Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Hepatotoxicity associated with statins: Reports of idiosyncratic liver injury post-marketing

Einar Björnsson[1,*], Elin I. Jacobsen[1], Evangelos Kalaitzakis[2]

[1]*Department of Internal Medicine, Section of Gastroenterology and Hepatology, The National University Hospital, Reykjavik, Iceland;*
[2]*Institute of Internal Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden*

See Editorial, pages 305–307

Background & Aims: Limited data exist on drug-induced liver injury (DILI) associated with statins.
Methods: Reports on adverse reactions suspected to be due to statins received by the Swedish Adverse Drug Reactions Advisory Committe 1988–2010 were analyzed. Only cases with >5 × upper limit of normal (ULN) in aminotransferases and/or alkaline phosphatase >2 × ULN were included.
Results: The most common types of ADRs suspected were DILI in 124/217 (57%) cases. A total of 73/124 (59%) cases had at least possible relationship, median age 64 years (57–73), 55% males, whereas 25/124 cases (20%) were excluded due to mild elevations of liver tests and 26 due to unlikely relationship and/or lack of data. A statin-related DILI episode was reported in 1.2/100,000 users. Atorvastatin was implicated in 30/73 (41%) cases, simvastatin in 28 (38%), fluvastatin (15%), and others. Two patients died of acute liver failure, one underwent liver transplantation and 25 (34%) had jaundice. Three patients were rechallenged with the same statin producing similar patterns of liver injury. The median duration of therapy was 90 days (30–120), 120 (39–248) for atorvastatin, and 75 (30–150) for simvastatin (NS). Cholestatic/mixed injury was more common with atorvastatin, 17/30 (56%) than with simvastatin, 7/28 (24%) ($p = 0.018$).
Conclusions: Idiosyncratic liver injury associated with statins is rare but can be severe. After recovery, a similar pattern of liver injury can be reproduced on re-exposure. Most patients experience liver injury 3–4 months after start of therapy. Atorvastatin is mostly associated with cholestatic liver injury whereas hepatocellular injury is more common with simvastatin.

Introduction

Statins are among the most commonly used types of drugs worldwide and have been shown to have a good safety record. Statins are the drugs of choice for patients with hypercholesterolemia and other risk factors for cardiovascular disease and have shown to be a life-reserving therapy in many of these patients [1–4]. A similar proportion of patients randomized to placebo and active treatment with statins in clinical trials have shown elevations in aminotransferases [1–4]. Although most trials assessing the cardiovascular efficacy of statins and their safety have included a large number of patients, they have been underpowered to detect clinically relevant drug-induced liver injury (DILI). It is well known that idiosyncratic DILI associated with drugs is generally detected in the post-marketing phase [5]. It has been convincingly shown that the risk of developing statin-induced DILI is not related to the presence of pre-existing liver abnormalities, mostly non-alcoholic fatty liver disease (NAFLD) [6]. On the contrary, the use of statins has been shown to be associated with improvement in liver test abnormalities and histology in patients with NAFLD [7–10]. The existence of statin-induced hepatotoxicity has been put into question and called a "myth" [11].

According to a recent review, only 40 cases with suspected statin-induced DILI have been reported in the literature [12]. The largest series of patients with suspected statin-induced DILI included only seven patients [13]. Thus, systematic assessment of DILI of these widely used drugs is largely lacking.

In Sweden, systematic monitoring of adverse effects of drugs has been conducted since 1966, with regular causality assessment offering the opportunity to evaluate a relatively large number of patients with DILI. We aimed to analyze the proportion of drug-induced liver injury (DILI), suspected to be due to statins out of all adverse reactions reported for this type of drugs, and to characterize the type of liver injury and clinical outcome. Furthermore, we wanted to calculate the incidence of liver injury in patients on statins based on spontaneous reporting and sale figures of statins during the study period.

Materials and methods

All reports of suspected adverse drug reactions received by the Swedish Adverse Drug Reactions Advisory Committee (SADRAC) from 1970 have been computerized and made available for analysis. Since 1975, the reporting of fatal, otherwise serious and new ADRs, has been compulsory. Full medical records, including laboratory results, and imaging studies are requested for the majority of serious and all fatal cases. All cases reported to the Swedish Adverse Drug Reactions Advisory

Keywords: Hepatoxicity; Statins; Drug-induced liver injury.
Received 19 April 2011; received in revised form 8 July 2011; accepted 26 July 2011
☆ DOI of original article: 10.1016/j.jhep.2011.08.016.
* Corresponding author. Address: The National University Hospital, 101 Reykjavik, Iceland.
E-mail address: einarsb@landspitali.is (E. Björnsson).

