MUSCULAR ADVERSE DRUG REACTIONS ASSOCIATED WITH PROTON PUMP INHIBITORS: A DISPROPORTIONALITY ANALYSIS USING THE ITALIAN NATIONAL NETWORK OF PHARMACOVIGILANCE DATABASE

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In 2001, after cerivastatin marketing withdrawal due to fatal cases of rhabdomyolysis (Staffa, Chang et al. 2002), statins represent the drug class most commonly associated with muscular adverse drug reactions (ADRs) (Conforti, Chiamulera et al. 2007). However, other drugs have been related to moderate and severe myopathies, including proton pump inhibitors (PPIs) (Clark and Strandell 2006). Unfortunately, these potential signals may be under-detected due to the masking effect of statins. To the best of our knowledge, disproportionality analysis on potential signals of muscular ADRs with PPIs are lacking. The aim of this study was to assess the reporting risk of muscular ADRs with PPIs on spontaneous reports recorded in the Italian National Network of Pharmacovigilance (Rete Nazionale di Farmacovigilanza - RNF) database. A case/non-case analysis, using data collected from July 1983 to May 2016, was performed. Published case reports, reports on adverse events following immunization (AEFI), low-quality reports and duplicate reports were excluded (Yue, Shi et al. 2014). Cases were identified by reports containing at least one muscular ADR. Non-cases were defined as all reports containing only ADRs other than muscular ones. In the primary analysis, reports where at least one PPI was considered the suspected drug(s) were classified as index reports. All other reports were included in the reference group. Reporting odds ratio (ROR) and 95% confidence intervals (CIs) were calculated as a measure of reporting risk (Piccinni, Gissi et al. 2015). A sub-analysis was performed only on reports that included rhabdomyolysis in the group of cases. In a secondary and tertiary analysis, we explored the association of PPIs with muscular ADRs after taking into account the masking effect (Maignen, Hauben et al. 2014) of statins. After unmasking, i.e. the exclusion of reports with statins as suspected drugs and the inclusion of cases with at least one PPI (both suspected and concomitant role), the RORs for the association of muscular ADRs with PPIs were calculated. Moreover, a possible interaction between PPIs and statins was also tested. RORs were adjusted by logistic regression including age, gender, number of drugs and thyroid diseases among co-variates. A total of 274,108 reports were analysed. In the primary analysis, the RORs of muscular ADRs for PPIs, adjusted for age and gender, was 1.484 (95%CI: 1.204-1.829; $p<0.001$), whereas the adjusted ROR for rhabdomyolysis was 0.621 (95%CI: 0.258-1.499). In the secondary analysis, after unmasking, similar results were obtained (adjusted ROR 1.200; 95%CI: 0.447-3.224). A potential association of PPIs with rhabdomyolysis was detected in the tertiary analysis, where PPIs were considered independently from their suspected or concomitant role (adjusted ROR: 1.667, 95%CI 1.173-2.369; $p<0.01$). No potential signal with PPI-statin interaction and muscular ADR/rhabdomyolysis was observed. The present study shows a potential signal of disproportionate reporting for muscular ADRs related to the overall class of PPIs. This disproportion was enhanced in the secondary analysis, where the eventual size of the masking effect of statins was confirmed. Notably, in the

present analysis the RORs of rhabdomyolysis did not reach the minimum criteria for signal detection. Only in the tertiary analysis, the frequency of rhabdomyolysis related to PPIs was higher than any other ADRs, when compared to reports not including PPIs or statins. Given the limitations of the tertiary analysis, this finding should be confirmed by further investigations.

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