ORIGINAL RESEARCH ARTICLE

Drug Safety 2006; 29 (12): 1163-1172
0114-5916/06/0012-1163/$39.95/0

Fluvastatin and Hepatic Reactions

A Signal From Spontaneous Reporting in Italy

Anita Conforti,[1] *Lara Magro*,[1] *Ugo Moretti*,[1] *Stefania Scotto*,[2] *Domenico Motola*,[3] *Francesco Salvo*,[4] *Barbara Ros*[5] and *Roberto Leone*[1]

1 Clinical Pharmacology Unit, Reference Centre for Education and Communication within the WHO Programme for International Drug Monitoring, University of Verona, Verona, Italy
2 Lombardy Centre of Pharmacovigilance, Milan, Italy
3 Department of Pharmacology, Interuniversity Research Centre for Pharmacoepidemiology, University of Bologna, Bologna, Italy
4 Department of Clinical and Experimental Medicine and Pharmacology, Section of Pharmacology, University of Messina, Messina, Italy
5 Pharmaceutical Service of Friuli Venezia Giulia Health Department, Trieste, Italy

Abstract

Background: Signal detection is a crucial element in recognising new adverse drug reactions (ADRs) as soon as possible. HMG-CoA reductase inhibitors ('statins'), the most potent cholesterol-lowering drugs, are generally well tolerated but can occasionally lead to liver toxicity. Pre- and postmarketing studies on statins revealed an incidence of 0.1–3% elevation in hepatic transaminase levels. However, these elevations are asymptomatic, reversible, dose related or probably due to other causes. Postmarketing studies clearly showed the lack of evidence of hepatotoxicity from statins, apart from some isolated case reports of serious hepatic damage described in the literature. It is still unclear whether serious hepatic reactions are dose related and more frequent than the expected rate in the general population.

Objective: In this study, the hypothesis that fluvastatin could cause serious liver injuries more than the other statins is investigated, in the light of a quantitative and qualitative signal analysis, drug consumption data and evidence from the literature.

Methods: The Italian Interregional Group of Pharmacovigilance (Gruppo Interregionale di Farmacovigilanza; GIF) is an example of signal detection within the Italian spontaneous ADR reporting system. The GIF database holds reports of suspected ADRs submitted by five Italian pharmacovigilance regional centres. In the GIF database, all reports of suspected ADRs are classified according to the WHO criteria for causality assessment. The reactions are coded according to the WHO Adverse Reaction Terminology and classified as serious or non-serious events on the basis of the WHO Critical Term List. Every 6 months the GIF database is analysed to extract potential signals through a qualitative case-by-case analysis and using a quantitative methodology called proportional reporting ratio (PRR). This methodology permitted us to identify the potential signal 'fluvastatin and hepatic reactions'.

Results: At 31 December 2004, the GIF database contained 35 757 reports with an annual reporting rate of 170 reports per million inhabitants. We found a total of

1260 reports of ADRs related to statins, including 178 of hepatic reactions. Sixty-nine reports were attributed to fluvastatin, which showed the highest PRR in comparison with the other statins. Fluvastatin was associated with 33 serious reactions, mainly hepatitis and cholestatic hepatitis. The number of reports of severe hepatotoxicity associated with fluvastatin started to increase from 2002. About half of them did not report other suspected or concomitant drugs and in one third the hepatotoxicity occurred after <1 month of therapy. Twenty-seven out of 33 patients were female, and fluvastatin was administered at 80 mg/day in 81% of cases reporting complete data on drug dosage.

Conclusion: In the literature, serious hepatic reactions are rarely described in patients taking statins; however, data gathered by GIF suggest that cases of hepatotoxicity are reported more often than expected. In addition, GIF data seem to reveal that fluvastatin is more likely to cause hepatic reactions than the other statins. However, this is a preliminary signal and future evaluations are certainly needed to confirm it and to quantify this possible risk.

