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HMG-CoA-reductase inhibitors and lichenoid eruption

Introduction

HMG-CoA-reductase inhibitors inhibit the enzyme HMG-CoA (3-hydroxy-methylglutaryl-coenzyme A-reductase, which plays an important role in the synthesis of cholesterol by catalysing the conversion from HMG-CoA to mevalonate [1]. HMG-CoA-reductase inhibitors are indicated for hypercholesterolemia. They are effective in both the primary and the secondary prevention of ischemic heart diseases and stroke prevention[2].
In general the HMG-CoA-reductase inhibitors are well tolerated. Two potentially serious adverse reactions are: elevation of the liver-enzymes (up to more than three times the upper normal level) and musculoskeletal abnormalities, including myalgia, myositis and rhabdomyolysis[3-7].

Spontaneously lichen planus is a relatively common skin disorder of unknown cause with an incidence of 0.9 to 1.2% in the general population. It affects men and women almost equally and it is likely to start in middle age [8]. On visual examination, the lesions of lichen planus might show similarities with psoriaform eruptions. However, they might also reassemble eczematous eruptions, pityriasis rosea, chronic-graft-versus-host disease, secondary syphilis, lupus erythematosus and plain warts[8]. Lichen planus is diagnosed on clinical symptoms and biopsy can confirm the diagnosis.

Drug-induced lichenoid eruptions usually differ from spontaneously lichen planus. Next to lichenoid elements, drug-induced lichenoid eruptions may be accompanied with papular, scaling and eczmatous lesions. Frequently the lichenoid eruptions occur a few months after starting the drug. Similar as in spontaneously lichen planus drug-induced lichenoid eruptions results in hyperpigmentation, which regresses slowly or even can be irreversible [9]. Lichenoid eruptions are not mentioned in the SPCs of Zocor®, Lipitor®, Selektine®, Lescol® and Crestor®[3-7] .

Reports

On June 9, 2004 the database of the Netherlands Pharmacovigilance Centre contained three reports concerning lichenoid eruptrion associated with the use of HMG-CoA-reductase inhibitors. Two reports involved simvastatin and one atorvastatin. In addition Lareb received one report of lichenification associated with the use of atorvastatin, but it is not sure whether this reaction concerned a lichenoid eruption.
In two of the four patients the symptoms appeared within two weeks after starting with the HMG-CoA-reductase inhibitor and in one patient the symptoms disappeared after discontinuation of the HMG-CoA-reductase inhibitor. This supports a causal relationship between the use of HMG-CoA reductase inhibitors and lichenoid eruptions. Table 1 gives an overview of the characteristics of these reports.

Other sources of information

Literature

A search in Medline revealed two case reports concerning lichenoid eruptions associated with the use of simvastatin [10,11] and one case report involving the use of pravastatin[12]. Roger *et al*. described a case of a 57-year-old woman who used simvastatin 10 mg once daily with a pruritic, erythematous eruption of papules on her wrists and elbows with a latency period of one month after starting. She used no concomitant medication. Patient did not recover after treatment with a topical corticosteroid. Simvastatin has been withdrawn and the rash resolved four weeks later. The rash reassembled a lichenoid drug eruption and histopathology was also compatible with a lichenoid eruption[10].

Surprisingly, Nazami recently suggested that HMG-CoA-reductase inhibitors may be useful in the treatment of several skin disorders, especially those characterised by infiltration of activated leucocytes into the skin, for example lichen planus and subacute cutaneous lupus

erythematosus. This could be due to the immunomodulatory activities of HMG-CoA-reductase inhibitors[13].

Table 1. reports of HMG-CoA-reductase inhibitors and Lichenoid dermatitis in the database

Patient, sex, age	Drug, Dose	Concomitant medication	Suspected ADR	Time to onset	Action taken, Outcome
A, F, 55	simvastatin, 20 mg 1 dd.	unknown	lichenoid toxicodermia	shortly after start	treated with betomethasone, symptoms improved
B, F, 58	atorvastatin, 20 mg 1 dd.	acetylsalicylic acid, ibuprofen	lichen planus	12 weeks after start	treated with clobetasol and clobetasone, not yet recovered
C, M, 66	atorvastatin, 20 mg 1 dd.	aetylsalicylic acid, metoprolol, isosorbidedinitrate and nitroglycerin	lichenification	two weeks	atorvastatin continued, unknown
D, ?, ?	simvastatin, 10 mg	diclofenac, diazepam	Lichenoid toxicodermia	unknown#	recovered after cessation

symptoms appeared after switching from Zocor® to a generic product

Databases

On June 9 2004, the Lareb database contained 1562 reports associated with the use of HMG-CoA-reductase inhibitors, including the above mentioned four cases. The reporting odds ratio (ROR) was 3.8 (95% CI 1.3 - 11.0), indicating that lichenoid eruptions for HMG-CoA-reducatase inhibitors are disproportionally present in the Lareb database.

The database of the Uppsala Monitoring Centre of the WHO contains 118 associations of HMG-CoA-reductase inhibitors and lichenoid eruptions (expressed as lichenoid dermatitis, lichen planus and lichenoid changes in mouth), which is disproportional (ROR 3.6; 95% CI 3.0 - 4.3). Of these 118 associations 49 concerned simvastatin and 19 concerned atorvastatin. The ROR for simvastatin and lichenoid eruptions was 4.5 (95% CI 3.4 - 6.0) and for atorvastatin 2.3 (95% CI 1.4 - 3.6) and therefore also disproportionally present in the database. Table 2 shows an overview of RORs of lichenoid eruptions and all HMG-CoA-reductase inhibitors.

Table 2. Reports of lichenoid eruptions in association with statins in the WHO database

HMG-CoA-reductase inhibitor	Reports Lichenoid eruptions	ROR (95% CI)
simvastatin	49	4.5 (3.4- 6.0)
atorvastatin	19	2.3 (1.4 -3.6)
pravastatin	26	7.0 (4.8 - 10.4)
fluvastatin	5	1.9 (0.77 - 4.5)
cerivastatin	2	not applicable
lovastatin	17	2.4 (1.5 - 3.9)
Total	**118**	**3.6 (3.0 - 4.3)**

Mechanism

The pathogenic mechanism of drug-induced lichen planus is yet unknown, but it is neither an allergic reaction nor a dose-dependent reaction [9].

Conclusion

Lareb received three reports of lichenoid eruptions and one report of lichenification associated with the use of HMG-CoA-reductase inhibitors. The association lichenoid eruptions and HMG-CoA-reductase inhibitors is disproportionally present in both the Lareb and the WHO database.

Case reports in literature support this association.

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