Committee (SADRAC), suspected to be due to statins since these drugs were put on market, were retrieved. Only cases with DILI reported to SADRAC were reviewed. Medical records and results of laboratory data were analysed, as well as duration of treatment, exclusion of competing causes, and clinical outcome such as potential death from the drug reaction and/or liver transplantation due to DILI. Only cases with >5 × upper limit of normal (ULN) in aminotransferases and/or ALP >2 × ULN or >2 ULN in bilirubin were included. This cut-off is based on a recent revision of case definitions and classification of DILI by a group of international experts [14].

Causality assessment was based on International Consensus Criteria (RUCAM) [15–16]. According to these criteria, the liver injury was classified into hepatocellular, cholestatic or mixed pattern, and the causal relationship classified as highly probable, probable, unlikely or excluded [15–16]. The methodology of the analysis of reports has been described in detail in a previous publication on DILI reported to SADRAC [17]. During the first years after marketing of statins from 1988–1991, a test for hepatitis C was not yet commercially available. However, in the following years, the vast majority of cases had hepatitis A, B, C, cytomegalovirus (CMV), and Epstein Barr virus (EBV) excluded and all serious cases, including cases with fatal outcome and cases with positive rechallenge. Given the association between overconsumption of alcohol and liver injury, alcoholic liver disease was always ruled out in these patients. It was almost without exception that it was stated in the report that patients did not have overconsumption of alcohol. However, information on the amount of alcohol used by the patient or whether or not the patient did not use alcohol at all, was often missing. Thus, usually it was difficult to give points for alcohol as a risk factor in RUCAM (which gives one point) and this leads therefore often to lower score due to this lack of information.

The search for drug interactions was carried out by entering drugs, that were, apart from statins, considered possible sources of liver injury and discontinued concomitantly with the statin drugs: cefadroxil, celecoxib, ciprofloxacin, daltaparin, estrogen, isoniazid, losartan, metformin, mexitil, nefazodon, amlodipine, enalapril, rofecoxib, sertraline, ticlopidine, and lisinopril as well as atorvastatin, simvastatin, rosuvastatin, and fluvastatin, into the Micromedex drug interaction database (Micromedex® Healthcare Series. (2.0.), retrieved January 20, 2011, from http://www.thomsonhc.com. Greenwood Village, CO: Thomson Reuters (Healthcare) Inc.) and by entering the same drug list into Stockley's Drug Interaction database (Baxter K (ed.), Stockley's Drug Interactions. [online] London: Pharmaceutical Press <http://www.medicinescomplete.com/> (Accessed on January 20, 2011). The four possible drug interactions with statins retrieved from these databases were investigated further by evaluating references from both databases [18–21] and by searching for a clinical relevance evaluation in the textbook by Hansten and Horn: "Drug Interactions Analysis and Management", [22] which provides evaluations of drug interactions selected on the basis of their potential to alter patient outcomes. Finally, a search for drug interactions, that are the result of competition for, or effects on the human cytochrome P450 system, was done by consulting the University of Indiana cytochrome P450 drug interaction table (Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). http://medicine.iupui.edu/clinpharm/ddis/table.asp. Accessed January 20, 2011).

Total sale figures and DDDs (estimated average daily dose for an adult patient) for the different statins marketed in Sweden were obtained from Swedish Drug Statistics Ltd., and DDDs (estimated average daily dose for an adult patient) and the National Board of Health and Welfare.

Statistics

The Fisher exact test was used to test diferences between groups regarding dichotomous variables. The Mann–Whitney test was used for continuous variables. All tests were two-tailed and were conducted at a 5% significance level. Results are presented as medians and IQR (interquartile range).

Results

The first statin drug was marketed in Sweden in 1988. During the period 1988–November 2010, SADRAC received a total of 239 reports of adverse effects suspected to be due to statins. 22/239 (9.2%) cases were considered by SADRAC to be of unlikely relationship whereas 217 had a possible causality according to SADRAC. The most common types of ADRs suspected, were: DILI in 124/217 (57%) of reports, rhabdomyolysis/myalgia in 42/217 (19%), pancreatitis (5%), dermatological (4.3%), gastrointestinal (4.3%) and neurological (3.3%) and urinary (2.9%) side effects.