Background

We can define pharmacovigilance as the continuous process of monitoring, evaluating, communicating and improving the safety of medicines in real conditions of usage by patients.[1] One of the first steps in pharmacovigilance is the systematic search for signals of drug toxicity in large postmarketing drug safety databases, which make it possible to recognise any new adverse drug reactions (ADRs) as soon as possible. Once such signals are detected, they have to be explored, verified and processed in the context of other relevant data, through specific pharmacoepidemiological studies.[2]

A number of publications have investigated the data-mining methods used to identify safety signals from spontaneous databases and the role of such methodologies is evolving.[3-6] Currently, there is evidence that data mining may be useful, but its value and real utility have to be confirmed by time and experience. As a basic requirement, adequate signal detection should be based on qualitative case-by-case analysis and on quantitative approaches that may differ in methodology and parameters. Among quantitative methods, proportional reporting ratio (PRR) and reporting odds ratio (ROR) are probably the most used, since these indices of disproportionality are easily calculated and have been proved to be effective in signal detection. It is well recognised that these measures can give comparable results.[6] Another measure of disproportionality is the information component (IC), calculated within the Bayesian Confidence Propagation Neural Network methodology, used by the Uppsala Monitoring Centre to scan incoming reports to the WHO database.[5] Eventually, all methodologies try to answer the question: "is a particular drug-ADR combination reported in the database more often than would be expected from the rest of the reports in the database?".

The Italian Interregional Group of Pharmacovigilance (Gruppo Interregionale di Farmacovigilanza; GIF) is an example of signal detection within the Italian spontaneous ADR-reporting system.[7] GIF is co-ordinated by the Veneto Regional Centre for Pharmacovigilance in Verona, Italy and its database holds reports of suspected ADRs submitted by five Italian Regional Centers for Pharmacovigilance (Emilia Romagna, Friuli Venezia Giulia, Lombardy, Sicily and Veneto), where active groups have been working on pharmacovigilance for some years.

The main goal of GIF is to identify potential signals, by a qualitative case-by-case analysis and using a quantitative methodology. GIF considers any "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously", to be a signal following the

WHO definition.[8] A signal may be also the observation of a change in the proportion of known reactions in terms of frequency, severity or outcome within a 'risk group' of patients, or in relation to a dose range, as well as a drug-ADR relationship already identified and analysed in the literature but little known among physicians. The signals of interest are periodically notified on the web site http://www.gruppogif.org and published when it is appropriate.[9,10] At the end of 2004, case-by-case analysis revealed a considerable number of hepatic reactions associated with fluvastatin and the combined signal detection raised the question of the possibly greater hepatotoxicity associated with this molecule compared with the other HMG-CoA reductase inhibitors ('statins') on the Italian market.

Statins, including lovastatin, simvastatin, atorvastatin, fluvastatin, pravastatin and rosuvastatin, are used for the treatment of hypercholesterolaemia, and they are among the most widely prescribed medicines in the world. Apart from lovastatin, all the aforementioned statins were available on the Italian market in 2004, and atorvastatin, simvastatin and pravastatin were among the 30 most commonly prescribed drugs.[11]

Large clinical trials and meta-analyses have confirmed that these drugs have significant potential benefits, leading to a reduction in cardiovascular morbidity and mortality.[12-14] The benefit of statin therapy is related to the absolute reduction in low-density lipoprotein (LDL) cholesterol level, above and beyond to the patient's individual risk. So, statins with higher potency in lowering LDL, or higher doses, are often required to achieve very low LDL levels, thereby increasing the potential risk of toxicity.[15]

Statins are considered to have low risk for causing serious adverse effects, but it is well known that they can rarely lead to severe muscle and liver toxicity.

Early clinical studies revealed an elevation, usually dose dependent, which was more than three times the upper limit of normal for liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) in about 3% of patients treated with statins.[16] However, recent reviews of data from large clinical trials show that elevations in hepatic enzyme levels are rare and do not lead to clinically significant liver disease.[17] Monitoring liver function is recommended by the authorities, but this position is not shared by everyone.[18,19] Isolated cases of serious hepatic damage (acute liver failure, hepatitis, jaundice) associated with statins are reported in the literature, but it is still unclear whether serious hepatic reactions are dose related or more frequent than the expected rate in the general population.[20-23]

In this paper, the hypothesis that fluvastatin could cause serious liver injuries more than the other statins will be discussed in the light of quantitative signal detection, single case report analysis, drug consumption data and evidence from the literature.

Methods

Sources of Data

At 31 December 2004, the GIF database contained 35 757 reports of ADRs (37% serious), 99% of which were submitted by physicians. In 2004, spontaneous reports collected through GIF represented >60% of the total number of Italian reports, with a reporting rate of 170 reports per million inhabitants.

In the GIF database, all reports of suspected ADRs are classified according to the WHO criteria for causality assessment[24] and only those with a 'certain', 'probable' or 'possible' causality assessment were included in this study. A 'probable' relationship is a clinical event with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs, and that follows a clinical reasonable response on dechallenge. The presence of predisposing conditions or consumption of drugs known for hepatotoxicity lead to a 'possible' classification, particularly where the information on drug withdrawal may be lacking or unclear.

