RHEUMATOLOGY

Letter to the Editor (Matters arising from published papers)

Comment on: Risk of giant cell arteritis and polymyalgia rheumatica following COVID-19 vaccination: a global pharmacovigilance study: reply

Dear Editor, We read with great interest the comment by Manzo and Castagna [1] on our study, entitled 'Risk of giant cell arteritis and polymyalgia rheumatica following COVID-19 vaccination: a global pharmacovigilance study' [2].

Safety-monitoring activities, including spontaneous reporting of suspected adverse drug reactions (ADRs) represent a major challenge for new drugs, especially for new vaccines and are foremost during the current pandemic. There is a major need for signal detection and transparency on vaccine safety profiles, which are essential for successful completion of the mass immunization campaign [3]. Hence, pharmacovigilance's first missions are signal detection, risk assessment and risk communication, with honesty and clarity [4]. Patient stories, discussed on fora or social media, are often manipulated or falsified, and feed anti-vaxx behaviour. We do believe that scientific findings, appropriately communicated and put into perspective, are essential to counterbalance fake news and fake stories. Hence, risk assessment and appropriate risk communication have appeared essential to restoring public confidence in vaccines in the past [4].

The main limitations of pharmacovigilance studies are inability to quantify real-life incidence of ADRs, difficulty to assess drug causality and under-reporting, which has been assessed to 94% for all ADRs and 85% for serious or severe ADRs [5, 6]. Since 2021 and the starting of the mass immunization campaign, the number of cases reported to pharmacovigilance systems worldwide increased by at least 60% compared with 2020 (2 642 810 reporting cases in 2020 and 4 182 137 reporting cases in 2021, up to 25 October 2021; unpublished data). However, it is very likely underreporting is still major. Nevertheless, our disproportionality analysis, based on a case/non-case approach that is similar to the concept of case/control studies, estimates whether an adverse event of interest is differentially reported for a specific drug compared with other drugs. Unlike '*Cum hoc vel post hoc, ergo propter hoc*', as mentioned by Manzo and Castagna, association is not causality. Nevertheless, disproportionality analyses have proven their efficacy to identify pharmacovigilance signals (i.e. unknown ADRs) and to assess relative risks [7]. Our study highlights a significant association between PMR reporting and COVID-19 vaccine use, compared with the reporting of any other adverse event. Underreporting is not likely to affect this finding as it is expected be balanced between PMR cases and other ADR (non-cases). Furthermore, this association is still significant when considering only cases reported by healthcare providers.

Another limitation of pharmacovigilance studies is notoriety bias. It is well known that the spontaneous reporting of suspected adverse effects could change over time in relation with mass media interventions or scientific communications, affecting the results of disproportionality analysis [8]. Nonetheless, our study was performed before the publication on 15 August by Manzo *et al.* of the first PMR case following COVID-19 vaccination and a notoriety bias would not affect our results.

We would like to clarify a result that seems insufficiently explicit. In Table 1 of our article, the line 'second vaccine administered' presented the proportion of PMR cases occurring after the second vaccine shot, that is, 19.3%. In our analysis we have insufficient data on patients who were reported to have PMR after the first dose, regarding the outcome after the second dose, if it has been administered. Further studies would provide longitudinal follow-up.

Early identification of safety signals also helps to anticipate risk and support individual risk benefit decision making about the use of COVID-19 vaccines (e.g. thrombosis and ChAdOx1 nCov-19 vaccine). At an individual level, it helps to identify a possible adverse reaction and to provide better patient care, as well as reduce medical errancy. For instance, due to the risk of persistent vision loss in GCA, it would be prudent to encourage patients to seek urgent medical assistance in case of GCA-related symptoms following COVID-19 vaccination, such as headache with scalp tenderness, pain in the jaw after chewing and vision problems.

To conclude, as real-life studies, pharmacovigilance studies allow us to observe associations, make assumptions and generate safety signals. Cohort studies or pharmaco-epidemiological studies on large databases are needed to further assess these safety signals.

Acknowledgements

LETTER

Data availability statement

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

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