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A case of atorvastatin-induced solar urticaria

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To the Editor:

Atorvastatin calcium (ATV) is a second-generation statin drug, which has been used as a lipid-lowering agent. This agent inhibits 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. Although the most common adverse effect of ATV is gastrointestinal disturbances, some clinical cases of cutaneous adverse reactions have also been reported, including photosensitive disorders (1) (2).

Herein, we report a case of ATV-induced solar urticaria.

A 21-year-old woman was referred to our dermatology department with the symptom of solar urticaria. She was diagnosed with familial hypercholesterolemia at the age of 14 years. Thereafter, she commenced taking ATV. When she was 18 years old, she presented with pruritic erythema or wheal on her sun-exposed skin, including dorsal sides of the hands, neck, legs upon 5 to 10 minutes of sun exposure. The rash disappeared within an hour. Laboratory examinations revealed increased serum levels of total cholesterol (221 mmol/L) and low-density lipoprotein cholesterol (137 mmol/L) under medication with 10 mg of ATV per day, whereas her triglyceride level was normal (104 mmol/L). Her

erythrocyte protoporphyrin level was 53 $\mu\text{mol/L}$ (reference value: 30–86 $\mu\text{mol/L}$).

Phototesting was conducted on the patient's back skin using a fluorescent lamp (Toshiba FL 32S BL/DMR; Toshiba, Tokyo, Japan) emitting 310 to 400 nm with a peak emission at 365 nm, demonstrated a minimal wheal dose (MWD) of 12 J/cm². Visible light exposure using a slide projector with a 300-W bulb at a distance of 15 cm induced wheals upon 20 minutes exposure. No urticarial response was observed after exposure to UVB range from Toshiba FL 32S E-30 lamps. Several cut-off glass filters (Toshiba Medical Supply, Tokyo) were also used in combination with a slide projector to define the wavelengths that produce and inhibit urticarial reactions. We obtained a prominent urticarial reaction on exposure to slide projector irradiation through a Y-45 glass filter and a less prominent wheal through a Y-48 glass filter. By contrast, no wheal but slight erythema was observed through a Y-50 glass filter, which cut off light shorter than 500 nm and transmit light longer than 500 nm. The phototest indicated that the action spectrum of this case ranged from 360 to 480 nm. Exposure to the action spectra followed by exposure to visible light with a R-60

filter induced neither erythema nor wheal, indicating an inhibition wavelength of >600 nm. Her symptom persisted despite treatment with antihistamines (fexofenadine). After 1 week from the discontinuation of ATV, UVA phototesting (6 and 12 J/cm²) yielded a negative result for urticarial reaction. When the ATV therapy was resumed, UVA phototesting at 6 J/cm² induced neither erythema nor wheal, although erythema and wheal were observed after UVA phototesting at 12 J/cm². Consequently, she declined to take ATV, and the drug was replaced with rosuvastatin, which did not induce any more urticarial reactions with sun exposure.

Solar urticaria is characterized by wheal and erythema confined on sun-exposed skin. The age of onset is varies; most patients develop symptoms in young adulthood. In most studies, female patients predominate (3). It does not seem to be limited to any particular race or ethnic. We assume that its pathogenesis involves a photoallergen produced by sunlight resulting in histamine release from mast cells. Most studies show action spectra between 300 and 500 nm, but other studies report infrared-induced urticaria (4). The inhibition spectrum in

solar urticaria was first reported by Hasei and Ichihashi (5). They suggested that irradiation with longer wavelength light than the action spectrum, immediately after exposure to the action spectrum, inhibited the wheal reaction. The inhibition spectrum in solar urticaria was mostly identified in Japanese patients with solar urticaria. Fukunaga et al (6) speculated that ligation of photoallergen with immunoglobulin E binding to mast cells was blocked by some unknown mechanisms by inhibition spectra irradiation.

Drug-induced solar urticaria is rare, and only several cases have been reported thus far, including chlorpromazine, benoxaprofen, coal tar and pitch, repirinast, tetracycline, and oral contraceptives (7). Some clinical cases of cutaneous adverse reactions of statin drugs have been reported, including photosensitivity disorders with lichenoid tissue reactions, chronic actinic dermatitis. But there has been no report of solar urticaria caused by statin drugs. ATV is a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, prescribed for hypercholesterolemia. The hydrophilic statin agents are pravastatin and rosuvastatin. Meanwhile, the lipid-soluble statin agents are simvastatin and

ATV. Morimoto et al supposed that the inactive prodrug of simvastatin, which is not distributed in the liver, and an active β -hydroxyacid metabolite excreted in the blood may be the sensitizers (8). Montanaro et al reported that the phototoxicity of ATV can be attributed to the phenanthrene-like intermediate of ATV as a photosensitizer characteristic (9). They also showed that laser flash photolysis of atorvastatin at both 266 and 308 nm led to the formation of intermediate, which showed absorption spectra of 340-600nm with a peak at $\lambda_{\max}$ of 460 nm, that goes along with the action spectrum for evoking urticarial wheal in our patient. After she was diagnosed with solar urticaria, she kept in mind a strict photoprotection, therefore her symptoms subsided either taking drug or discontinuing the drugs as long as she prevented from sun-exposure. However, she must take a lipid lowering agents for her lifetime because she was diagnosed with familial hypercholesteremia at the age of 14 years old, and carrying out strict photoprotection throughout her lifetime is extremely inconvenient. Then we suggested changing the lipid-lowering drug. The fact that her symptoms became subsided, after changing the drug, is also a supportive evidence that her solar urticaria was probably caused by atorvastatin. We should

keep in mind that ATV is a solar urticaria-causing drug in clinical practice.

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Legends

Figure 1.

Conventional phototesting using UVA, UVB and visible light sources.

- (a) UVA phototesting demonstrated a minimal whealing dose of 12 J/cm². The UVB phototesting result was negative for urticarial reaction. (b) Visible light emitted from the slide projector induced wheals upon 20 minutes of exposure.

Figure 2.

Demonstration of action spectrum and inhibition spectrum using glass filters.

(a)–(c) Prominent urticarial reaction was induced by slide projector irradiation through a Y-45 glass filter, and a less prominent wheal was induced through a Y-48 filter, whereas no wheal was observed through a Y-50 filter. (d) The area was first exposed to the action spectra. Then, the left half was shielded, and the right half was exposed to visible light with a R-60 filter. It markedly reduced the wheal reaction, although slight wheal was observed on the left half.