The drugs were grouped using the Italian Codifa System and the Anatomical Therapeutic Chemical classification. The reactions were coded according

Table I. Total and hepatic adverse reaction reports associated with HMG-CoA reductase inhibitors ('statins') in the GIF database

Drug	Year of marketing	Total no. of reports	No. or reports of hepatic reactions (% over total reports)	Percentage of hepatic reactions classified as 'serious'
Simvastatin	1989	444	50 (11)	28
Atorvastatin	1997	385	37 (10)	22
Fluvastatin	1995	194	69 (36)	48
Pravastatin	1990	176	16 (9)	25
Rosuvastatin	2004	61	6 (10)	67

GIF = Gruppo Interregionale di Farmacovigilanza (Italian Interregional Group of Pharmacovigilance).

to the WHO Adverse Reaction Terminology (WHO-ART) and classified as serious or non-serious events on the basis of the WHO Critical Term List.[25] WHO-ART has a hierarchical structure starting with body system/organ level, within which there are grouping terms (general or high level), which are useful for the broadest view of drug problems. Within these broad categories the specific, frequently used 'preferred terms' allow precise identification of adverse reactions and are those mainly used in entering and searching the data.

The statin consumption data were obtained by the Pharmaceutical Service of Friuli Venezia Giulia Health Department, through the 'Progetto Sfera' of Italian Ministry of Health.

Signal Detection

Every 6 months, the GIF database is analysed to filter out potential signals. Signal detection is done by qualitative case-by-case analysis and by using, as quantitative methodology, the PRR. PRR compares the proportion of an ADR by a drug with the corresponding proportion for all drugs in the database. PRR is currently used for signal generation from spontaneous reporting data, because it is easy to calculate and interpret.[26,27] A large PRR for a specific drug-ADR association indicates that ADR has been disproportionately reported for that drug. A significant increase in PRR, supported by any other information on a particular drug-ADR combination, contributes to the creation of a signal.

At the end of 2004, case-by-case analysis in the GIF database revealed a considerable number of cases of hepatitis associated with fluvastatin, so this signal was examined closely, by calculating the PRR of all hepatic reactions at system organ level (liver is coded as 0700 in the WHO-ART classification) for each statin in the whole database.

Results

As of December 2004, in the GIF database there were in total 1260 reports of ADRs related to statins available on the Italian market. Another 250 reports related to cerivastatin, which was withdrawn from the market in August 2001, were not included in this analysis. As shown in table I, we found a total of 178 reports of statin-related adverse hepatic reactions, with the highest number (69 reports) attributed to fluvastatin. Furthermore, nearly 50% of reports of hepatic reactions related to fluvastatin were serious.

The number of reports associated with a drug in a spontaneous reporting database, is clearly affected by the length of time it has been on the market and also by how much it is used. The national statin consumption in Italy during the last 4 years of the study period indicated that simvastatin and atorvastatin were the most widely used lipid-lowering drugs (table II). Pravastatin and fluvastatin were less commonly used, even if prescriptions for the latter increased considerably between 2002 and 2004. Three delayed-delivery formulations of fluvastatin 80mg

Table II. National HMG-CoA reductase inhibitor ('statin') consumption in Italy in 2001–4. Data are expressed as defined daily dose/1000 inhabitants/day

Drug	2001	2002	2003	2004
Simvastatin	9.79	12.52	14.58	16.62
Atorvastatin	7.69	10.42	13.44	20.76
Pravastatin	3.73	4.80	6.02	6.95
Fluvastatin	0.43	2.31	4.00	4.87
Rosuvastatin				2.14

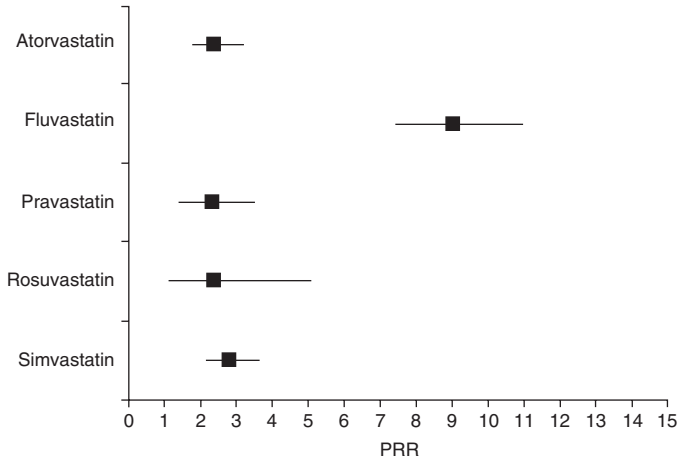

Fig. 1. Proportional reporting rate (PRR) values of HMG-CoA reductase inhibitor ('statin') hepatic reactions. The lines represent the 95% CI.

entered the Italian market in September 2001 and were mainly responsible for the observed increase.

