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Overview of rosuvastatin reports

Introduction

Rosuvastatin (Crestor®) was granted a market authorisation for the Netherlands on November 6, 2002 by the Dutch Medicines Evaluation Board (MEB). The Netherlands acts as Reference Member State for rosuvastatin.
Rosuvastatin is a potent HMG-CoA reductase inhibitor (statin), indicated for *the treatment of primary hypercholesterolemia including heterozygous and homozygous familiarly hypercholesterolemia and familiarly combined hyperlipidemia* [1]. Rosuvastatin is the fifth currently marketed statin in the Netherlands in addition to simvastatin, pravastatin, fluvastatin and atorvastatin. It differs structurally from other statins, containing a polar methane sulfonamide group which confers relative hydrophilicity. The drug is less lipophilic than most other statins, being similar in this regard to pravastatin. The relative hydrophilicity of rosuvastatin imparts greater selectivity for uptake into hepatic versus nonhepatic cells [2].
Rosuvastatin is not extensively metabolised, with little or no transformation by cytochrome P450 isoenzymes in contrast with atorvastatin and simvastatin. The elimination half-life in humans is between 13 and 21 hours and 90% is eliminated unchanged in the faeces.
The aim of this report is to review the adverse drug reactions reported to the Netherlands Pharmacovigilance Centre Lareb and to compare them with the adverse drug reactions listed in the Dutch SPC.

Reports

Between approval and the 24th of February 2004, the Netherlands Pharmacovigilance Centre Lareb received 79 reports on 116 adverse drug reactions (ADRs) attributed to rosuvastatin (table 1). Twenty-five serious reports containing 47 ADRs were received of which seven reports originated from healthcare professionals and 18 (dutch) reports from the manufacturer.

One fatal case was reported by the manufacturer: the death of a male aged 79 years who experienced rhabdomyolysis, renal insufficiency and hypotension with a latency period of 1 month after starting rosuvastatin. This individual had a medical history of cardiovascular disease (PTCA in LAD, coronary angioplasty) and concomitant medication included atenolol, clopidogrel, carbasalate calcium and furosemide.

Table 1. number (n) of adverse drug reactions on rosuvastatin reported to Lareb per frequently reported MedDRA system organ classes (SOC's)relative to the ADRs listed in the Dutch SPC and relative to the ADRs listed in the US package insert for Crestor®.

SOC	ADR	n	SPC[1]
Blood	Coagulopathy	2	i
	Vasculitis Henoch-Schonlein like	1	nl
Eye	Diplopia	1	nl
	Vision blurred	1	nl
	Eyes tearing	1	nl
Gastr	Abdominal pain	4	c
	Constipation	2	c
	Vomiting	2	nl
	Nausea	2	c
	Diarrhoea	2	nl
Genrl	Oedema	4	nl
	Death	**1**	nl
	Fatigue extreme	1	nl
	Chest discomfort	1	nl
	Malaise	1	c
Hep. Bil.	Hepatic function abnormal	6	l
Infec	Hepatitis	1	nl
Inv	Blood CPK increased	3	r
	Heart rate irregular	1	nl
	Coagulation time prolonged	2	i
	Blood in stool	1	nl
	Hypotension	1	nl
	Hepatic enzyme increased	2	r
	GGT increased	1	r
Metab	Hyperglycaemia	1	nl
Nerv	Headache	8	c
	Stroke	1	nl
	Paraesthesia	1	nl
	Depressed level consciousness	1	nl
	Dizziness	6	c
Musc	Myalgia	15	c
	Rhabdomyolysis	4	r
	Muscular weakness	3	nl
	Muscle cramp	1	nl
	Myopathy	1	r
	Muscle rigidity	1	nl
	Arthralgia	3	nl
	Polymyalgia rheumatica	1	nl
Psych	Agitation	2	nl
Renal	Renal impairment	1	l
	Renal insufficiency	1	r
Respir	Epistaxis	1	nl
Skin	Rash vesicular/ maculo-papular	2	u
	Sweating increased	3	nl
	Pruritus	4	u
	skin reaction (local)	1	nl
	Alopecia	1	nl
	Exanthem	1	u l
	Skin ulceration	1	nl
	Rash	2	u
	Angiooedema	1	nl
	Urticaria	2	u
Vasc	Haemorrhage	1	nl
	Haematoma	1	nl
Total		116	

[1] c = common (>1/100, < 1/10)
u = uncommon (> 1/1.000, <1/100)
r = rare (> 1/10.00, < 1/1.000)
l = listed (without frequency)
nl = not listed
i = listed under interactions (SPC §4.5

Other sources of information

WHO database

ADR reports in the database of the WHO (n= 231) show a similar profile of adverse drug reactions of rosuvastatin. The WHO database contains ADR reports in SOCs which are absent in the Lareb data on rosuvastatin:

- Cardiovascular disorders, general (7 reports equals 3%)

- Heart rate and rhythm disorders (10 reports equals 4%)

Discussion

The distribution of adverse drug reactions reported to Lareb according SOC shows striking similarities between all statins marketed in the Netherlands. The reflection of the ADR profile of the reports on rosuvastatin to Lareb is markedly improved in the current, recently reviewed Dutch SPC of rosuvastatin. The previous Dutch SPC of rosuvastatin suggested a more favourable ADR profile of rosuvastatin as compared to the other currently marketed statins in the Netherlands. Because of this prescribers might have been compelled to give preference to rosuvastatin above other statins. At least six reports to Lareb concern individuals who experienced an ADR after they switched to rosuvastatin after previous treatment with a different statin (pravastatin: 3, atorvastatin: 2, simvastatin: 1).

The Netherlands Federation of Hemostasis Services (NFT) was notified by Lareb of the reports on coagulation disorders in patients concomitantly using coumarin anticoagulants and rosuvastatin. A preliminary pilot-screening by the NFT in Hilversum and Utrecht identified 3 cases of increased INR out of 15 coumarin-rosuvastatin users. This prompted the NFT to issue a warning for this possible drug-drug interaction[3]. It is surprising to see warfarin to be specifically mentioned in the Dutch SPC in the interactions section 4.5 and not acenocoumarol or fenprocoumon, the commonly prescribed coumarins in the Netherlands. Especially since the latter two coumarins are actually mentioned in the Dutch patient information leaflet ("patiëntenbijsluiter") of Crestor® [4].

Conclusion

The profile of ADR reports attributed to rosuvastatin fits within the safety profile as described in the Dutch SPC.

References
1. 1B tekst van Crestor http://www.cbg-meb.nl/IB-teksten/26872-26873-26874.PDF (accessed 09-03-2004)
2. McTaggart F, Buckett L, Davidson R et al: Preclinical and clinical pharmacology of rosuvastatin, a new 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor. Am J Cardiol 2001; 87(suppl):28B-32B.
3. http://www.fnt.nl/ (accessed 12-02-2004)
4. patiëntenbijsluiter van Crestor®.[http://www.cbg-meb.nl/Bijsluiters/26872-26873-26874.PDF(accessed 09-03-2004)