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ORIGINAL RESEARCH ARTICLE

Characterization of Statin-Associated Myopathy Case Reports in Thailand Using the Health Product Vigilance Center Database

Pornwalai Boonmuang · Surakit Nathisuwan · Nathorn Chaiyakunapruk · Wimon Suwankesawong · Pattreya Pokhagul · Nattawat Teerawattanapong · Pairin Supsongserm

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Abstract

Background HMG-CoA reductase inhibitors [statins], a widely prescribed cholesterol-lowering therapy, are associated with muscle-related adverse events. While characteristics of such events are well documented in Western countries, little data exists for the Thai population.

Objective The aim of this study was to determine the characteristics of patients, type and dosing of statin, and to identify patterns of drug use that may be associated with such adverse events using the national pharmacovigilance database known as Thai Vigibase.

Method Muscle-related adverse events involving statins in the Thai Vigibase from 1996 to December 2009 were identified. For each report, the following information was extracted: patient demographics, co-morbidities, detailed information of adverse event, detailed information of suspected drug, treatment and outcome, as well as causality assessment and quality of reports. Descriptive statistics were performed for all study variables.

Results A total of 198 cases of statin-associated muscle-related adverse events were identified. Mean age was 61.4 ± 12.4 years of age and 59.6 % were female. Simvastatin, atorvastatin, rosuvastatin and cerivastatin were implicated as the suspected drug in 163 (82.3 %), 24 (12.1 %), 10 (5.1 %) and 1 (0.5 %) cases, respectively. Rhabdomyolysis accounted for 55.6 % of all muscle-related adverse events. Drug interactions known to enhance such toxicity of statins were identified in 40.9 % of the total set of reports. Similar to studies from Western countries, fibrates, HIV protease inhibitors, non-dihydropyridine calcium channel blockers, azole antifungals and macrolides were commonly found in such cases. Interestingly, colchicine has been identified as the second most common drug interaction in our database. Case fatality rates were 0.9, 1.6 and 16.7 %, when there were 0, 1 and ≥2 interacting drugs, respectively.

Conclusions Characteristics of muscle-related adverse events with statins in the Thai population showed some similarities and differences compared with Western countries. Such similarities included advanced age, female sex, certain co-morbidities and drug interactions. While the majority of interacting drugs are well known, a big proportion of cases of statin-colchicine interaction attributed to long-term use of colchicine in Thailand was noted and should be further investigated. Based on these results, an attempt to

P. Boonmuang
Faculty of Pharmacy, Prince of Songkla University, Songkla, Thailand

S. Nathisuwan (✉) · P. Supsongserm
Faculty of Pharmacy, Mahidol University, 447 Sri-ayutthaya Road, Rajthewi, Bangkok 10400, Thailand
e-mail: surakit.nat@mahidol.ac.th

N. Chaiyakunapruk
Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Center of Pharmaceutical Outcomes Research, Naresuan University, Phitsanulok, Thailand

N. Chaiyakunapruk
School of Population Health, University of Queensland, St. Lucia, QLD, Australia

N. Chaiyakunapruk
School of Pharmacy, University of Wisconsin-Madison, Madison, WI, USA

W. Suwankesawong · P. Pokhagul
Health Product Vigilance Center, Food and Drug Administration, Ministry of Public Health, Nonthaburi, Thailand

N. Teerawattanapong
Faculty of Pharmaceutical Sciences, Naresuan University, Phitsanulok, Thailand

avoid dangerous and well-known drug interactions among statin users should be implemented nationwide.

1 Background

Statins, or HMG-CoA reductase inhibitors, are a widely prescribed cholesterol-lowering drug class [1]. These drugs are with well documented benefits in cardiovascular risk reduction [2]. With wider approved indications along with 'the lower is the better' [3] concept of cholesterol reduction, statins usage has increased dramatically in recent years worldwide including Thailand [4–7]. Statins are often perceived as safe medications with minor adverse effects. However, their safety remains an issue of concern when considering the large number of patients being exposed to statins [8].