Figure 1 shows PRR values for the hepatic reactions calculated for each statin, by using as reference group all drugs in the database. Fluvastatin had the highest PRR (8.99; 95% CI 7.39, 10.96) compared with atorvastatin (2.36; 95% CI 1.73, 3.21), simvastatin (2.78; 95% CI 2.13, 3.63), pravastatin (2.21; 95% CI 1.38, 3.53) and rosuvastatin (2.38; 95% CI 1.11, 5.09). It is worth noting that all PRR values were statistically significant. PRR calculated only with serious hepatic reactions data leads to same results (data not shown).

Table III illustrates the distribution of the different types of hepatic reactions to each statin at the preferred terms level. We can observe that the most common hepatic effect is an elevation in liver enzyme levels. As shown, fluvastatin was associated with a high number of serious reactions, mainly hepatitis and cholestatic hepatitis. Rosuvastatin caused the highest percentage of serious hepatic reactions, but the number of reports was too small for conclusions to be drawn. Sixty-three reports out of 178 satisfied the WHO criteria for classification as serious reactions, mainly hepatitis (75%) and cholestatic hepatitis (13%).

In table IV, the 63 cases of serious hepatic reactions associated with the five statins are described, focusing on some characteristics that can help in interpreting these associations. Causality assessment of single reports, as established by the coordinating centre, was 'possible' in 70% of reports,

Table III. Number of reports of HMG-CoA reductase inhibitor ('statin')-related hepatic reactions (WHO-ART preferred term) in the GIF database

Hepatic ADR	Atorvastatin	Fluvastatin	Pravastatin	Rosuvastatin	Simvastatin
Hepatic enzymes increased	26	30	10	2	34
Hepatic function abnormal	3	5	2	0	2
Hepatic necrosis[a]	0	1	0	0	0
Hepatitis[a]	5	26	2	4	10
Hepatitis cholestatic[a]	2	5	2	0	4
Hepatitis chronic active	0	1	0	0	0
Hepatocellular damage[a]	1	1	0	0	0
Total	37	69	16	6	50

a Serious ADRs (according to the WHO Critical Term List).

ADR = adverse drug reaction; **GIF** = Gruppo Interregionale di Farmacovigilanza (Italian Interregional Group of Pharmacovigilance); **WHO-ART** = WHO Adverse Reaction Terminology.

Table IV. Characteristics of reports of serious[a] HMG-CoA reductase inhibitor ('statin')-related hepatic reactions present in the GIF database

Drug	No. of reports	No. of reports/ year	No. of males/ females	Age (mean ± SD) [y]	Statin dose	Onset of reaction	No. of reports with no concomitant drugs (%)	No of reactions confirmed by laboratory values (%)	Causality assessment
Atorvastatin	8	2002: 3	3/5	60.7 ± 11.7	10mg: 2	1–2d: 1	2 (25)	7 (88)	Probable: 3
		2003: 1			20mg: 1	8–30d: 3			Possible: 5
		2004: 4			40mg: 2	>90d: 3			
					60mg: 1	Missing: 1			
					Missing: 2				
Fluvastatin	33	Before 2000: 1	6/27	63.8 ± 7.7	20mg: 1	1–2d: 9	15 (45)	28 (85)	Certain: 1
		2001: 2			40mg: 4	3–7d: 3			Probable: 14
		2002: 7			80mg: 22	8–30d: 8			Possible: 18
		2003: 12			Missing: 6	31–90d: 9			
		2004: 11				>90d: 4			
Pravastatin	4	Before 2000: 2	1/3	58.8 ± 10.6	20mg: 1	8–30d: 2	0	2 (50)	Possible: 4
		2002: 1			40mg: 2	>90d: 2			
		2004: 1			Missing: 1				
Rosuvastatin	4	2004: 4	2/2	69.5 ± 12.7	10mg: 4	8–30d: 2	1 (25)	3 (75)	Probable: 1
						31–90d: 2			Possible: 3
Simvastatin	14	Before 2000: 3	10/4	63.4 ± 15.3	10mg: 6	8–30d: 6	2 (14)	11 (79)	Possible: 14
		2000: 2			20mg: 4	31–90d: 3			
		2001: 4			40mg: 1	>90d: 5			
		2003: 2			Missing: 3				
		2004: 3							

a According to the WHO Critical Term List.

d = days; **GIF** = Gruppo Interregionale di Farmacovigilanza (Italian Interregional Group of Pharmacovigilance).

