

RESEARCH LETTERS

Sitagliptin-Associated Drug Allergy: Review of Spontaneous Adverse Event Reports

Sitagliptin (Januvia; Merck and Co Inc, Whitehouse Station, New Jersey) was the first dipeptidyl peptidase-4 inhibitor (DPP-4) to gain approval from the Food and Drug Administration (FDA) in October 2006 for the treatment of type 2 diabetes mellitus.¹ In October 2007, approved labeling for sitagliptin was updated to note the appearance of spontaneous adverse event reports of hypersensitivity reactions (ie, anaphylaxis, angioedema, serious skin reactions) and noted that most reported events occurred within the first 3 months after initiation of treatment, including some following the first dose.¹ The objective of our study was to construct a case series of sitagliptin-associated allergic reactions within an empirical model for the assessment of events consistent with drug allergy.

Methods. The Adverse Event Reports System (AERS) database of the FDA was searched for all reports of potential drug allergy (including domestic and foreign reporters) with outcomes of (1) death, (2) life-threatening conditions, (3) disability, (4) hospitalization, or (5) intervention required to prevent permanent impairment. Reports of drug allergy occurring within 6 weeks following the initiation of sitagliptin therapy that suggested at least a *possible* causal relationship between the adverse event and sitagliptin use, as described in the World Health Organization (WHO) criteria,² were retained as cases. Previously published criteria were modified for classification of cases into 1 of the following 4 categories to build case definitions suitable for examination of spontaneous adverse event reports, which frequently have partial or limited information. Explicit inclusion and exclusion criteria for each category are outlined as follows:

- **Anaphylaxis:** We defined anaphylaxis as any unexplained episode of hypotension or respiratory compromise with or without angioedema or a clinical diagnosis by a health care professional. Reports that were confounded by a major concurrent illness were excluded.

- **Angioedema Without Upper Airway Obstruction/Symptomatology:** Patients who rapidly developed unexplained swelling of skin or mucosa without any signs of respiratory compromise were included under this category. We excluded reports of anaphylaxis and angioedema that were confounded by concomitant use of antibiotics or in which therapy with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker was started within 1 month of onset of the hypersensitivity reaction, since these drugs most commonly cause angioedema during this period.

- **Serious Skin Reactions:** Reports of Stevens-Johnson syndrome or toxic epidermal necrolysis diagnosed by a health

care professional and bullous, desquamative, blistering, exfoliative, urticarial, or exanthematous skin reactions were classified as cases. We excluded those cases that included the following concomitant therapies: antibiotics, carbamazepine, barbiturates, phenylbutazone, piroxicam, allopurinol, amithiozone, nevirapine, and lamotrigine because these agents are frequently cited as causes of Stevens-Johnson syndrome or toxic epidermal necrolysis.

- **Hypersensitivity Vasculitis:** Reports were included as cases within this category based on a clinical diagnosis of vasculitis primarily involving skin by a reporting clinician. This definition was based on diagnostic criterion for diagnosis of hypersensitivity vasculitis established by the American College of Rheumatology.³ Reports with concomitant therapy with antibiotics, phenytoin, or allopurinol or a concurrent diagnosis of hepatitis B, hepatitis C, human immunodeficiency virus, and chronic bacteremia were excluded.

Because there is no consensus regarding timing of allergic reactions with regard to initiation of drug treatment, we further categorized cases based on time to onset.

Results. From initial marketing of sitagliptin in October 16, 2006, through November 24, 2008, the AERS database contained 186 reports that satisfied the specified search criteria. After reviewing each report, 48 reports satisfied all predefined criteria for inclusion and exclusion as cases. Among the 48 cases, 38 cases were from the United States and 10 cases were from foreign sources. Selected demographic and clinical attributes are given in the **Table** (stratification by primary symptom category [$n=4$]), and the **Figure** (report count by latency). Twelve reports (25%) noted a history of allergy to other drugs, including 9 cases with penicillin allergy. Most of the cases were reported by physicians (33 cases) and other health care providers, such as pharmacists and nurses (11 cases).

Although there were no deaths, among all 48 cases in this case series, 37 (77%) were hospitalized because of the hypersensitivity reaction and 4 (8%) required ventilator support, intensive care unit treatment, or use of pressors to maintain blood pressure. Fourteen case reports noted that steroids were administered for treatment. Five cases reported recurrence of reaction on resuming sitagliptin therapy. Reporters noted that the reaction resolved in 36 cases (75%) after the withdrawal of sitagliptin. Based on WHO criteria for causality,² 5 cases were classified as "certain," 30 as "probable," and 13 as "possible" in relation to sitagliptin use.

