Response to: 'Correspondence on 'Concomitant use of oral glucocorticoids and proton pump inhibitors and risk of osteoporotic fractures among patients with rheumatoid arthritis: a population-based cohort study" by Zheng

We thank Dr Zheng for his comments on our recently published article in the *Annals of the Rheumatic Diseases* entitled 'Concomitant use of oral glucocorticoids and proton pump inhibitors and risk of osteoporotic fractures among patients with rheumatoid arthritis: a population-based cohort study'.[1 2] Our main goal in this study was to bring more clinical insight into the simultaneous use of these two common medications in patients with rheumatoid arthritis (RA), that is, oral glucocorticoids (GCs) and proton pump inhibitors (PPIs), using data from a large primary care database and pharmacoepidemiological methodologies.

Our results showed that there was an interaction in the risk of osteoporotic (OP) fractures with concomitant use of oral GCs and PPIs in patients with RA. Based on the adjusted hazard ratios and according to the formula proposed by Rothman *et al*,[3] the relative excess risk due to interaction (RERI) was: 1.60 – 1.23 – 1.22 + 1 = 0.15. We now have also calculated the CIs and the statistical significance of this index using the method proposed by Hosmer and Lemeshow.[4 5] The lower and upper limits of the 95%CI of the RERI were −0.16 and 0.45, respectively, and the p value was 0.36. This means, although we observed a 15% more risk of OP fracture with concomitant use of oral GCs and PPIs in addition to the single use of each drug versus non-use of both, this additive interaction was not statistically significant.

As we discussed in our paper, there is currently no proven biological mechanism for an action of PPIs on bone or falling,[6] while the effects of GCs on bone and the musculoskeletal system are quite established. Our secondary analyses (ie, lower fracture risk with long-term or higher daily doses of PPIs compared with short-term or lower daily doses) did not support the few proposed potential mechanisms, such as hypochlorhydria and calcium malabsorption, or an increased fall risk due to malabsorption of magnesium or vitamin B_{12}. This is important to consider when interpreting a potential additive interaction between oral GCs and PPIs on fracture risk. Without this basic knowledge, it would be extremely difficult to confer any conclusions on a plausible synergistic action of these two drugs, since it would sound more as a methodological reasoning rather than a clinical explanation.

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Correction notice This article has been corrected since it published Online First. Reference 3 has been corrected.

Handling editor Josef S Smolen

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Contributors SA and JD conducted the data analysis. All authors contributed to data interpretation. SA wrote the manuscript. All authors were involved in editing or quality control. All authors are accountable for their own contribution, in addition to all aspects of the manuscript. All authors have approved the submitted version of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests JvdB reports grants from Amgen, Eli Lilly and UCB, outside the submitted work. AB received research grants to her department from Celgene and AbbVie, and speakers' fees or honoraria from Sandoz, UCB, Lilly, Novartis and Biogen, and Gilead also to her department, not related to the current study. FdV supervises 3 PhD students who are employed with F. Hoffmann La Roche Ltd (Basel, Switzerland/Welwyn Garden City, UK). He has not received any fees or reimbursements for this, and the topics of their PhD thesis are not related to the current study proposal. SA, JD, AMB, PCS and TPvS have no competing interests.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

To cite Abtahi S, Driessen JHM, Burden AM, *et al*. *Ann Rheum Dis* 2023;**82**:e94.

Received 25 January 2021
Accepted 26 January 2021
Published Online First 8 February 2021

Linked

► http://dx.doi.org/10.1136/annrheumdis-2020-219797

Ann Rheum Dis 2023;**82**:e94. doi:10.1136/annrheumdis-2021-219856

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