Among various adverse events of statins, muscle-related adverse events are of significant importance since these events can range from mild to severe reaction. Although mild symptoms of myalgia are more common and relatively benign, severe forms of muscle-related adverse events, such as myositis and rhabdomyolysis, can also occur. These severe events may result in hospitalization and even death in some cases. Data from randomized, controlled trials indicated that muscle symptoms associated with statin therapy occur in 1.5–3 % of patients with myalgia as the predominant event [9]. Data from a recent meta-analysis of statin trials comparing standard versus intensive treatment suggested that the incidence of rhabdomyolysis ranges from 0.01–0.04 %, respectively [3]. However, such incidence in real-world practice may be higher as a result of the exclusion of patients who are at high risk of muscle toxicity from clinical trials [10]. Concerns about these adverse events have been reinforced following the withdrawal of cerivastatin from the US market in August 2001 after numerous cases of serious myositis, including life-threatening rhabdomyolysis, were reported [11]. The risk appeared to be high among patients receiving the full dose (0.8 mg/day) and those receiving gemfibrozil concomitantly [11].

The importance of characterizing these muscle-related adverse events is underscored by the prevalence of statin use [4–7] and frequency of such events among the reported adverse events of statins [12]. To date, a number of studies have identified risk factors for severe muscle-related adverse events [13–16]. Schech et al. [13] conducted a nested case-control study among 252,460 new users of lipid-lowering therapy in the US. Using a conditional logistic regression analysis, the investigators found that age $\geq$65 years, high dose of statin, renal disease and female sex were associated with increased risk of hospitalization from rhabdomyolysis [13]. Cziraky et al. conducted a case-control study using an administrative managed-care claims database among 474,343 patients who received lipid-lowering therapy to evaluate risk factors for muscle, liver and renal adverse events requiring hospitalization. In addition to identifying hypertension and diabetes as risk factors, the investigators also reported a sixfold increase in myopathy requiring hospitalization due to concomitant use of cytochrome P450 (CYP) 3A4 inhibitors which highlighted a strong impact of drug interaction [14]. Other factors such as hypothyroidism, pre-existing myopathies, excessive alcohol consumption, liver dysfunction, use of certain addictive drugs, serious infection, major trauma and intensive muscle activity have been either reported or postulated to increase the risk of muscle-related adverse events [17]. Nevertheless, these factors have not been confirmed through any formal studies with robust epidemiological methods.

A spontaneous reporting system for adverse events is a method of postmarketing surveillance. Despite know limitations such as underreporting and limited quality of reports, the system is a valuable mechanism in identifying adverse events and their characteristics, which may lead to regulatory actions to improve patient safety [18–21]. Concerning muscle-related adverse events of statins, national spontaneous reporting databases have been analysed to describe demographic characteristics and drug interaction patterns of reported cases in various countries [15, 22, 23]. Using the Australian Adverse Drug Reaction database, Ronaldson et al. [15] reviewed the frequency of known risk factors among 96 and 39 cases of simvastatin and atorvastatin users, respectively, who suffered from rhabdomyolysis. Risk factors included in their analysis were age $\geq$70 years, statin dose $\geq$40 mg, pre-existing hepatic dysfunction, diabetes mellitus, hyperkalemia, hypothyroidism and interacting drugs. Overall, 95 % of cases were with at least one risk factor. Drug interaction was identified as a risk factor for 77 and 44 % of simvastatin and atorvastatin users, respectively [15]. The most common interacting drugs were gemfibrozil, diltiazem and ciclosporin (cyclosporine). Such a high frequency of drug interaction was also seen in previously published reports from other countries [22, 23].

Currently, there has been no formal study evaluating the risk factors of muscle-related adverse events among the Asian population. Data from a pharmacokinetic study has previously reported a twofold increase in rosuvastatin plasma level in the Asian population compared with the Caucasian population [24]. In addition, several studies also suggested heightened response to statins in the Asian population because of genetic differences in statin metabolism involving CYP and drug transporters [25–27]. Difference in drug use pattern, along with popularity of traditional medicine and herbal use among Asians [28],

reinforces the need for more information on such important events in this population.

