



Rosuvastatin

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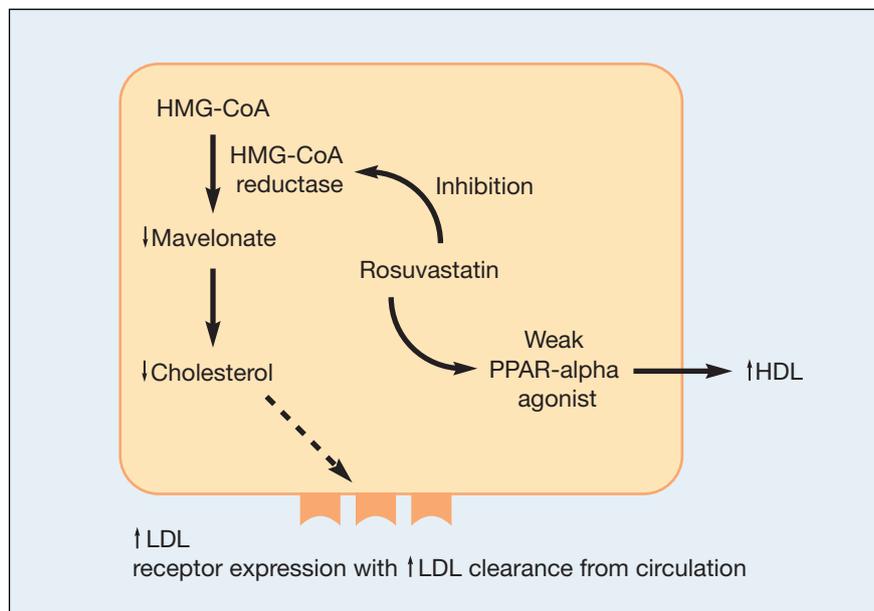
Introduction

There is considerable evidence to support the use of statins in patients with diabetes to reduce cardiovascular risk both in primary and secondary prevention, and there is good evidence that even patients with 'normal' cholesterol values benefit from further reduction. Several statins are now available and trials have demonstrated that pravastatin, simvastatin and atorvastatin are effective in reducing the incidence of cardiovascular events in patients with diabetes. Rosuvastatin is one of the newest and most potent statins. Its potency has been considered favourable in those aiming for aggressive lipid lowering; however, concerns were initially raised over its safety in comparison to other statins.

Pharmacology

Figure 1 outlines the pharmacological action of rosuvastatin in the hepatocyte. Rosuvastatin like other statins acts as a reversible inhibitor of HMG-CoA reductase to reduce cholesterol synthesis. This promotes expression of the LDL receptor thus increasing clearance of LDL and VLDL from the circulation. It acts as a weak peroxisome proliferator-activated receptor-alpha (PPAR-alpha) agonist to increase apoA1 lipoprotein expression and hepatic production of HDL. The half-life is 19 hours so, unlike pravastatin and simvastatin, it can be taken at any time of day. The clinical activity is not influenced by the cytochrome P450 system so does not have clinically significant drug interactions through this route. Treatment should commence at the lowest dose of 10mg and the dose titrated up to a maximum of 40mg according to clinical response. A lower starting

Figure 1. Pharmacological action of rosuvastatin in the hepatocyte



dose of 5mg is recommended in elderly people and in Asian patients.

Trials of safety and efficacy in diabetes

Several studies have examined the lipid lowering effects of rosuvastatin compared to other statins in patients with type 2 diabetes mellitus. The ANDROMEDA study was a 16-week, double-blind, randomised multicentre UK trial of 695 subjects with type 2 diabetes.¹ It compared two groups given either rosuvastatin 10mg or atorvastatin 10mg for eight weeks followed by rosuvastatin 20mg or atorvastatin 20mg for a further eight weeks. Rosuvastatin was significantly more effective at reducing LDL at eight and 16 weeks (51% and 53% reduction) compared with atorvastatin (39% and 46% reduction). Rosuvastatin also significantly reduced total cholesterol, non-HDL and apoB lipoproteins. More patients

achieved 2003 European lipoprotein guidelines of LDL <2.5mmol/L and total cholesterol <4.5mmol/L on rosuvastatin than atorvastatin (96% and 87% respectively). The ANDROMEDA study showed that C-reactive protein (CRP), a predictor of cardiovascular events, was significantly decreased by both rosuvastatin and atorvastatin but there was no difference between the two groups.