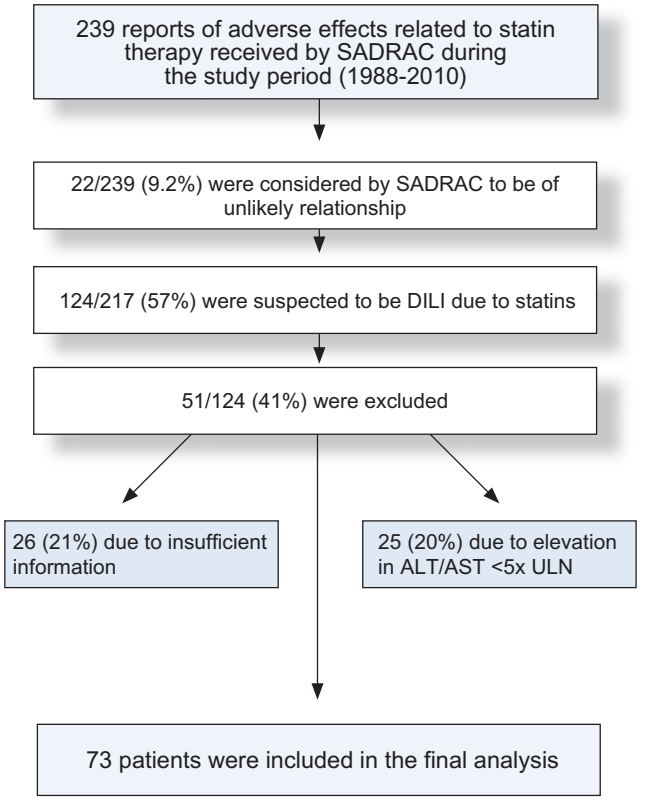

Fig. 1. A flow diagram of the patients showing reasons for the elimination of cases and those who were included in the final analysis.

Out of 124 reports considered to be potentially related to the statin therapy, 51/124 (41%) cases were excluded, 26 due to insufficient information making a causality assessment according to RUCAM impossible, whereas in the remaining cases, elevation of aminotransferases (AST and/or ALT) was less than five times ULN as well as ALP <2 × ULN (Fig. 1). Thus, a total of 73 cases were included in the final analysis.

Two patients died and one underwent liver transplantation associated with statin therapy (Table 1). Three other patients were rechallenged with the same statin which produced a similar pattern of liver injury as experienced by the patients during the first liver injury associated with the statin treatment (Table 1). This occurred approximately one month after the start of the re-exposure (Table 1). The rechallenge was in these cases inadvertent, as the responsible physicians were either not certain whether the previous liver injury was due to the statin (n = 2) or did not take the previous liver reaction seriously. All these patients had a very thorough diagnostic work-up. None had suspicion of alcoholic liver disease, viral markers for a recent infection with hepatitis A, B, C, CMV, and EBV were negative, and none had suffered from hypotension prior to the reaction.

According to the causality assessment, 52 (71%) patients had a possible relationship, 14 (19%) probable and 7 (10%) highly probable. In the total study cohort, a total of 43 (59%) patients were of hepatocellular type, 22 (30%) were of chole-

Table 1. Demographics, drugs, duration of treatment before the diagnosis of DILI as well as liver tests in patients who died or underwent liver transplantation from DILI as well as patients with a positive rechallenge. Liver tests: AST, ALT, ALP and total bilirubin are shown in the multiples of the upper limit of normal. Both values after the first reaction and after re-exposure of statins are shown in the three rechallenge cases.

	Drug	Duration (days)	Causality	AST	ALT	ALP	Bilirubin	Outcome
M 63	Simvastatin (20 mg)	90	Highly probable	45	36	2	20	Liver transplantation
M 78	Simvastatin (20 mg)	92	Highly probable	40	38	1.5	10	Death
F 39	Atorvastatin (10 mg)	120	Possible	2.0	1.8	5.5	26.6	Death
M 58	Simvastatin (20 mg)	28 (second treatment)	Highly probable	1.9/2.8	2.1/2.9	2.5/4.2	normal	Positive rechallenge
F 60	Atorvastatin (40 mg)	30 (second treatment)	Highly probable	11/33	15/53	1.1/1.99	normal/2.0	Positive rechallenge
F 52	Atorvastatin (10 mg)	30 (second treatment)	Highly probable	5.5/35	10/57	1.2/1.5	normal/1.2	Positive rechallenge

static type and 8 (11%) were of mixed type. The vast majority of reports of statin-induced hepatotoxicity were due to atorvastatin (n = 30) and simvastatin (n = 28). Other statin-associated liver injuries were due to fluvastatin (n = 11), pravastatin (n = 2) and rosuvastatin (n = 2). The clinical and biochemical characteristics of the total study cohort are shown in Table 3. The majority of patients (55%) were males and the median time from the start of the statin treatment until abnormal liver tests were detected was 3 months (Table 2). Approximately 35% had jaundice at presentation and the median ALT elevation was 10 × ULN (Table 2).