In Thailand, the Health Product Vigilance Center (HPVC) was established under the Thai Food and Drug Administration, Ministry of Public Health, in 1983 (http://thaihpvc.fda.moph.go.th). The HPVC is responsible for the management and maintenance of the spontaneous reporting system concerning drugs and health products marketed in Thailand. Thai Vigibase was developed by the HPVC as the national database collecting all case reports submitted from both spontaneous reporting systems, intensive monitoring programs and clinical trials [29]. Healthcare professionals from all health facilities are urged to report suspected adverse events to the HPVC. Reports can be submitted either via an adverse event reporting form or via an online reporting system. Currently, a total of more than 30,000 reports are received and evaluated annually, and the Thai Vigibase now contains over 350,000 reports [30]. Recently, a surveillance study on herbal medicine use in Thailand carried out by Saokaew et al. [28] has used Thai Vigibase as an important source of the surveillance system and should be explored further in other dimensions.

2 Objective

Given the lack of information concerning muscle-related adverse events among statin users in Thailand, such a study is warranted. In this descriptive study, the Thai Vigibase was analysed with the aim of determining the characteristics of patients, type and dosing of implicated statins, and identifying signals or patterns of drug use that may be associated with statin-associated muscle events.

3 Methods

3.1 Data Source

The Thai Vigibase was used for this analysis; the database included all case reports of suspected adverse events submitted by health professionals throughout the country to the HPVC since the launch of Thai Vigibase in 1983 through December 2009. However, the first case related to statins was reported in 1996. Under the spontaneous reporting system, adverse event reports were collected nationwide via a national network covering more than 900 public and private hospitals and health service centres [29].

3.2 Criteria for the Selection of Cases

Reports were identified for all statins marketed in Thailand (i.e. atorvastatin, cerivastatin, fluvastatin, rosuvastatin, simvastatin) by generic name or trade name of statin-containing products in single or combined formulation. Since standardized terms for muscle-related adverse events of statins did not exist until recently, along with the lack of information on creatinine kinase levels in most reports, we were limited to performing case identification using only the terms reported by the reporters. These terms were myopathy, myositis, creatine phosphokinase increase, myoglobinuria, rhabdomyolysis, polymyositis or the WHO adverse reactions terminology (WHO-ART) preferred term code: 0072, 0074, 0748, 0791, 1002, 1210 and 1245. Data in Thai Vigibase were in Oracle® format. A unique HPVC number identified each unique report. From each report, the following information was extracted: patient demographics, co-morbidities, suspected reactions, suspected drug as well as concomitant treatments, dosage, route of administration and duration of treatment of the suspected drug, date of onset of the adverse event, outcome as well as causality assessment and quality of reports. We were unable to completely obtain the reason for use of the statins because of the limited information in most reports. When a patient experienced more than one of the events of interest, the most severe event was selected. For drug interaction assessment, the investigators used a standard reference [31] to evaluate presence and severity of drug interaction manually. Based on such reference, significance ratings of drug interaction were classified into five categorical levels, ranging from the highest (level 1) to the lowest severity of interaction as follows: 1 is a severe and well documented interaction; 2 is an interaction with moderate severity and suspected/well documentation; 3 is an interaction with minor severity and suspected/well documentation; 4 is an interaction with major/moderate severity and possible documentation; 5 is an interaction of no more than unlikely or possible documentation [31].

3.3 Method for Assessing Quality of Reports

Qualities of reports were assessed by the HPVC according to WHO-Uppsala Monitoring Centre (WHO-UMC) documentation grading [32]. Reports were classified into four grades (0, 1, 2 and 3) depending on data completeness. Reports that lack mandatory data for grading (case identification and data source), at least one suspected drug, and one adverse event term were classified as grade 0. For grade 1, reports must include data on patient identification, at least one suspect drug and at least one adverse event term. The reports also had to contain information on onset and treatment dates. For grade 2, indication for treatment must be additionally provided. For grade 3, information on positive rechallenge had to be given. Regardless of the grade, all reports were included in the analysis.

3.4 Data Analyses

The data were managed using Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA) and subsequently imported into STATA® version 10.1 (StataCorp LP, College Station, TX, USA) for analysis. All variables were analysed using descriptive statistics to determine total number of reports; mean age and number in each age group; percentage of sex, co-morbidities, distribution of muscle-related adverse events associated to each type of statin used, mean daily dose of each statin, time to onset of reaction, types and frequencies of concomitant treatment that may potentially interact with statin or precipitate muscle-related adverse events, clinical outcome and quality of reports.

