

Statins and lichenoid drug eruption

Introduction

Statins 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. Statins are indicated for *hypercholesterolemia*. They are effective in both *the primary and the secondary prevention of ischemic heart diseases and stroke prevention*. Among the statins simvastatin (Zocor[®]) was granted marketing authorization in the eighties, atorvastatin (Lipitor[®]), pravastatin (Selektine[®]) and fluvastatin (Lescol[®]) in the nineties, rosuvastatin (Crestor[®]) in 2002 and pitavastatin (Vezeptra[®], Livazo[®]) in 2010. Common adverse skin reactions in this group are urticaria, eczema, dermatitis, skin eruption, pruritus, alopecia and angioneurotic edema. Beside these, several serious skin reactions are described [1-7].

Lichen planus (LP) is an inflammatory, pruritic disease of the skin and mucous membranes, which can be either generalized or localized. It is characterized by distinctive purplish, flat-topped papules having a predilection for the trunk and flexor surfaces. On the surface often white stripes (Wickham's striae) might be visible. The lesions may be discrete or coalesce to form plaques. Histologically, there is a "saw-tooth" pattern of epidermal hyperplasia and vacuolar alteration of the basal layer of the epidermis along with an intense upper dermal inflammatory infiltrate composed predominantly of T-cells. The etiology is unknown. It occurs in the general population at a rate of 0.9-1.2 % and oral lesions may be seen in 30-70 % of these patients. It affects men and women almost equally and it is likely to start in middle age. It is diagnosed on clinical symptoms and biopsy can confirm the diagnosis. It is a self-limiting disease, but recovery might be slow and remission occurs in 1-2 years; oral lichen seems to follow a more chronic course, with a mean duration of 4.5 years [8,9].

Drug induced lichenoid eruptions (LDE)* can differ in clinical (and histological) aspects from lichen planus; next to lichenoid elements, LDE may be accompanied with papular, scaling and eczematous lesions. The predilection sites are rarely involved. On the other hand LDE produces lesions that might be clinically and histologically indistinguishable from idiopathic LP. The two conditions can be differentiated only by the time course of skin or mucous membrane involvement in relation to drug administration and by re-challenging with the suspected agent. Frequently the lichenoid eruptions occur a few months after starting the drug, but the latency may vary between days to several years. Clearance of symptoms can occur within a few weeks after withdrawal of the drug; in some reports the healing period stretched from less than a week to many months. In some single case reports, symptoms cleared without discontinuation of the drug, in another study with oral LDE patients did not recover after withdrawal of the drug. Similar as in idiopathic lichen planus LDE results in hyperpigmentation, which regresses slowly or even can be irreversible. Histologic differences between LP and LDE are often subtle and not reliable. The dermal infiltrate (as well as peripheral blood) may contain eosinophils and plasma cells and may sometimes be distinguished from the infiltrate in LP [8,10].

* A reliable differentiation between lichenoid drug eruption and drug induced lichen planus cannot be made, therefore the term lichenoid drug eruptions (LDE) is used [8].

The current observation describes the association between statins and lichenoid drug eruptions in 13 patients. A previous report regarding this association in 4 patients has been sent to the Medical Evaluation Board in 2004 [11].

Reports

Lareb received 13 reports of lichen planus or lichenoid dermatitis associated with the use of statins, in a period from July 18, 1996 till April 3, 2014. The reports are listed in Table 1. In one patient (D) biopsy results confirmed the diagnosis. In four other cases (B,E,I,L) the diagnosis was confirmed by a dermatologist.

