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Risk Management of Simvastatin or Atorvastatin Interactions with CYP3A4 Inhibitors

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Abstract

Background: Co-administration of cytochrome P450 (CYP) 3A4 inhibitors with simvastatin or atorvastatin is associated with increased risk of developing myopathy or rhabdomyolysis.

Objective: To detect co-prescriptions of CYP3A4 inhibitors with simvastatin or atorvastatin in community pharmacies and assess the risk-preventive actions taken by the prescribing physicians who were alerted about the co-prescription by the pharmacist.

Methods: This naturalistic study was performed during four separate 6-week periods in 2004 and 2005, and involved 110 Norwegian community pharmacists (25–30 in each period). Co-prescription of the selected CYP3A4 inhibitors diltiazem, verapamil, clarithromycin, erythromycin, fluconazole, itraconazole and ketoconazole with either simvastatin or atorvastatin was detected with the aid of a simple computer programme. In instances where the pharmacist alerted the prescribing physician about the co-prescription, information on possible strategies to minimize the risk associated with the interaction was also provided. Odds ratios (ORs) were estimated to describe the associations between prescription variables and frequencies of physician information and prescription change, respectively.

Results: In total, 245 co-prescriptions of CYP3A4 inhibitors with simvastatin (134 events) or atorvastatin (111) were detected. Diltiazem (86 events), verapamil (72), erythromycin (48) and clarithromycin (29) were the most commonly co-prescribed CYP3A4 inhibitors. Physicians were informed in 168 out of 245 cases (68.6%). The prescription was subsequently changed in 100 out of 168 cases (59.5%). Another 50 physicians (29.8%) responded that they would consult the patient and monitor potential adverse effects, while only 18 physicians (10.7%) replied that they had already managed the interactions or considered the issue as irrelevant. The adjusted OR for the informing of the physician was 1.89 (95% CI 0.98, 3.63) in patients receiving a daily HMG-CoA reductase inhibitor ('statin') dose of ≥40 mg compared with patients receiving a statin dose of <40 mg/day. The adjusted OR for prescription change was 4.98 (95% CI 2.36, 10.52) if co-prescription was detected prior to the initiation of concurrent use compared with if it was detected during concurrent use.

Conclusion: Nine out of ten physicians changed prescriptions or monitored potential adverse effects when informed by community pharmacists about the risk associated with co-prescription of CYP3A4 inhibitors with simvastatin or atorvas-

tatin. This suggests that an important risk factor for myotoxicity due to these statins could be minimized through interdisciplinary co-operation.

Background

HMG-CoA reductase inhibitors ('statins') are generally well tolerated drugs, but a concern with these drugs is the potential for muscular adverse effects.[1-4] These adverse effects range from diffuse muscle pain or weakness without elevation of creatine kinase levels, to serious myopathy with elevation of creatine kinase levels to more than ten times the upper limit of normal, a condition that may progress to rhabdomyolysis and occasionally, death.[1-4] Serious adverse muscular events have been rare in large randomized clinical trials of statins (observed in 0.1–0.6% of the patients).[5] However, risk factors such as interacting drugs have been excluded in the study protocols.

Cerivastatin was withdrawn from the global market in 2001 due to its being shown to be associated with an elevated risk of rhabdomyolysis compared with other statins.[6] In about 50% of the rhabdomyolysis cases associated with cerivastatin, gemfibrozil was involved as an interacting drug.[7] Atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin comprise the currently available statins. The statins that are currently used most extensively worldwide, atorvastatin and simvastatin, are both metabolized by cytochrome P450 (CYP) 3A4.[8] Concurrent use of CYP3A4 inhibitors, such as ketoconazole,[9,10] itraconazole,[11-13] fluconazole,[14,15] diltiazem,[16-18] verapamil,[19] amiodarone,[20-22] ritonavir,[23,24] nelfinavir,[25,26] clarithromycin[27-30] and erythromycin,[19,28,31] with atorvastatin or simvastatin is associated with increased systemic statin exposure and increased risk of myopathy, with the latter of the two statins being the most sensitive to the interaction. Moreover, gemfibrozil and ciclosporin are additional drugs that increase systemic exposure of simvastatin and atorvastatin by inhibition of alternative pathways, i.e. via CYP2C8, glucuronidation, P-glycoprotein and/or organic anion transporting polypeptide 1B1.[8] A recent study by Rätz-Bravo et al.,[32] which investigated the prevalence of statin interactions in Switzerland, found that nearly one in every ten patients treated with simvastatin (n = 763) or atorvastatin (n = 886) was co-prescribed either CYP3A4 inhibitors, ciclosporin or fibric acid derivatives (fibrates). CYP3A4 inhibitors were by far the most commonly prescribed interacting drugs and were co-prescribed in 7–8% of the patients.[32]

