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Safety Profile of Rosuvastatin

Results of a Prescription-Event Monitoring Study of 11 680 Patients

Rachna Kasliwal,[1] *Lynda V. Wilton*,[1,2] *Victoria Cornelius*,[1] *Beate Aurich-Barrera*[1] and *Saad A.W. Shakir*[1,2]

1 Drug Safety Research Unit, Southampton, UK
2 University of Portsmouth, Portsmouth, UK

Abstract

Background and objective: Rosuvastatin is a lipid-lowering drug, the newest of a class of drugs called HMG-CoA reductase inhibitors, or 'statins', launched in the UK in March 2003. Our objective was to monitor the post-marketing safety of this drug, prescribed in primary care in England, using prescription-event monitoring.

Methods: An observational cohort study in which patients were identified from dispensed prescriptions issued by primary care physicians/general practitioners (GPs) between August and December 2003. Demographic and clinical-event data were collected from questionnaires posted to GPs at least 6 months after the date of first prescription for each patient. Stratified analysis of specific events by starting dose of rosuvastatin was conducted. Follow-up and causality assessment of medically significant events was undertaken.

Results: The cohort comprised 11 680 patients (median age 64 years); 50.3% were males (5880 of 11 680). The median period of treatment was 9.8 months. Of these patients, 72.7% (n = 8494) were started on rosuvastatin 10 mg/day. A total of 17.5% (n = 2047) of the patients were reported to have stopped treatment with rosuvastatin. Myalgia was the most frequent reason for stopping rosuvastatin and the most frequently reported clinical event. A 2.5-fold increase in the rate of abnormal liver-function tests (LFTs) was observed for patients started on rosuvastatin 40 mg/day compared with those started on 10 mg/day (2.71; 95% CI 1.53, 4.53). No case of rhabdomyolysis was reported in this cohort.

Conclusion: Rosuvastatin was considered to be a reasonably well tolerated drug. In the majority of patients, rosuvastatin was prescribed in line with recommendations. Abnormality of LFTs was found to be more frequent with the 40 mg/day dosage of rosuvastatin. Results from this study should be taken into account together with those of other clinical and pharmacoepidemiological studies of rosuvastatin.

Cardiovascular disease has been projected to become the number one cause of death worldwide by 2020, causing 36% of all deaths.[1] Because coronary artery disease (CAD) is the most common type of cardiovascular disease, its primary as well as secondary prevention is of paramount importance.

Low-density lipoprotein (LDL) cholesterol is established as an important risk factor in the development of atherosclerosis and so are other types of lipoproteins such as very low-density lipoprotein (VLDL).[2] On the other hand, both human and animal studies have shown that an inverse relationship exists between high-density lipoprotein (HDL) level and the development of atherosclerosis.[3]

Rosuvastatin is a new lipid-lowering drug which belongs to the HMG-CoA reductase inhibitor class of drugs also called 'statins'. Rosuvastatin acts by inhibiting HMG-CoA reductase, the rate limiting enzyme that converts HMG-CoA to mevalonate, a precursor of cholesterol. Launched in the UK in March 2003, rosuvastatin is indicated in patients with high lipid levels. It is the sixth statin to be marketed in the UK and has been reported to have higher efficacy than other available statins in reducing total cholesterol, LDL, VLDL and triglyceride levels and increasing HDL levels.[4]

Although statins are extremely beneficial drugs in reducing the risk of ischaemic heart disease and stroke,[5] a number of safety issues have surrounded this class of drugs. Statins have been associated with muscular events that may range from a simple muscle ache to an acute and potentially fatal condition of skeletal muscle necrosis called rhabdomyolysis.[6] Cerivastatin was withdrawn from the market in 2001 after being linked to a number of deaths resulting from rhabdomyolysis.[7] A number of cases of rhabdomyolysis have been reported with use of rosuvastatin,[8-10] particularly at dosages ≥40 mg/day. Other safety concerns that have been expressed with rosuvastatin include renal effects such as tubular proteinuria and the potential for renal failure and hepatic effects such as an increase in hepatic transaminases.[11]

In view of these safety concerns, the Drug Safety Research Unit (DSRU) conducted a post-marketing observational cohort study to examine the safety and use of rosuvastatin in general practice in England.

Methods

An observational cohort study was conducted in England, using the technique of prescription-event monitoring (PEM), described in more detail previously.[12]

Between August and December 2003, exposure data were collected from dispensed National Health Service prescriptions for rosuvastatin issued by primary care physicians/general practitioners (GPs) in England and supplied in confidence to the DRSU by the Prescription Pricing Division (a part of the National Health Service Business Services Authority). At least 6 months after the initial prescription, questionnaires, known as green forms, were sent to prescribing GPs requesting information (outcome data) on any events [1] that had occurred since the initiation of rosuvastatin. GPs were also requested to provide information on: patient demographics; indication for prescribing rosuvastatin; dosage at the time of starting rosuvastatin and at event; start and stop dates; and, if applicable, reason(s) for stopping rosuvastatin and cause of death. GPs completed the green forms on a voluntary basis.

All reported events were entered onto the DSRU database using the DSRU event dictionary that has a hierarchical structure arranged by system-organ class. The terminology used by the GP (doctor summary term) is grouped under 'lower-level' terms, which are in turn grouped under broader, 'higher-level' terms that are linked to the respective system-organ classes.