4 Results

A total of 198 case reports of statin-associated muscle-related adverse events were identified. Most reports of such adverse events were submitted by physicians (80.0 %) followed by pharmacists (12.0 %) and nurses (8.0 %). Characteristics of reported cases are provided in Table 1. Age ranged from 15–90 years, with a mean age of 61.4 ±12.4 years and 59.6 % were female. More than half of the cases were >60 years of age. Eighty-five percent had no previously documented history of drug allergy. Diabetes (12.6 %), hypertension (12.1 %), ischaemic heart disease or history of myocardial infarction (5.1 %), gout (4.0 %) and HIV infection (3.5 %) were the five most common co-morbidities. Diabetes and hypertension accounted for a noteworthy fraction of patients with statin-associated rhabdomyolysis.

Simvastatin was the most commonly implicated drug. No reports of pravastatin or fluvastatin were found in the database. The average daily doses of each statin were 26.5 ± 17.0 mg/day for simvastatin, 11.5 ± 4.6 mg/day for atorvastatin and 13.6 ± 11.8 mg/day for rosuvastatin. Times to onset of reaction were 6.1 ± 9.2, 2.9 ± 4.3 and 2.9 ± 4.6 months for simvastatin, atorvastatin and rosuvastatin, respectively.

The most frequently reported muscle-related adverse events were rhabdomyolysis ($n = 110$), myopathy ($n = 50$) and myositis ($n = 38$). Causality of most reported events were classified as probable (73.7 %) according to the Naranjo's probability scale. Regarding quality of reports, most were graded at quality level 2 (64.1 %) [Table 1].

Sixty-one percent (121/198) of reported events were classified as serious, in which the majority (100/121) required hospitalization. There were 17 cases where the events were considered as either life-threatening (12/198)

Table 1 Demographic and clinical characteristics from Thai Vigibase of 198 statin-treated patients who experienced muscle-related adverse events

Parameter	Number of reports (%) [$N = 198$]
Age (years)	
Mean ± SD	61.4 ± 12.4
15–30	2 (1.1)
31–45	18 (9.1)
46–60	66 (33.3)
61–75	78 (39.4)
75–90	27 (13.6)
Not reported	7 (3.5)
Sex	
Female	118 (59.6)
Male	77 (38.9)
Not reported	3 (1.5)
Co-morbidities[a]	
Diabetes mellitus	25 (12.6)
Hypertension	24 (12.1)
IHD or history of myocardial infarction	10 (5.1)
Gout	8 (4.0)
HIV infection	7 (3.5)
Chronic kidney diseases	6 (3.0)
Acute coronary syndrome	4 (2.0)
Cerebrovascular disease	3 (1.5)
Atrial fibrillation	2 (1.0)
Asthma/COPD	2 (1.0)
Others[b]	4 (2.0)
Type of statins (mean daily dose ± SD)	
Simvastatin (26.5 ± 17.0 mg/day)	163 (82.3)
Atorvastatin (11.5 ± 4.6 mg/day)	24 (12.1)
Rosuvastatin (13.6 ± 11.8 mg/day)	10 (5.1)
Cerivastatin (NA)	1 (0.5)
Type of muscle-related adverse events	
Rhabdomyolysis	110 (55.6)
Myopathy	50 (25.2)
Myositis	38 (19.2)
Use of concomitant drugs	
Mean number of concomitant drugs (items)	3.2 ± 2.3
1–2 items	99 (50.0)
3–5 items	64 (32.3)
>5 items	35 (17.7)
Naranjo's probability scale	
Certain (score 9–10)	6 (3.1)
Probable (score 5–8)	146 (73.7)
Possible (score 1–4)	46 (23.2)
Quality of reports[c]	
3	5 (2.5)
2	127 (64.2)
1	55 (27.8)
0	11 (5.5)

COPD chronic obstructive pulmonary disease, *IHD* ischaemic heart disease, *NA* data not available, *SD* standard deviation, *WHO-UMC* World Health Organization-Uppsala Monitoring Centre

[a] Each case may have >1 co-morbidities

[b] Others include benign prostatic hyperplasia (1), osteoarthritis of knee (1), vessel disease (1), valvular heart diseases (1)

[c] WHO-UMC documentation grading [29]

Table 2 Severity of muscle-related adverse events among 198 reported cases

Severity of events	Number of cases (%)
Serious[a]	121 (61.1)
Hospitalization	100 (50.5)
Life-threatening	12 (6.1)
Death	5 (2.5)
Non-serious	76 (38.4)
Not reported	1 (0.5)

[a] Detailed data on severity for four serious cases were missing

or resulting in death (5/198) (see Table 2). Of important note, all five fatal cases suffered from rhabdomyolysis.