Table 1. Reports of lichenoid drug eruptions associated with the use of statins

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 14687 F, 51-60 years Hospital Pharmacist	simvastatin, 20mg daily pure hypercholesterolaemia		dermatitis lichenoid	unknown ("soon") no change recovering
B 35066 F, 51-60 years Pharmacist	atorvastatin 20mg daily	carbasalate calcium ibuprofen	lichen planus	12-14 weeks discontinued not yet recovered
C 37816 M, 61-70 years General Practitioner	atorvastatin 20mg daily pure hypercholesterolaemia	carbasalate calcium diclofenac nitroglycerin isosorbide dinitrate metoprolol	dermatitis lichenoid	2 weeks no change unknown
D 43561 M or F General Practitioner	simvastatin 10mg daily	diazepam diclofenac	therapeutic response unexpected with drug substitution, dermatitis lichenoid	unknown discontinued recovered
E 48214 F, 51-60 years Specialist doctor	simvastatin 20mg daily pure hypercholesterolaemia		lichen planus	15 years no change unknown
F 53337 F, 51-60 years Pharmacist	atorvastatin 40mg daily hypercholesterolaemia ezetimibe 10mg hypercholesterolaemia	furosemide, captopril acetylsalicylic acid esomeprazole metoprolol nitroglycerin - transdermal betahistin	lichen planus	6 years 4 months both discontinued recovering
G 119392 F, 71 years and older	simvastatin 20mg daily hypercholesterolaemia	macrogol/ electrolytes vitamin B1, B6, B12,	lichen planus	2-3 months no change not recovered

Pharmacist		lamotrigine, miconazole vaginal oxazepam omeprazole, metoprolol telmisartan/hydro- chlorothiazide sucralfate		
H 129411 F, 51-60 years Consumer	atorvastatin 20mg daily hypercholesterolaemia		lichen planus	3 months discontinued recovering
I 133942 F, 51-60 years Consumer	simvastatin 10 mg daily hypercholesterolaemia	metformin irbesartan	lichen planus	< 2 years discontinued recovering
J 136378 F, 61-70 years Pharmacist	simvastatin 20mg daily hypercholesterolaemia	omeprazole enalapril amlodipine	lichen planus on lower legs and arms	18 months discontinued not yet recovered*
K 146716 M, 61-70 years Pharmacist	simvastatin 20 mg daily hypercholesterolaemia		dermatitis lichenoid	6-7 years discontinued unknown**
L 148414 F, 61-70 years Specialist doctor (student)	atorvastatin 20 mg daily hypercholesterolaemia	enalapril triamterene/hydrochl orothiazide 50/25 metoprolol	dermatitis lichenoid	1 week discontinued recovered
M 172669 F, 51-60 years Pharmacist	simvastatin 20 mg daily hypercholesterolaemia	bisoprolol fluticasone carbasalate calcium ranitidin	lichen planus	1 year discontinued recovering

* Report sent at date of discontinuation

**Patient switched to atorvastatin

Other sources of information

SmPC

Lichenoid drug eruptions, including lichen planus, are not mentioned in the SmPCs of atorvastatin, fluvastatin, pravastatin, rosuvastatin, simvastatin and pitavastatin [1-7].

Literature

Case reports of lichenoid drug eruptions have been described in association with simvastatin [12,13] pravastatin [14,15], fluvastatin and lovastatin [16]. Roger *et al.* described a case of a 57-year-old woman with a pruritic, erythematous eruption of polygonal papules on her wrists and elbows one month after starting simvastatin 10 mg once daily. 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 [12].

Stoebner *et al.* described a 63-year-old man, who was treated with simvastatin for hypercholesterolemia. After one month he developed a pruriginous and bullous lichenoid eruption. Histological and direct immunofluorescent features were consistent with the diagnosis of lichen planus pemphigoides. After two months use, simvastatin was discontinued. He was treated with a topical class II corticosteroid during one week. Four weeks hereafter the itching had vanished and no new lesions had appeared. Three months later he had recovered with only some hyperpigmented sequelae [13].

Pravastatin-induced LDE was first reported in a 75-year-old black patient who developed a lichenoid rash, on the extensor surfaces of the arms and dorsal aspect of the hands, 3 weeks after starting pravastatin at a dose of 10 mg daily. Clinical examination revealed multiple scattered, polygonal, erythematous plaques and papules with a translucent, shiny scale and the diagnosis of a lichenoid drug eruption was confirmed on histopathological examination of a skin biopsy. Discontinuation of pravastatin led to resolution with mild postinflammatory hyperpigmentation in two weeks' time. Upon re-challenge, the rash reappeared within 1 week [14].

A case of pravastatin-induced diffuse and numerous pigmented macules on the face and upper back was described in a 64 year old woman. Histopathological examination showed a lichenoid dermatitis. Three months before, pravastatin had been added to her treatment regime, because of an acute coronary syndrome. Cessation of pravastatin resulted in gradual fading of pigmentation over a 9 months period. All other chronic medications, including furosemide and candesartan – which both can cause also LDE- had been continued [15].