All returned green forms were reviewed by medically qualified staff and events that required additional information for further assessment were followed-up. These included: selected events of medical interest (e.g. muscular, hepatic and renal events); serious[13] or unlabelled events that were suspected adverse drug reactions (ADRs); and events with unknown aetiology (e.g. jaundice). Events for which an alternate cause was specified on the green form were not followed-up. Follow-up questionnaires

1 The term 'event', as used in PEM, is defined as: "any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction, any alteration of clinical importance in laboratory values, or any other complaint that was considered of sufficient importance to enter in the patient's notes."

gathered information on dose, whether the event was pre-existing, risk factors for the event, concomitant medication (e.g. ciclosporin, fibric acid derivatives and other drugs), past/present medical history, relevant laboratory results and dechallenge information. GPs were offered £15 as reimbursement for completing follow-up questionnaires.

All reported pregnancies were followed-up to ascertain the outcome of pregnancy. Deaths for which the cause was not specified were followed-up to ascertain the cause of death.

Causality assessment was conducted independently by two physicians for all follow-up questionnaires returned with clinical information; cases where the two physicians disagreed were deferred to a third physician at the DSRU. Categories used for causality assessment were: probable, possible, unlikely or unassessable. Criteria taken into account included: temporal relationship; pharmacological plausibility; clinical and pathological characteristics of the event; other risk factors for the event; concomitant drugs; past/present medical history; and dechallenge/rechallenge information.[14]

Statistical Analysis

Incidence Density (ID) Analysis

Incidence densities (IDs) were calculated for all events reported during treatment within specified time periods and expressed as the number of first reports of an event per 1000 patient-months of exposure. IDs for events occurring in the first month of treatment (ID_1), during months 2–6 of treatment ($ID_{2–6}$) and for events occurring during the overall treatment period (ID_A) were calculated. Patient-months of exposure were calculated from data for those patients for whom either the date of stopping the drug was known or who continued to take the drug until the end of the study period. The difference between ID_1 and $ID_{2–6}$ and the 99% confidence intervals (CIs) for this difference were calculated. A significant positive difference between ID_1 and $ID_{2–6}$ showed that the rate of events during month 1 was significantly greater than during months 2–6, thus indicating that the event may have been an early-onset event with rosuvastatin.

Analysis of Specific Event IDs Stratified by Starting Dose

To investigate the effect of starting dose of rosuvastatin on selected events, the data were stratified by three dosage categories (10 mg/day, 20 mg/day and 40 mg/day), and IDs were calculated for these groups for each event of interest during the entire treatment period of rosuvastatin. The IDs for 20 mg/day and 40 mg/day were then compared with the 10 mg/day group by computing ID ratios and 95% CIs for these ratios. Events of interest occurring with a frequency >10 in the total cohort were included in the stratified analysis. Only those patients for whom the GP had specified a starting dose could be included in this analysis.

Power

The ability to detect an event is dependent on the expected incidence of the event in those exposed to the drug, the background rate in those not exposed to the drug and the total number of patients. A cohort of at least 10 000 patients would allow with 95% certainty the conclusion that events not observed in the cohort occurred less frequently than one in 3333 cases.[15] In addition, a cohort of 10 000 patients should allow for the detection of at least three cases of an event with 85% power if the event occurs at a rate of at least one in 2000 patients (assuming the background rate is zero).[16]

Ethics

This study was conducted in accordance with Guidelines for Biomedical Research (Council for International Organizations of Medical Sciences/World Health Organization)[17] and those issued by the Royal College of Physicians.[18] The DSRU is recognised by the UK General Medical Council as an organisation to which relevant information should be provided by physicians, wherever possible, for the purpose of monitoring public health.[19]

Table I. Age distribution and sex of patients

Age range	Male		Female		Not specified		Total	
(y)	number	%	number	%	number	%	number	%
0–39	186	3.2	99	1.7	3	5.4	288	2.5
40–49	652	11.1	305	5.3	3	5.4	960	8.2
50–59	1 423	24.2	1 047	18.2	9	16.4	2 479	21.2
60–69	1 709	29.1	1 754	30.5	9	16.4	3 472	29.7
70–79	1 094	18.6	1 551	27.0	10	18.2	2 655	22.7
80+	218	3.7	390	6.8	1	1.8	609	5.2
Not specified	598	10.2	599	10.4	20	36.4	1 217	10.4
Total	5 880	100.0	5 745	100.0	55	100.0	11 680	100.0

Results

Information Derived from Green Forms

Study Cohort

Of the 31 228 green forms sent, 12 543 (40.2%) were returned. Of these, 863 (6.9%) were classified as void and excluded from the study. Lack of clinical information was the main reason for exclusion. Thus, the study cohort comprised 11 680 patients. The cohort consisted of 50.3% (n = 5880) male patients, 49.2% (n = 5745) female patients; for 0.5% (n = 55), the sex was not specified. The median age of the cohort was 64 years (interquartile range 56–72 years) and the age range was 17–101 years. The only patient aged 17 years was a male who was prescribed rosuvastatin for familial hypercholesterolaemia. Table I gives an overview of the age and sex distribution of the cohort. The median treatment period was 9.8 months (interquartile range 8.6–11.7 months).

Indication and Starting Dose of Rosuvastatin

The indications reported for prescribing rosuvastatin and the reported starting doses are summarised in table II and table III.

