Internal and Emergency Medicine (2021) 16:799–800
https://doi.org/10.1007/s11739-021-02677-0

CE-LETTER TO THE EDITOR

Adverse drug reactions in SARS-CoV-2 hospitalised patients: a case-series with a focus on drug–drug interactions-reply

Giada Crescioli[1,2] · Cecilia Lanzi[3] · Guido Mannaioni[1,3] · Alfredo Vannacci[1,2] · Niccolò Lombardi[1,2,3]

Received: 11 February 2021 / Accepted: 15 February 2021 / Published online: 26 February 2021

Dear Editor,

We read with great interest the comment written by Pardo-Cabello and colleagues [1], replying to our original article entitled "Adverse drug reactions in SARS-COV-2 hospitalised patients: a case series with a focus on drug–drug interactions" [2] and we would like to make some comments regarding their considerations.

As the authors correctly point out, data on the overall number of patients hospitalised for COVID-19 during the study period were not available at the time of writing. For this reason, only those patients for whom a pharmacological and toxicological counselling was requested by clinicians working in COVID-19 Units were considered. Of course, knowing the overall number of patients treated, and consequently, the prevalence rate of adverse drug reactions, could improve the assessment of burden due to pharmacological treatments in COVID-19 inpatients. Currently, we are able to retrieve the total number of patients hospitalised in the COVID-19 Units during the different phases of the SARS-CoV-2 pandemic, from the last Smart Consensus Conference organised by Careggi University Hospital, Florence (Italy) available online [3]. In particular, during the first wave (I semester 2020), a total of 472 patients were hospitalised, with a mean age of 72 years and an average hospital stay of 14.2 days. Of them, 27% ($n=127$) were managed in the intensive care units, with an overall mortality of 25.6% (mean age of 77 years) [3]. Considering that all cases ($n=23$) reported in our original article were critically ill patients, managed in the intensive care units, the overall prevalence of adverse drug reactions was 18.1% (23/127). Instead, considering the total number of patients, including those not hospitalised in intensive care units, the prevalence of adverse drug reactions was 5% (23/472), which can be considered relevant as well from a clinical point of view during a pandemic emergency. Considering our study, we would like to underline four relevant aspects: (1) adverse drug reactions occurred in highly critically ill patients; (2) they all required pharmaco-toxicological consultation; (3) during the pharmaco-toxicological consultation, the drugs responsible for these adverse reactions and the underlying drug–drug interactions were identified; (4) the adverse drug reactions coincided with the effects of the drug–drug interactions. Therefore, the fact that a pharmaco-toxicological consultation was necessary to deal with adverse drug reactions and that drug–drug interactions were identified, both in the clinical toxicology evaluation phase and in the data analysis phase (through the application of the respective tools), makes these interactions real and not potential. These evidences are further strengthened by data registered during the second wave (II semester 2020) of SARS-CoV-2 pandemic. In fact, during this phase, a total of 473 patients were hospitalised, with a mean age of 67 years and an average hospital stay of 9.1 days. Of them, 19% ($n=90$) were managed in intensive care units, with an overall mortality of 15.6% (mean age of 82 years) [3]. Noteworthy, likely due to an increased knowledge of the disease, better management and more appropriate use of drugs, no pharmaco-toxicological consultations were required during this phase. In addition, the use of drugs responsible for the majority of drug–drug interactions observed in our sample during the first phase, in particular, hydroxychloroquine and antivirals, was suspended by the Italian Medicines Agency on May 29th, 2020 [4].

In conclusion, we strongly agree with the last consideration reported by Pardo-Cabello and colleagues concerning

✉ Niccolò Lombardi
niccolo.lombardi@unifi.it

1 Department of Neurosciences, Psychology, Drug Research and Child Health, Section of Pharmacology and Toxicology, University of Florence, Florence, Italy

2 Tuscan Regional Centre of Pharmacovigilance, Florence, Italy

3 Toxicology Unit and Poison Centre, Careggi University Hospital, Florence, Italy

the limitation of Naranjo's scale in the assessment of causal relationship between the suspected drugs and adverse reactions, particularly in case of patient's death. Pharmacovigilance specialists and the other healthcare professionals should always take into consideration all clinical covariates and risk factors of each patient, and this was done in our case, during the pharmaco-toxicological consultation. Nevertheless, for a better general understanding and a wide comparability between settings, Naranjo scale still plays a role, although, as stated in several pharmacovigilance studies, the scale presents numerous well-known application limits [5]. Finally, as reported in Table 2 [2], none of adverse drug reactions described in our study were assessed as "certainly" associated with the suspected drugs.

Funding The authors have received no financial support or other benefits from commercial sources for the work reported here, and the authors have no other financial interests that could create a potential conflict of interest or the appearance of a conflict of interest regarding the present study.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and animal rights statement This article does not contain any studies with humans and participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

References

1. Pardo-Cabello AJ, Manzano-Gamero V, Belda-Rustarazo S, Giner-Escobar P (2021) Adverse drug reactions in SARS-COV-2 hospitalised patients: a case series with a focus on drug–drug interactions—comment. Intern Emerg Med. https://doi.org/10.1007/s11739-021-02645-8
2. Crescioli G, Brilli V, Lanzi C et al (2020) Adverse drug reactions in SARS-CoV-2 hospitalised patients: a case-series with a focus on drug–drug interactions. Intern Emerg Med. https://doi.org/10.1007/s11739-020-02586-8
3. Careggi University Hospital (2020) Smart Consensus Conference COVID-19 AOUC. https://www.youtube.com/watch?v=9kN6eUjAFUQ&list=PLeNf4JKSus9nv8t8CkjCYup-3jgxdEEAV. Accessed 10 Feb 2021
4. Italian Medicines Agency (2020) Medicines usable for treatment of COVID-19 disease. https://www.aifa.gov.it/en/aggiornamento-sui-farmaci-utilizzabili-per-il-trattamento-della-malattia-covid19. Accessed 10 Feb 2021
5. Lombardi N, Crescioli G, Bettiol A et al (2020) Italian Emergency Department Visits and Hospitalizations for Outpatients' adverse drug events: 12-year active pharmacovigilance surveillance (the MEREAFaPS study). Front Pharmacol. https://doi.org/10.3389/fphar.2020.00412