# 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*

In a recent case series, Mathian *et al* reported on 17 patients suffering from systemic lupus erythematosus and COVID-19.[1] All of these patients received long-term hydroxychloroquine treatment and initial signs and symptoms of COVID-19 were similar to those previously described. However, as 50% of the patients remained hospitalised at the time of publication, the authors cannot comment on the duration and eventual outcome of COVID-19 in all of their patients. Furthermore, it is emerging that hydroxychloroquine does not alter COVID-19.[2–4] As such, we actually believe that other immunosuppressive, antirheumatic medications require more attention. Mathian *et al* rightfully pointed out that besides long-term hydroxychloroquine treatment, steroids and other baseline immunosuppressant drugs are often present in patients with rheumatic diseases. In this context, we found an altered immune response and noticeable prolongation of COVID-19 from the onset of symptoms to intensive care unit (ICU) admission in two patients pretreated with rituximab (RTX) (table 1).

Patient A (aged 40–60 years) suffered from rheumatoid arthritis, treated with daily doses of leflunomide and low-dose prednisolone. RTX was administered every 6 months. The patient was admitted to ICU 33 days after the onset of COVID-19 symptoms with severe acute respiratory distress syndrome and massively elevated interleukin-(IL-) 6 levels. A good response to low-dose circulatory support with norepinephrine and prone positioning improved the clinical situation. Extubation was successful on day 41 and the patient could be discharged from the ICU on day 44 in stable condition. Patient B (aged 40–60 years) presented himself to a regional hospital 19 days after the onset of fever and dyspnoea. COVID-19 was diagnosed and mechanical ventilation became necessary. Four months prior, the patient received an autologous haematopoietic stem cell transplantation due to a mantle cell lymphoma. Chemotherapy among others included RTX. Despite ARDS treatment and the use of IL-1 receptor antagonist anakinra to treat macrophage-activation-like syndrome, the clinical condition worsened. Transfer to tertiary care ICU was necessary on day 34. Massively elevated IL-6 and ferritin levels indicated hyperinflammation and treatment with tocilizumab was initiated. Moreover, the patient received hydrocortisone, convalescent plasma, granulocyte colony stimulating factor and immunoglobulins. After a complex clinical course, including acute renal failure, massive bilateral pulmonary embolism, episodes of ventricular tachycardia and a subarachnoid haemorrhage, the patient was successfully weaned from mechanical ventilation and finally discharged from ICU on day 58 without major respiratory or neurological residues.

Both patients had severe lymphocytopenia on ICU admission and B cell depletion persisted throughout the course of treatment, as repeatedly confirmed via flow cytometry. The patients were neither able to establish any anti-SARS-CoV-2-spike-receptor binding domaine (RBD) antibody titres, nor to eliminate the virus, as pharyngeal swabs and tracheal aspirates tested positive for SARS-CoV-2 until ICU discharge (figure 1).

**Table 1** Clinical course

| Demographics and ICU course | Patient A | Patient B |
|---|---|---|
| Age (years) | 50–55 | 50–55 |
| Body mass index (kg/m²) | 29.4 | 25.7 |
| Rituximab | | |
| Indication | Rheumatoid arthritis | Mantle cell lymphoma |
| Last infusion (months prior to COVID-19 infection) | 4 | 1 |
| Dose (mg) | 1000 | 828.75 |
| B cell depletion | Complete | Complete |
| Gammaglobulin, baseline (mg/dL) | 140 | 447 |
| Further comorbidities | Hypertension | None |
| Tertiary care ICU admission | | |
| Preceding length of COVID-19 symptoms (days) | 33 | 34 |
| Preceding hospital stay (days) | 3 | 15 |
| SARS-CoV-2 confirmation by RT-PCR | Yes | Yes |
| Mechanical ventilation | Yes | Yes |
| $PaO_2/FiO_2$ (mm Hg) | 72 | 178 |
| SOFA score | 9 | 15 |
| APACHE II score | 31 | 39 |
| Leucocytes (×1000/µL) | 5.6 | 3.9 |
| Lymphocytes (×1000/µL) | 0.2 | 0.7 |
| Thrombocytes (×1000/µL) | 95 | 16 |
| Erythrocytes (×1000/µL) | 2.7 | 2.7 |
| IL-6 (pg/mL) | 641 | 518 |
| Ferritin (µg/L) | 6757 | 23 986 |
| Tertiary care ICU course | | |
| ICU stay (days) | 9 | 25 |
| Mechanical ventilation (days) | 6 | 10 |
| Renal replacement therapy | None | Intermittent |
| SARS-CoV-2 RNA, airway material | Cont. positive | Cont. positive |
| SARS-CoV-2 RNA, serum | Cont. positive | Cont. negative |
| Anti-SARS-CoV-2-Spike-RBD antibodies | Not detectable | Not detectable |
| Complications | Haemorrhage | Urinary tract infection |
| | PE | |
| | SAB | |
| | VT | |
| Survival on ICU discharge | Yes | Yes |