Reasons for Stopping Rosuvastatin

A total of 2047 (17.5% of total cohort) patients were reported to have stopped treatment with rosuvastatin. GPs recorded 2037 reasons for stopping rosuvastatin in 1754 patients; for the remaining 293 patients, the reason(s) for discontinuing was not specified. Musculoskeletal events accounted for 20.3% (414 of 2037) of the reasons for discontinuing rosuvastatin. Overall, myalgia was the most frequent reason reported for discontinuing rosuvastatin (277 cases, 13.6% of all reasons specified) and was followed by: patient request (n = 144; including patient's request/decision/preference); drug information (n = 123; including adverse publicity/reports in media); drug not effective (n = 105); and 'non-formulary' (n = 91; including change in GP/primary care trust prescribing policy). Table IV lists the most frequently reported clinical events for stopping rosuvastatin therapy. The numbers of events given as reasons for stopping rosuvastatin within the musculoskeletal, hepatic and renal system-organ classes are shown in table V.

Table II. Indication for prescribing rosuvastatin

Indication	Number	% of total cohort
Hypercholesterolaemia/ hyperlipidaemia[a] or the context for prescribing a lipid-lowering drug (e.g. IHD)	4 281	36.6
Inadequate response/intolerance to previous lipid-lowering drug	180	1.5
Reasons unrelated to lipid-lowering[b]	12	0.1
Rosuvastatin started in drug trial	4	<0.1
Patient's request	1	<0.1
Unspecified	7 202	61.7
Total	11 680	100.0

a This includes 81 patients who were prescribed rosuvastatin for familial hypercholesterolaemia/hyperlipidaemia.

b These include: congestive heart failure (n = 5); osteoarthritis (n = 2); Alzheimer's disease (n = 1); dyspepsia (n = 1); atrial fibrillation (n = 1); abnormal liver-function tests (n = 1) and valve incompetence (n = 1).

IHD = ischaemic heart disease.

Table III. Frequency of patients by starting dose of rosuvastatin

Starting dose (per day)	Number	%
5mg	8	0.1
10mg	8 494	72.7
20mg	1 141	9.8
30mg	2	<0.1
40mg	446	3.8
Other doses[a]	2	<0.1
Dose not specified	1 587	13.6
Total	11 680	100.0

a Other doses reported were 4 mg/day and 8 mg/day (1 patient each).

ID Analysis

The number of events reported during treatment, together with the IDs for month 1 of treatment, months 2–6 of treatment and the overall time period, are shown in table VI. Myalgia was the event with the highest ID during month 1 (ID_1 7.70 per 1000 patient-months of treatment) and the highest ID for the entire treatment period. There were six clinical events (shown in bold in table VI) for which the rate of event in month 1 was significantly greater than the rate of event in months 2–6.

Analysis of Specific Event IDs Stratified by Starting Dose

Table VII lists the frequency of events and IDs, stratified by dosage group (10 mg/day, 20 mg/day or 40 mg/day), ID ratios and 95% CIs. The rate of abnormal LFT results in the 40 mg/day group was approximately 2.5-fold higher than that in the 10 mg/day group (2.71; 95% CI 1.53, 4.53) and the difference was statistically significant.

Information Derived from Follow-Up Questionnaires

A total of 685 questionnaires were posted to prescribing GPs, of which 585 (85%) were returned. For 53 questionnaires (9% of those returned), the GP either returned a blank questionnaire or was unable to complete the questionnaire. Medically important events reviewed within the musculoskeletal, hepatic and renal system-organ classes are listed in table V; some of these events are described in more detail below.

Muscular Events

A wide range of muscular events were followed-up and a high proportion of these were assessed as 'probably related to rosuvastatin' (table V). No case of rhabdomyolysis was found is this cohort. Of the 64 events of elevated creatine kinase (CK) reported,

Table IV. The most frequent clinical events reported as reasons for stopping rosuvastatin

Higher-level term[a]	Lower-level term[a]	Count
Myalgia		277
	Myalgia	277
Intolerance[b]		86
	Intolerance	86
Malaise, lassitude		85
	Malaise	56
	Lassitude	29
Nausea, vomiting		62
	Nausea	56
	Vomiting	6
Abnormal LFT		57
	Abnormal LFT	57
Unspecified side effects[b]		45
	Unspecified side effects	45
Headache, migraine		42
	Headache	40
	Migraine	2
Cramp		36
	Cramp	36
Dizziness		36
	Dizziness	36
Abnormal laboratory test[c]		34
	Abnormal laboratory test[c]	34
Diarrhoea		33
	Diarrhoea	33
Abdominal pain		33
	Abdominal pain	33

a The terminology used by the GP (doctor summary term), is grouped under 'lower-level terms'(LLTs), which are in turn grouped under broader, 'higher-level terms' (HLTs) that are linked to the respective system-organ classes.

b The GP did not specify the exact clinical event but reported that the patient had intolerance to/unspecified side effects with rosuvastatin.

c Includes 33 events of elevated CK and one event of poor INR control.

CK = creatine kinase; **GP** = general practitioner; **INR** = international normalised ratio; **LFT** = liver-function test.