In a total of five cases, information was available about a switch to another statin after recovery of liver tests. This was possible in all cases without elevation of liver tests while on therapy (with more than three months of follow-up in all). In three patients, atorvastatin was replaced by pravastatin (n = 2) and in one by simvastatin. Two patients with rosuvastatin-induced liver injury were able to use simvastatin and atorvastatin, respectively.

A comparison between patients who suffered liver injury from atorvastatin and simvastatin is shown in Table 2. Duration of treatment tended to be longer with atorvastatin compared to simvastatin (approximately 4 *vs.* 3 months) (Table 2). A significantly higher proportion of patients on atorvastatin had cholestatic/mixed type of liver injury compared with those treated with simvastatin (Table 2). Otherwise, no significant differences were revealed between the two groups.

In 19/73 (26%) cases, another drug was discontinued together with statin. The following drugs were also implicated: cefadroxil, celecoxib, ciprofloxacin, daltaparin, estrogen, isoniazid, losartan, metformin, mexitil, nefazodon, amlodipine, enalapril (n = 3), rofecoxib, sertraline, ticlopidine, and lisinopril. In Table 3, drugs discontinued with the specific statins are illustrated. Some of these drugs interact with the metabolism of simvastatin and atorvastatin through the cytochrome P450 isoenzyme CYP3A4. The interaction is either by inhibition of the isoenzyme or by competition for the enzyme. However, no clinically relevant interactions were found that could explain the DILI associated with statins (Table 3).

Calculation of the incidence of DILI associated with statins based on the spontaneous reporting to SADRAC and the sale figure of statins during the study period is shown in Table 4. Reactions were more frequent with fluvastatin compared to the total study group (p <0.05). Overall, a statin-related DILI episode was reported in 1.6/100,000 person–years (Table 4) and in 1.2/100,000 users (Table 4).

Discussion

In the current study, we could confirm that idiosyncratic liver injury associated with statins is rare but can be associated with severe outcome. After recovery, a similar pattern of liver injury can be reproduced on re-exposure. Most patients experienced liver injury 3–4 months after start of therapy. Atorvastatin and simvastatin are the most common statins associated with DILI, which is probably due to the fact that these are the most commonly used statins. Atorvastatin is mostly associated with cholestatic liver injury whereas hepatocellular injury is more common with simvastatin.

In patients on statins, mild elevations of liver enzymes are observed in approximately 1–3% of patients, but in the vast majority of cases this is not clinically significant and rarely requires discontinuation of therapy [23,24]. In the current study, all patients had their statin therapy withdrawn and the analysis was only based on those who had >5 × ULN of AST and ALT, which is considered to reduce false positive signals such as concomitant occurrence of NAFLD and other chronic liver diseases. Moreover, despite the fact that reporting serious and life-threatening adverse drug reactions is mandatory in Sweden, the completeness of the SADRAC registry has not been validated. Thus, we believe that our cases represent an under-estimation of the real incidence of liver injuries with these drugs.

Disregarding very rare side effects as non-existing is unreasonable [11]. In fact, extrapolating the incidence of liver injury from clinical trials is confounded by several factors. Exclusion criteria, such as co-morbidities, alcohol use, age, pre-existing liver disease as well as relatively small sample size in clinical trials, make any conclusions about safety at best pre-mature [25]. Thus, severe DILI has very rarely been observed within the context of a clinical trial. It has been pointed out that as many patients as the reciprocal of the true incidence rate must be observed almost three times in order to have at least 95% possibility of detecting one patient with a relatively rare problem as severe DILI [26].

Large retrospective [17] and prospective [27–28] studies on DILI have included patients with suspected liver injury due to statins. In a large series from Sweden, based on spontaneous reporting of adverse effects to the authorities, 8/747 (1%) DILI patients (with jaundice) had suspected statin-induced DILI, in two cases leading to liver transplantation and death, respectively [17]. In the Spanish Hepatotoxicity Registry, 18/461 (3%) lipid lowering agents were implicated as the cause of DILI [27]. These cases had a mean of 16 times ULN in ALT and a mean of 6 mg/dl in bilirubin at presentation [27]. In the prospective DILIN study,

Table 2. Comparison between patients with atorvastatin- and simvastatin-induced liver injury in terms of gender, duration of treatment, liver tests and type of liver injury. Clinical and laboratory data in the total study population are shown. Liver laboratory values are expressed as multiples of ULN (upper limit of normal), medians and interquartile range. Age and duration of treatment are also expressed as medians and interquartile range.

