Risk of Myopathy Associated With DPP-4 Inhibitors in Combination With Statins: A Disproportionality Analysis Using Data From the WHO and French Spontaneous Reporting Databases

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Recently, a pharmacovigilance safety warning was released by the European Medicines Agency concerning the risk of myopathy and rhabdomyolysis associated with the use of dipeptidyl peptidase 4 (DPP-4) inhibitors (1,2). The warning was based on several cases in which DPP-4 inhibitors were used in association with statins; a drug-drug interaction was suggested (3). As statin use is likely to be common in patients with diabetes, it is important to investigate this potential serious risk and the underlying drug-drug interaction hypothesis. This need is enforced by the recent marketing in several countries of fixed combinations containing both statins and DPP-4 inhibitors (4). The aim of the study, therefore, was to assess the association between myopathy and the use of DPP-4 inhibitors, alone and in combination with statins, by analyzing data from two pharmacovigilance spontaneous reporting databases.

Data from the French Base Nationale de Pharmacovigilance (BNPV) and the World Health Organization (WHO) global individual case safety reports database, VigiBase, were analyzed for the 2009–2015 time period. Cases consisted of all reported adverse drug reactions (ADRs) of muscular injury, which were identified in both databases by using the dedicated Standardized MedDRA Queries ("myopathy/rhabdomyolysis"). All reports of other ADRs were considered noncases. The exposures of interest were the use of DPP-4 inhibitors along with statins at the time the ADR occurred, as we were investigating a potential drug-drug interaction between DPP-4 inhibitors and statins. We conducted complementary analyses considering exposures to all noninsulin antidiabetes agents other than DPP-4 inhibitors and to fibrates. As other noninsulin antidiabetes agents share indications with DPP-4 inhibitors, the absence of an association between those drugs and myopathy would argue against a potential indication bias in which DPP-4 inhibitors might seem to be associated with myopathy owing to specific susceptibility among patients with type 2 diabetes; the same would hold true for fibrates, statins, and patients with dyslipidemia as a background influence.

In the BNPV, disproportionality analyses based upon the case/noncase approach were performed (5). Unconditional logistic regression was used to derive reporting odds ratios (RORs) adjusted for age, sex, use of glucose-lowering drugs (DPP-4 inhibitors or other noninsulin antidiabetes agents), and use of lipid-lowering drugs (fibrates or statins) for each drug combination being evaluated. The likelihood that a given ADR resulted from a suspected drug-drug interaction was estimated by the ROR value for the drug combination being evaluated. According to the interaction additive model (6), a ROR value for coexposure that exceeds the sum of the RORs estimated for each individual class of drug supports a potential drug-drug interaction.

In VigiBase, analyses used the Bayesian estimators specifically developed by the WHO Uppsala Monitoring Centre for this database: the information component for evaluating the association between a given ADR and an individual drug and the omega value for estimating the relationship between a given ADR and a drug combination.

In BNPV, the use of DPP-4 inhibitors without statins and without fibrates was significantly associated with reports of myopathy. Conversely, no increase in reports of myopathy was found for other noninsulin antidiabetes agents in the same conditions. Assessment of drug-drug interaction showed an increase in reports of myopathy for the concomitant use of DPP-4 inhibitors and statins, but it was lower than that found for statins alone and thus did not support a potential drug-drug interaction according to the additive model (Table 1). In this database, concomitant use of DPP-4 inhibitors and statins had been reported in 19 ADR cases (12 were serious, 4 of them associated with renal

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Table 1—Crude and adjusted RORs for the risk of myopathy associated with the use of antidiabetes agents and lipid-lowering agents, separately and in combination, according to data in the BNPV