The presence of interacting drugs has been shown to be a common factor associated with simvastatin- and atorvastatin-induced rhabdomyolysis.[33,34] An analysis of 173 Australian cases of rhabdomyolysis associated with these statins conducted by Ronaldson et al.[33] showed that interacting drugs were involved in 77% of such events in patients receiving simvastatin and 44% of such events in patients receiving atorvastatin. The most frequently co-prescribed drugs were gemfibrozil (41 events altogether), diltiazem (32), ciclosporin (19), macrolides (11), verapamil (10) and amiodarone (8).[33] CYP3A4 inhibitors were prescribed in 42% of the simvastatin-treated patients and 25% of the atorvastatin-treated patients.[33] These frequencies of co-prescription are several-fold higher than those reported by Rätz-Bravo et al.,[32] but geographical differences and inclusion of different CYP3A4 inhibitors prohibit a direct comparison. However, a recent US study by Cziraky et al.[35] found a 6-fold relative increase in risk of hospitalization due to myopathy in patients co-treated with CYP3A4 inhibitors in a cohort of almost 500 000 lipid-treated patients, where more than two-thirds received atorvastatin or simvastatin. Thus, there is convincing evidence that concurrent use of CYP3A4 inhibitors escalates the risk of rhabdomyolysis in patients receiving simvastatin or atorvastatin.

Several authors have recently addressed the importance of implementing practical procedures to minimize the risk associated with concurrent use of CYP3A4 inhibitors and simvastatin or atorvastatin.[5,32,33,35] This is particularly important considering the trend towards more aggressive lipid-lowering therapy and a growing number of elderly statin users. The aim of the present study was to systematically detect co-prescription of CYP3A4 inhibitors with simvastatin or atorvastatin in community phar-

macies and assess the risk-preventive actions taken by physicians who were alerted.

Methods

Participants

In total, 110 pharmacists from 69 community pharmacies in the southern part of Norway were recruited during four separate 6-week study periods in 2004 and 2005 (25–30 pharmacists participated during each period). The pharmacists completed a 2-day introductory course where the practical procedures and devices were demonstrated. They also received an update on the theory and management of drug interactions, including mechanisms, inter-individual variability, risk considerations and patient/physician communication. Statin interactions with CYP3A4 inhibitors were included as case examples, and high dosages and advanced patient age were mentioned as potential risk factors for adverse interactions. The course was developed and presented by one of the investigators (Espen Molden) in cooperation with the Department of Postgraduate and Continuing Education at School of Pharmacy, University of Oslo.

Norwegian pharmacists are defined by law as healthcare professionals with an obligation to provide information that stimulates correct and safe drug use, and this quality assurance project was conducted in accordance with requirements of the regional ethics committees in Norway.

Procedures

Seven CYP3A4 inhibitors were included in the study: the macrolide antibiotics clarithromycin and erythromycin; the calcium channel blockers diltiazem and verapamil; and the azole antifungals fluconazole, itraconazole and ketoconazole. Although their relative CYP3A4 inhibitory potency varies (itraconazole and ketoconazole are the most potent), all the included inhibitors had been reported to interact with simvastatin and/or atorvastatin in the literature, either in clinical interaction studies or detailed case reports on rhabdomyolysis following inhibitor co-administration (table I). Amiodarone, telithromycin, ritonavir, indinavir and nelfinavir are additional CYP3A4 inhibitors that were not included in the study for various reasons: published interaction data with statins were lacking for amiodarone when the study was planned, telithromycin was not approved for use, and HIV protease inhibitors were dispensed from community pharmacies to a very limited extent.

