NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

Volume 4; Number 11 **August 2010**

MHRA DRUG SAFETY UPDATE: SIMVASTATIN 80MG AND MYOPATHY

PACEF Recommendations: Review of Simvastatin 80mg following MHRA *Drug Safety Bulletin* (May 2010)

(1) All patients currently prescribed simvastatin 80mg should be reviewed at their next consultation. Patients should only remain on simvastatin 80mg if they fulfil MHRA criteria (i.e. they should have severe hypercholesterolaemia and be at high risk of CV complications; they should be free from muscle pain, tenderness or weakness).

(2) For secondary prevention of CVD, patients on simvastatin 80mg who do not fulfil the MHRA criteria should be stepped down to simvastatin 40mg and their lipid levels checked after four weeks. If after four weeks the patient has reached the QOF target of 5mmol/l (Total Cholesterol) (and 3mmol/l LDL-C), maintain on simvastatin 40mg. If lipid levels are above the QOF target, initiate atorvastatin 20mg and titrate up as necessary to achieve the QOF target.

(3) For patients with acute coronary syndrome who do not fulfil the MHRA criteria for continuation of simvastatin 80mg, step down to simvastatin 40mg. PACEF and ULHT Drug and Therapeutics Committee have not approved atorvastatin 80mg as an alternative statin for ACS due to concerns over lack of comparative evidence between simvastatin 40mg/80mg and atorvastatin 80mg in ACS and the significant additional cost (in excess of £0.3Mpa for new patients alone). Patients with ACS should be started on simvastatin 40mg and titrated up as designated for other secondary prevention of CVD patients (see (2)).

(4) For patients with diabetes with or without CVD, treat as for secondary prevention of CVD (see (2)).

(5) For primary prevention of CVD, doses of simvastatin above 40mg are unnecessary.

(6) After review, patients currently taking simvastatin 80mg within MHRA criteria and without problem can be approved to continue treatment at the discretion of the prescriber. New initiations of simvastatin 80mg are no longer recommended, although simvastatin 80mg continues to be designated GREEN for appropriate patients within MHRA criteria.

Introduction

Over the last few months both the American Food and Drug Administration (FDA) and our own Medicines and Healthcare products Regulatory Agency (MHRA) have been reviewing data from the as yet unpublished Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine trial (SEARCH). It is this purpose of this issue of the *PACE Bulletin* to outline the findings of the SEARCH study, review the advice of the FDA and the MHRA and draw some conclusions relating to the implications for our local statin prescribing policy.

The SEARCH trial

SEARCH was a multicentre, double blind study that evaluated over 6.7 years the number of major vascular events (MVEs) (heart attack, revascularisation, and CV death) in 6,031 post-MI patients taking 80mg simvastatin compared to 6,033 post-MI patients taking 20mg simvastatin. The results showed that treatment with simvastatin 80mg did not provide any significant benefits over simvastatin 20mg. The incidence of MVEs was similar for 80mg (24.5%) and 20mg (25.7%). There was no evidence of increased total or cause-specific mortality, vascular mortality, non-vascular mortality or higher risk of cancer or haemorrhagic stroke with the high dose simvastatin. Preliminary results identified 52 cases of myopathy (0.9%) in the simvastatin 80mg group compared to 1 case (0.02%) in the 20mg simvastatin group; similarly, eleven (0.2%) of patients in the simvastatin 80mg group developed rhabdomyolysis compared to none in the simvastatin 20mg group.

Myopathy and rhabdomyolysis

Of particular concern to both the FDA and the MHRA was the incidence of myopathy and rhabdomyolysis associated with simvastatin 80mg. Myopathy is an identified dose-related side effect with all statins. The risk of myopathy increases with the dose of statin used and as a result of certain interactions of simvastatin with other drugs. The risk of myopathy is greater in:

- the elderly (>65).
- women.
- patients with renal impairment or hypothyroidism.
- patients who excessively consume alcohol.
- those with a history of previous muscle problems on statins (and other lipid-lowering drugs).
- those with a family history of muscle disorders.

Rhabdomyolysis is the most serious form of myopathy. Muscle fibres break down releasing myoglobin that can cause kidney damage and even fatal kidney failure. Known risk factors for rhabdomyolysis are: age (>65 years), low thyroid hormone levels (hypothyroidism) and poor kidney function. Rhabdomyolysis is very rare.

MHRA advice for healthcare professionals

Following their review of SEARCH, the MHRA issued the following advice:

- Simvastatin 80mg should be considered only in patients with severe hypercholesterolaemia and high risk of CV complications who have not achieved their treatment goals on lower doses, when the benefits are expected to outweigh the potential risks.
- Prescribers treating patients who are taking simvastatin 80mg or who are being considered for up-titration to that dose may need to review their treatment during their next consultation.
- Patients currently taking simvastatin 80mg should not stop taking their medicine. Patients should be advised to contact their doctor immediately if they experience unexplained muscle pain, tenderness or weakness.