Comment. This review of spontaneous adverse event reports includes 48 cases consistent with drug allergy associated with the use of sitagliptin. There are several potential limitations in our study. First, owing to the voluntary nature of reporting, spontaneous adverse event reporting systems, which were used to collect cases for this study, have numerous biases, and the information content or quality is highly variable.⁴ Such systems are designed to collect rare and serious events and remain important tools for drug regulation. Second,

Table. Patient Characteristics Stratified by Primary Symptoms Category^a

Characteristic	Serious Skin Reactions	Anaphylaxis	Angioedema Without Upper Airway Obstruction/Symptomatology	Vasculitis
Cases, No. (%)	26 (54)	15 (31)	4 (9)	3 (6)
Age				
Mean, y	65	64	40 ^b	59
Median (range), y	67 (41-87)	65 (38-84)	40 (40-40)	57 (55-66)
Sex				
Male	13	6	1	1
Female	12	9	2	2
Unknown	1	0	1	0
Onset of symptoms from initiation of therapy				
Mean, d	14	8	10	18
Median (range), d	13 (0-30)	5 (0-40)	7 (0-25)	14 (9-30)
Dose,				
25 mg	1	0	0	0
50 mg	3	0	0	0
100 mg	14	12	2	3
Unknown	8	3	2	0
Hospitalization				
Hospitalized	23	8	3	3
Not hospitalized	2	7	1	0
Unknown	1	0	0	0
Type of reaction (No. of patients)	SJS (2), TEN (2), other (22)	With angioedema (5), without angioedema (9), hypotension (1)	Swelling of tongue (2), face (1), and hand (1)	Cutaneous vasculitis (3)
Resolution				
Resolved	17	15	3	1
Unresolved	6	0	0	2
Unknown	3	0	1	0

Abbreviations: SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

^aData are given as number of patients unless otherwise specified.

^bOnly 1 of 4 cases reported age.

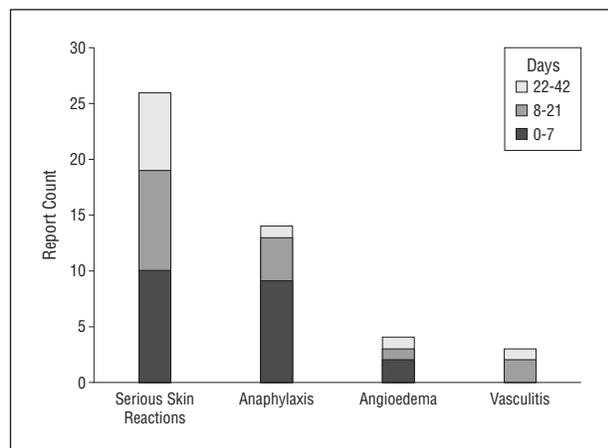


Figure. Distribution of report count by latency (median time to onset from initiation of therapy) by symptom category.

the case definitions used in this case series were modified from current clinical case definitions. This raises concerns about inadvertently including or excluding potential cases and the introduction of misclassification bias into the case series. To address this issue, we independently reviewed all case reports and included only those for which there was agreement among the authors. Also, we identified common confounders for each diagnosis and included those within each case definition as exclusion criteria.

Definite pathogenesis of allergic reactions in patients taking sitagliptin is unknown. The DPP-4 molecule is expressed on certain subsets of CD4 and CD8 T cells, B cells, and natural killer cells. Lymphocyte activation leads to up-regulation of DPP-4 enzyme.⁵ These data raise concerns that DPP-4 inhibitors could modulate immune function, though there is presently no definite evidence for this hypothesis.

In conclusion, spontaneous adverse event reports of allergic reactions among patients taking sitagliptin received to date are characterized by serious morbidity. More studies are needed to determine incidence and predisposing factors for allergic reactions in patients taking sitagliptin.

Shrey Desai, MD, MPH
 Allen Brinker, MD, MS
 Joslyn Swann, PharmD
 Solomon Iyasu, MD, MPH

Author Affiliations: Community Health Project, SEWA-Rural (Society for Education, Welfare and Action-Rural), Jhagadia, Gujarat, India (Dr Desai); and Division of Drug Risk Evaluation, Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, Maryland (Drs Brinker, Swann, and Iyasu).

Correspondence: Dr Desai, SEWA-Rural, Jhagadia, District Bharuch, Gujarat State 393110, India (sdesai1977@yahoo.com).

Author Contributions: Study concept and design: Desai, Brinker, and Iyasu. Acquisition of data: Brinker. Analysis and interpretation of data: Desai, Brinker, and Swann. Drafting of the manuscript: Desai and Brinker. Critical revision of the manuscript for important intellectual content: Desai, Brinker, Swann, and Iyasu. Statistical analysis: Desai. Administrative, technical, and material support: Brinker and Swann. Study supervision: Brinker and Iyasu.