Co-prescription of simvastatin or atorvastatin with the included CYP3A4 inhibitors was detected with the aid of a simple computer programme installed at the study pharmacies. The programme automatically produced a coded message on the computer screen when a CYP3A4 inhibitor was dispensed. When a message appeared on the screen, the pharmacist identified whether the patient was receiving either simvastatin or atorvastatin by checking the patient's drug history in the pharmacy's electronic prescription database. In addition, patients were consulted about drugs received at other pharmacies to identify possible simvastatin or

Table I. Relative exposure to atorvastatin or simvastatin and reports of rhabdomyolysis when these drugs were administered with cytochrome P450 (CYP) 3A4 inhibitors included in the study

CYP3A4 inhibitor	Effect on HMG-CoA reductase inhibitor ('statin') exposure		Reports of rhabdomyolysis associated with drug combination	
	atorvastatin	simvastatin	atorvastatin	simvastatin
Fluconazole	NR	NR	✓[15]	✓[14]
Itraconazole	3-fold[11]	20-fold[12]	NR	✓[13]
Ketoconazole	NR	NR	NR	✓[9,10]
Diltiazem	NR	5-fold[16]	✓[17]	✓[18]
Verapamil	NR	3-fold[19]	NR	NR
Clarithromycin	2-fold[29]	10-fold[27]	✓[30]	✓[28,36]
Erythromycin	1.5-fold[31]	4-fold[19]	NR	✓[28]

NR = not reported; ✓ indicates reported rhabdomyolysis.

atorvastatin use that would not be detected by the electronic check.

All prescriptions of CYP3A4 inhibitors were registered regardless of simvastatin or atorvastatin co-prescription (statin prescriptions were only registered when co-prescribed with inhibitors). In cases of co-prescription, the pharmacists recorded information about the type of statin, the type of CYP3A4 inhibitor, the doses of each of these drugs, co-prescription history (already in use or not yet in use), gender and age in a standardized study form (no patient-sensitive or traceable data were recorded). The pharmacists performed independent case assessments and there were no predefined criteria for contacting the prescribing physicians. When the pharmacists alerted the physicians about the potential interactions, they also provided information on possible strategies to minimize the risk associated with the interaction. The risk prevention strategies were available for the pharmacists in a folder developed for the study. The folder included documented information about potential drug alternatives with limited CYP3A4 metabolism/inhibition and published potencies of the interactions (similar to table I) as a basis for interaction risk assessments/rational dose reductions. Regarding potential drug alternatives, the following information was made available in the folder:

- Pravastatin and fluvastatin are statins not metabolized by CYP3A4 to any clinically relevant extent.[1,8,12,20,27,37]
- Azithromycin and spiramycin are macrolides that do not inhibit CYP3A4 to any clinically relevant extent.[29,38-40]
- Dihydropyridine calcium channel blockers (e.g. amlodipine, felodipine and nifedipine) display limited ability to inhibit CYP3A4 compared with diltiazem and verapamil,[41-43] but the indications for their use may differ.

The responses and/or actions of the informed physicians were recorded in the study form and categorized into 'prescription change', 'monitoring of potential adverse effects' and 'already managed/not relevant'. In cases where the physicians decided to change the prescription, the kind of change was also recorded. Moreover, the pharmacists indicated on the study form whether they had advised the patients to be aware of potential muscular symptoms (pain/fatigue) and to contact their physician if they experienced such symptoms.

Statistical Analyses

The frequencies of co-prescription of simvastatin or atorvastatin with each CYP3A4 inhibitor were calculated and compared within the same drug class of inhibitors (e.g. diltiazem vs verapamil) by two-tailed chi-square tests. In addition, odds ratios (ORs) with 95% CIs were estimated to describe the associations between prescription variables and frequencies of physician information and prescription change, respectively. Prescription and patient variables included in the analyses were statin type (simvastatin = '1'; atorvastatin = '0'), statin dose (≥40 mg daily = '1'; <40 mg daily = '0'), co-prescription history (not yet in use = '1'; already in use = '0'), gender (female = '1'; male = '0') and age (≥70 y = '1'; <70 y = '0'). The potency of CYP3A4 inhibitors was not included as a prescription variable due to limited observations of high-potency agents (itraconazole/ketoconazole). The response variables were information of the physician (informed = '1'; not informed = '0') and prescription change (changed = '1'; not changed = '0'). Unadjusted ORs were estimated individually for each prescription variable, while adjusted ORs were estimated by logistic regression analyses including all covariates as explanatory variables. In the logistic regression models, the following covariate interactions were tested: 'age × dose', 'age × statin' and 'statin × dose'.

