Interactions between vaccines against influenza and drugs for chronic diseases: the analysis of the Vaccine Adverse Event Reporting System (VAERS) and VigiBase

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Annual vaccination against influenza is the primary means of preventing influenza and its complications in fragile patients i.e. children, pregnant women, elderly and patients with chronic disorders. The most frequently reported Adverse Events (AEs) include reversible local pain or tenderness, fatigue and fever (Whalley et al., 2011). However, an increasing number of reports suggests that vaccines against influenza may influence drug metabolism, through the release of inflammatory cytokines modifying cytochrome activity in the liver leading to significant changes in serum concentrations of specific drugs (Pellegrino et al., 2014). This issue is of particular importance for largely-used drugs administered chronically in poly-treated patients, as warfarin or direct-acting oral anticoagulant (DOACs), anticonvulsants and statins, for which frequent monitoring of interactions with vaccination is not likely to be feasible in clinical practice (Khuo et al., 2012; Diaz et al., 2008; Shah et al., 2010). To date, the impact and the AEs characteristics of vaccine-drug interactions observed in the real world clinical practice have not been investigated.

The aim of the study is to explore this pharmacological hypothesis and preliminary assess the clinical significance of these interactions, trough the case-by-case analysis of the AEs reports from the VAERS database (collecting data on vaccine-related AEs) and the WHO-Vigibase, recording worldwide reports on drug-related adverse events, including vaccines.

We collected Adverse Event Following Immunization (AEFI) reports for individuals receiving all available types of vaccines against the influenza virus, recorded as a suspect in the AEFI submitted to VAERS (from 1990 to 2016) and VigiBase (from 2009 to 2016). Data related to a suspect increased toxicity of interacting drugs (statins and DOACs) with influenza vaccines were retrieved through the Standard MedDRA Queries for “haemorrhages” and “rhabdomyolysis/myopathy”, applying a narrow search for specificity of case retrieval. The reports of the suspect increased toxicity of antiepileptics were searched using a pre-specified list of signs and symptoms related to anticonvulsant overdose. We applied the established criteria for AEFI causality and the validated Algorithm to assess drug-drug interactions (Drug Interaction Probability Scale-DIPS).

Of 132.739 AEFI reports submitted to VAERS related to influenza vaccines, 110 were included in our analysis since likely to be related to an increased drugs toxicity (16 reports involved statins therapy, 16 anticonvulsant and 78 DOACS and/or warfarin). Statins and anticonvulsants were related to the highest number of indeterminate (68.7%; 81.3%) and possible/probable (62.5%; 50.1%) cases according to the AEFI and DIPS, respectively. Of importance, the majority of cases occurred within the first week after vaccine administration (5-7 days), i.e. the estimated time interval within which the vaccine induces dysregulation of inflammatory cytokines on CYP regulation. 83 reports from Vigibase were also included in our analysis (12 were related to statins,

12 to anticonvulsant and 42 to warfarin/DOACs) supporting VAERS data; there was a female predominance in all validated reports, and the highest number of serious cases for reports involved statins (71.4%) and anticonvulsant (66.6%).

We have highlighted that potential interactions between influenza vaccines and drugs (most likely with anticonvulsant and statins) for chronic diseases are likely to occur, but appear to be rare, thus confirming that the overall benefit largely outweighs this risk. Considering the characteristics of cases (seriousness and onset interval) and the importance of vaccination in chronically ill and elderly patients, the risk of vaccine–drug interaction should not be disregarded, but clinical monitoring should be considered especially within the first week following vaccine administration to prevent relevant clinical effects.

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