'probable' in 28% and 'certain' in only one report. Apart from those related to pravastatin, >75% of reports included laboratory values confirming liver injury, on the basis of an increase of more than twice the upper limit of the normal range in ALT level or a combined increase in AST, alkaline phosphatase and total bilirubin levels, provided that one of them was twice of the upper limit of the respective normal ranges.[28]

Other concomitant drugs, mainly cardiovascular agents (e.g. antiplatelet agents, calcium channel antagonists, β-adrenoceptor antagonists, diuretics), were administered in 68% of patients. We cannot exclude the possible role of these drugs in the onset of ADRs, in particular in the case of ticlopidine, an antiplatelet agent with some evidence of hepatotoxicity.

The number of reports of severe hepatotoxicity associated with fluvastatin started to increase from 2002. About half of these cases report the use of other suspected or concomitant drugs, but not of ticlopidine. Twenty-seven out of 33 patients were female, and fluvastatin was administered at 80 mg/day in 81% of cases reporting complete data on drug dosage. The other statins are administered at lower doses, according to their different potency. The early onset of reaction (<7 days from starting fluvastatin treatment) in 12 patients could be related to a toxic effect or to an immunoallergic reaction. Unfortunately, we do not know if these patients had been previously exposed to fluvastatin. Fluvastatin was withdrawn in 28 cases, after which the ADR symptoms improved in all patients except one. Other information such as alcohol consumption or serological analysis are not usually requested in spontaneous reporting systems, even if doctors often excluded viral hepatitis by referring to serological data.

Discussion

The spectrum of drug-induced liver injury is broad, with imitations of almost all liver disorders, from mild and asymptomatic increases in liver enzyme levels to serious hepatotoxicity that is disabling or life-threatening or that requires hospitalisation.[29]

Statins are considered to be well tolerated drugs, but rare major adverse effects include liver and muscle damage. High values of liver enzyme levels (more than three times the upper reference limit) were observed during clinical trials in 0.1–3% of patients and were dose related.[16,19,30,31] Alterations in laboratory values for liver function, mainly slight elevations of ALT level, have been observed during the premarketing clinical trials of statins.[31,32] For that reason, all statins are contraindicated in patients with active liver disease and should be used with caution in those with a history of liver disease or high alcohol intake.[33] In particular, leaflets of statins report hepatitis and elevations in liver function values (more than three times the upper reference limit) as possible adverse reactions to statins with incidence of 0.01% and 1–2%, respectively.[34] Postmarketing pharmacovigilance experience suggested that elevated liver enzyme levels are reversible and asymptomatic.[19,31,33] Moreover, transient asymptomatic transaminase elevations have been observed in response to all classes of antihyperlipidemic drugs and may be secondary to cholesterol reduction within the hepatocytes, representing a transient pharmacological effect and not a toxic consequence.[19] It has also been argued that the elevation in aminotransferase enzyme levels in patients with hyperlipidaemia could be related to the commonly coexisting condition called non-alcoholic fatty liver disease, and that such patients do not appear to be at increased risk of statin-associated hepatotoxicity.[35]

Meta-analyses of randomised controlled trials[14,36] and a placebo-controlled trial[37] with simvastatin in 20 536 patients did not show any difference between placebo and statins (especially at low doses) in the incidence of raised ALT levels (about 1% of patients), and no cases of serious liver disease were reported. For these reasons and in consideration of their substantial cost, screening and monitoring of asymptomatic elevation of transaminase levels do not appear to be justified to many authors.[16,18,19]