The URANUS study was a 16-week, double-blind, randomised, multicentre Swedish trial of 469 subjects with type 2 diabetes.² It compared patients given rosuvastatin 10mg and atorvastatin 10mg for four weeks then escalating doses of each up to rosuvastatin 40mg and atorvastatin 80mg. Rosuvastatin resulted in a significantly greater reduction in LDL (52% reduction with rosuvastatin 40mg compared to 46% reduction with atorvastatin 80mg). There were also significant reductions in

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total cholesterol, non-HDL cholesterol and apoB/apoA1 ratio (a recognised predictor of myocardial infarction). More patients achieved European guidelines with rosuvastatin than atorvastatin (65% vs 33% at 10mg doses).

The CORALL study was a 24-week, open-label, randomised, multi-centre Dutch trial of 263 subjects with type 2 diabetes.³ Patients were given escalating doses of either rosuvastatin 10mg, 20mg and 40mg or atorvastatin 20mg, 40mg and 80mg for six weeks at each stage. The primary endpoint was change in the apoB/apoA1 ratio. Rosuvastatin led to a significantly greater reduction in the ratio at 20mg and 40mg. Again, there was a greater reduction in LDL with rosuvastatin at all doses (46%, 51%, 54% for rosuvastatin as compared with 41%, 46% and 48% for atorvastatin). Greater numbers in the rosuvastatin group met European guidelines.

In all three trials rosuvastatin was well tolerated with no significant difference between atorvastatin and rosuvastatin groups in the incidence of adverse effects. Up to 6% of patients reported myalgia but there were no cases of rhabdomyolysis or significant increases in creatine kinase. There were no clinically relevant increases in liver enzymes.

There have been concerns about adverse renal effects, with previous early studies reporting increase in tubular protein excretion with rosuvastatin. The URANUS study examined urinary albumin excretion and glomerular filtration rate in 344 patients and found no significant increase for either rosuvastatin or atorvastatin over four months. Seventeen patients (nine rosuvastatin and eight atorvastatin) in the ANDROMEDA study had clinically significant increases in serum creatinine. The CORALL study did not examine renal data.

The above studies show good evidence of the efficacy of rosuvastatin in reducing LDL in patients with type 2 diabetes. These populations included patients controlled with diet, oral agents and insulin. All had reasonable glycaemic control at baseline with HbA_{1c} 5% to 9% in ANDROMEDA and 6.5% to 8.5% in

CORALL. HbA_{1c} values were not available for URANUS. In the ANDROMEDA study, rosuvastatin was associated with a significantly greater increase in mean HbA_{1c} levels but the difference was slight (6.9% to 7.3%) and the CORALL study showed no change in HbA_{1c} levels.

Discussion

The trials above have demonstrated that rosuvastatin is more effective at reducing LDL cholesterol, improving additional lipid parameters and achieving European lipoprotein guidelines than atorvastatin. These reductions can be achieved at low doses and there is no significant difference in adverse effects compared to atorvastatin. However, data to establish whether this reduction in LDL translates into reduced cardiovascular morbidity and mortality, as has been established with other statins, are not yet available.

The recently published CORONA study was a large randomised, placebo-controlled, multinational trial comparing 10mg rosuvastatin with placebo in 5011 subjects aged over 60, with moderate or severe heart failure caused by ischaemia.⁴ In all, 1477 subjects had coexisting diabetes mellitus. It is the only study to date specifically examining endpoints of cardiovascular morbidity and mortality. Despite demonstrating significant reductions in LDL cholesterol and CRP, rosuvastatin had no effect on cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. In this study rosuvastatin was well tolerated.

The CORONA study suggests there is no benefit in cardiovascular endpoints; however, it is difficult to make accurate conclusions as this involved a specific heart failure population. Such a population has not previously been sufficiently examined in trials of statin therapy and raises uncertainty about the benefits of statins for secondary prevention in patients with heart failure.

There are ongoing trials with rosuvastatin assessing cardiovascular endpoints in other populations. These include the role of rosuvastatin in primary prevention in the JUPITER study (Justification for the Use of statins in Primary

Key points

- Rosuvastatin is a potent statin reducing LDL cholesterol at all doses
- The LDL cholesterol lowering effect of rosuvastatin is seen in patients with diabetes
- Compared with other statins there is no evidence that treatment with rosuvastatin improves cardiovascular outcomes and therefore it should be used for patients with diabetes who do not reach LDL cholesterol targets with less potent statins

prevention: an Intervention Trial Evaluating Rosuvastatin) and in patients with end-stage renal failure in the AURORA study (A study to evaluate the Use of Rosuvastatin in subjects On Regular haemodialysis: an Assessment of survival and cardiovascular events). The results of these trials are awaited to further establish the benefits of rosuvastatin as compared with other statins, and at present rosuvastatin should be reserved for patients with diabetes who fail to reach targets with other less potent statins.

Conflict of interest statement

Dr Cowan and Dr McKay have no conflicts of interest to declare. Dr Fisher has received lecture fees from Astra Zeneca.

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