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Philippe Guilpain, Clément Le Bihan, Vincent Foulongne, Patrice Taourel,
Nathalie Pansu, Alexandre Thibault Jacques Maria, Boris Jung, R. Larcher,
Kada Klouche, Vincent Le Moing

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Response to: 'Severe COVID-19 associated pneumonia in 3 patients with systemic sclerosis treated with rituximab' by Avouac *et al*

We read with deep interest the comments by Avouac and colleagues¹ and their report of severe cases of COVID-19 in three patients with systemic sclerosis (SSc) under rituximab treatment. The heterogeneous profile of patients as well as the potential implication of comorbidities appear to be the hallmarks of this viral outbreak. Applied to the field of SSc, the absence of pre-existing interstitial pneumonia is an illustration of the viral ability to surprise and challenge our classic thinking. A singular profile of patients with both autoimmune disease and COVID-19 has not yet emerged, and each patient may be a special case when faced with COVID-19, considering the gathering and interplay of pathophysiological mechanisms and clinical features of the rheumatic disease, comorbidities,² viral aggression and immune response against coronavirus.³ The weight of comorbidities is at least illustrated by the high number (until today: 323) of referenced papers on PubMed, while numerous risk factors are suspected and debated.² To date, large data concerning rituximab during the pandemic are lacking, and whether rituximab is associated with a specific risk of more severe COVID-19 is not yet established.

However, this is a reasonable possibility when considering the impairment of the numerous functions of B cells (particularly those related to humoral response) by rituximab, as commented by Monti *et al.*⁴ While interesting data on T cell-specific responses are emerging,⁵ antibody response remains crucial for neutralising virus, although higher antibody titres may be associated with bad outcome in some individuals,^{3,4} possibly through the phenomenon of antibody-dependent enhancement (implicating non-neutralising virus-specific IgG). However, the delayed worsening (up to day 23) of COVID-19 in the rituximab-treated patients described by Avouac and colleagues¹ as well as in our patient⁶ is intriguing and raises additional comments.

Indeed, the median duration from symptom onset to intensive care unit (ICU) is classically about 10 days.^{7,8} The median time to ICU may depend on the cause of the worsening and varies from 8 to 15 days with a median of 12 days, in the series by Zhou *et al.*⁷ In addition, heterogeneous presentation of COVID-19 as well as atypical symptoms (anosmia, ageusia, digestive, neurological, cutaneous manifestations and so on) make possibly difficult the dating of the very first symptom. Consequently, the date of worsening may be approximative in some patients from the general population published in literature studies, and thus delayed worsening might occur sometimes. In addition, our observations might be rather related to the specific recruitment of our departments, as a bias of selection. However, since B cells are essential in primary and secondary immune responses, the implication of rituximab should be further discussed.

First of all, it is noteworthy that the critical severity of COVID-19 is mainly related to the development of inflammatory cytokine storm, implicating interleukin (IL)-1, IL-6, tumour necrosis factor, interferons and many immune cells (monocytes, macrophages, T helper (Th) lymphocytes and antigen-presenting cells such as dendritic cells).³ Notably, during a normal immune response and besides the production of autoantibodies, B lymphocytes also play the role of antigen-presenting cells, through the B cell receptor recognition and internalisation of antigens, and the processing and presentation of peptides to Th lymphocytes using major histocompatibility complex (MHC)

class II molecules. So the presentation of coronavirus antigens might be impaired by rituximab and the activation of immune cells consequently delayed, holding up the onset of the cytokine storm. Furthermore, B cells also play key roles in cellular interactions. In their recent study, Wen and colleagues⁹ observed that B cells could secrete IL-6 and thus initiate an inflammatory cascade involving T cells and monocytes, leading to the inflammatory cytokine production. Comparing early and late recovery states, the authors suggested that the interactions between immune competent cells may accelerate or delay the recovery from COVID-19.

Taken together, these elements suggest that the delayed worsening observed in our rituximab-treated patients may not occur by pure chance. Whether rituximab exhibits specific effects in COVID-19 (especially compared with other immunosuppressants) remains to be established. We can hope that future studies and national/international registries (in France, the French rheumatic and musculoskeletal diseases (RMD) COVID-19 cohort (FAI2R/SFR/SNFMI consortium) and its future contribution to the European League Against Rheumatism registry) will provide answers to the dramatic question of the tolerance for this immunosuppressive drug, as well as for the others.

Philippe Guilpain,^{1,2} Clément Le Bihan,³ Vincent Foulongne,⁴ Patrice Taourel,⁵ Nathalie Pansu,³ Alexandre Thibault Jacques Maria,^{1,2} Boris Jung,^{6,7} Romaric Larcher,^{6,7} Kada Klouche,^{6,7} Vincent Le Moing³

¹Internal Medicine: Multi-Organic Diseases, Local Referral Center for Systemic Autoimmune Diseases, Montpellier University Hospital, Université Montpellier, Medical School, Montpellier Cedex 5, France

²IRMB, Université Montpellier, INSERM, Montpellier, France

³Tropical and Infectious Diseases, Hôpital Saint Eloi, CHRU de Montpellier, Montpellier Cedex 5, Hérault, France

⁴Pathogenesis and Control of Chronic Infections, Inserm, Université Montpellier 1 Faculté de Médecine Montpellier-Nîmes, Montpellier, Languedoc-Roussillon, France

⁵Osteoarticular Medical Imaging Section, Department of Medical Imaging, University Hospital Centre Montpellier, Montpellier, Languedoc-Roussillon, France

⁶Department of Intensive Care Medicine, Lapeyronie University Hospital, and PhyMedExp, University of Montpellier, INSERM, CNRS, Montpellier, France

⁷Lapeyronie University Hospital, and PhyMedExp, University of Montpellier, INSERM, CNRS, Montpellier, France

Correspondence to Dr Alexandre Thibault Jacques Maria, Internal Medicine: Multi-Organic Diseases, Local Referral Center for Systemic Autoimmune Diseases, Montpellier University Hospital, Univ Montpellier, Medical School, Montpellier Cedex 5, France; alexandremaria@hotmail.fr

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REFERENCES

- 1 Avouac J, Airó P, Matucci-Cerinic M, *et al.* Severe COVID-19 associated pneumonia in 3 patients with systemic sclerosis treated with rituximab. *Ann Rheum Dis* 2021;80:e37.
- 2 Jordan RE, Adab P. Who is most likely to be infected with SARS-CoV-2? *Lancet Infect Dis* 2020:S1473309920303959.
- 3 Vabret N, Britton GJ, Gruber C, *et al.* Immunology of COVID-19: current state of the science. *Immunity* 2020:S1074761320301837.
- 4 Monti S, Balduzzi S, Delvino P, *et al.* Clinical course of COVID-19 in a series of patients with chronic arthritis treated with immunosuppressive targeted therapies. *Ann Rheum Dis* 2020;79:667–8.
- 5 Grifoni A, Weiskopf D, Ramirez SI, *et al.* Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals. *Cell* 2020.
- 6 Guilpain P, Le Bihan C, Foulongne V, *et al.* Rituximab for granulomatosis with polyangiitis in the pandemic of covid-19: lessons from a case with severe pneumonia. *Ann Rheum Dis* 2021;80:e10.
- 7 Zhou F, Yu T, Du R, *et al.* Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395:1054–62.
- 8 Yang X, Yu Y, Xu J, *et al.* Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020;8:475–81.
- 9 Wen W, Su W, Tang H, *et al.* Immune cell profiling of COVID-19 patients in the recovery stage by single-cell sequencing. *Cell Discovery* 2020;6:1–18.