On average, most patients were taking more than three other drugs concomitantly with a suspected statin. These concomitant drugs were analysed, and potential drug interactions that may precipitate muscle-related adverse events are shown in Table 3. Overall, 81 of 198 cases (40.9 %) received at least one potential interacting drug. Totally, there were 103 pairs of drug interaction presented among these 81 cases. The most common interacting drugs were gemfibrozil (with average dose of 900.0 ±428.0 mg/day, and duration of use 3.7 + 4.5 months [$n = 59$]), colchicine (with average dose of 0.9 ± 0.4 mg/day, and duration of use 7.9 ± 13.4 months [$n = 11$]), HIV protease inhibitors ($n = 10$), other fibrates ($n = 9$), non-dihydropyridine calcium channel blockers ($n = 5$), azole antifungals ($n = 3$) and clarithromycin ($n = 1$). Case fatality rates were 0.9, 1.6 and 16.7 %, when there were 0, 1 and ≥2 interacting drugs, respectively (Table 4).

5 Discussion

While statins have been used extensively worldwide, little information is available on the safety aspect of these drugs among the Asian population. To date, there is only one large, randomized, controlled trial evaluating the efficacy and safety of low-dose pravastatin (10–20 mg) in 7,832 Japanese [33]. In this study, no cases of rhabdomyolysis were reported while information on other muscle-related adverse events were also not reported. In a long-term observational study on the effect of low-dose simvastatin (5 mg) among 51,321 Japanese hypercholesterolaemic patients, musculoskeletal adverse reactions were reported to be 0.45 % at the end of the 10-year follow-up period, with any cases of rhabdomyolysis being reported [34]. However, due to the unusually low dose being used in these studies, the application of such data to the standard dose would be limited. In addition, there have never been any published studies specifically evaluating the muscle-related adverse events of statins in spontaneous reporting systems of any Asian countries prior to this study.

Based on the finding of our study, patterns of statin-associated muscle-related events in Thailand shared some similar characteristics as those seen with studies from Western countries [13, 16]. Although we were unable to perform formal statistical analysis due to the lack of control, certain co-morbidities known to be risk factors for statin-associated myopathy were found in our study, including diabetes mellitus, hypertension and chronic kidney disease.[13–16, 22, 23] Other biases that might confound conclusions include co-morbid conditions and reasons for statin use. Simvastatin was the most commonly suspected statin. This may be a reflection of a larger patient pool exposed to simvastatin because it was, for a long time, the only statin with generic availability listed in the Thai National Essential Drugs list [35]. Interestingly, the mean simvastatin dose of 26.5 mg/day in our study was relatively low when compared with studies from Western countries. Analysis of rhabdomyolysis reports from the Australian Adverse Drug Reaction Database showed that approximately 50 and 30 % of cases were using simvastatin at a dose of 40–60 mg/day and 80 mg/day, respectively [15]. Another analysis of statin-associated rhabdomyolysis cases during the period 2004–2008 from Health Canada's Canadian Vigilance Program and the US FDA's Adverse Event Reporting System indicated that the mean simvastatin dose and atorvastatin dose used in these cases was 55 mg/day and 30.5 mg/day, respectively [36].

There are at least two potential explanations for this observation. First, the Asian race may be more susceptible to statin-associated myopathy. Data supporting this hypothesis is from an interim observation from the ongoing Heart Protection Study 2 Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) [37], which showed a higher incidence of myopathy among Chinese descendants (0.43 %) compared with non-Chinese patients (0.03 %) receiving a similar dose of simvastatin plus niacin. [38] The second possibility is that some drug interactions may result in a rise in simvastatin plasma concentrations sufficient to cause simvastatin-associated myopathy, even in those taking low-dose statins. For our study population, herbal drug interactions could also be an important issue.

