Evaluation of reporting risk for myopathy using the Italian Adverse Drug Reaction Spontaneous Reporting Database: proton pump inhibitors and their interaction with statins

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Muscular adverse reactions are well known adverse effects of statins. A weaker evidence exists also about the potential association between exposure to proton pump inhibitors (PPIs) and development of myopathies. Current knowledge rises the hypothesis that a treatment with PPIs might enhance the risk of developing drug-induced muscular injuries in patients receiving statins. This study was performed to assess the risk of muscular adverse reactions due to PPIs, either in the absence or in the presence of concomitant treatment with statins, in the Italian pharmacovigilance system database. A case/non-case analysis was performed using spontaneous reports collected in the Italian Adverse Drug Reaction (ADRs) Spontaneous Reporting Database between January 1988 and July 2014. Cases were identified by reports containing at least one muscular ADR. Reports of severe myopathies (MedDRA important medical event, IME) and rhabdomyolysis were also considered for a sub-analysis. Non-cases were defined as all reports containing ADRs other than muscular ones. The reports were divided in three index groups: 1) patients exposed to PPIs (omeprazole, pantoprazole, lansoprazole, esomeprazole, rabeprazole) but not statins; 2) patients exposed to statins (lovastatin, simvastatin, fluvastatin, pravastatin, cerivastatin, atorvastatin, rosuvastatin) but not PPIs; 3) patients exposed to both PPIs and statins. The reference group consisted of patients using neither PPIs nor statins. For comparison of the index and reference groups, the reporting odds ratio (ROR) was used as a measure of reporting risk. The analysis was carried out on 255,548 reports. RORs were adjusted for age, gender and drugs known to interact with statins. The adjusted RORs (aRORs) of muscular ADRs (myopathy, IME and rhabdomyolysis) for each index group are displayed in the Table. When considering single PPIs, the reporting risk of rhabdomyolysis was significant for lansoprazole (aROR:2.687, 95%CI:1.778-4.062, P<0.001) and omeprazole (aROR:1.996, 95%CI:2.027-4.428, P<0.001). The combinations atorvastatin-omeprazole (aROR:13.309, 95%CI:8.036-22.042, P<0.001) and pravastatin-esomeprazole (aROR:14.543, 95%CI:1.927-109.754, P<0.01) were associated with an increased aROR for rhabdomyolysis, as compared to the respective statin alone (atorvastatin aROR:11.967, 95%CI:9.377-15.273, P<0.001; pravastatin aROR:11.474, 95%CI:7.218-28.238, P<0.001). This preliminary study suggests that the class of PPIs is involved in reports of myopathy, rather than any other adverse drug reaction, more frequently than any non-statin drug. When considering specific PPIs, only omeprazole and lansoprazole displayed a significant aROR for rhabdomyolysis. Concomitant treatments with statins and PPIs do not appear to enhance the aROR of myopathy associated with statins, with the exception of the combinations atorvastatin-omeprazole and pravastatin-esomeprazole. Further studies are required to confirm the signal.

Table. Adjusted ROR for the occurrence of muscular adverse reactions in the Italian Adverse Drug Reaction Spontaneous Reporting Database between January 1988 and July 2014.

	Statins no PPIs Adjusted[a] ROR (95% CI)	**PPIs no statins** Adjusted[b] ROR (95% CI)	**Statins and PPIs** Adjusted[a] ROR (95% CI)
Myopathy	20.762 (19.445-22.167)*	1.237 (1.101-1.389)*	3.898 (3.366-4.514)*
IME	14.499 (12.355-17.014)*	1.851 (1.427-2.401)*	6.256 (4.704-8.318)*
Rhabdomyolysis	15.973 (13.511-18.884)*	2.125 (1.630-2.770)*	6.803 (5.078-9.114)*

[a]Adjusted for age, gender and drugs known to interact with statins
[b]Adjusted for age and gender
*p<0.001
CI: confidence interval; IME: important medical event; ROR: reporting odds ratios