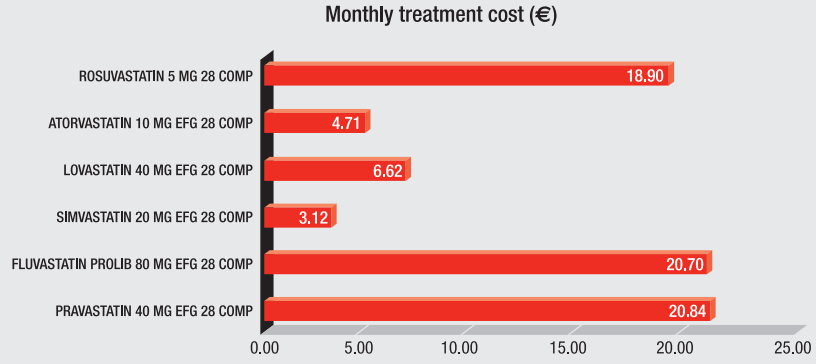
www.dtb.navarra.es

04/2011

Rosuvastatin▲ (Crestor®)

Another statin! Expensive, potent and doubts on safety



- Rosuvastatin is the seventh commercialized statin in Spain.
- Its capacity to lower cholesterol levels is similar to other statins at equivalent doses.
- No advantage has been shown compared to other statins with regard to morbidity and mortality.
- Its safety profile has caused controversy since the drug was marketed and the 40 mg dose should be restricted.
- It is considerably more expensive than simvastatin and atorvastatin.

Therapeutic indications[1]

It is indicated as an adjunct to diet in patients with primary hypercholesterolemia and mixed dyslipidemia when management with diet and other non-pharmacological treatments have not proven sufficient. Homozygous familial hypercholesterolemia in combination with diet and other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are inappropriate.

As an adjunct to other treatments to correct risk factors in the prevention of major cardiovascular events in patients considered at high risk of suffering a first cardiovascular event.

Mechanism of action and pharmacokinetics[1]

Rosuvastatin is a competitive and selective inhibitor of HMG-CoA reductase. The bioavailability of rosuvastatin is approximately 20%. Its clearance is renal in 28% and hepatic in 72%. The elimination half-life is about 19 hours and it is excreted mainly through the feces.

Simvastatin remains the elective management option, backed by evidence and price

Posology and administration[1]

The initial recommended dose is 5-10 mg once daily. The choice of the dose should be made considering the cholesterol levels of the patient, the calculated cardiovascular risk profile, and possibility of adverse reactions. Rosuvastatin can be administered at any hour of the day, with or without food. The maximum authorized dose is 40 mg daily.

Clinical efficacy

There are no clinical trials that have compared morbidity and mortality in primary or secondary prevention of cardiovascular disease in hypercholesterolemic patients with other statins or with placebo. The only comparative data available show reductions in cholesterol levels, especially LDL-c, in dose-ranging studies. These were similar to equivalent doses (rosuvastatin 5 and 10 mg compared to atorvastatin 10 and 20 mg, respectively).

JUPITER trial[2]

During this trial 17,802 healthy patients with normal cholesterol levels, but with high sensitivity CRP (hs-CRP) >2 mg/L were randomly allocated either to placebo or rosuvastatin 20 mg daily. The primary endpoint

The qualification assigned to the drug was agreed by the Drug Assessment Committees of Andalusia, Basque Country, Catalonia Institute of Health, Aragon and Navarre. The current report is based on the available information and is susceptible to be updated according to the latest evidence. Let us remind the reader about the importance of notifying the Pharmacovigilance Centre when there are suspicions of adverse reactions to drugs.

was a composite of acute myocardial infarction (MI), stroke, arterial revascularization, hospital admission for unstable angina, and cardiovascular death. This endpoint showed significant results but of questionable clinical relevance (ARR = 0.59% per year, NNT=82 patients for 1.9 years). On the contrary, the incidence of diabetes was 3% vs 2.4% in the rosuvastatin and placebo groups, respectively (p=0.01), NNH=165. Moreover, the trial presented some possible biases such as the premature interruption with less cases than expected from the protocol, and the value of hs-CRP as a marker of cardiovascular disease has been highly questioned[3].

The indication *"prevention of major cardiovascular events in patients who have an estimated high-risk profile to suffer a first cardiovascular event"* is based on the results of a post-hoc analysis. In this analysis, the use of rosuvastatin was associated with a reduction by 50% of suffering a MI, stroke or cardiovascular death in those participants with a basal risk of >20% according to the Framingham tables [HR = 0.50 (0.27-0.93)] and a reduction of 43% given a risk of 5% measured with the SCORE tables [HR = 0.57 (0.43-0.78)]. In these subgroups a substantial reduction in LDL-c levels and hs-CRP was observed consistent with the results from the main study[4].