Table V. Number of events that occurred whilst on treatment with rosuvastatin, number given as reason for stopping rosuvastatin, number followed-up, number of valid follow-up questionnaires (Qn) returned and causality assessment terms (probably and possibly related to rosuvastatin) for the mascular, hepatic and renal system-organ classes

Event	No. 'on' treatment	No. given as reason for stopping	No. events followed-up	No. of valid Qn returned	DSRU causality assessment	
					probable[a]	possible[b]
Muscular events						
Myalgia	370	277	280	229	128	69
Limb pain	83	27	28	23	5	13
Elevated CK	64	33	61	47	18	26
Cramps	62	36	32	26	13	12
Muscle weakness	15	4	5	5	2	3
Muscular spasm	5	1	1	1		1
Myositis	3	3	3	3	2	1
Myopathy[c]	2	2	2	0		
Hepatic events						
Abnormal LFT	171	57	136	101	19	48
Jaundice[d]	5	5	1	1		1
Autoimmune liver disease	1		1	1		1
Cirrhosis[e]	1	1	1	1		
Hepatitis[f]	1	1	0			
Renal events						
Raised urea/creatinine	43	3	31	25		5
Haematuria	10	2	10	7		3
Proteinuria	11	1	10	9	1	1
Renal failure[g]	1		2	0		

a Probable: a clinically and/or pathologically well defined event, with reasonable time-sequence in relation to administration of rosuvastatin, which is more likely to be attributed to rosuvastatin than to concurrent disease or other drugs and dechallenge or rechallenge is positive.[14]

b Possible: an event with reasonable clinical and/or pathological definition, with a reasonable time-sequence in relation to administration of rosuvastatin, but which could also be explained by concurrent disease/other drugs or chemicals. Information on dechallenge/rechallenge may be inconclusive/not fully available.[14]

c Myopathy: for one patient, the starting rosuvastatin dosage and the dosage at event was 40 mg/day; for the other patient, the starting and event dosages were 10 mg/day. The follow-up questionnaire was not returned for either of the cases and causality could therefore not be assessed.

d Jaundice: an alternative cause for four cases of jaundice was reported on the green form; therefore, these cases were not followed-up. The single case that was followed-up also had abnormal LFTs.

e Cirrhosis: the case was alcohol-induced and therefore assessed as unlikely to be due to rosuvastatin.

f Hepatitis: an alternative cause (alcohol) for the event was reported on the green form; therefore, the event was not followed-up.

g Renal failure: one case was reported to have occurred while the patient was taking rosuvastatin. Another case of renal failure was reported as the cause of death, but it was not known whether the patient was taking rosuvastatin at that time. For both cases, it was not specified whether the renal failure was acute or chronic. The follow-up questionnaire was not returned for either case and, therefore, causality could not be assessed.

CK = creatine kinase; **DSRU** = Drug Safety Research Unit; **LFT** = liver-function test.

18 were assessed as 'probably related to rosuvastatin' and one of these had a CK value >10 times the upper limit of normal (ULN). In this case, the event consisted of an asymptomatic rise in CK from 200 U/L, prior to starting rosuvastatin, to 2478 U/L, 2.5 months after starting rosuvastatin 40 mg/day. The patient was taking clofibrate concomitantly. No other risk factor for the event was reported. Rosuvastatin was stopped because of the event and dechallenge was positive.

Table VI. Incidence densities (ID) for the ten most frequent clinical events in patients taking rosuvastatin, ranked in order of ID_1 (statistically significant results for ID_1 versus $ID_{2–6}$ are shown in bold)

Higher-level term[a]	N_1	$N_{2–6}$	ID_1	$ID_{2–6}$	$ID_1–ID_{2–6}$	99% CI min	99% CI max	N_A	ID_A
Myalgia	**80**	**179**	**7.70**	**3.70**	**4.00**	**1.67**	**6.33**	**370**	**3.65**
Malaise, lassitude	**40**	**76**	**3.85**	**1.57**	**2.28**	**0.64**	**3.91**	**168**	**1.66**
Dizziness	**30**	**48**	**2.89**	**0.99**	**1.90**	**0.49**	**3.30**	**99**	**0.98**
Nausea, vomiting	**28**	**56**	**2.70**	**1.16**	**1.54**	**0.17**	**2.91**	**114**	**1.12**
Intolerance[b]	**27**	**43**	**2.60**	**0.89**	**1.71**	**0.38**	**3.04**	**89**	**0.88**
Headache, migraine	**26**	**52**	**2.50**	**1.08**	**1.43**	**0.11**	**2.75**	**111**	**1.09**
Abdominal pain	24	55	2.31	1.14	1.17	−0.10	2.45	115	1.13
Dyspepsia	23	64	2.21	1.32	0.89	−0.37	2.15	132	1.30
Abnormal liver-function test	23	91	2.21	1.88	0.33	−0.96	1.62	171	1.69
Joint pain	21	86	2.02	1.78	0.24	−1.00	1.48	193	1.90

a The terminology used by the general practitioner (GP) [doctor summary term], is grouped under 'lower-level terms' (LLTs), which are in turn grouped under broader, 'higher-level terms' (HLTs) that are linked to the respective system-organ classes.

b The GP did not specify the exact clinical event but reported that the patient had intolerance to rosuvastatin.

N_1 = number of first reports of each event during month 1 of treatment; **$N_{2–6}$** = number of first reports of each event during months 2–6 of treatment; **ID_1** = incidence density for each event during month 1 of treatment; **$ID_{2–6}$** = incidence density for each event during months 2–6 of treatment; **$ID_1–ID_{2–6}$** = arithmetic difference between ID_1 and $ID_{2–6}$; **99% CI** = 99% confidence intervals for $ID_1–ID_{2–6}$; **N_A** = number of first reports of each event during the total treatment period; **ID_A** = incidence density for each event for the total treatment period.