In addition the FDA has recommended simvastatin dose limitations with interacting medicines to minimise the risk. Prescribers are reminded of the following table from the simvastatin (Zocor) Summary of Product Characteristics:

Drug interactions Associated with Increased Risk of Myopathy/ Rhabdomyolysis

Interacting agents	Prescribing recommendations
Potent CYP3A4 inhibitors: Itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin	Contraindicated with simvastatin
HIV protease inhibitors	Contraindicated with simvastatin
Nefazodone	Contraindicated with simvastatin
Gemfibrozil or other fibrates	Avoid but if necessary, do not exceed 10mg simvastatin daily.
Ciclosporin	Do not exceed 10mg simvastatin daily
Danazol	Do not exceed 10mg simvastatin daily
Amiodarone	Do not exceed 20mg simvastatin daily
Verapamil	Do not exceed 20mg simvastatin daily
Diltiazem	Do not exceed 40mg simvastatin daily
Amlodipine	Do not exceed 40mg simvastatin daily
Fusidic acid	Patients should be closely monitored; temporary suspension of simvastatin treatment may be considered.
Grapefruit juice	Avoid grapefruit juice when taking simvastatin

Patients of Chinese origin who are taking cholesterol modifying doses of niacin containing products are contra-indicated for simvastatin 80mg due to an increased risk of myopathy. Similarly, simvastatin 40mg is a caution within this context.

PACEF Comment:
All statins cause myopathy and to a much lesser extent rhabdomyolysis. These adverse effects are dose related with the incidence increasing as the dose increases. Nonetheless, equipotent doses of atorvastatin and rosuvastatin are linked to a lower incidence of myopathy and rhabdomyolysis than simvastatin 80mg. The following tables summarize incidence of myopathy and rhabdomyolysis and comparative potencies and cost. Equipotent doses of atorvastatin and rosuvastatin to simvastatin 80mg are highlighted in bold.

Comparison of incidence of myopathy and rhabdomyolysis with key statins

Statin	Incidence of myopathy	Incidence of rhabdomyolysis
Simvastatin 20mg	0.02%	Negligible
Simvastatin 40mg	0.4%	
Simvastatin 80mg	**0.9%**	**0.2%**
Atorvastatin 10mg	0.4%	0.01 to 0.1%
Atorvastatin 20mg	**0.4%**	**0.01 to 0.1%**
Atorvastatin 40mg	0.4%	0.01 to 0.1%
Atorvastatin 80mg	0.5%	0.01 to 0.1%
Rosuvastatin 5mg	0.2%	0.01 to 0.1%
Rosuvastatin 10mg	**0.1%**	**0.01 to 0.1%**
Rosuvastatin 20mg	0.1%	0.01 to 0.1%
Rosuvastatin 40mg	0.2%	0.01 to 0.1%
Rosuvastatin 80mg	1.0%	0.4%

(Myopathy and rhabdomyolysis incidence figures are quoted from SEARCH and information provided by Pfizer and AstraZeneca; very little of this data derives from head-to-head studies).

PACEF Comment

Prescribers are also reminded that approximately half of the myopathy cases identified with simvastatin 80mg in SEARCH occurred within the first year of treatment; the incidence of myopathy in each subsequent year was approximately 0.1%. This emphasizes that the bulk of the risk with simvastatin 80mg is with new initiations within the first year of treatment; patients established on simvastatin 80mg for more than a year without a problem are at much lower risk of going on to develop myopathy. This information may be helpful when undertaking a risk-benefit assessment of continued simvastatin 80mg treatment in an individual patient long-established on therapy.

Cost Comparison and Percentage Reductions in LDL Cholesterol and Total Cholesterol

Statin	28 day cost	Percentage reduction in LDL-C	Percentage reduction in total cholesterol	Incidence of myopathy
Atorvastatin 10mg	£13.00	37%	32%	0.4%
Atorvastatin 20mg	**£24.64**	**43%**	**36%**	**0.4%**
Atorvastatin 40mg	£24.64	49%	42%	0.4%
Atorvastatin 80mg	£28.21	55%	47%	0.5%
Pravastatin 40mg	£3.82	29%	29%	
Rosuvastatin 5mg	£18.03	38%	33%	0.2%
Rosuvastatin 10mg	**£18.03**	**43%**	**37%**	**0.1%**
Rosuvastatin 20mg	£26.02	48%	40%	0.1%
Simvastatin 40mg	£1.64	37%	31%	0.4%
Simvastatin 80mg	**£3.01**	**42%**	**35%**	**0.9%**

(Prices quoted are from the *Drug Tariff*, August 2010)

References

MHRA *Drug Safety Update*, Simvastatin: Increased risk of myopathy at high dose (80mg) (May 2010)
United States Food and Drug Administration, *Drug Safety Communication*. Ongoing safety review of high-dose Zocor (simvastatin) and increased risk of muscle injury (March 2010)

Acknowledgements

Many thanks to: Dr Richard Andrews, Dr David O'Brien and Alun Roebuck from Cardiology at ULHT for their help during the compilation of this *Bulletin.*

Stephen Gibson
Head of Prescribing and Medicines Management August 2010