	Atorvastatin (n = 30)	Simvastatin (n = 28)	*p* value	Total study cohort (n = 73)
Age	67 (55-74)	63 (56-71)	n.s.	64 (57-73)
Gender (Females %)	15/30 (50%)	10/28 (36%)	n.s.	33/40
Duration of treatment (days)	120 (39-248)	90 (30-180)	n.s.	90 (30-210)
Bilirubin	3.7 (2.0-4.7)	4.0 (1.8-8.9)	n.s.	3.2 (2.0-6.5)
AST	5.7 (2.6-11)	8.1 (4.5-19.7)	n.s.	5.9 (3.6-16.5)
ALT	10 (5.2-20)	11.9 (7.0-28)	n.s.	10 (5.7-20)
ALP	3.0 (1.6-3.6)	2.1 (1.6-3.6)	n.s.	2.5 (1.6-3.6)
Cholestatic/mixed	17/30 (57%)	7/28 (25%)	0.0182	30/73 (41%)

liver injury was considered to be due to lipid lowering agents in 3.4% of cases [28]. Considering the common use of statins worldwide, clinically important liver injury is probably very rare but there seems little doubt that the use of statins can be associated with severe DILI.

The current series, which is by far the largest series of statin-induced DILI, does support that clinically important idiosyncratic liver injury can occur in patients treated with statins. A total of 73 patients in the current study can be compared with only 40 cases with statin-induced DILI which have been reported as case reports or small case series [12]. Among our patients, two died and one underwent liver transplantation. Two of these cases had a highly probable relationship with the drug according to the RUCAM causality assessment method. Three case reports have been published with serious suspected atorvastatin-induced DILI [13,29–30]. Recently, the combination of simvastatin–ezetimibe was reported to lead to liver failure requiring liver transplantation [31]. Moroever, among patients put on the liver transplant list in the US between 1990 and 2002, three patients had a transplant in whom statins were implicated as the responsible agents [32]. Furthermore, a recent report from the Acute Liver Failure (ALF) Study Group, showed that a statin was the only implicated agent in 6 patients (4.5%) among all those patients with ALF from DILI [33]. In the DILIN study, in 2/27 (7.4%) patients, who died from liver failure or underwent liver transplantation, statins were the implicated agents [28].

Perger *et al.* reviewed reports of the Adverse Event Reporting System of the World Health Organization for deaths resulting from serious liver injury attributable to statin therapy and calculated reporting rates of fatal liver injury from data on prescriptions in the US [29]. They found that fatal liver failure was an existing but rare event among statin users with reporting rates much lower than one death per million prescriptions for all statins [29]. In a paper on statin safety, the incidence of statin-associated DILI episode was estimated to be 1 per million person–years of use [34]. Based on the sales of statins in Sweden during the study period, we found that the incidence of statin-associated DILI episode was instead 1.6 cases per 100,000 person–years of use. Thus, our results indicate that the estimation on the risk of liver failure undertaken by Law and Rudnicka (1 per million person-years of use) is probably under-estimation, particularly given the huge under-reporting of adverse effects such as DILI [5].

Three patients in our series had a positive rechallenge with the same statin they had recovered from suspected DILI. This occurred approximately one month after re-initiation of therapy but all recovered after the second discontinuation. Very limited previous experience has been reported with rechallenge of statins. However, a fatal liver failure has been reported with a rechallenge of atorvastatin, which originally was withdrawn due to jaundice [30]. Interestingly, the patient developed liver injury approximately one month after re-exposure as it was the case in our three patients with positive rechallenge. Thus, it seems to be unsafe and can even be life threatening to suggest "if the ALT returns to normal, it is almost certainly safe to rechallenge the patient with the same or a different statin" [35]. A panel of expert hepatologists came to the conclusion that "if a causal relationship between significant liver injury and statins therapy cannot be excluded, then re-initiation of statin therapy is not recommended" [36]. Concerning crossreactivity and the risk of adverse effects of statins, the information in the literature is very scarce. In the current series, information was available in five cases, with suspect liver injury to one type of statin, who were able to tolerate another statin without development of liver injury. This suggests a lack of class effect and it seems to be safe to switch to another statin although numbers are small. We think this is an important information and adds to the existing literature in the field.