SPSS version 14.0 (SPSS Inc., Chicago, IL) was the software used for statistical analyses.

Results

Among the 2045 reviewed CYP3A4 inhibitor prescriptions, 245 co-prescriptions with simvastatin or atorvastatin were detected. Simvastatin and atorvastatin were involved in 134 and 111 co-prescription events, respectively. The male/female case distribution was 121/124, and 43.7% of the patients were ≥70 years old (14.7% ≥80 years old). Patients aged ≥70 years comprised 41.7% of the atorvastatin-treated population and 52.2% of the simvastatin-treated population. The mean daily dose was 28 mg in patients treated with simvastatin and 24 mg in

patients treated with atorvastatin. Daily statin doses ≥40 mg and detection prior to starting concurrent use comprised 29.8% and 36.7% of the cases, respectively. Macrolide antibiotics were involved in the majority of co-prescriptions detected prior to starting concurrent use (77 of 90).

Table II lists the number of simvastatin/atorvastatin co-prescriptions for each CYP3A4 inhibitor and the respective management outcomes. Calcium channel blockers and macrolide antibiotics comprised the majority of the co-prescriptions and were involved in 158 (64.5%) and 77 (31.4%) events, respectively. Although the total number of diltiazem prescriptions was lower than that for verapamil, diltiazem was involved in more cases and significantly more frequently co-prescribed with simvastatin or atorvastatin compared with verapamil (36.8% vs 16.7%; $p < 0.0001$). Similarly, clarithromycin was less frequently prescribed than erythromycin, but significantly more frequently co-prescribed with simvastatin or atorvastatin (11.1% vs 5.3%; $p < 0.001$).

The pharmacists informed the physicians of the co-prescription in 168 out of 245 cases (68.6%; figure 1). Unadjusted and adjusted ORs for the informing of physicians are provided in table III. The most consistent finding was of more frequent informing of the physician in patients receiving a daily statin dose of ≥40 mg (adjusted OR 1.89; 95% CI 0.98, 3.63). Moreover, there was a weak tendency towards the physician being more likely to be informed if the co-prescription was detected prior to the initiation of concurrent use of the statin and the CYP3A4 inhibitor (adjusted OR 1.55; 95% CI 0.84, 2.85). The covariate interactions tested did not provide any additional information of interest regarding the likelihood of physicians being informed of the co-prescription. When the physicians were not informed by the pharmacists, the majority of the patients (64 of 77) were instructed to be aware of potential muscular symptoms and contact their physician if they experienced such symptoms.

The physicians who were informed about the risk of drug interaction changed the prescription in 100 out of 168 cases (59.5%; figure 1). Among these prescription changes, 43 were a switch of statin to pravastatin or fluvastatin, 33 were a switch of CYP3A4 inhibitor to a therapeutic alternative without relevant inhibition of CYP3A4 (23 macrolide switches, 10 diltiazem switches, 0 verapamil switches), and 24 were dose reductions or temporary interruptions of statin treatment. Temporary interruption of statin therapy was not included as a possible risk-reduction strategy in the study folder, but was regarded by several physicians to be a rational action during short-term treatment with a CYP3A4 inhibitor.

Unadjusted and adjusted ORs for prescription change are provided in table IV. The odds of prescription change were significantly increased if co-prescription was detected prior to starting concurrent use of the statin and the CYP3A4 inhibitor (adjusted OR 4.98; 95% CI 2.36, 10.52). There was also a trend towards a greater likelihood of prescription change if simvastatin was detected as the co-prescribed statin (adjusted OR 1.85; 95% CI 0.92, 3.72). The covariate interactions tested did not provide any additional information of interest regarding

Table II. Co-prescriptions and respective management outcomes with atorvastatin/simvastatin for each cytochrome P450 (CYP) 3A4 inhibitor

CYP3A4 inhibitor	Total prescriptions (%)	Atorvastatin			Simvastatin		
		no. of cases	informed physician	changed prescription	no. of cases	informed physician	changed prescription
Diltiazem	86/234 (36.8)	39	27	10	47	35	18
Verapamil	72/431 (16.7)	27	17	9	45	28	13
Clarithromycin	29/262 (11.1)	15	10	8	14	10	9
Erythromycin	48/909 (5.3)	25	19	11	23	18	18
Fluconazole	9/181(5.0)	5	2	2	4	1	1
Ketoconazole	0/21 (0)	0	0	0	0	0	0
Itraconazole	1/7 (14.3)	0	0	0	1	1	1
All CYP3A4 inhibitors	245/2045 (12.0)	111	75	40	134	93	60

