Response to: 'Correspondence on Recovery from COVID-19 in a patient with spondyloarthritis treated with TNF-alpha inhibitor etanercept. A report on a COVID-19 patient with psoriatic arthritis receiving ustekinumab' by Messina *et al*

We thank Messina *et al* for their interest in our article reporting a benign evolution of COVID-19 in a patient with spondyloarthritis (SPA) treated with a combination of disease-modifying antirheumatic drugs (DMARDs), methotrexate and a tumour necrosis factor (TNF)-alpha inhibitor, etanercept.[1 2] We read with deep interest their report on a patient with psoriatic arthritis treated with ustekinumab, an antagonist of the interleukin (IL)-12/23 axis, who developed a moderate form of COVID-19, with full recovery.[1]

Of interest, a Th17 immune response with overexpression of IL-17, among other cytokines, has been shown elsewhere associated with COVID-19-related cytokine release syndrome (CRS).[3–6]

The authors are balancing an apparent paradox of an increased risk of infection, because of a potential compromised viral clearance, in patients exposed to ustekinumab, contrasting with a potential 'protective' effect of IL-12/23 inhibition, which might limit a deregulated Th1 and Th17 immune response leading to CRS associated with severe evolution of COVID-19.[1 6 7]

Presumably, this phenomenon might not be restricted to IL-12/23 inhibitors, but is likely to be extended for a broader panel of conventional, biological or targeted synthetic DMARDs, particularly anticytokine drugs, echoing our observation.[2] In addition, recent registry data have shown lower hospitalisation rates in patients treated with TNF-alpha inhibitors.[8] Conversely, concerns have recently been raised suggesting a detrimental effect, with an increased risk of severe evolution and mortality, in patients treated with B-cell depleting monoclonal antibodies, such as the anti-CD20 rituximab (RTX).[9–11]

Collectively, these emerging data, along with the experience of rheumatologists regarding the risk of infection in patients undergoing immunosuppressive therapies, support the current European League Against Rheumatism (EULAR) recommendations relative to the management of patients with rheumatic and musculoskeletal diseases (RMDs) in the context of COVID-19.[12]

We report here characteristics and outcomes of patients with RMDs followed and treated in our centre (Hôpitaux civils de Colmar; France) who developed COVID-19 under DMARDs (table 1).

A total of 17 patients, including 8 patients with rheumatoid arthritis (RA), 6 patients with SPA, 2 patients with primary Sjögren's syndrome and 1 patient with Still's disease, were confirmed for COVID-19, either by real-time retrotranscription (RT)-PCR on nasopharyngeal swabs performed in 10 symptomatic patients (58.8%), or retrospectively, by serology for detection of SARS-CoV-2 IgM and/or IgG in 5 patients (29.4%) with a history of symptoms highly suggestive of SARS-CoV-2 infection, or based solely on a typical bilateral pneumonia pattern on CT-scan for 2 patients (11.8%).

Immunomodulatory treatment regimens consisted on csDMARDs for 13 patients (76.5%), including methotrexate in 9 patients (52.9%), leflunomide in 3 patients (17.6%), azathioprine in 1 patient (5.9%) and hydroxychloroquine in 1 patient (5.9%). A total of 10 patients (58.8%) were treated with bDMARDs including TNF inhibitors in 6 patients (35.3 %), IL-6 receptor inhibitor, tocilizumab, in 3 patients (17.6 %) and anti-CD20 monoclonal antibody, rituximab, in 1 patient (5.9%). One patient (5.9%) was treated with a tsDMARD, the Janus Kinase (JAK) inhibitor baricitinib in combination with methotrexate 20 mg, subcutaneous, weekly. Seven patients (41.2%) were treated with an association of csDMARDs and bDMARDs/tsDMARDs. In our study, no patients treated with IL-17A or IL-12/23 inhibitors have been confirmed for SARS-CoV-2 infection.

Overall, 16 patients out of the 17 analysed (94.1%) fully recovered, regardless of the type of RMD and the type of immunomodulation considered. A benign evolution was observed in 13 patients (76.5%), while 3 patients (17.6%) developed a moderate form requiring hospitalisation but without the need for invasive ventilation.

