

Dear Editor

Maculopapular-Type Drug Eruption Caused by Sitagliptin Phosphate Hydrate: A Case Report and Mini-Review of the Published Work

Sitagliptin phosphate hydrate (Januvia; MSD, Tokyo, Japan) is an oral hypoglycemic drug, classified as a dipeptidyl peptidase IV (DPP IV) inhibitor for patients with type 2 diabetes.¹ It is a relatively new drug that was approved in the United States of America, the European Union, and Japan in 2006, 2007, and 2009, respectively. It is currently approved in 120 countries and regions worldwide (as of March 2013). Here, we report the case of a 63-year-old woman diagnosed with maculopapular eruption caused by sitagliptin phosphate hydrate, and review this case together with 4 cases reported in the English language literature.

A 63-year-old Japanese woman was referred to our department for diagnosis of pruritic eruptions on the trunk and extremities. She stated that she had taken glimepiride (Amaryl; Sanofi, Tokyo, Japan), voglibose (Basen; Takeda Chemical Industries, Osaka, Japan), and metformin hydrochloride (Metgluco; Dainippon Sumitomo Pharma, Osaka, Japan) for 10 years and sitagliptin phosphate hydrate for 4 months for type 2 diabetes mellitus, and pravastatin sodium (Mevalotin; Daiichi Sankyo, Tokyo, Japan) for 1 year for hyperlipemia. Three months before her first visit to our department, she noticed the eruptions. At her former hospital, she was started on prednisolone 15 mg/day for 4 days followed by 10 mg/day for 7 days. In an in-

itial physical examination at our department, erythematous and maculopapular lesions were present on the trunk and extremities (Fig. 1a, b), but there were no mucosal lesions associated with Stevens-Johnson syndrome. Based on the medical history, drug eruption caused by sitagliptin phosphate hydrate was suspected. Administration of sitagliptin phosphate hydrate was discontinued. A skin biopsy obtained from an erythematous papule on the back showed liquefaction degeneration at the dermal-epidermal interface, slight edema in the upper dermis, and mild lymphocytic infiltrate with admixed eosinophils around small vessels in the upper dermis, but there were no specific findings from the middle dermis to the fatty tissue (Fig. 1c). Laboratory tests, including complete blood cell count and liver and kidney functions, were within normal limits. Elevated hemoglobin A1c level (8.4%; normal range, 4.6-6.2) was seen. The prednisone dose was decreased to 5 mg/day and oral administration of olopatadine hydrochloride (10 mg/day) and topical application of 0.05% difluprednate were started. After 12 days, the prednisone was discontinued. The pruritic eruptions disappeared in 1 month after discontinuation of sitagliptin phosphate hydrate. A positive lymphocyte transformation test (LTT) reaction (stimulation index 2.0; normal <1.8) with sitagliptin phosphate hydrate was obtained using blood samples taken 7 days after discontinuation of oral prednisolone. We diagnosed this case as maculopapular-type drug eruption caused by sitagliptin phosphate hydrate.

In addition to this case, there have been 4 reports of drug eruption caused by sitagliptin phosphate hydrate in the literature (Table 1).¹⁻⁴ The patients (2 males and 3 females) were aged 59 to 66 years (mean

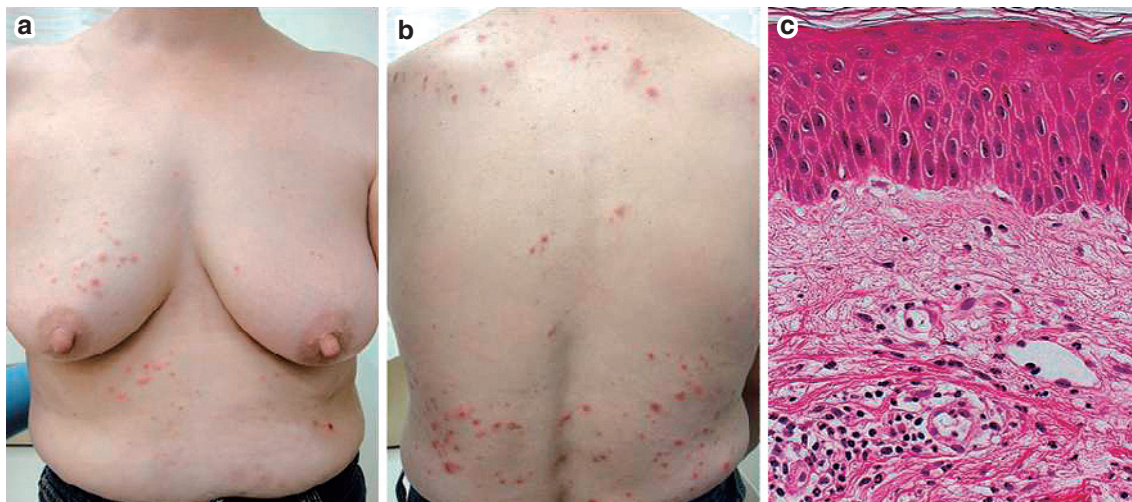


Fig. 1 Clinical photographs (a, b) and histopathological study (c). (a, chest and abdomen; b, back) At first visit. (c) The histopathological findings were consistent with maculopapular eruption (hematoxylin and eosin staining; original magnification $\times 200$).