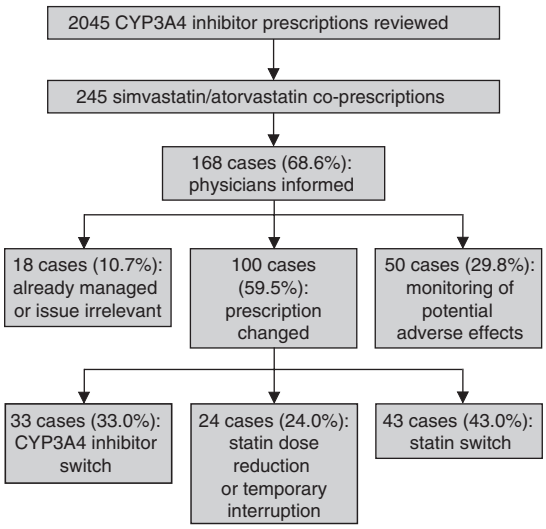

Fig. 1. Summary of the study outcome. **CYP** = cytochrome P450.

the likelihood of prescription change. When the prescription was not changed, 50 of 168 physicians (29.8%; figure 1) responded that they would consult the patient and monitor potential adverse effects. In the remaining 18 cases (10.7%), the physicians either replied that they had already managed the interaction risk or did not consider the issue relevant.

Discussion

Co-administration of CYP3A4 inhibitors with simvastatin or atorvastatin is associated with an increased risk of developing myopathy or rhabdomyolysis.[1,8,33-35] To prevent events of unpleasant and potentially dangerous muscular adverse effects in vulnerable patients, systematic management of the drug interaction risk is necessary. In the present study, a group of Norwegian community pharmacists detected co-prescription of CYP3A4 inhibitors with simvastatin or atorvastatin as part of routine practice. When the physicians were alerted, the pharmacists also informed them about possible strategies to minimize the risk associated with the interaction.

In total, 245 co-prescriptions of CYP3A4 inhibitors with simvastatin or atorvastatin were detected during all four 6-week study periods. The prescribing physicians were informed in two-thirds of the cases and 59.5% of these led to a change in prescription. Another 29.8% of the physicians responded that they would consult the patient and monitor potential adverse effects, while only 10.7% replied had already managed the interaction risk or did not consider the issue as relevant. This indicates that Norwegian physicians generally do not recognize the drug interaction risk associated with co-administration of CYP3A4 inhibitors and simvastatin or atorvastatin, despite warnings in the prescribing information of these drugs,[44,45] but acknowledge it when they are informed. As efforts to ensure treatment safety were made by nine out of every ten physicians who were alerted, the study suggests that the interaction risk associated to concurrent use of CYP3A4 inhibitors with these statins could be minimized through interdisciplinary co-operation.

While the concept of pharmacists alerting physicians about potential drug interactions has a long

Table III. Association between prescription variables and frequency of physician contact

Variable	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Sex		
Female vs male	1.07 (0.63, 1.84)	1.07 (0.61, 1.88)
Age (y)		
70 vs <70	0.77 (0.45, 1.33)	0.86 (0.48, 1.53)
Statin type		
Simvastatin vs atorvastatin	1.09 (0.64, 1.87)	0.96 (0.54, 1.71)
Statin dose (mg)		
≥40 vs <40	1.92 (1.01, 3.64)	1.89 (0.98, 3.63)
Co-prescription history		
Not yet in use vs already in use	1.70 (0.96, 3.00)	1.55 (0.84, 2.85)

OR = odds ratio.