Hepatic Events

A number of hepatic events were reported in this cohort. Information on these is presented below and in table V.

Abnormal Liver-Function Tests

Of the 101 events of abnormal LFTs for which follow-up information was available, there were nine events in which AST or ALT or both were >3 × ULN. Three of these were assessed as probably related to rosuvastatin and six were assessed as possibly related to rosuvastatin.

One patient was reported to have jaundice with a bilirubin of >100 μmol/L, raised alkaline phosphatase (1048 U/L) and raised ALT (149 U/L). This event was assessed as possibly related to rosuvastatin.

Autoimmune Liver Disease

One case of autoimmune liver disease was reported in this cohort and assessed as possibly related to rosuvastatin. The event was detected 4 months after starting rosuvastatin 10 mg/day. In this case, LFTs were reported to be normal, anti-smooth mus-

Table VII. Incidence density ratios (IDRs) for specific events on 20 mg/day and 40 mg/day starting dosages of rosuvastatin compared with 10 mg/day with 95% CIs (where information on starting dosage was available)

Events	ID_{10}[a] (no. of events)	ID_{20}[b] (no. of events)	ID_{40}[c] (no. of events)	$IDR_{20/10}$ (95% CI)	$IDR_{40/10}$ (95% CI)
Myalgia	3.59 (271)	3.12 (32)	3.45 (14)	0.87 (0.58, 1.26)	0.96 (0.52, 1.64)
Limb pain	0.82 (62)	0.97 (10)	0.74 (3)	1.19 (0.54, 2.33)	0.90 (0.18, 2.76)
Elevated CK	0.62 (47)	0.58 (6)	0.74 (3)	0.94 (0.33, 2.20)	1.19 (0.24, 3.70)
Cramp	0.57 (43)	1.07 (11)	0.25 (1)	1.88 (0.88, 3.71)	0.43 (0.01, 2.55)
Abnormal LFT	1.55 (117)	1.56 (16)	4.19 (17)	1.01 (0.56, 1.70)	2.71 (1.53, 4.53)
↑ urea/creatinine	0.43 (32)	0.59 (6)	0.49 (2)	1.38 (0.47, 3.35)	1.17 (0.14, 4.57)
Haematuria	0.08 (6)	0.10 (1)	0.25 (1)	1.23 (0.03, 10.11)	3.12 (0.07, 25.61)
Proteinuria	0.09 (7)	NA (0)	0.49 (2)	NA (0)	5.33 (0.54, 27.98)

a ID_{10} = incidence density for event where starting dosage of rosuvastatin was 10 mg/day.

b ID_{20} = incidence density for event where starting dosage of rosuvastatin was 20 mg/day.

c ID_{40} = incidence density for event where starting dosage of rosuvastatin was 40 mg/day.

CK = creatine kinase; **LFT** = liver-function test; **NA** = not applicable; ↑ indicates raised.

cle antibodies were found to be positive and a hepatitis screen was negative. When previously taking atorvastatin, the patient had had abnormal LFTs, auto-antibodies and abnormal immunoglobulin, all of which reverted to normal on stopping atorvastatin.

Hepatic Failure and Liver Transplantation

No cases of hepatic failure or liver transplantation were reported in this cohort.

Renal Events

Proteinuria

Amongst the renal events followed-up, only one event of proteinuria was assessed as probably related to rosuvastatin. This event, which was given as a reason for stopping rosuvastatin, occurred 10 months after starting the drug, when the patient was receiving rosuvastatin 40 mg/day. The event did not pre-date rosuvastatin, no other risk factors were reported and dechallenge was positive.

Other Events

Pancreatitis

Two events of pancreatitis were reported during treatment with rosuvastatin, one of which was specified as acute pancreatitis. Both events were reviewed and assessed as unlikely to be related to rosuvastatin.

Raised International Normalized Ratio

Two events of raised international normalized ratio (INR) [occurring 1 and 2 months after starting rosuvastatin] and one event of 'difficulty controlling INR on warfarin' were reported. The latter event was given as a reason for stopping rosuvastatin 4 months after starting the drug and was followed-up. The GP reported that the "patient was on long-term warfarin for atrial fibrillation and was stable – couldn't re-stabilise on statin". The INR stabilised after stopping rosuvastatin and the event was assessed as probably related to rosuvastatin.

Other Events Assessed as 'Probably Related to Rosuvastatin'

A small number of events assessed as 'probably related to rosuvastatin' but which are not listed in the 'Undesirable effects' section of the UK Summary of Product Characteristics (SPC) for rosuvastatin[11] were reported. These were (number assessed as probable/number of events for which causality was assessed): muscular cramps (n = 13/32); muscle weakness (n = 2/5); myositis (n = 2/3); hallucination (n = 1/1); tremor (n = 1/1); palpitation (n = 1/5); dyspnoea (n = 1/1) and oesophageal reflux (n = 1/1).

Use of the 40 Mg/Day Dosage when Contraindicated

Of the 446 patients who were prescribed rosuvastatin 40 mg/day, the product was prescribed in situations in which its use is contraindicated in eight patients. These are summarised in table VIII.