Sebök described a case of a 59-year old woman with bilateral pruritic, papulous eruption on the dorsal side of her forearms, hands and on the volar surfaces of her wrists, on the soles and to a lesser extent on her trunk and thighs four weeks after starting fluvastatin. Topical steroids had only a temporary effect. The antihypertensive treatment, perindopril, was continued. After discontinuation of fluvastatin and treatment with mometasone-furoate, the lesions cleared after three weeks. Two weeks later, lovastatin was introduced, because of an increase in cholesterol levels. The eruption recurred. Biopsy showed a lichenoid dermatitis. After stopping lovastatin, recovery was observed within three weeks, leaving post-inflammatory hyperpigmented macules [16].

Databases

Table 2. Reports of lichen planus/lichenoid dermatitis with statins in the databases of the Netherlands Pharmacovigilance Centre Lareb, the WHO- and Eudravigilance (EMA) database [17,18].

Database	Preferred Terms	Number of reports	ROR (95% CI)
Lareb	Lichen planus	8	4.3 (2.3-10.4)
	Lichenoid dermatitis*	5	5.7 (2.2-15.1)
WHO	Lichen planus	91	5.3 (4.3-6.6)
Eudravigilance	Lichen planus	31	3.2 (2.3 -4.7)

*Lichenoid dermatitis is the Lower Level Term; the corresponding MedDRA Preferred Term Lichenoid keratosis is not appropriate

Prescription data

Table 3. Number of patients using statins in the Netherlands between 2009 and 2013 [19].

Drug	2009	2010	2011	2012	2013
simvastatin	826,190	930,700	980,250	1,044,000	1,084,000
pravastatin	164,470	170,080	169,640	170,760	171,410
fluvastatin	23,113	22,181	21,667	21,474	20,937
atorvastatin	394,750	375,810	364,900	383,670	412,580
rosuvastatin	179,010	181,230	191,890	209,550	221,690
Total	1.507.000	1.594.000	1.662.000	1.751.000	1.827.000

Mechanism

The pathogenic mechanism of LDE is not well understood, a type IV allergy is sometimes involved. A dose dependency is suggested. Some drugs change surface antigens, whereas other drugs change enzyme systems. These aberrations may precipitate an immune response, in which cytotoxic CD8+ T cells are activated, which then cause epidermal damage [8,10]. For statins no specific mechanism is described.

Discussion and conclusion

Lareb has received 13 reports of lichen planus and lichenoid dermatitis in association with statins; in one case a lichenoid dermatitis occurred after drug substitution of simvastatin and in one case also ezetimibe was reported as suspected drug.

In one patient (D) biopsy results confirmed the diagnosis. In four other cases (B,E,I,L) reporting was done by a dermatologist or patients had been referred to a dermatologist, therefore a reliable diagnosis was assumed.

As is described by Ellgehausen it is difficult to distinguish LDE from idiopathic lichen planus, clinically as well as histologically [8]. The time course in relation to drug administration of the suspected agent might be of help, but may also vary between days and years. In the reported cases to Lareb, the latency in most patients was several weeks.

According to Ellgehausen, the clearance of symptoms in LDE might vary from a week to many months or can be irreversible. Therefore idiopathic lichen planus cannot be ruled out easily. Of the thirteen cases reported to Lareb, five had recovered or were recovering after discontinuation of the statins at the moment of reporting; in one case also the suspected ezetimibe was discontinued. Four of these patients had also been treated with either topical corticosteroids, light treatment or acupuncture. Recovery took weeks to several months. In three of these patients several concomitant medications were used, which are known to be associated with lichenoid eruptions as well, including bisoprolol, metoprolol, hydrochlorothiazide and/or enalapril/captopril. These medications were however continued during the recovering phase, which strengthens an association with the statin.

The association was supported by the WHO- and Eudravigilance data and by several publications; in one of these even a positive re-challenge was observed after re-introduction of a statin.

It is of importance to acknowledge the possible role of statins in a patient with lichenoid eruption, which might have a major influence on well-being.

Discontinuation of these statins might result in a substantial improvement in symptoms.

For this reason, it is suggested statins might have a causative role in the occurrence of lichenoid drug eruption.

- Lichenoid drug eruptions should be mentioned in the SmPC of statins

References

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This signal has been raised on October 2014. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbqmeb.nl/cbq/en/default.htm