Statins have different potency, and the following equivalent doses are generally used to compare their efficacy: rosuvastatin 5mg = atorvastatin 10mg = simvastatin 20mg = pravastatin 40mg = fluvastatin 80 mg.[38] Reviews on small and large doses of single statins, particularly focused on high dose atorvastatin and lovastatin, confirm that elevation of liver enzyme levels is rare and does not lead to clinically significant disease.[17,31] Interestingly, a recent meta-analysis by de Denus et al.[39] on 13 randomised, placebo-controlled trials with four statins (fluvastatin, lovastatin, pravastatin and simvastatin), showed that the proportion of patients having liver function test (LFT) abnormalities was low in both groups and the risk with statin therapy, as a class, was no greater than that with placebo (OR: 1.26; 95% CI 0.99, 1.62; p = 0.07). The data on single statins supported previous observations that pravastatin, lovastatin and simvastatin, at low-to-moderate doses, were not associated with a significant risk of LFT abnormalities, whereas fluvastatin was associated with a significant increase in the odds of having LFT abnormalities (fluvastatin 1.13% vs placebo 0.29%; OR: 3.54; 95% CI 1.1, 11.6; p = 0.04) compared with placebo. It should be emphasised that the doses used in trials evaluating lovastatin, pravastatin and simvastatin were ≤40mg, whereas fluvastatin was evaluated in two trials, one of them using 80mg. According to the authors, the distinctive effect of fluvastatin on the liver could be due to the fact that fluvastatin is the only statin metabolised by cytochrome P450 (CYP) 2C9. Recent data[40] suggest that polymorphism of CYP2C9 may influence the pharmacokinetics of fluvastatin in healthy volunteers and this could lead this group of patients to experience ADRs. However, the clinical implications of this finding should be investigated in a larger group of patients treated with fluvastatin.

Compared with the large number of trials and reviews on minor elevations of liver enzyme levels associated with statins, the reports of more serious hepatic toxicity are few and anecdotal. Hepatitis is reported as rare, probably no more frequent than with other common drugs (1 per 100 000 patient-treatment years).[32] Isolated cases of hepatocellular toxicity and jaundice were reported in the literature in association with the most commonly used statins,[20-22] and single cases of fatal liver failure[41] and autoimmune hepatitis[42] with atorvastatin have also been described.

Screening for signals in the GIF database shows a higher-than-expected number of reports of hepatotoxicity in patients treated with statins in the last 4 years. The elevation in liver enzymes was the reaction most commonly reported overall, but a considerable number of serious hepatic abnormalities were also signalled. Quantitative analysis from each statin report, obtained through PRRs calculation, raised the hypothesis that fluvastatin was more hepatotoxic than the other molecules in the group and we have no reason to suspect over-reporting of hepatotoxicity from fluvastatin more than from other statins by Italian physicians.

In WHO ADR database (accessed online on February 2006), maintained by the Uppsala Monitoring Centre, there are 2303 reports of serious and 9748 reports of non-serious hepatic ADRs associated with statins (except cerivastatin), which underline the potential for statin-induced hepatotoxicity. Among these reports, 968 involve fluvastatin; of which, 22% were serious hepatic ADRs, a percentage similar to that of other statins. In the absence of worldwide drug-utilisation data, and considering the different prescribing patterns and different reporting rates from various countries, it is difficult to compare the ADR pattern among statins. However, an analysis of the WHO database performed in the first quarter of 2001 showed a higher IC for fluvastatin-induced hepatitis, hepatitis cholestatic and hepatocellular damage than for other statins.[43]

Furthermore, a recent analysis on the US FDA's MedWatch reporting program shows that, in the period 2002–4, the "report proportion" of liver failure/hepatitis is higher (0.061 per million prescriptions) for fluvastatin than for other statins.[44]

Information from the single case reports did not allow identification of specific differences in patients treated with each statin. However, fluvastatin reports from the GIF database would support a possible relation with the 80mg daily dose, since most

of them occurred with the 80mg formulation, in concomitance with the marketing in Italy of three delayed-delivery formulations of fluvastatin. This hypothesis is strengthened by national drug-use data, confirming that the consumption of fluvastatin increased 10-fold from 2001 to 2004, although it remained very low in comparison with atorvastatin and simvastatin. On the other hand, we cannot exclude the hypothesis that these formulations were administered to a select group of patients with a genetic predisposition or other unknown risk factors for hepatotoxicity. Given that the proportion of females was higher in the patients with fluvastatin-related hepatic reactions, we also hypothesise a possible causal role for sex, but we have no further data to confirm this hypothesis. The onset of serious hepatotoxic reactions from starting fluvastatin therapy was highly variable, suggesting potential multiple underlying mechanisms. Generally, the latency time for type A reactions ranges between days and weeks, whereas for type B reactions this time period may be months.[45] However, all fluvastatin reports were compatible with the accepted criteria of diagnosis of hepatic ADRs in relation to duration of exposure.[46]

Conclusion

Our analysis of the GIF database indicates that fluvastatin-related hepatic reactions may be more frequent and serious than those caused by other statins. Previously only one meta-analysis[39] showed differences between fluvastatin and other statins. It should be remembered that spontaneous reporting does not make it possible to calculate the incidence of ADRs; therefore, this signal should be considered as preliminary. Further evaluations are certainly needed to confirm it and to quantify the possible risk in any patient population.