Some reports suggested that interaction between statins and other drugs leads to higher risk for DILI [12]. We were only able to study this for those drugs that were discontinued concomitantly with statins and were considered as likely cause of liver injury. By careful analysis of the potential interactions that might lead to higher concentrations of statins, we found very little evidence for this as an important potential mechanism, as only two drugs were found to have a clinically relevant interaction.

Interestingly, DILI was the highest adverse effect reported to SADRAC, whereas myopathy has been reported to be the most common side effect [37]. We do not have an explanation for this. In Sweden, the strategies of spontaneous reporting of adverse effects are first and foremost serious adverse effects and also new or previously unknown adverse effects. It is conceivable that because effects of statins on muscle are well known, this might reduce the spontaneous reporting of that type of side effects.

Table 3. The concomitant drug and the statin discontinued in patients with other drugs possible for the DILI. The potential interactions, possible consequences and the evidence for this are described.

Statin	Concomitant drug	Interaction	Possible consequence	Evidence
Simvastatin	Nefazodone	Inhibiton of CYP3A4	Rhabdomyolysis Transaminitis due to raised serum levels of simvastatin [18]	Several case reports, not clinically relevant regarding the liver
Simvastatin	Amlodipine	Possible competition for CYP3A4	Slight raise in AUC for statin – not clinically relevant [19]	One case report
Simvastatin	Mexiletine	None	-	-
Simvastatin	Rofecoxib	None	-	-
Simvastatin	Ciprofloxacin	Possible inhibiton of CYP3A4 and P-glycoprotein competitive inhibiton	Myopathy Rhabdomyolysis due to raised serum levels of simvastatin [20]	One case report
Simvastatin	Metformin	Unknown	One study [21]	Not clinically relevant
Simvastatin	Isoniazid	None	-	-
Simvastatin	Estrogen	None	-	-
Simvastatin	Ticlopidine	None	-	-
Atorvastatin	Enalapril	None	-	-
Atorvastatin	Dalteparin	None	-	-
Atorvastatin	Premarina	None	-	-
Atorvastatin	Sertraline	None	-	-
Atorvastatin	Cefadroxil	None	-	-
Atorvastatin	Losartan	None	-	-
Rosuvastatin	Enalapril	None	-	-
Fluvastatin	Lisinopril	Unlikely	-	-

Most DILI reports were associated with atorvastatin, which is in line with the fact that out of 40 case reports, 18 were in atorvastatin treated patients [12]. Similarly, among statins, atorvastatin has generally been the most common statin reported in earlier series [17,27,28]. We also found that atorvastatin was significantly more commonly associated with DILI than simvastatin. Compared with DILIs in the total study cohort, fluvastatin had proportionally the highest number of DILI episodes. However, the fact that this drug is used less often than simvastatin and atorvastatin makes the interpretation of this comparison difficult.

In the current study, cholestatic/mixed pattern of liver injury was significantly more common with atorvastatin than with simvastatin, which is also in line with previous studies showing this to the most common type of liver injury with atorvastatin [29].

Statins are very important drugs in cardiovascular medicine and in large clinical trials they have been found to prevent a significant proportion of cardiovascular deaths [2–4]. Thus, given their potency, the occurrence of rare adverse effects such as DILI associated with statins has to be put into perspective. There is a risk for "myths" on either extremes. One "myth" might be the overzelous definition of DILI based on low threshold of raised ALT in a patient on statin that can certainly have other causes [10]. The other extreme is to dismiss statin DILI entirely based on comparing ALT elevations in the setting of a clinical trial [11], which, as mentioned above, are underpowered to detect very rare side effects. Thus, it is important to establish a sound assessment based on clinical data from a large number of patients from the post marketing phase. Although DILI can occur in patients on statins, this should not *discourage* people to use statins. Given that these reactions are extremely rare, it is hardly cost-effective to perform liver tests in patients on statins but this paper does not answer the question whether or not monitoring is reasonable. Measurements of liver tests should as always be based on the clinical scenario and suspicion of a liver disease.

The current study has some limitations. First of all, the retrospective nature of the study makes it difficult to obtain complete clinical information. However, we excluded a significant proportion of patients who had too limited clinical information in order to be able to calculate the RUCAM score. The causality assessment used (RUCAM) in the current study has been the most widely used instrument in DILI studies but it is problematic for several reasons. Ambiguity of instructions and considerable variability among raters are among the problems that limit its reliability [38]. Expert opinion produced a higher agreement rates but still had some inter-observer variability [38]. However, a recent study found RUCAM to have a good correlation with another scale that has been used in DILI and showed good agreement with clinical judgment [39]. Thus, giving the lack of better causality assessment instruments, RUCAM is probably the best validated and its use in the current study is unlikely to have had any major influence on the results. However, causality assessment is the Achilles' heel of the science of DILI and it is very difficult to prove that a liver reaction is actually caused by a drug, except when you have a positive rechallenge. Hopefully, in the

Table 4. Reports of statin-associated DILI according reports to SADRAC during the study period. Reactions were significantly more frequent in patients taking fluvastatin (p <0.05 compared to the total group). DDD, defined daily dose.