Table IV. Association between prescription variables and frequency of prescription change

Variable	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Sex		
Female vs male	0.87 (0.47, 1.62)	0.95 (0.48, 1.88)
Age (y)		
≥70 vs <70	0.86 (0.46, 1.60)	1.11 (0.55, 2.24)
Statin type		
Simvastatin vs atorvastatin	1.59 (0.86, 2.96)	1.85 (0.92, 3.72)
Statin dose (mg)		
≥40 vs <40	0.84 (0.44, 1.61)	0.71 (0.35, 1.45)
Co-prescription history		
Not yet in use vs already in use	4.31 (2.17, 8.56)	4.98 (2.36, 10.52)

OR = odds ratio.

tradition, little is known about the actual impact of pharmacy-based information on the management of interaction risks by physicians. In order to obtain constructive communication, it is fundamental that the pharmacists do not act as controllers when physicians are alerted. Moreover, we believe it is important that the pharmacists not only communicate potential problems, but also provide information about possible strategies as to how the interaction could be prevented. However, physicians are responsible for the selection and monitoring of drug treatment, and decide whether changes should be undertaken, based on clinical benefit-risk assessments. About 30% of the physicians in the study did not implement changes, but responded that they would consult the patient and monitor for potential adverse effects. There are several rational reasons for this; for instance, that the treatment was well titrated and therapeutic alternatives were not considered to be equivalent in terms of indication, clinical effect or documentation. Nevertheless, monitoring for possible adverse effects should be regarded as a valuable strategy in the management of drug interactions.

The pharmacists completed a 2-day course prior to the study. In addition to demonstration of the study procedures and devices, they received an update on the theory and management of drug interactions. Time since graduation was variable among the participants and the pre-study update was performed to limit differences in basic knowledge. However, the study was naturalistic and the pharmacists made independent decisions on when to contact the physicians. The findings indicated that statin dose and prescription history were associated with their decisions, but it should be noted that physicians may be difficult to reach in the time that patients wait for their prescriptions to be filled (frequency of being informed only takes into account cases where physicians were reached).

Co-administration of CYP3A4 inhibitors increases systemic exposure to simvastatin and atorvastatin several-fold (table I). As the incidence of muscular side effects is dose dependent, at least for simvastatin,[44] concurrent use of a certain CYP3A4 inhibitor is generally considered as more risky when there is high baseline statin exposure.[8,33,36] Thus, the higher odds (OR = 1.89; 95% CI % CI 0.98, 3.63) for informing physicians of a co-prescription in patients receiving a daily statin dose of ≥40 mg is rational. However, administration of simvastatin or atorvastatin at lower dosages in combination with a highly potent CYP3A4 inhibitor, such as itraconazole or ketoconazole, would provide a risk equal to that when a higher statin dose is administered with less potent CYP3A4 inhibitors. In this study, only a single event was detected in association with itraconazole/ketoconazole. The potential impact of CYP3A4 inhibitor potency on the management outcome was therefore not tested.

Simvastatin is more sensitive to the effects of CYP3A4 inhibitors than atorvastatin, in terms of plasma concentration increases during concomitant administration (table I). In a study of cases of rhabdomyolysis reported in Australia, CYP3A4 inhibitors were more often involved in events associated with simvastatin (42%) than atorvastatin (25%).[33] In line with this, myopathy was recently reported after switching from atorvastatin to simvas-

tatin in a patient treated with diltiazem.[46] We observed a tendency towards a higher frequency of prescription change by physicians in patients receiving simvastatin than those receiving atorvastatin (adjusted OR 1.85; 95% CI 0.92, 3.72) in the present study, possibly reflecting the higher interaction risk of simvastatin than atorvastatin with CYP3A4 inhibitors.

Advanced age is also considered an important risk factor for muscular adverse effects of statins,[3,33] but patient age was not significantly associated with the actions of the pharmacists or the physicians in this study. As multiple risk factors are often present in reported cases of rhabdomyolysis,[33] it is important to be aware of advanced age in the management of drug interactions with simvastatin or atorvastatin. Patients aged ≥70 years comprised a relatively high proportion (43.7%) of detected cases of co-prescription in this study. This could reflect the fact that elderly individuals represent almost half of the statin-treated population in Norway, but it is also possible that older patients are more often co-prescribed CYP3A4 inhibitors than younger patients, due to an increasing degree of multiple drug treatment with age. Another age-related issue was the trend of relatively higher simvastatin use in patients aged ≥70 years. As previously mentioned, simvastatin is more sensitive than atorvastatin to the effects of CYP3A4 inhibition, and the possible combination of more frequent simvastatin use and more frequent co-prescription of CYP3A4 inhibitors could make older patients particularly vulnerable to adverse muscular effects.