We found only one case of myopathy from cerivastatin. The reason for this was the fact that cerivastatin had been marketed in Thailand for just 1 year before it was withdrawn in 2001 [11]. Additionally, we did not find any reports on myopathy from pravastatin and fluvastatin. Potential explanations include low usage rates of both agents in Thailand or chemical properties of the drugs result in lower incidences of statin-associated myopathy [22].

Table 3 Potential drug interactions identified among statin-treated patients who experienced severe muscle-related adverse events from Thai Vigibase

Potentially interacting drugs	No. of cases (significance ratings)[a]				
	CYP3A4-metabolized statins				
	Simvastatin	Atorvastatin	Cerivastatin	Rosuvastatin	Total (% of 81 pts)[b]
Fibrates	*55*	*6*	*1*	*6*	*68* (*84.0*)
Gemfibrozil	52 (1)	4 (1)	1 (NA)	2 (1)	59
Fenofibrate	1 (1)	2 (1)		4 (1)	7
Bezafibrate	2 (NA)				2
Colchicine	*8* (*4*)	*3* (*4*)			*11* (*13.6*)
HIV protease inhibitors	*8*	*2*			*10* (*12.4*)
Indinavir	4 (1)	1 (2)			5
Ritonavir	3 (1)	1 (2)			4
Lopinavir/ritonavir	1 (1)				1
Non-DHP CCBs	*5*				*5* (*6.2*)
Diltiazem	4 (2)				4
Verapamil	1 (2)				1
Azole antifungals	*3*				*3* (*3.7*)
Fluconazole	1 (1)				1
Itraconazole	1 (1)				1
Ketoconazole	1 (1)				1
Antiarrhythmic agents	*3*				*3* (*3.7*)
Amiodarone	1 (1)				1
Digoxin	2 (NA)				2
Calcineurin inhibitors	*2*				*2* (*2.5*)
Ciclosproin (cyclosporine)	1 (1)				1
Tacrolimus	1 (4)				1
Clarithromycin	*1* (*1*)				*1* (*1.2*)
Total	*85*	*11*	*1*	*6*	*103*

CYP cytochrome P450. *NA* data not available, *Non-DHP CCBs* non-dihydropyridine calcium channel blockers, *pts* patients

[a] Each case may receive ≥1 interacting drugs

[b] Eighty-one patients received interacting drugs

Table 4 Severe muscle-related adverse events stratified by number of drug interaction pairs and corresponding case fatality rates

Number of drug interaction pairs	Number of cases	Type of AEs [number of cases (%)]			Case fatality rates (%)
		Rhabdomyolysis	Myopathy	Myositis	
0	117	52 (26.3)	36 (18.2)	29 (14.7)	1/117 (0.9)
1	63	43 (21.7)	11 (5.6)	9 (4.6)	1/63 (1.6)
≥2	18	15 (7.6)	3 (1.5)	–	3/18 (16.7)

AEs adverse events

Similar to previous published reports [13–16, 22, 23], drug interactions were commonly identified in our study. For interacting drugs, most drugs identified in our study were similar to those reported in literature from Western countries.[13–16, 22, 23] These include fibrates, particularly gemfibrozil, HIV protease inhibitors, non-dihydropyridine calcium channel blockers, azole antifungals and macrolide antibiotics. Of important note, 13.6 % (11/81 cases) of the reports include colchicine as a concomitant drug, which is the second most common drug interaction in our database. Although there have been several case reports highlighting the potential drug interaction between statin and colchicines [39–46], only one [15] of six reports of Western pharmacovigilance studies [13–16, 22, 23] identified colchicine as an interacting drug. Colchicine, when used long-term, can by itself lead to muscle damage, including rhabdomyolysis, especially in patients with impaired renal function [47].