CORONA study[5]

This study aimed at studying the effects of treatment with rosuvastatin in patients with heart failure of ischemic origin. The primary endpoint was the combination of cardiovascular death, non fatal MI and non fatal stroke. Despite the considerable lowering of LDL-c (45%, p<0.001) and hs-CRP levels (37%, p<0.001) there were no significant differences either in the primary endpoint [HR=0.92 (0.83-1.02)] or among its individual components. This data was confirmed by the GISSI-HF study[6].

Safety

Adverse effects

Frequent (1-10%): headache, nausea, abdominal pain, myalgia, extreme tiredness, diabetes (treatment with rosuvastatin has been associated with an increased risk of developing diabetes in patients with a fasting glycemia between 100 and 124 mg/dL or 5.5 and 6.9 mmol/L).

Rare (0,01-0,1%): pancreatitis, pruritus, rash and urticaria, myopathy and rhabdomyolysis, hypersentivity reactions including angioedema.

A dose-dependent increase in transaminase enzymes has been observed in a reduced number of patients treated with rosuvastatin. The incidence of adverse reactions to this drug tends to be dose-dependent.

Contraindications

Hypersensitivity to rosuvastatin or any of its excipients, active liver disease, severe renal failure (Cr Cl <30 mL/min), myopathy, concomittant treatment with cyclosporine. The 40 mg dose is moreover contraindicated in patients with a predisposition for myopathy/rhabdomyolisis.

Special precautions

Renal function should be checked during follow-up of those patients taking rosuvastatin 40 mg. Rosuvastatin should be taken with precaution in patients that consume excessive quantities of alcohol and/or present a history of liver disease. Liver function tests should be performed before starting treatment and three months after. Should serum transaminase levels exceed three times the upper limit then treatment should be either discontinued or the dose decreased.

Interactions

Significant interactions occur with cyclosporine, vitamin k antagonists (producing increments in INR), gemfibrozil and other fibrates, and niacin, ezetimibe, protease inhibitors, anti-acid agents (should be taken at least two hours after rosvastatin), erythromycin, oral contraceptive agents and hormone replacement therapy.

Special situations

No dose adjustments are necessary in patients with mild to moderate renal failure. In patients with moderate renal failure (Cr Cl< 60 mL/min) the initial recommended dose is 5 mg while the 40 mg dose is contraindicated. In patients with severe renal failure the use of rosuvastatin is contraindicated at any dose. In cases of liver failure no dose adjustments are required when patients present Child-Pugh scores of ≥7. In patients of Asian origin the initial recommended dose is 5 mg and the 40 mg dose is contraindicated. No dose adjustments are necessary in elderly patients, although in those patients >70 years, the recommended dose is 5 mg. Rosuvastatin is contraindicated during pregnancy and breastfeeding. It is not recommended in children under 10 years of age.

Place in therapeutics

Rosuvastatin is the seventh statin commercialized in Spain (including the withdrawn cerivastatin). It is a potent drug in lowering total cholesterol levels, especially the LDL-c and non HDL cholesterol fractions. However, this powerful effect has generated many doubts concerning its safety profile, especially at the 40 mg dose[7,8,9]. There are no trials comparing it with other statins in terms of clinically relevant variables. The greatest clinical benefit of statin therapy is obtained from their use at standard doses in secondary prevention in patients with high levels of total cholesterol or LDL-c and low HDL-c. Clinical trials evaluating statins on the prevention of cardiovascular disease carried out on patients with hypercholesterolemia have shown to be equivalent with regard to coronary mortality and morbidity[10] and the most efficient agent currently is simvastatin[11,12].

The indication for the use of rosuvastatin 20 mg in primary prevention in high cardiovascular risk patients with normal cholesterol levels was obtained after a post hoc analysis of a trial that had raised many doubts with respect to the data presented and the early interruption of the trial. Given the absence of clinical trials with regard to primary and secondary prevention in patients with hypercholesterolemia, and the absence of comparative data of hard endpoints with other statins, rosuvastatin does not offer any benefit among the management options. New agents for chronic diseases should show significant improvements when compared to the standard treatment in morbidity and mortality and/or an improvement in the quality of life. Here this is not the case. Rosuvastatin has therefore a very limited place in current therapy given the ample amount of options, experience and cost of the other available statins.

Presentations

Crestor® (AstraZeneca) 5 mg 28 tablets 18.90 €, 10 mg 28 tablets 25.95 €, 20 mg 28 tablets 38.92 €. Prescription medicine only.

References

A complete report on rosuvastatin can be consulted at: http://www.dtb.navarra.es

Servicio Navarro de Salud
Osasunbidea

INFORMATION:
Servicio de Prestaciones Farmacéuticas Plaza de la Paz s/n, 4ª planta - 31002 Pamplona **T** 848429047 **F** 848429010