

Urticarial Vasculitis from Simvastatin: What Is the Alternative Drug?

To the Editor:

Statins are the first-choice drugs in the cholesterol-lowering treatment for patients with coronary heart disease, cardiovascular risk factors, and cerebrovascular and peripheral vascular diseases.^{1,2} They are divided into two groups. The fungal metabolite compounds (lovastatin, pravastatin, and simvastatin) are characterized by a hexahydronaphthalene ring with two major side chains: one chain is common to all compounds and contains a hydroxy acid that forms a six-membered analog of the intermediate compound in the hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase reaction; the other is a methyl butyrate ester (lovastatin and pravastatin) or a dimethyl butyrate ester (simvastatin).³ The synthetic compounds (atorvastatin, rosuvastatin, and fluvastatin) have a heptanoic acid side chain that forms a structural analog of the HMG-CoA intermediate.³ The most frequent adverse statin reactions are hepatotoxicity, myopathy, and rhabdomyolysis.⁴

A 79-year-old man treated with ramipril, atenolol, acetylsalicylic acid, and simvastatin in the previous 7 months for hypertension and coronary heart disease was admitted for a severe urticaria that appeared 1 week previously. The erythematous and firm wheals with sharp edges lasted more than 24 hours and resolved with hyperpigmentation (Fig 1). The clinical results of corticosteroid and antihistamine treatments had not been satisfactory. Physical examination and results of laboratory investigations (routine blood tests, paraneoplastic markers, antinuclear antibodies, hepatitis B and C markers, and serum immunofixation) were normal. Histopathologic examination of a biopsy specimen from a recent-onset wheal showed a fibrinoid necrotizing

venulitis, with endothelial swelling, erythrocyte diapedesis, perivenular neutrophilic cellular infiltrate, and leukocytoclasia. After the discontinuation of all systemic drugs and a short course of oral methylprednisolone (1 week), the urticaria quickly resolved. One month later, as all patient drugs were considered vital and to find the responsible compound, exposure tests were performed in an environment with emergency equipment and after written informed consent. Oral rechallenge with each drug taken by the patient was carried out every 10 days in the following sequence: atenolol, acetylsalicylic acid, ramipril, and simvastatin. The doses of each drug were gradually increased (1/1,000, 1/100, 1/10, and the single therapeutic dose) at hourly intervals. A slight urticaria was observed only after the administration of simvastatin (0.2 mg). Patch tests and prick tests with the statins marketed in Italy (Table 1) showed a positive reaction to lovastatin. As lovastatin is chemically related to simvastatin, an oral challenge test with a synthetic statin was performed. The daily dose of atorvastatin (40 mg) was fractionated in five administrations over 4 days (day 1, 0.04 mg; day 2, 0.4 mg and 4 mg; day 3, 20 mg; day 4, 40 mg). No side effects were observed. Currently, after 5 months, the drug is still being taken by the patient without problems.

Cutaneous side effects from statins have been reported.⁴ To our knowledge, urticarial vasculitis from statins and simvastatin in particular is not reported in the literature. For patients sensitized to statins, it is difficult to prescribe an alternative antilipidemic therapy

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Figure 1. Erythematous firm wheals and hyperpigmented spots on the trunk.

Table 1. Results of Skin Tests with Statins

Statins	Results	
	Patch Test (*)	Prick Test (†)
Fungal metabolites		
Lovastatin	–	++(‡)
Pravastatin	–	–
Simvastatin	–	–
Synthetic statins		
Atorvastatin	–	–
Rosuvastatin	–	–
Fluvastatin	–	–

(*) 4% in petrolatum; readings at day 2 and day 4

(†) 4% in saline; readings at 20 min and 24 h

(‡) no positive reactions in 20 healthy volunteers

because bile-acid sequestrants or resins (cholestyramine and colestipol) and ezetimibe (an inhibitor of cholesterol absorption by enterocytes in the small intestine) are less effective than statins in preventing coronary heart disease.⁵ These drugs lower cholesterol but do not have other very important effects on atherosclerotic plaque, which, on the contrary, is stabilized by statins.⁵ Based on what is illustrated above, we would like to emphasize the results of the oral challenge test in our patient. They underline the possibility of administering a chemically different statin in subjects with cutaneous adverse statin reactions, using a fungal metabolite compound in patients sensitized to the synthetic statins

(or vice versa). However, further investigations are necessary to confirm our recommendation.

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