Response to: 'Presence of anti-phospholipid antibodies in COVID-19: a case series study' by Amezcua-Guerra *et al*

We thank Amezcua-Guerra *et al* for their interest in our study reporting on the course of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease 2019 (COVID-19) in a case series of patients with systemic lupus erythematosus under long-term treatment with hydroxychloroquine.[1 2] Complementary to our work, Amezcua-Guerra *et al* address the issue of anti-phospholipid antibodies (anti-PL abs) during the course of COVID-19. Indeed, despite adequate thromboprophylaxis, COVID-19 is associated with a high rates of venous, as well as arterial, thromboembolic events, in particular in patients hospitalised in an intensive care unit.[3–5] This state of hypercoagulation has been linked to an important systemic inflammatory response syndrome, with elevated serum levels of fibrinogen, factor VIII and D-dimers.[6 7] Several reports, including the study by Amezcua-Guerra *et al*[2] have emphasised the high frequency of serum anti-PL abs and lupus anti-coagulant (LA) in a case series of patients with severe COVID-19, however with surprisingly heterogeneous results.

Amezcua-Guerra *et al* report a high frequency (57%) of both conventional (ie, those included in the antiphospholipid syndrome (APS) classification criteria) and non-conventional anti-PL abs in patients with severe and critical COVID-19, which appear to be associated with a hyperinflammatory state. An association with pulmonary thromboembolism has also been suggested although this concerned only 2 (17%) of the 12 patients who had at least one type of circulating anti-PL abs.[2] More recently, Zuo *et al*, measuring serum levels of eight different types of anti-PL abs in 172 patients hospitalised with COVID-19, detected anti-cardiolipin (anti-CL) IgM in 23%, anti-PS/PT IgG in 24% and anti-PS/PT IgM in 18% of the patients, with at least one type of anti-PL abs present in 52%.[8] In contrast, Galeano-Valle *et al* reported a very low prevalence of conventional serum anti-PL abs among patients experiencing venous thromboembolism during the course of severe COVID-19.[9] The results from their study were confirmed and extended by Borghi *et al* who also reported a low prevalence of anti-β_2GPI IgG, IgA and IgM in patients with COVID-19 at a frequency of 15.6, 6.6 and 9.0%, respectively, as well as anti-CL IgG (5.7%) or IgM (6.6%), that was not associated with major thrombotic events.[10] In the latter study, anti-PL abs were mainly directed against β_2GPI, but they displayed an epitope specificity different from that of anti-PL abs present in APS.[10] The explanation for the observed discrepancy between the rates of anti-PL abs reported in these studies might rely on the possibility that their generation is linked to the severity of COVID-19. In this respect, Bertin *et al* reported in a cohort of 56 patients with COVID-19 that such differences were found for anti-CL IgG whose presence were significantly associated with a severe form of the disease.[11] This observation was confirmed by Xiao *et al*, who showed that anti-PL abs, mostly anti-β_2GPI and aCL IgA, were detected in 47.0% of critically ill patients, but not in patients with non-critical conditions.[12] Surprisingly, in the latter study, LA was detectable in only 2 of 66 critically ill patients. The presence of multiple anti-PL abs with a moderate serum titres of at least one type of anti-PL ab, was found to be statistically associated with a higher incidence of cerebral infarction.[12] Of note, anti-PL abs were mainly of the IgA isotype which suggest a cross-reactivity and/or breakdown of mucosal immune tolerance induced by SARS-CoV-2 because of the pulmonary and intestinal mucosal tropism of this virus.

Meanwhile, many studies have shown a significant presence of LA in patients with severe COVID-19, mainly in critically ill conditions. In the study of Bowles *et al*, 31 patients (14%) were shown to be positive for an LA assay in a series of 216 patients with severe COVID-19 with only two patients having a confirmed or suspected venous thrombosis.[7] Harzallah *et al* reported 25 patients (45%) positive for LA in a series of 56 critically ill patients with COVID-19,[13] whereas in the study of Helm *et al*, 50 patients (33%) tested positive for an LA assay in a series of 150 patients with COVID-19-related acute respiratory disease syndrome (ARDS).[3] These important rates of LA in critically ill patients with COVID-19 should however be interpreted with caution. Indeed, the extrapolation of LA results from patients receiving anticoagulants, which is now current clinical practice in the vast majority of patients hospitalised for COVID-19, is subject to discussion.[14] Furthermore, one should be aware of false-positive LA testing results in patients with COVID-19 because many assays are sensitive to the presence of C-reactive-protein resulting in false positives.[15]

We recently reported, on a series of 25 patients with refractory COVID-19-related ARDS, 23 cases (92%) of LA. Anti-CL or anti-β_2GPI abs were observed in 13 (52%) and 3 (12%) cases, respectively.[16] Three patients (12%) were triple positive for LA, anti-CL and anti-β2GP1 abs, whereas massive pulmonary embolism was diagnosed in six patients, all positive for the presence of anti-PL abs.

During acute infection, thrombosis or inflammation, serum levels of different anti-PL abs may transiently arise. Strikingly, however, this elevation of anti-PL abs and/or LA titres reported in a major proportion of patients with severe COVID-19 has rarely been observed in other pathologies. Nevertheless, the involvement of anti-PL abs in the induction of a hypercoagulable state and the possibility that SARS-Cov-2 may trigger the development of 'COVID-19-induced APS-like syndrome' have to be confirmed in large clinical series. Notwithstanding, the high frequency and wide variety of anti-PL abs observed in patients with COVID-19 cannot be ignored.

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