If co-prescription was detected prior to starting concurrent use, the adjusted OR of an immediate prescription change was 4.98 (95% CI 2.36, 10.52). This is rational because switching to an alternative drug is clinically more straightforward when a drug combination is not yet in use compared with situations of pre-existing ongoing combination therapy. In accordance with their short-term use, macrolide antibiotics were involved in >80% of the co-prescriptions detected prior to starting concurrent use. However, it should be added that co-prescription of any CYP3A4 inhibitor could be detected prior to starting concurrent use if a systematic approach is applied over time.

Short-term use of the macrolide antibiotics clarithromycin and erythromycin has been associated with rhabdomyolysis in association with simvastatin and atorvastatin, resulting in several months of hospitalization in susceptible patients.[23,28,36] In the present study, clarithromycin was significantly more frequently co-prescribed with simvastatin and atorvastatin than was erythromycin. This is in accordance with previous observations,[47] and indicates that clarithromycin is more often prescribed for the treatment of infections in statin-treated patients than erythromycin. However, it is important to note that erythromycin, due to its more extensive overall use, was associated with more cases of co-prescription than clarithromycin.

The calcium channel blockers diltiazem and verapamil were the most frequently involved CYP3A4 inhibitors in the study. These were also the CYP3A4 inhibitors most commonly implicated in the Australian reports of rhabdomyolysis associated with simvastatin and atorvastatin that were reviewed by Ronaldson et al.[33] However, while diltiazem was listed in 18% of the reports of rhabdomyolysis, verapamil was listed in 6% of the reports.[33] This difference possibly results from diltiazem being more frequently co-prescribed with statins than verapamil, as suggested by the present study. The significantly higher frequency of statin interaction cases amongst prescriptions of diltiazem is probably due to the different use of these calcium channel blockers in patients with different types of cardiovascular disease.

It is important to be aware that simvastatin and atorvastatin interact with drugs other than those included in the present study, e.g. amiodarone,[20-22] HIV protease inhibitors,[23-26] gemfibrozil,[7,8] and ciclosporin.[8] HIV protease inhibitors were not included in the study because these drugs are dispensed to a very limited extent from community pharmacies. In the case of amiodarone, interaction data with statins lacked when the study was planned, but recent reports with simvastatin have clearly shown that amiodarone is an important CYP3A4 inhibitor to consider regarding interactions with statins.[20-22] Gemfibrozil and ciclosporin, which interact with statins mainly via other mechanisms than CYP3A4 inhibition,[8] are also important to consider, but were not included in this Norwegian study

because gemfibrozil is not approved for use and because pravastatin or fluvastatin are considered first-line statins in transplant patients.

Even though the procedures in the study were aimed at preventing the interaction-induced adverse effects of simvastatin and atorvastatin, there is a possibility that some of the interventions were unnecessary and potentially unfavourable for the patients. Examples of how this might be so are unnecessary pharmacist interventions with a potential negative impact on the patient-physician relationship, and unnecessary prescription changes potentially resulting in unwanted effects on lipid parameters. The appropriateness of the individual decisions made by the pharmacists and physicians were not reviewed by external experts, and the presence of potentially unfavourable decisions was not evaluated. However, the logistic regression analyses showed that the actions taken by physicians and pharmacists were associated with statin dosage, statin type and co-prescription history. This indicates that, in general, the decisions regarding when to act in order to prevent possible adverse interactions in this study were rational.

Conclusion

Co-administration of CYP3A4 inhibitors is associated with several-fold increases in the risk of developing myopathy or rhabdomyolysis in patients treated with simvastatin or atorvastatin. Even though most subjects are likely to tolerate increased statin exposure during concurrent use of a CYP3A4 inhibitor, systematic management of the interaction risk is necessary to prevent unpleasant and potentially dangerous muscular adverse effects in vulnerable patients. This is particularly important considering the trend towards more aggressive lipid-lowering therapy and a growing number of older statin users.

In the present naturalistic study, nine out of every ten physicians performed prescription changes or responded that they would monitor potential adverse effects when informed by primary care pharmacists about the interaction risk of co-prescribed CYP3A4 inhibitors with simvastatin or atorvastatin. This suggests that an important risk factor for myotoxicity with these extensively used statins could be minimized through interdisciplinary co-operation.

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