskeletal AEs. Of these, 51.6% had musculoskeletal AEs that were associated with simvastatin-drug interactions. Gemfibrozil, colchicine and amlodipine were the most common interacting drugs associated with these events. This result is consistent with the association shown in previous studies (Cziraky et al., 2006; Tirkkonen et al., 2008; Boonmuang et al., 2013). In particular, the data from the Thai Vigibase showed that among 198 cases of statin-related muscular AEs, 40% of the cases received at least one potential interacting drug (Boonmuang et al., 2013). The most common interacting drugs indicated were gemfibrozil and colchicines (Boonmuang et al., 2013).

Simvastatin, when taken orally is converted from its inactive lactone form to the active β-hydroxy acid via hydrolysis (Neuvonen et al., 2006; Shitara and Sugiyama, 2006; Chatzizisis et al., 2010; Bellosta and Corsini, 2012). Simvastatin is intensively metabolized to inactive forms by CYP3A4 in the intestinal wall and liver (Neuvonen et al., 2006; Shitara and Sugiyama, 2006). Apart from CYP3A4-mediated drug interaction, transporting proteins may involve simvastatin disposition and pharmacokinetic drug interaction. Notably, simvastatin is a substrate of P-glycoprotein (P-gp) and organic anion transporting polypeptide (OATP) 1B1 (Neuvonen et al., 2006; Shitara and Sugiyama, 2006). The former is expressed in the intestinal wall and may contribute to simvastatin pre-systemic extraction, while OATP1B1 is the protein that uptakes simvastatin into the liver (Neuvonen et al., 2006; Shitara and Sugiyama, 2006). Thus, co-administration of simvastatin with CYP3A4 and/or transporter inhibitors may potentially increase the exposure of simvastatin and potentiate the risk of musculoskeletal AEs.

Apart from its myotoxicity, gemfibrozil can also interfere simvastatin pharmacokinetics. Although gemfibrozil does not inhibit CYP3A4, it can inhibit OATP1B1 transporter-mediated hepatic uptake (Neuvonen et al., 2006; Shitara and Sugiyama, 2006) and UGT-mediated lactonization (Prueksaritanont et al., 2002) suggesting that gemfibrozil can increase the plasma concentrations of simvastatin which may increase the risk of musculoskeletal AEs (Corsini, 2005; Bellosta and Corsini, 2012). According to Drug Interaction Facts 2011, the interaction between simvastatin and gemfibrozil is highly significant (level 1) and also in the contraindication list as indicated in the USFDA 2011 warning. Although severe musculoskeletal AEs were not found in this study, rhabdomyolysis during concomitant use of simvastatin and gemfibrozil has been previously reported (Graham et al., 2004; Enger et al., 2010; Boonmuang et al., 2013).

Amlodipine was shown to be a weak CYP3A4 inhibitor (Katoh et al., 2000). Several studies showed that the area under the plasma concentration/time curve of simvastatin was increased when co-administered with amlodipine (Nishio et al., 2005; Son et al., 2014). A higher exposure to simvastatin when taken with amlodipine may increase the risk of statin-induced myopathy. The recommendation from the USFDA is to limit the dose of simvastatin to no more than 20 mg when co-administered with amlodipine; however, according to Drug Interaction Facts 2011, amlodipine does not interact with simvastatin.

The interaction between colchicine and simvastatin can be explained by both pharmacokinetic and pharmacodynamic mechanisms. Colchicine itself can induce myotoxicity (Kuncl et al., 1987). In addition, colchicine is a substrate of CYP3A4 and P-glycoprotein (Niel and Scherrmann, 2006), and thus, it may

interfere with simvastatin clearance leading to an elevated plasma level of simvastatin. The interaction between colchicine and simvastatin has a level 4 significance rating according to Drug Interaction Facts, whereas the USFDA does not define any contraindications or dose limitations for colchicine when combined with simvastatin. However, acute myopathy was reported in patients receiving long-term treatment with simvastatin after adding colchicine to the treatment regimen (Hsu et al., 2002; Baker et al., 2004). Notably, previous report from the Thailand database indicated that colchicine has been identified as the second most common interacting drug associated with statin-induced myopathy (Boonmuang et al., 2013).

To our knowledge, this is the first study that used the Drug Interaction Probability Scale (DIPS) as a tool to assess the causality of statin interaction-induced AEs. The causality can be classified as doubtful, possible, probable and highly probable. DIPS was developed from the Naranjo algorithm (Horn et al., 2007), the nomogram for the estimation of the probability of adverse drug reactions. Since 2007, case reports have often used DIPS to assess the causality of drug interactions and AEs. One such study reported a case of severe rhabdomyolysis that was associated with a possible interaction between simvastatin and ketoconazole (Watkins et al., 2011). Hu et al. reported two cases of myopathy related to a possible simvastatin-diltiazem interaction using DIPS assessment (Hu et al., 2011). With DIPS, the case reports illustrated that the probability of drug interactions was in primarily listed in the "possible" level (Hu et al., 2011; Watkins et al., 2011). Consistent with these reports, we found that the musculoskeletal AEs associated with simvastatin-drug interactions were mostly found in the "possible" level (15 cases), and only 1 case was found to be in the "probable" level. Our study found that the association of simavastatin-drug interactions and musculoskeletal AEs was considered to be doubtful (scores less than 2) for approximately 40% of cases. The low DIPS scores can be explained by two major factors, including alternative factors that can trigger myopathy such as concomitant diseases and heavy physical exertion, and the timing of co-medication and the onset of AEs. In addition, there are 3 out of 10 topics that cannot be assessed, including "dechallenge and rechallenge of interacting drugs", "consistence of interaction and simvastatin plasma concentration" and "magnitude of interaction when increase or decrease the dose of precipitant drugs".

We are aware that our research may have some limitations. Firstly, the data that were retrospectively reviewed in phase 1 of our study were retrieved from medical records, and thus, medication from the other sources (i.e., drug stores) cannot be accounted for. Secondly, as this study was conducted in a community hospital, the prevalence and pattern of drug interactions obtained from tertiary care or university hospital settings may differ from our data. Finally, because of the small number of patients recruited in phase 2, we cannot evaluate the association of patient demographics and musculoskeletal AEs. In addition, a study using the DIPS tool to assess the causality of drug interactions and AEs should be further investigated in a larger population.

5. Conclusions

Potential simvastatin-drug interactions have been identified in Thai patients with a prevalence that is consistent with previous reports. Gemfibrozil, colchicine and amlodipine were the most common interacting drugs observed in this study. The combination of these drugs with simvastatin may potentiate musculoskeletal AEs. The musculoskeletal AEs identified in this study consisted of myalgia, asymptomatic increase in CK, and myositis. Using the DIPS tool, we found that about half of the musculoskeletal AEs were associated with simvastatin-drug interactions.

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