

## Response to: 'Correspondence on 'Onset of rheumatoid arthritis after COVID-19: coincidence or connected?' by Roongta *et al*

We thank Roongta *et al*<sup>1</sup> for the interest taken in our work and for bringing this interesting case of seropositive rheumatoid arthritis (RA) after COVID-19 to the attention. They describe a patient who developed polyarthritis after proven SARS-CoV-2 infection, with seroconversion for both rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) between 2 weeks and 6 months after infection. This raises the question whether seroconversion (becoming seropositive for ACPA and RF) might occur more often after COVID-19.

In our study, three out of five patients presenting with polyarthritis post-COVID were already autoantibody positive at first presentation to the rheumatologist, on average 8.3 weeks after COVID-19.<sup>2</sup> Unfortunately, there was no serum available from the time before COVID-19 or from timepoints between SARS-CoV-2 infection and presentation to the rheumatologist, precluding any investigation into seroconversion after COVID-19 in these patients. However, detailed investigations into the characteristics of their ACPA response revealed the presence of multiple ACPA isotypes and a high amount of variable-domain glycosylation,<sup>2</sup> indicating that the autoimmune response had undergone a prolonged maturation phase with great similarity to the ACPA response in patients with RA without preceding COVID-19.<sup>3</sup> In addition, we investigated seroconversion in a cohort of 61 post-COVID-19 patients 5 weeks after hospitalisation. None of the patients tested positive for ACPA, except two patients previously diagnosed with ACPA-positive RA. Thus, in this cohort we could not observe an increase in ACPA positivity after COVID-19.<sup>2</sup>

We agree with Roongta *et al* that it is tempting to speculate that the severe (pulmonary) inflammation in COVID-19 could be a trigger for the break of tolerance to citrullinated proteins. Proinflammatory cytokine levels and neutrophil extracellular trap formation can indeed provide a source of citrullinated proteins in an inflammatory pulmonary environment, but one could also argue that these potential triggering factors subside as the SARS-CoV-2 infection wanes. This could diminish the likelihood that they would still be involved in inducing an ACPA response many months later. Although several recent findings point towards a potential role of the pulmonary immune system in the development of (seropositive) RA, for example, the presence of ACPA in sputum of some patients with RA<sup>4</sup> and preceding respiratory disease being a risk factor for RA,<sup>5</sup> the underlying pathophysiological mechanisms are still unknown.<sup>6</sup> Therefore, it remains difficult to hypothesise on the chain of events based on independent associations and findings.

Furthermore, it seems important to keep the bigger epidemiological picture in mind. RA is not a rare disease; the global annual age-standardised incidence rates of RA was estimated at 14.9 per 100 000 in 2017.<sup>7</sup> When a substantial part of the population contracts an infectious disease, as is the case during this still ongoing SARS-CoV-2 pandemic, some individuals will develop RA within a half year after infection based on chance alone. Therefore, it appears likely that cases of post-COVID-19 RA will occur even if there is no causal connection between RA and COVID-19. Considering the millions (currently over 100 million) of individuals that have survived COVID-19, perhaps

one would have expected even more cases of seropositive RA to have emerged if there would be a causal link.

In conclusion, in our study involving 61 individuals we did not find evidence of seroconversion for ACPA and RF 5 weeks after SARS-CoV-2 infection. Furthermore, in the patients presenting with seropositive RA after COVID-19, the autoantibody characteristics greatly resembled those of regular patients with RA. Nevertheless, the hypothesis that pulmonary inflammation, due to COVID-19 or other inflammatory triggers, might be involved in the break of tolerance against citrullinated proteins remains very interesting and the topic of ongoing investigations. Although it appears likely that more cases of seropositive RA post-COVID will be reported in the future based on epidemiology alone, this in itself does not prove a causal relationship. Time will tell whether a plausible connection between these two events exists, or whether it may be coincidence.

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