In addition to additive muscle toxicity, this interaction may also be the result of pharmacokinetic interactions of these drugs [44, 48]. Simvastatin, when taken orally, will be converted from its inactive lactone form to the active β-hydroxy simvastatin acid via hydrolysis [49]. This active form is then further metabolized via CYP3A4 into

inactive metabolites [49]. In addition to CYP3A4, P-glycoprotein, an important drug transporter regulating both bioavailability and metabolism of various drugs [50], and glucuronidation also play an important role in the metabolism of simvastatin acid [51]. For atorvastatin, the parent compound is an active form and does not require bioactivation to take effect. Atorvastatin shares similarities with simvastatin in its metabolism pathway, including CYP3A4, P-glycoprotein and glucuronidation [50, 52]. Colchicine is metabolized by CYP3A4 and excreted by P-glycoprotein [53]. It can therefore potentially hinder the metabolism of the active form of simvastatin and atorvastatin via interference with CYP3A4 and P-glycoprotein, leading to an elevated level of these statins [44, 48].

One potential explanation of why colchicine was identified in our database may be related to prescribing guidelines of colchicine across countries. In Western countries [54, 55], colchicine is generally recommended for the treatment of acute gout attacks and prevention of gout attacks during the initiation of uric acid-lowering treatment, which is generally limited to less than 6 months. However, the Thai Rheumatology Association recommends the use of long-term colchicine therapy to prevent frequent exacerbations of gout attack for up to 12 months [56]. Such prolonged use may enhance the risk of statin-colchicine interaction. Interestingly, all 11 cases with statin-associated myopathy who received colchicine were taking colchicine for an average duration of 7.9 ± 13.4 months, with an average dose of 0.9 mg/day. This is in contrast to previous published reports where the duration of colchicine use ranged from 8 days to 4 weeks [39–46]. Further studies are needed to fully elucidate the relationship between colchicine and statin interaction and its importance on statin safety.

Similar to other pharmacovigilance studies [57, 58], case reports of suspected adverse events may be affected by various types of bias. Underreporting had been an important limitation for the Thai healthcare system during the early years of Thai Vigibase implementation. The limited quality of reports, especially incomplete data, may also affect our analysis. Inherent limitation of the spontaneous reporting system also limits firm interpretation of reaction frequency or rate of statin-associated myopathy among different types of statins.

Despite the general limitations mentioned above, important limitations that are specific to our study should be clearly noted. Firstly, we performed case identification using only terms reported by the reporters. This was a result of the lack of standardized terms for muscle-related adverse events of statins in the early years of the Thai Vigibase. We had made an attempt to extract laboratory data to perform further analysis but were unable to do so due to the lack of such data in a large proportion of the reports. As a result, our study may suffer from mischaracterization of types of reaction reported and severity of adverse events.

There are a large number of rhabdomyolysis cases reported in the Thai Vigibase compared with other muscle-related adverse events. Several issues may help explain such finding. First, rhabdomyolysis is a severe reaction and usually leads to hospitalization. In the early years of adverse event monitoring, monitoring activities tended to focus on hospitalized patients. Mild and benign reaction not requiring treatments or hospitalization generally received less attention from healthcare professions and were underreported. Second, mischaracterization due to the lack of standardized terms of muscle-related adverse events may also contribute to the high number of rhabdomyolysis reports.

Despite such limitations, we performed a separate analysis specifically on rhabdomyolysis cases to evaluate whether there were any important differences from the overall reports. Such analysis revealed that rhabdomyolysis and non-rhabdomyolysis cases were similar in most characteristics. However, a higher proportion of cases with rhabdomyolysis were classified as having a serious event and all five fatality cases in our study were among those who suffered from rhabdomyolysis.

6 Conclusion

Our study helps characterize the nature of muscle-related adverse events of statins in a developing Asian country where no data has been available before. There appeared to be a surprisingly high number of rhabdomyolysis cases reported in the study which warrant further investigation. Overall, our results showed that some risk factors for such events in the Thai population are similar to those identified in published reports from Western countries. The implicated doses of statin in our reports appeared to be less than those reported from Western countries. Drug interactions resulting in heightened risk of such events were similarly common. While the majority of interacting drugs are well-known, a large proportion of statin-colchicine interactions are uniquely noted. While this interaction is mechanistically possible, this signal should be further investigated and validated. Until more data is available, attempts should be made to make clinicians aware of such potential interactions that few have known before, both in Thailand and perhaps other Asian countries where long-term colchicine therapy is commonly employed. In addition, a systematic campaign to screen, detect, warn and avert well-known dangerous statin drug interactions should be implemented on a wide scale in Thailand.

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