APACHE, acute physiology and chronic health evaluation; cont., continuously; ICU, intensive care unit; IL-6, interleukin 6; PE, pulmonary embolism; RBD, receptor binding domaine; RT-PCR, reverse transcription PCR; SAB, subarachnoid haemorrhage; SOFA, sequential organ failure assessment; VT, ventricular tachycardia.

Previously a prolonged course of COVID-19[5] was attributed to the lack of B cell antigen presentation, which might concomitantly impair activation of immune cells and cytokine production.[6] We rather observed excessive immune activation and cytokine release with high proinflammatory markers. Hyperinflammation in the absence of B cells underlines the predominant role of the myeloid and T cell system in COVID-19 cytokine storm. The second interesting finding was that both patients could probably not completely clear the virus. This highlights the role of the B cell system and antibody production for virus elimination, as potentially neutralising anti-SARS-CoV-2-Spike-RBD antibodies were not detectable in both RTX patients. Nonetheless, the clinical situation improved, indicating that deterioration

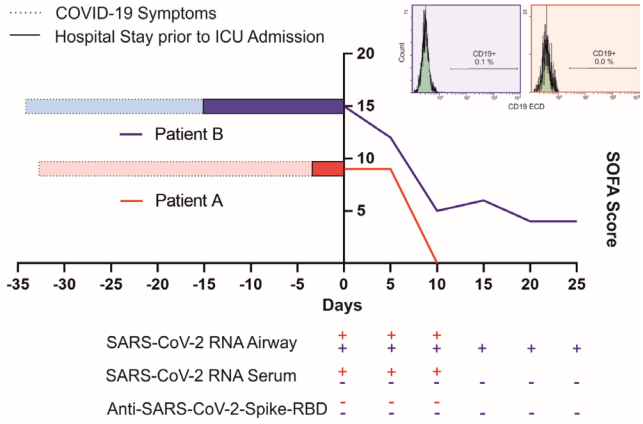


**Figure 1** The prolonged clinical courses of the two patients are shown. Day 0 represents the admission on tertiary care intensive care unit (ICU). The onset of COVID-19 is marked with light red and blue bars; hospitalisation in a secondary care centre is highlighted in blue and red bars. The clinical course on ICU is represented by sequential organ failure assessment score with a line in corresponding colours. The line stops at the time of discharge from ICU. Patients had a continuous B cell depletion after rituximab treatment, as repeatedly confirmed via flow cytometry (representative inlays in corresponding colours, CD19 positivity indicated B cells). RNA from SARS-CoV-2 was positive (+) during the whole ICU stay. Anti-SARS-CoV-2-spike-receptor binding domaine (RBD) antibodies were negative (–) at all time.

was rather driven by the immune system and not by sheer presence of virus.

Overall, the case series by Mathian *et al* and our observations indicate that the presence of complex antirheumatic drug regimens further complicates COVID-19. However, the question if these patients are at risk of a more severe or just delayed course of COVID-19 remains unanswered. Larger and adequately powered studies are required, which concomitantly would provide evidence on how to handle immunosuppression in times of COVID-19.

## COMPLIANCE WITH ETHICAL STANDARDS

The institutional ethic board of the University of Wuerzburg waived the need for a specific approval due to the context of sole retrospective chart review within standard care (63/20-kr 25.03.2020). Both patients have consented to the submission of this article to the journal. On behalf of all authors, the corresponding author states that there is no conflict of interest relating to the current work.

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