	Atorvastatin	Fluvastatin	Pravastatin	Rosuvastatin	Simvastatin	Total
No. of reactions	30	11	2	2	28	73
DDDs (x10^6)	370.7	23.2	131.5	42.9	1097.8	1666.1
Person-years (x10^4)	10.29	0.64	3.65	1.19	30.49	46.26
Incidence (x10^{-6} DDDs)	0.081	0.474	0.015	0.047	0.026	0.044
Incidence (x10^{-4} person-years)	2.9	17	0.5	1.6	0.9	1.6

future the subjective judgment and the scientific immaturity of all causality assessment current work in DILI can be replaced by objective markers of drug injury such as drug protein adducts and pharmacogenomics. Given the fact that a large number of the general population is taking statins and cases with idiopathic acute liver failure (ALF) do occur, it cannot be excluded that in some cases we are dealing with the background noise of idiopathic ALF.

In summary, we were able to show that although idiosyncratic liver injury associated with statins is rare, it can be associated with severe outcome. After recovery, a similar pattern of liver injury can be reproduced on re-exposure. There seems little doubt that certain individuals for unknown reasons may develop this rare side effect. Responsible physicians should perform liver tests in patients taking statins, who present with newly developed symptoms such as nausea, severe lethargy and abdominal pain.

Conflict of interest

The authors who have taken part in this study do not have a relationship with the manufacturers of the drugs involved either in the past or present and did not receive funding from the manufacturers to carry out their research.

References

[1] Bradford RH, Shear CL, Chremos AN, Dujovne C, Downton M, Franklin FA, et al. Expanded Clinical Evaluation of Lovastatin (EXCEL) study results. I. Efficacy in modifying plasma lipoproteins and adverse event profile in 8245 patients with moderate hypercholesterolemia. Arch Intern Med 1999;151 (1):43–49.

[2] Wright RA, Flapan AD, McMurray J, Slattery J, White HD, Spaulding C, et al. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344 (19):1383–1389.

[3] Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. JAMA 2001;285 (13):1711–1718.

[4] Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med 1995;333 (20):1301–1307.

[5] Larrey D. Epidemiology and individual susceptibility to adverse drug reactions affecting the liver. Semin Liver Dis 2002;22:145–155.

[6] Chalasani N, Aljadhey H, Kesterson J, Murray MD, Hall SD. Patients with elevated liver enzymes are not at higher risk for statin hepatotoxicity. Gastroenterology 2004;126 (5):1287–1292.

[7] Rallidis LS, Drakoulis CK, Parasi AS. Pravastatin in patients with nonalcoholic steatohepatitis: results of a pilot study. Atherosclerosis 2004;174 (1):193–196.

[8] Hyogo H, Tazuma S, Arihiro K, Iwamoto K, Nabeshima Y, Inoue M, et al. Efficacy of atorvastatin for the treatment of nonalcoholic steatohepatitis with dyslipidemia. Metabolism 2008 Dec;57 (12):1711–1718.

[9] Ekstedt M, Franzén LE, Mathiesen UL, Holmqvist M, Bodemar G, Kechagias S. Statins in non-alcoholic fatty liver disease and chronically elevated liver enzymes: a histopathological follow-up study. J Hepatol 2007;47 (1):135–141.

[10] Athyros VG, Tziomalos K, Gossios KD, Griva D, Anagnostis P, kargiotis K, et al. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post-hoc analysis. Lancet 2010;376:1916–1922.

[11] Bader T. The myth of statin-induced hepatotoxicity. Am J Gastroenterol 2010;105 (5):978–980.

[12] Russo MW, Scobey M, Bonkovsky HL. Drug-induced liver injury associated with statins. Review. Semin Liver Dis 2009;29 (4):412–422.

[13] Clarke AT, Mills PR. Atorvastatin associated liver disease. Dig Liver Dis 2006;38 (10):772–777.

[14] Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, et al. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther. 2011;89:806–815.