Unfortunately, 1 patient (5.9%), an 83-year-old man with a spondyloarthritis treated with golimumab, a TNF-alpha inhibitor monoclonal antibody, experienced a severe form of COVID-19, complicated by a fatal acute respiratory distress syndrome. In accordance with data obtained in the general population, age and cardiovascular comorbidities appear to be the dominating risk factors of severe evolution and death related to COVID-19. We presume that in this patient, age and hypertension might have accounted, more likely than TNF-alpha inhibition, for the unfavourable outcome.

Furthermore, in our study, only one patient treated with the anti-CD20 monoclonal antibody RTX developed COVID-19, with mild symptoms and a favourable outcome. To date, no other patient treated with RTX from our centre was confirmed for COVID-19 either by RT-PCR, CT-scan or serology.

Data concerning COVID-19 outcomes in patients treated with RTX are still scarce. It is conceivable that while some immunomodulating agents (eg, anti-TNF; anti-IL6R; anti-IL1; anti-IL17A; anti-IL12/23; JAKi) might confer an advantage over the exaggerated immune response and cytokine storm triggered by SARS-CoV-2, other agents, including those acting on cells responsible for humoral immunity, would appear to be detrimental in the context of COVID-19. In addition, as suggested by Mathian *et al*[13] and Avouac *et al*[10] in their reports of COVID-19 in systemic lupus erythematosus and systemic sclerosis, respectively, severe autoimmune diseases, especially when associated with organ damages are probably at higher risk of developing severe forms of COVID-19, in comparison to patients with SPA or RA. Nonetheless, subgroups of patients with RA, especially those receiving RTX seem to be at higher risk than patients with RA treated with other cs/b/tsDMARDs.[11] Organ damages associated with age, a long-standing evolution of the disease, cardiovascular risk factors and interstitial lung disease (ILD) that are likely to be found in higher proportions in this population, along with the impaired B-cell response and reduced antibody production raised against the SARS-CoV-2, might explain the potential detrimental effect reported in the subgroup of patients with RA treated with anti-CD20. Clarifying whether this plausible increased risk related to RTX use is due to B-cell depletion or to comorbidities represents an important issue that is not fully resolved yet.

Our results, although collected on a limited number of patients, are consistent with the data in the literature so far available on COVID-19 and RMDs.[14–16] If it is not protective, at least no warnings suggestive of a pejorative evolution of COVID-19 have been detected. However, these studies do not fully clarify whether or not patients with RMDs are at increased risk of developing severe forms of COVID-19 compared with the general population.[17 18]

Table 1 Clinical characteristics of patients with rheumatic and musculoskeletal diseases (RMDs) treated with disease-modifying antirheumatic drugs (DMARDs) and COVID-19 outcomes

