Response to: 'Antirheumatic drugs, B cell depletion and critical COVID-19: correspondence on 'Clinical course of coronavirus disease 2019 (COVID-19) in a series of 17 patients with systemic lupus erythematosus under long-term treatment with hydroxychloroquine by Mathian *et al*' by Notz *et al*

We thank Notz *et al* for their interest in our study reporting on the course of 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] Notz *et al* report on two patients who had been treated with the anti-CD20 monoclonal antibody rituximab (RTX), prior to SARS-CoV-2 infection, and who presented an exacerbated immune response, a noticeable prolongation of the COVID-19 course and a need for intensive care unit (ICU) admission and mechanical ventilation. Neither one of the patients was able to generate an anti-SARS-CoV-2 spike receptor-binding domain serum antibody response or to eliminate the virus prior to ICU discharge. Because our case series did not include patients receiving B cell depletion therapy, we can only make a general comment on the authors' very interesting observations.

At the start of the epidemic in Europe, it was already suggested that RTX may expose rheumatic disease patients to a significant increased risk of hospital admission.[3] In their study, Nuño *et al* reported that all seven patients under treatment with RTX in a cohort of 122 patients with rheumatic inflammatory disease infected with SARS-CoV-2 needed hospital admission and that one died.

This observation was corroborated by several other observations made in severe, sometimes fatal, COVID-19 in patients receiving RTX for the treatment of different pathologies, including rheumatoid arthritis,[4] granulomatosis with polyangiitis,[5 6] systemic sclerosis[7] and haematological malignancies.[8] Recently, Loarce-Martos *et al* confirmed that COVID-19 is not only common, but also particularly severe in patients with rheumatic disease who had been on treatment with RTX.[9] Indeed, in an observational study they reported that 13 out of 76 (17.1%) patients with rheumatic disease treated in their centre with RTX in the last 12 months prior to screening for the presence of SARS-CoV-2 had suspected or confirmed infection. A total of eight of these patients (61.5%) developed severe COVID-19 leading to hospitalisation, from which five (38.5%) fulfilled the acute respiratory distress syndrome criteria, whereas three (23.1%) eventually died. These findings underscore that while the innate immune system[10] and T cells[11] are paramount in the early antiviral response, B cells have also an important role to play in the anti-viral response. B cell depletion agents, while not improving the cytokine storm that causes severe morbidity, may dramatically inhibit the protective antibody immunity following infection and vaccination. This process is probably largely involved in cases of a prolonged and/or atypical course of COVID-19 characterised by a negative or delayed serological response against SARS-CoV-2 in B cell depleted patients.[12–15] It is of note however that many, non-serious, cases of COVID-19 in patients under treatment with RTX have been reported as well.[16 17]

Until further studies will help us to understand the risk with respect to COVID-19 severity, treatment with biological disease-modifying drugs, such as RTX, will have to be applied with particular caution in patients with rheumatic or auto-immune disease, especially if they suffer from other comorbidities which render them particularly at risk.

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