Table VIII. Use of rosuvastatin 40 mg/day when contraindicated

Event followed-up	Age	Sex	Ethnicity	Causality assessment
In patients with hypothyroidism				
Myalgia	71	Female	Caucasian	Possible
Myalgia and elevated CK	60	Female	Caucasian	Possible
In patients concomitantly taking a fibric acid derivative				
Elevated CK (>10 times ULN)	62	Male	Caucasian	Probable
Cramp	50	Male	Caucasian	Probable
Abnormal LFT	63	Female	Caucasian	Probable
↑ urea/creatinine	50	Male	Caucasian	Possible
↑ urea/creatinine	50	Male	Caucasian	Possible
In patients with hypothyroidism and concomitantly taking a fibric acid derivative				
Elevated CK (>3 times ULN)	56	Male	Caucasian	Probable

CK = creatine kinase; **LFT** = liver-function test; **ULN** = upper limit of normal; ↑ indicates raised.

Pregnancy

One pregnancy was reported. The patient was exposed to rosuvastatin for the first 2 months of pregnancy. The pregnancy was unplanned, but the patient was reported not to be taking an oral contraceptive or any other medication during pregnancy. The patient had a spontaneous abortion in the third month of pregnancy and no fetal abnormalities were reported.

Deaths

A total of 115 (1% of the total cohort) deaths were reported on the green forms. Of these, 43 were reported during treatment with rosuvastatin, 16 were reported after stopping treatment; however, for 56 patients, it was not known whether they were continuing rosuvastatin at the time of death. Ischaemic heart disease was the most frequently reported cause of death (n = 19 'on' rosuvastatin and 10 not known whether 'on' rosuvastatin at time of death). None of the deaths was attributed to rosuvastatin by the reporting GP.

Discussion

This study examined the 'real life' use of rosuvastatin in 11 680 patients who were prescribed rosuvastatin under primary care in England between August and December 2003.

Principal Strengths and Limitations of This Study

PEM is an observational cohort technique, used for the post-marketing surveillance of newly marketed drugs. One of the major strengths of PEM is that it uses data from day-to-day clinical practice. There are no exclusion criteria, i.e. all patients prescribed and dispensed the study drug are eligible for inclusion. The PEM cohort in this study comprised all patients for whom a completed questionnaire was returned by the GP. This resulted in a cohort with a wide age-range of patients (17–101 years) and without exclusion of those with co-morbidities or those on co-prescribed medicines. Furthermore, the methodology of PEM is non-interventional, in that it does not influence the prescribing practices of GPs because the patients are identified from dispensed prescriptions. Another strength of the methodology is that PEM is based upon 'event' monitoring and is therefore capable of identifying signals for events that were not necessarily suspected as being ADRs to the drug being studied. The methodology also readily permits follow-up for additional data on events of interest and also in case of death to ascertain the cause of death.

A limitation of this study was the low response rate of 40%. This is lower than the average response rate of 56% for the 90 completed PEM studies. As rosuvastatin is the sixth statin to be marketed in the UK, GPs have had a long clinical experience of using this class of drugs and this may be a possible explanation for the low response rate. A postal survey of the reasons for non-response by GPs in PEM studies was conducted by the DSRU in 2002.[20] The survey found that the most frequent reasons for non-response were: 'GP too busy', non-payment and that the GPs received too many green forms. It is not possible to assess the effect of low-response rate on the results of this study. However, we have no reason to believe that non-response bias was differential, i.e. whether GPs' response to the questionnaire was affected by the event profiles of their patients.

Another limitation of the methodology is that the data are limited to experience in general practice, i.e. patients in whom the treatment was initiated in hospital were not included, unless treatment was continued by the patient's GP. Also, as in any observational study, it was not possible to estimate the degree of compliance with the prescribed medication.

Green Form Information

The cohort consisted of similar proportions of male (50.3%) and female patients (49.2%) and 68% of the cohort was aged >60 years.

Although the indication for prescribing rosuvastatin was not specified for 62% of the patients, the licensed indications of hypercholesterolaemia/hyperlipidaemia were the most frequently reported

indications. There is an ongoing debate about the cognitive improvements in patients with Alzheimer's disease who are taking statin therapy.[21] Alzheimer's disease was given as an indication for prescribing rosuvastatin in one patient in this cohort.

The 10 mg/day dosage was the recommended starting dosage for rosuvastatin at the time the study was started (rosuvastatin SPC, March 2003); subsequently, the 5 mg/day dosage was marketed and introduced as an acceptable starting dosage alongside the 10 mg/day dose.[11] Where starting dosage was specified (n = 10 093), the majority of the patients were started on the recommended starting dosage of 10 mg/day (84.1%; 8494 of 10 093), however, 4.4% (446 of 10 093) and 11.3% (1141 of 10 093) of patients were started on 40 mg/day and 20 mg/day dosages of rosuvastatin, respectively. Given the dose relationship of some ADRs with rosuvastatin, starting some patients on the 40 mg/day dosage gives cause for concern. The company reminded doctors (May 2004) that the starting dose of rosuvastatin should not exceed 10 mg/day, and use of a starting dose of 20 mg/day or 40 mg/day is a matter which requires continued monitoring and action if this pattern of prescribing persists. In addition, eight patients were reported to have been started on the 5 mg/day dosage of rosuvastatin, even though this dosage was not available in the UK at the time of the study. It is possible that these patients may have been started on this dosage as part of a drug trial.