Table 1 Cases of sitagliptin phosphate hydrate-induced drug eruption.

Ref.	Case no	Year	Age	Sex	Underlying disease	Clinical manifestations	Time interval [‡]	Was sitagliptin stopped?	Treatment	RP	LTT	Patch test	Oral challenge test	Re-currence
1	1	2012	62	F	DM type 2, HT	MPE	15 d	Yes	Topical steroid	1 w	-	-	ND	nw
2	2	2012	66	M	DM type 2, Urticaria	Generalized skin eruption	6 m	Yes	Oral steroid, Topical steroid	1 m	-	nw	nw	nw
3	3	2012	65	M	DM [†]	Persistent edematous-plaque photosensitivity	2 w	Yes	Prevention of light transmittance	2 y	nw	-§	nw	nw
4	4	2012	59	F	DM type 2, HT, Sarcoidosis	Psoriasiform eruption	6 d	No	Topical steroid	3 w	nw	nw	nw	-
Our case	5	2013	63	F	DM type 2, Hyperlipemia	MPE	1 m	Yes	Oral steroid, Topical steroid, Oral antihistamine	1 m	+	ND	ND	-

[†]Detailed information is not described in the case report.

[‡]Time interval between start of sitagliptin phosphate hydrate and onset of symptoms.

[§]Photopatch test.

d, day; DM, diabetes mellitus; F, female; HT, hypertension; LTT, lymphocyte transformation test; M, male; m, month; MPE, maculopapular eruption; ND, not done; nw, not written; Ref, reference; RP, recovery period; w, week; y, year.

63.0, median 63.0 years) and 4 patients had used sitagliptin phosphate hydrate for treatment of type 2 diabetes mellitus. Types of eruptions included psoriasiform eruption, generalized skin eruption, persistent edematous-plaque photosensitivity, and maculopapular eruption. Time interval between start of sitagliptin phosphate hydrate and onset of symptoms ranged from 6 days to 6 months, but it was ≤ 1 month in 4 of the 5 patients, suggesting that the drug eruption may commonly occur within a relatively short period of time after intake of sitagliptin phosphate hydrate. In 4 of the 5 patients, the sitagliptin phosphate hydrate was discontinued. The drug eruptions resolved within 1 month, except for one patient with persistent edematous-plaque photosensitivity. In one patient reported by Mas-Vidal *et al.*,⁴ the psoriasiform eruption caused by sitagliptin phosphate hydrate resolved in 3 weeks after starting topical steroid without stopping the causative drug, suggesting that an eruption might disappear despite continuance of a causative drug. The eruptions were mainly treated with topical steroids, oral steroids, and oral antihistamines. In one patient reported by Stricklin *et al.*,³ prevention of light transmittance was effective for treatment of the eruption. LTT with sitagliptin phosphate hydrate was positive in 1 of 3 evaluable cases, and negative patch test results were reported in 2 evaluable cases. There was no useful information from the oral challenge test. In 2 evaluable cases, no eruption recurrence was seen.

Desai *et al.*⁵ summarized sitagliptin-associated drug allergy from initial marketing of sitagliptin in October 16, 2006, through November 24, 2008, in the Adverse Event Reporting System database of the

Food and Drug Administration. Twenty six serious skin reactions including 2 cases of Stevens-Johnson syndrome and 2 cases of toxic epidermal necrolysis, 15 anaphylaxis, 4 angioedema, and 3 cutaneous vasculitis were confirmed.

In our case, the drug eruption caused by sitagliptin phosphate hydrate was diagnosed based on a positive LTT result. However, in other reports, the diagnosis was based on the medical history, eruption, and clinical course. This case is the first report of drug eruption caused by sitagliptin phosphate hydrate with a positive LTT. It is still unclear whether allergy tests, including LTT and patch test, are useful or not because there have been only a limited number of reported cases. In our case, the drug eruption may have been caused by a type IV allergic reaction based on a positive LTT result. DPP IV is expressed on B and natural killer cells, and a specific set of T cells after activation. It is also expressed on a restricted subpopulation of dendritic cells in lymph nodes draining the skin and intestine.⁶ Therefore, DPP IV inhibitor might modulate immune responses. Therefore, further accumulation of data and careful observation of the clinical course are required to improve the understanding of drug eruption caused by sitagliptin phosphate hydrate. This case also illustrates the importance of medical practitioners being aware of sitagliptin phosphate hydrate as a potential cause of drug eruption.

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