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1. Physicians' Desk Reference. 62nd ed. Januvia (sitagliptin) tablets: Merck & Co Inc. Montvale, NJ: Thompson Healthcare Inc; 2008:1492-1499.
2. Uppsala Monitoring Centre. The use of the WHO-UMC system for standardized case causality assessment. <http://www.who-umc.org/graphics/4409.pdf>. Accessed January 20, 2009.
3. Calabrese LH, Michel BA, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of hypersensitivity vasculitis. *Arthritis Rheum.* 1990;33(8):1108-1113.
4. Sachs RM, Bortnichak EA. An evaluation of spontaneous adverse drug reaction monitoring systems. *Am J Med.* 1986;81(suppl 5B):49-55.
5. Lambeir A-M, Durinx C, Scharpé S, De Meester I. Dipeptidyl-peptidase IV from bench to bedside: an update on structural properties, functions and clinical aspects of the enzyme DPP IV. *Crit Rev Clin Lab Sci.* 2003;40(3):209-294.

Physical Activity at Midlife and Health-Related Quality of Life in Older Men

A recent study in the *Archives*¹ investigated associations of midlife physical activity and health status in older age, and the results showed a strong association between midlife leisure time physical activity and successful survival and exceptional health status in later life. However, this cohort was limited to women, and although health-related quality of life (HRQoL) was assessed with the 36-Item Short-Form Health Survey (SF-36), these results were not reported. Because the SF-36, with its 8 domains, may give detailed information of the effects of physical activity on both physical and mental dimensions in old age aspects, we investigated long-term associations between leisure-time physical activity in midlife and HRQoL in old age in the Helsinki Businessmen Study.²

See Invited Commentary at the end of this letter

Methods. In 1974, clinically healthy middle-aged men (born in 1919-1934; median age, 47 years) of similar socioeconomic status were assessed with questionnaires and clinical and laboratory examinations as described previously.² The men were asked how they rated their present health on a 5-step scale ("very good," "good," "fair," "poor," and "very poor"), and a global description of leisure time physical activity was assessed with the following 4-step scale:

1. Activity mainly reading, watching television, or other sedentary activity.

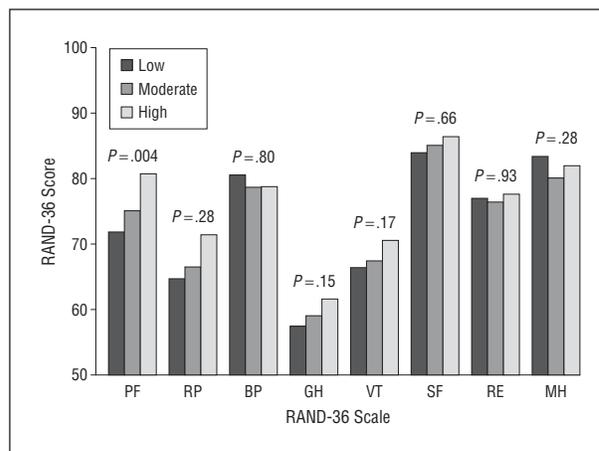


Figure. RAND-36 scores in old age in the year 2000 (n=552) according to leisure time physical activity (low, intermediate, or high) in healthy middle-aged men (in 1974). The scores are adjusted for age, smoking, self-rated health at baseline, and Charlson comorbidity index in old age. Numbers above bars denote P values between physical activity groups. BP indicates body pain; GH, general health; MH, mental health; PF, physical function; RE, role emotional; RP, role physical; SF, social function; VT, vitality.

2. Walking, cycling, gardening, or other light exercise weekly.
3. Jogging, skiing, tennis, or similar exercise weekly on a regular basis.
4. Regular vigorous/competitive exercise several times a week on a regular basis.

Details of physical activity were available for 782 clinically healthy men with various cardiovascular risk factors. Men answering yes to question 1 were categorized as low activity (n=148); yes to question 2, as moderate activity (n=398); and yes to questions 3 and 4, as high activity (n=236 [among whom only 11 men had a competitive activity level]). After a 26-year follow-up in 2000 (median age, 73 years; range, 66-81 years), 552 men (91% of survivors at that time [deaths were verified from the Central Population Register]) could be reassessed using a mailed questionnaire. The questionnaire included queries about anthropometric measures, housing, prevalence of chronic diseases, medication, and lifestyle factors. The Finnish version of the RAND-36 Item Health Survey 1.0, which is practically the same as SF-36 and validated in the Finnish population,³ was embedded into the questionnaire. From the responses, a summary comorbidity index was also assessed according to the method of Charlson et al.⁴ The 8 domains of RAND-36 were physical function, role physical, bodily pain, general health, vitality, social function, role emotional, and mental health. Analyses were performed using NCSS 2004 statistical software (NCSS, Kaysville, Utah). Analysis of covariance was used to compare baseline activity groups, and $P < .05$ was considered statistically significant.

Results. In 2000, men with a low physical activity in midlife reported significantly higher prevalences of coronary artery disease ($P = .02$), cerebrovascular disorders ($P = .046$), and chronic obstructive pulmonary disease ($P = .04$). Of the adjusted HRQoL scales in old age (in the year 2000), only physical function was significantly related to physical activity in midlife (**Figure**). Further adjustment for individual diseases (history of coronary ar-