In any case, patients and physicians should be aware of this possible serious hepatotoxicity in their respective use and prescription of high doses of fluvastatin.

Acknowledgements

We are very grateful to the Pharmaceutical Departments of Emilia Romagna, Friuli Venezia Giulia, Lombardy, Sicily and the Veneto and their local Health Districts for collecting the adverse reaction forms. We would also like to thank the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden, for allowing us to consult the WHO database and, in particular, Anne Kiuru for providing us the first quarter 2001 analysis of hepatic reactions reported with statins in the WHO database.

No sources of funding were used in the preparation of this article. The authors have no conflicts of interest that are directly relevant to the content of this manuscript.

References

1. Meyboom RH, Egberts AC, Gribnau FW, et al. Pharmacovigilance in perspective. Drug Saf 1999; 21 (6): 429-47
2. Meyboom RH, Lindquist M, Egberts CG, et al. Signal selection and follow-up in pharmacovigilance. Drug Saf 2002; 25 (6): 459-65
3. Chan KA, Hauben M. Signal detection in pharmacovigilance: empirical evaluation of data mining tools. Pharmacoepidemiol Drug Saf 2005; 14 (9): 597-9
4. Coulter DM. Signal generation in the New Zealand Intensive Medicines Monitoring Programme: a combined clinical and statistical approach. Drug Saf 2002; 25 (6): 433-9
5. Bate A, Lindquist M, Edwards IR, et al. A data mining approach for signal detection and analysis. Drug Saf 2002; 25 (6): 393-7
6. Almenoff J, Tonning JM, Gould AL, et al. Perspective on the use of data mining in pharmacovigilance. Drug Saf 2005; 28 (11): 981-1007
7. Spontaneous reporting in GIF regions of Italy during 2004. Reactions Weekly 2005; 1063: 2
8. Edwards IR, Biriell C. Harmonisation in pharmacovigilance. Drug Saf 1994; 10 (2): 93-102
9. Leone R, Venegoni M, Motola D, et al. Adverse drug reactions related to the use of fluoroquinolone antimicrobials: an analysis of spontaneous reports and fluoroquinolone consumption data from three Italian regions. Drug Saf 2003; 26 (2): 109-20
10. Leone R, Conforti A, Venegoni M, et al. Drug-induced anaphylaxis: case non-case study based on an Italian pharmacovigilance database. Drug Saf 2005; 28 (6): 547-56
11. Ministero della Salute. Drug utilization in Italy. National Report year 2004 [online]. Available from URL: http://www.ministerosalute.it/medicinali/osmed/osmed.jsp [Accessed 2005 Nov 21]
12. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med 1995; 333 (20): 1301-7
13. Baigent C, Keech A, Kearney PM, et al. Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005; 366 (9493): 1267-78
14. Law R, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ 2003; 326 (7404): 1423-9

15. Grundy SM. The issue of statin safety: where do we stand? Circulation 2005; 111 (23): 3016-9

16. Gotto AM. Safety and statin therapy: reconsidering the risks and benefits. Arch Intern Med 2003; 163 (6): 657-9

17. Waters DD. Safety of high-dose of atorvastatin therapy. Am J Cardiol 2005; 96 (5A): 69F-75F

18. Smith CC, Bernstein LI, Davis RB, et al. Screening for statin-related toxicity: the yield of transaminase and creatine kinase measurements in a primary care setting. Arch Intern Med 2003; 163 (6): 688-92

19. Sniderman AD. Is there value in liver function test and creatine phosphokinase monitoring with statin use? Am J Cardiol 2004; 94 (9A): 30F-4F

20. Hartleb M, Rymarczyk G, Januszewski K. Acute cholestatic hepatitis associated with pravastatin. Am J Gastroenterol 1999; 94 (5): 1388-90