Variable	Spondyloarthritis	Rheumatoid arthritis	Sjögren's syndrome	Still's disease	All RMDs
Number of patients	6	8	2	1	17
Sex, female, n (%)	2 (33.3)	6 (75)	2 (100)	1 (100)	11 (64.7)
Age at COVID-19 onset, median (range)	54.5 (53–83)	57 (49–71)	63.5 (59–68)	35	55 (35–83)
Comorbidities and risk factors					
Hypertension, n (%)	2 (33.3)	4 (50)	1 (50)	0	7 (41.2)
Diabetes, n (%)	0	1 (12.5)	0	0	1 (5.9)
BMI, median (range)	28.6 (26.9–34)	26.2 (20.7–45.5)	39.4 (31.6–47.2)	18.97	28 (18.97–47.2)
COVID-19 diagnosis					
Positive SARS-CoV-2 RT-PCR, n (%)	3 (50)	4 (50)	2 (100)	1 (100)	10 (58.8)
Positive SARS-CoV-2 serology, n (%)	2 (33.3)	3 (37.5)	0	0	5 (29.4)
Positive CT-scan, n (%)	2 (33.3)	3 (37.5)	0	1 (100)	6 (35.3)
Positive CT-scan and serology, n (%)	0	1 (12.5)	0	0	1 (5.9)
Positive CT-scan and RT-PCR, n (%)	1 (16.7)	1 (12.5)	0	1 (100)	3 (17.6)
Positive CT-scan without RT-PCR or serology available, n (%)	1 (16.7)	1 (12.5)	0	0	2 (11.8)
Rheumatic disease treatment previous to COVID-19					
csDMARDs, n (%)	4 (66.7)	7 (87.5)	2 (100)	0	13 (76.5)
Methotrexate	4 (66.7)	5 (62.5)	0	0	9 (52.9)
Leflunomide	0	2 (25)	1 (50)	0	3 (17.6)
Hydroxychloroquine	0	1 (12.5)	0	0	1 (5.9)
Azathioprine	0	0	1 (50)	0	1 (5.9)
bDMARDs, n (%)	5 (83.3)	3 (37.5)	1 (50)	1 (100)	10 (58.8)
TNF inhibitors, n (%)	5 (83.3)	1 (12.5)	0	0	6 (35.3)
Adalimumab	1 (16.7)	0	0	0	1 (5.9)
Etanercept	1 (16.7)	1 (12.5)	0	0	2 (11.8)
Golimumab	2 (33.3)	0	0	0	2 (11.8)
Infliximab	1 (16.7)	0	0	0	1 (5.9)
IL-6 receptor inhibitors, n (%)	0	1 (12.5)	1 (50)	1 (100)	3 (17.6)
Tocilizumab	0	1 (12.5)	1 (50)	1 (100)	3 (17.6)
Anti-CD20 monoclonal antibodies, n (%)	0	1 (12.5)	0	0	1 (5.9)
Rituximab	0	1 (12.5)	0	0	1 (5.9)
tsDMARDs, n (%)	0	1 (12.5)	0	0	1 (5.9)
JAK inhibitors, baricitinib	0	1 (12.5)	0	0	1 (5.9)
Combination of csDMARD and bDMARD/tsDMARD, n (%)	3 (50)	3 (37.5)	1 (50)	0	7 (41.2)
COVID-19 evolution and outcomes, n (%)					
Benign	4 (66.7)	6 (75)	2 (100)	1 (100)	13 (76.5)
Moderate	1 (16.7)	2 (25)	0	0	3 (17.6)
Severe	1 (16.7)	0	0	0	1 (5.9)
Recovery	5 (83.3)	8 (100)	2 (100)	1 (100)	16 (94.1)
Death	1 (16.7)	0	0	0	1 (5.9)

bDMARDs, biological disease-modifying antirheumatic drugs; BMI, body mass index; csDMARDs, conventional synthetic DMARDs; IL-6, Interleukin 6; JAKi, Janus Kinase inhibitors; RMDs, rheumatic and musculoskeletal diseases; TNF-α, tumour necrosis factor-alpha; ; tsDMARDS, targeted synthetic DMARDs.

Given the limited data, case reports and case series contribute to increase knowledge on the impact of immunomodulatory treatments in patients with autoimmune and rheumatic diseases. Importantly, in this context of uncertainty, and while waiting for wider datasets, each patient may reveal unique features when exposed to COVID-19 and should be scrupulously collected and considered.

However, data derived from monocentric case series should be interpreted with care, given the limited number of patients, which is prompt to impair statistical power. In addition, selection bias and 'centre/hotspot-effect' might compromise extrapolation of the results. As a consequence, robust data collected on a large amount of patients, with a rigorous analysis adjusted on identified risk factors, especially age, body mass index, cardiovascular risk factors (eg, diabetes mellitus; hypertension), ILDs and treatment regimens are needed to draw further and reliable conclusions.

Collecting data globally is a major challenge. There is no doubt that the impressive responsiveness and collective effort of the rheumatology community, as reflected by the 'COVID-19-Global-Rheumatology-Alliance' and national/international registries (in France, the 'French RMD COVID-19 cohort' (FAI2R/SFR/SNFMI consortium)) and its future contribution to the 'EULAR-COVID-19-Database', will provide new insights regarding the course of SARS-CoV-2 infection occurring in patients with autoimmune and rheumatic diseases but also the impact of DMARDs on COVID-19 outcomes.

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