This study found that 17% (2047 of 11 680) of the cohort stopped treatment with rosuvastatin during the study. Clinical reasons for stopping are important because they suggest that the GP or the patient suspected rosuvastatin to be the cause of the event and therefore stopped the drug. Myalgia and other musculoskeletal events constituted the most frequent reasons for stopping rosuvastatin. Abnormal LFTs were the fifth most common clinical reason for stopping rosuvastatin. Of the five leading overall reasons for stopping rosuvastatin, three terms, 'drug information', 'non-formulary' and 'patient request', were related to the publicity associated with rosuvastatin after its launch, showing how the media and published literature may influence prescribing practices as well as patient preferences.

Six events (myalgia, malaise/lassitude; dizziness; nausea/vomiting; intolerance; and headache/migraine) were identified as early-onset events with rosuvastatin. This is because the rate of the event in month 1 was significantly greater than the rate during months 2–6. All six events are listed in the SPC for rosuvastatin.[11] Myalgia had the highest ID in month 1 (ID_1 = 7.70) as well as for the entire treatment period (ID_A = 3.65).

According to the Drug Analysis Print (DAP) [2] for rosuvastatin, which is the cumulative information collected from the 'yellow card scheme' by the Medicines and Healthcare products Regulatory Agency (MHRA), 13 cases of rhabdomyolysis associated with rosuvastatin had been reported in the UK as at April 2006.[9] However, no case of rhabdomyolysis was reported in this cohort. One explanation is that our cohort comprised patients who were prescribed rosuvastatin between August and December 2003, and it is possible that the cases of rhabdomyolysis occurred in patients prescribed rosuvastatin outside this period. Secondly, the response rate was low and GPs whose patients had rhabdomyolysis may have been amongst the non-responders. Thirdly, PEM only covers England; it is possible that some of the cases of rhabdomyolysis reported to the regulatory authority were from other parts of the UK (Scotland, Wales and Northern Ireland). Fourthly, the cases of rhabdomyolysis may have developed >6 months after starting rosuvastatin. Finally, in some of the cases of rhabdomyolysis it is likely that treatment may have been initiated by doctors in the hospital and not continued by the patients' GPs.

Analysis of Specific Event IDs Stratified by Starting Dose

Consistent with the SPC for rosuvastatin, a 2.5-fold increase in the rate of abnormal LFT results

2 It should be noted that DAPs present data on *suspected* ADRs to drugs.

(2.71; 95% CI 1.53, 4.53) for patients started on rosuvastatin 40 mg/day compared with those started on rosuvastatin 10 mg/day was observed in this study. For other events such as elevated CK, raised urea/creatinine, haematuria and proteinuria, the ID ratios for rosuvastatin 40 mg/day compared with rosuvastatin 10 mg/day showed an increase in the rates; however, the confidence intervals around the ID ratio point estimates were wide because of the small number of events. Although skeletal muscle effects of rosuvastatin are seen with all doses, but in particular with doses >20 mg/day,[11] no differences in the rates of myalgia, limb pain or cramps were observed between the three dosage groups in this study.

Follow-Up Questionnaire Information

A high response rate of 85% was attained for the follow-up questionnaires and one reason for this could be that doctors are more likely to respond to questions they consider to be clinically important. In addition, unlike for the green form, a small sum of money was offered to GPs for completing these questionnaires.

Musculoskeletal Events

The exact mechanism by which statins cause musculoskeletal adverse effects is not known. However, statins are thought to cause myopathy or rhabdomyolysis by lowering the concentration of coenzyme Q_{10}, the reduction of which may in turn lead to a severe deficit in mitochondrial energy metabolism.[22]

While on the one hand some authors have defined myopathy as muscular symptoms combined with a CK level >10 × ULN,[6,23] others have reported, albeit in only a small number of patients, biopsy-confirmed cases of myopathy with normal CK levels.[24] The rosuvastatin DAP reports nine cases of myopathy as a suspected ADR to rosuvastatin.[9] In our study, one case of asymptomatic rise in CK >10 × ULN was reported and assessed as probably related to rosuvastatin. This patient was taking rosuvastatin 40 mg/day concomitantly with a fibric acid derivative, which is a contraindication according to the latest SPC.[11] Two cases of myopathy were reported in this cohort; for one case, the CK level was not specified and for the other it was only slightly raised (green form information). Follow-up information was not available for either of the cases and therefore causality could not be assessed. No case of rhabdomyolysis was reported in this study.

Overall, musculoskeletal events were the most frequently reported events and reasons for discontinuing rosuvastatin. Where causality assessment was conducted, a high proportion of musculoskeletal events were assessed as probably or possibly related to rosuvastatin.

Hepatic Events

As the primary site of cholesterol synthesis is the liver, statins are hepatospecific.[25] Rosuvastatin has been found to increase transaminase (AST and ALT) levels in a dose-dependent manner,[11] with increases to >3 × ULN being considered clinically significant. Rarely, use of statins has been associated with jaundice, hepatotoxicity and autoimmune hepatitis.[26,27] A case report of a possible association between rosuvastatin use and development of autoimmune hepatitis has also been published.[28] In this study, one case of autoimmune hepatitis and another case of jaundice, raised alkaline phosphatase and ALT were assessed as possibly related to rosuvastatin.