[15] Danan G, Benichou C. Causality assessment of adverse reactions to drugs-I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. J Clin Epidemiol 1993;46 (11):1323–1330.

[16] Benichou C, Danan G, Flahault A. Causality assessment of adverse reactions to drugs-II. An original model for validation of drug causality assessment methods: case reports with positive rechallenge. J Clin Epidemiol 1993;46 (11):1331–1336.

[17] Björnsson E, Olsson R. Outcome and prognostic markers in severe drug-induced liver disease. Hepatology 2005;42 (2):481–489.

[18] Karnik N, Maldonado J. Antidepressants and statin interactions: a review and case report og simvastatin and nefazodone-induced rhabdomyolysis and transaminitis. Psychosomatics 2005;46:565–568.

[19] Preston R et al. A ranomized, placebo-controlled trial to evaluate the efficacy, safety, and pharmacodynamic interaction of coadministered amlodipine and atorvastatin in 1660 patients with concomitant hypertension and dyslipidemia: The respond trial. J Clin Pharmacol 2007;47:1555–1569.

[20] Sawant R. Rhabdomyolysis due to an uncommon interaction of ciprofloxacin with simvastatin. Can J Clin Pharmacol 2009;16:e78–e79.

[21] Alsheikh-Ali A, Abourjaily H, Karas R. Risk of adverse events with concomitant use of atorvastatin or simvastatin and glucose-lowering drugs (thiazolidinediones, metformin, sulfonylurea, insulin and acarbose). Am J Cardiol 2002;89:1308–1310.

[22] Hansten P, Horn J. Drug interactions analysis and management. St. Louis, Missouri: Wolters Kluwer Health, Inc.; 2008.

[23] Chalasani N. Statins and hepatotoxicity: focus on patients with fatty liver. Hepatology 2005;41:690–695.

[24] Bader T. Liver tests are irrelevant when prescribing statins. Lancet 2010;376 (9756):1882–1883.

[25] Davern TJ, Chalasani N. Drug-induced liver injury in clinical trials: as rare as hens' teeth. Am J Gastroenterol 2009;104 (5):1159–1161.

[26] Senior J. Drug hepatotoxicity from a regulatory perspective. Clin Liver Dis 2007;11:507–524.

[27] Andrade RJ, Lucena MI, Fernández MC, Pelaez G, Pachkoria K, García-Ruiz E, et al. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. Spanish Group for the Study of drug-induced liver disease. Gastroenterology. 2005;129:512–521.

[28] Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, et al. Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Drug Induced Liver Injury Network (DILIN). Gastroenterology 2008;135:1924–1934.
[29] Perger L, Kohler M, Fattinger K, Flury R, Meier PJ, Pauli-Magnus C. Fatal liver failure with atorvastatin. J Hepatol 2003;39 (6):1095–1097.
[30] Sreenarasimhaiah J, Shiels P, Lisker-Melman M. Multiorgan failure induced by atorvastatin. Am J Med 2002;113:348–349.
[31] Tuteja S, Pyrsopoulos NT, Wolowich WR, Khanmoradi K, Levi DM, Selvaggi G, et al. Simvastatin-ezetimibe-induced hepatic failure necessitating liver transplantation. Pharmacotherapy 2008;28:1188–1193.
[32] Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug induced liver injury in the United States. Liver Transpl 2004;10 (8):1018–1023.
[33] Reuben A, Koch DG, Lee WM. Drug-induced acute liver failure: results of a US multicenter, prospective study. Hepatology 2010;52 (6):2065–2076.
[34] Law MR, Rudnicka AR. Statin safety: evidence from the published literature. Am J Cardiol 2006;97 (Suppl. 8A):52C–60C.
[35] Tolman KG. Reply to Dr. Dujovnes editorial. Am J Cardiol 2002;89:1451.
[36] Cohen DE, Ananina FA, Chalasani N. An assessment of statin therapy by hepatologists. Am J Cardiol 2006;97 (Suppl.):77C–81C.
[37] Knopp RH. Drug treatment of lipid disorders. N Engl J Med 1999;341:498–511.
[38] Rockey DC, Seeff LB, Rochon J, Freston J, Chalasani N, Bonacini M, et al. Causality assessment in drug-induced liver injury using a structured expert opinion process: comparison to the Roussel-Uclaf causality assessment method. Hepatology 2010 Jun;51:2117–2126.
[39] Miljkovic MM, Dobric S, Dragojevic-Simic V. Consistency between causality assessments obtained with two scales and their agreement with clinical judgments in hepatotoxicity. Pharmacoepidemiol Drug Saf 2011;20:272–285.