Response to: Correspondence on 'Anticardiolipin and other antiphospholipid antibodies in critically ill COVID-19 positive and negative patients' by Trahtemberg *et al*

We thank Dr Yudong Liu[1] for commenting on our manuscript and on many of the same issues we raised.[2] There are, however, some comments that require clarification and a response. It is true that antiphospholipid antibodies (aPLs) of various specificities and immunoglobulin isotypes have been reported in COVID-19.[3] However, despite a historical connection of aPLs with coagulopathies and antiphospholipid syndrome (APS), to date there has been no convincing evidence that aPLs has this in vivo pathogenic effect in COVID-19. In our patients, despite the presence of aPLs (eg, IgG anticardiolipin), there was no link to thrombotic events, a finding echoed by other referenced studies[4] and recently reviewed.[3 5] The recent publication by Chang *et al*[6] is mentioned, but it is important to appreciate that their results were compared with 'normal' controls and no clinical features (coagulopathy or APS) were reported, precluding any inferences to autoimmune diseases; it is a stand-alone description of COVID-19 findings. Like the Chang *et al*[6] manuscript, we also reported an extensive array of autoantibodies in COVID-19, but when we used sera from contemporaneous patients without COVID-19 of similar disease severity as comparator controls, we did not find significant differences in the autoantibody repertoire between the COVID-19 positive and negative cohorts.[7] Many individuals displayed 'certain autoimmune features' but that cannot be taken to be equivalent to autoimmune disease. Indeed, patients with COVID-19 have developed Guillain-Barré (not a COVID-19-specific condition) and there are anecdotal reports of other autoimmune diseases, but it is very important to realise that temporarily is not the same as causality.[3]

Last, it is opined that our study 'failed to detect aβ2-GP1 in patients with COVID-19, but other studies reported the existence of these (aPLs)'. However, this comment does not seem to appreciate that we used an assay that detected antibodies to domain 1 of β2-glycoprotein 1 (β2-GP1), which is known to have higher specificity for and more clearly linked to the pathogenesis of APS than antibodies to other β2-GP1 domains.[8] As we clarified in our manuscript, these findings are consistent with those of Borghi *et al*,[4] who detected antibodies to β2-GP1 domains 2 and 4 but found no association with thrombotic events in 122 patients with severe COVID-19, once again challenging the notion that anti-β2-GP1 has any pathogenic role in COVID-19.[3]

As to the dynamic and temporal/chronological sequence of autoantibody and APLA appearance, we clearly stated that 'clinical data and serum samples were collected longitudinally at days 0, 1, 3, 5, 7 and 10; after day 10 or discharge from intensive care (IC)'. Our data (table 2) and discussion on APLA[2] and other autoantibodies[7] showed that in some patients autoantibodies were present on admission to IC, while in others they appeared during the stay in IC and in some the autoantibodies fell to within normal/reference range while in IC. Hence, the chronological autoantibody responses are quite heterogeneous. We concur that important studies are still required, especially the assessment of whether autoimmunity evolves to autoimmune diseases in COVID-19 or following vaccination, as well as in long COVID and multi-inflammatory syndrome.

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Contributors Both authors contributed to and edited the response 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 None declared.

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 Fritzler MJ, Trahtemberg U, . *Ann Rheum Dis* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/annrheumdis-2021-221780

Received 3 November 2021
Accepted 4 November 2021

Linked

► http://dx.doi.org/10.1136/annrheumdis-2021-221711

Ann Rheum Dis 2021;**0**:1. doi:10.1136/annrheumdis-2021-221780

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