Drug-drug interaction of interest	Exposure	Cases* (N = 3,252)	Noncases (N = 187,035)	Crude ROR (95% CI)	Adjusted† ROR (95% CI)
DPP-4is and statins	No DPP-4is, no statins	2,452	174,582	ref	ref
	DPP-4is, no statins	23	1,099	1.5 (1.0–2.3)	2.1 (1.3–3.3)
	Statins, no DPP-4is	758	10,850	5.0 (4.6–5.4)	6.2 (5.7–6.8)
	DPP-4is and statins	19	504	2.7 (1.7–4.3)	4.5 (2.7–7.6)
DPP-4is and fibrates	No DPP-4is, no fibrates	3,140	184,153	ref	ref
	DPP-4is, no fibrates	39	1,553	1.5 (1.1–2.1)	1.6 (1.1–2.4)
	Fibrates, no DPP-4is	70	1,272	3.2 (2.5–4.1)	4.4 (3.4–5.6)
	DPP-4is and fibrates	3	57	3.1 (1.0–9.9)	6.3 (1.9–20.7)
nAOs and statins	No nAOs, no statins	2,416	169,809	ref	ref
	nAOs, no statins	59	5,872	0.7 (0.5–0.9)	0.6 (0.4–0.8)
	Statins, no nAOs	697	9,095	5.3 (5.0–5.9)	6.3 (5.7–6.9)
	nAOs and statins	80	2,259	2.5 (2.0–3.1)	2.7 (2.1–3.5)
nAOs and fibrates	No nAOs, no fibrates	3,048	177,837	ref	ref
	nAOs, no fibrates	131	7,869	1.0 (0.8–1.2)	0.5 (0.4–0.6)
	Fibrates, no nAOs	65	1,067	3.6 (2.8–4.6)	4.5 (3.5–5.5)
	nAOs and fibrates	8	262	1.8 (0.9–3.6)	1.8 (0.9–3.8)

DPP-4is, DPP-4 inhibitors; nAOs, noninsulin antidiabetes agents other than DPP-4is. *Cases of myopathy. †Adjusted for age and sex, statins or fibrates depending on the lipid-lowering exposure of interest, and DPP-4is or nAOs depending on the glucose-lowering exposure of interest.

failure). The mean age of the patients was 68 years, and 57.9% were women. Most reported cases occurred in patients using sitagliptin with atorvastatin or rosuvastatin.

In VigiBase, use of DPP-4 inhibitors was also associated with the risk of myopathy, as indicated by positive values for the information component and the lower limit of 95% CI, in contrast to the use of other noninsulin antidiabetes agents. All omega values and lower 95% CI limits were negative, indicating no potential drug-drug interactions.

These results showed a significantly increased risk of reports of myopathy for DPP-4 inhibitor use that was not found for other noninsulin antidiabetes agents; there was no evidence of an interaction between DPP-4 inhibitors and statins. Consistent findings in both databases support a potential intrinsic muscular toxicity of DPP-4 inhibitors. Indeed, existing knowledge of the metabolic and pharmacokinetic characteristics of these drugs does not support a potential drug-drug interaction; some studies actually showed no difference in either statins' pharmacokinetic parameters after administration of DPP-4 inhibitors or DPP-4 inhibitors' parameters after statin administration (7).

The study suffers from some limitations inherent to analyses of spontaneous reporting data, most of them deriving from a presumed selective underreporting (8). Even if adjusting for age, sex, and comedications by using multivariable logistic regression controlled for important potential confounders, this probably would not be sufficient to neutralize the likely effect of factors such as comorbidity, dose, and duration of exposure, which are seldom recorded in pharmacovigilance databases. In this context, it was important to perform complementary analyses to study whether patient background could have affected the probability of ADR reports for drugs indicated in type 2 diabetes. The negative results found for other noninsulin antidiabetes agents did not support the existence of such indication bias. An important strength of this study is the combined use of two databases and the consistency of the results between them. The BNPV has the distinction of containing medically validated information; VigiBase presents the obvious advantage of being representative of the worldwide real-life use of drugs.

To date, the literature provides little information on the potential mechanism that could underlie the muscular toxicity of DPP-4 inhibitors. It is suggested that these drugs may have pleiotropic effects and be implicated in lipid synthesis (9,10); if so, the mechanism could involve the cholesterol synthesis pathway, similar to that suspected for statins or fibrates.

This study confirms a potential muscular toxicity of DPP-4 inhibitors and advocates for pharmacoepidemiological studies to be conducted in order to further explore this potential risk. Meanwhile, physicians and patients should remain vigilant concerning this putative risk, regardless of whether DPP-4 inhibitors are used in combination with statins.

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