Furthermore, 19 and 48 events of abnormal LFT results were assessed as probably or possibly related to rosuvastatin, respectively. Of these, three events assessed as 'probable' and six assessed as 'possible' had levels of AST or ALT or both >3 × ULN. No sequelae were reported for any of the abnormal LFT cases assessed as probably or possibly related to rosuvastatin. Rosuvastatin was either stopped because of the abnormal LFT or the LFTs were being monitored by the GP.

Renal Events

Proteinuria detected on dipstick testing has been noted with rosuvastatin (≤40 mg/day) at a similar incidence to that found with other statins.[29,30] The incidence of proteinuria has been reported to be <1% in patients taking rosuvastatin 10 mg/day and 20 mg/day and approximately 3% in those treated with rosuvastatin 40 mg/day.[11] The incidence of

proteinuria with the 80 mg/day dose of rosuvastatin (dose not marketed) has been reported to be as high as 12%.[30] The proteinuria associated with use of rosuvastatin is said to be tubular in origin and not predictive of acute or progressive renal disease.[11,30]

The incidence of proteinuria in this cohort was <0.1% (11 of 11 680) overall and 0.4% (2 of 446) in patients taking rosuvastatin 40 mg/day. The true incidence of proteinuria with rosuvastatin is unlikely to be correctly measured by any study without pro-active testing of protein in the urine; this testing would be more frequent in a clinical trial setting compared with 'real life' general practice. This could be one explanation for the low reported incidence of proteinuria in this cohort.

Of the 11 cases detected, one case of proteinuria was assessed as probably and one as possibly related to rosuvastatin; no sequelae were reported for either case. Two cases of renal failure were also reported but because of lack of follow-up information, causality was 'unassessable'. Furthermore, of the 25 events of raised urea/creatinine for which follow-up information was available, five were assessed as possibly but none as probably related to rosuvastatin.

Other Events

The UK SPC of rosuvastatin lists pancreatitis as a rarely occurring undesirable effect.[11] One case report of acute pancreatitis possibly induced by rosuvastatin has been published.[31] In this cohort, two events of pancreatitis were reported but both were assessed as unlikely to be associated with rosuvastatin.

Use of rosuvastatin with concomitant warfarin has been found to increase the INR.[32] The rosuvastatin SPC[11] highlights this drug interaction and recommends appropriate monitoring of INR and discontinuation or down-titration of rosuvastatin. One case of 'difficulty controlling INR on warfarin' was reported in this cohort and was assessed as probably related to rosuvastatin.

Use of Rosuvastatin

Although use of rosuvastatin in children has not been recommended because of lack of experience with the drug in this age group,[11] one patient aged 17 years was prescribed the drug in this cohort. Rosuvastatin was used for familial hypercholesterolaemia in this patient.

According to the current SPC,[11] the 40 mg/day dose of rosuvastatin is contraindicated in a number of situations which are predisposing factors for myopathy/rhabdomyolysis, for example hypothyroidism and concomitant fibric acid derivative use. Eight patients with hypothyroidism and/or using concomitant fibric acid derivatives were prescribed rosuvastatin 40 mg/day in this cohort. Five of these patients had muscle-related events (myalgia/elevated CK/cramps). It should be noted that the above information was obtained from patients that were followed-up for specific events. Therefore, potentially there may be other patients (those not followed-up) in this cohort taking rosuvastatin 40 mg/day when this is contraindicated.

As cholesterol and other products of cholesterol biosynthesis are essential for fetal development, rosuvastatin is contraindicated in pregnancy.[11] According to recommendations, rosuvastatin should be immediately discontinued if a patient becomes pregnant.[11] One patient in this study was reported to have taken rosuvastatin for the first 2 months of gestation. The patient had a spontaneous abortion in the third month of pregnancy and no fetal abnormalities were reported.

Conclusion

This study examined the post-marketing safety of rosuvastatin in 11 680 patients when used in general practice in England and depicts 'real life' use of rosuvastatin.

Use of the recommended starting dosage of 10 mg/day for the majority of patients reflects that most GPs prescribed rosuvastatin according to the prescribing information. In some patients, the initial dosage of rosuvastatin was 40 mg/day and in a small number, rosuvastatin was prescribed when its use was contraindicated. Abnormality of LFT results was found to be more frequent with the 40 mg/day dosage of rosuvastatin.

Although musculoskeletal events were the most frequently reported clinical events and reasons for

discontinuing rosuvastatin, no case of a life-threatening muscle event/rhabdomyolysis was reported in this cohort. After myalgia, reasons related to adverse publicity for rosuvastatin constituted the most frequently reported reasons for discontinuing the drug. All events which are considered to be signals for early-onset events with rosuvastatin are listed in the SPC for the drug and none of the labelled events were reported at a frequency greater than that given in the rosuvastatin SPC. However, it is not possible in PEM to estimate accurately the incidence of proteinuria.

Overall, the results of this study suggest that rosuvastatin is a reasonably well tolerated drug. Results from this study should be taken into account together with those of other clinical and pharmacoepidemiological studies of rosuvastatin.

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Correspondence and offprints: Dr *Rachna Kasliwal*, Drug Safety Research Unit, Clinical Research Fellow, Bursledon Hall, Blundell Lane, Southampton, SO31 1AA, UK.
E-mail: rachna.kasliwal@dsru.org