21. Geddes JA. Cholestatic jaundice associated with lovastatin (mevacor) therapy. CMAJ 1990; 143 (1): 13-4

22. Nakad A, Bataille L, Hamoir V, et al. Atorvastatin induced acute hepatitis with absence of cross-toxicity with simvastatin. Lancet 1999; 353 (9166): 1763-4

23. Newman C, Tsai J, Szarek M, et al. Comparative safety of atorvastatin 80mg versus 10mg derived from analysis of 49 completed trials in 14,236 patients. Am J Cardiol 2006; 97 (1): 61-7

24. Uppsala Monitoring Centre. Safety monitoring of medicinal products: guidelines for setting up and running a pharmacovigilance centre. Uppsala: the Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring, 2000

25. Olsson S. Role of WHO programme on International Drug Monitoring in coordinating worldwide drug safety efforts. Drug Saf 1998; 19 (1): 1-10

26. Evans SJ, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiol Drug Saf 2001; 10 (6): 483-6

27. Banks D, Woo EJ. Burwen DR, et al. Comparing data mining methods on the VAERS database. Pharmacoepidemiol Drug Saf 2005; 14 (9): 601-9

28. Benichou C. Criteria of drug-induced liver disorders. Report of an international consensus meeting. J Hepatol 1990; 11 (2): 272-6

29. Navarro VJ, Senior JR. Drug-related hepatotoxicity. N Engl J Med 2006; 354 (7): 731-9

30. Gershovich OE, Lyman AE. Liver function test abnormalities and pruritus in a patient treated with atorvastatin: case report and review of the literature. Pharmacotherapy 2004; 24 (1): 150-4

31. Tolman KG. The liver and lovastatin. Am J Cardiol 2002; 89 (12): 1374-80

32. Bandolier. Statins and the liver [online]. Available from URL: http://www.jr2.ox.ac.uk/bandolier/booth/cardiac/statliv.html [Accessed 2005 Dec 14]

33. Kiortsis DN, Nikas S, Hatzidimou K, et al. Lipid-lowering drugs and serum liver enzymes: the effects of body weight and baseline enzyme levels. Fundam Clin Pharmacol 2003; 17 (4): 491-4

34. Repertorio Farmaceutico Italiano [CD ROM]. 14th ed. Milan: OEMF, 2005

35. Chalasani N, Aljadhey H, Kesterson J, et al. Patients with elevated liver enzymes are not at higher risk for statin hepatotoxicity. Gastroenterology 2004; 126 (5): 1287-92

36. LaRosa JC, He J, Vupputuri S. Effects of statins on risk of coronary heart disease: a meta-analysis of randomized controlled trials. JAMA 1999; 282 (24): 2340-6

37. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002; 360 (9326): 7-22

38. Kendrach MG, Kelly-Freeman M. Approximate equivalent rosuvastatin doses for temporary statin interchange programs. Ann Pharmacother 2004; 39: 1286-92

39. de Denus S, Spinler SA, Miller K, et al. Statins and liver toxicity: a meta-analysis. Pharmacotherapy 2004; 24 (5): 584-91

40. Kirchheiner J, Kudlicz D, Meisel C, et al. Influence of CYP2C9 polymorphisms on the pharmacokinetics and cholesterol-lowering activity of (-)-3S,5R-fluvastatin and (+)-3R,5S-fluvastatin in healthy volunteers. Clin Pharmacol Ther 2003; 74 (2): 186-94

41. Perger L, Kohler M, Fattinger K, et al. Fatal liver failure with atorvastatin. J Hepatol 2003; 39 (6): 1095-7

42. Pelli N, Setti M, Ceppa P, et al. Autoimmune hepatitis revealed by atorvastatin. Eur J Gastroenterol Hepatol 2003; 15 (8): 921-4

43. Restricted document, contact the UMC (www.who-umc.org) for details

44. Davidson MH, Clark JA, Glass LM, et al. Statin safety: an appraisal from the adverse event reporting system. Am J Cardiol 2006; 97 (8A): 32C-43C

45. Ward F, Daly M. Hepatic disorders. In: Lee A, editor. Adverse drug reactions. London: Pharmaceutical Press, 2001: 77-97

46. Davis M. Hepatic disorders. In: Davies DM, Ferner RE, de Glanville H, editors. Davies's textbook of adverse drug reactions. London: Chapman & Hall Medical, 1998: 275-338

Correspondence and offprints: Dr *Roberto Leone*, Clinical Pharmacology Unit, Policlinico G.B. Rossi, Piazzale L. Scuro 10, 37134 Verona, Italy.
E-mail: rleone@sfm.univr.it