## Use of rituximab in a multicentre cohort of patients with rheumatic diseases during the outbreak of novel SARS-COV-2 infection

Sirs,

We have recently published the findings of a retrospective multicentre study describing the association between SARS-COV-2 infection and the use of biological drugs or small molecules in 7,204 patients with rheumatic diseases enrolled by ten Italian Rheumatology Departments. 56.5% receiving anti-TNFα treatment, 11.1% CTLA4–Ig, 8.7% anti-IL-6 molecules, 8.8% small molecules, 5.4% anti-IL17 agents, 4.5% anti-CD20 agents, 2.6% anti IL-1 molecules, 1.6% anti-IL12/23 agents and 0.8% anti-BAFF agents (1). Forty-seven patients (0.65%) were infected by SARS-COV-2 (17 males and 30 females, mean age 60.6±15.9 years): 48.94% with rheumatoid arthritis (RA), 38.30% with spondyloarthritis, 8.50% with connective tissue disease and 4.26% with auto-inflammatory disease. The crude case fatality risk (CFR) rate of 14.9% was not statistically different from the 18.3% ($p$=0.076) recorded in the Lombardy COVID-19 surveillance data relating to the same period.

There were two cases (0.6%) among the 325 patients receiving rituximab (RTX), a chimeric monoclonal antibody against the CD20 molecules expressed on the surface of B cells, whose main function is to deplete mature B cells and B cell precursors, and which is approved worldwide to treat non-Hodgkin lymphoma, chronic lymphocytic leukaemia, rheumatoid arthritis, granulomatosis with polyangiitis, and pemphigus vulgaris. As stated in the recent review by Cohen *et al*., RTX has an acceptable safety profile with a low rate of serious infectious events and rare opportunistic infections (2), but the impact of SARS-COV-2 infection on RTX-treated patients is unclear (particularly its direct or indirect effects on B lymphocytes), as is the possible effect of RTX on the production of immunoglobulins for long-term immunity and immunological memory (3).

During the Italian COVID-19 outbreak, EULAR recommended continuing the use of glucocorticoids and synthetic and biological disease-modifying anti-rheumatic drugs in rheumatic patients without suspected/confirmed COVID-19 in order to avoid the increased risk of relapse and morbidity, but did not make any specific suggestions concerning patients newly requiring an RTX cycle or retreatment. On one hand, there is the awareness that continuing immunosuppressive therapy is essential to control the autoimmune disease, while on the other hand the concern of favouring the spreading of COVID-19 infection (4-6).

In May 2020, a group of Italian experts suggested that RTX treatment should also be discontinued in COVID-19 negative rheumatic patients, and Schulze-Koops *et al*. recommended particular caution when using RTX to treat patients with rheumatic diseases (7, 8).

**Table I.** Patients affected by COVID-19 undergoing rituximab treatment.

| | Patient 1 | Patient 2 |
|---|---|---|
| Age | 55 | 32 |
| Sex | Female | Female |
| Smoker | No | No |
| Rheumatological diagnosis | RA + cryoglobulinaemia | Scleroderma |
| Disease duration | 10 years | 8 years |
| Co-morbidities | Arterial hypertension (ischaemic stroke, DVT in protein S deficiency, HCV infection treated with DAA) | Interstitial lung disease |
| Rheumatological treatment | RTX | RTX, iloprost |
| Months from last RTX cycle | 10 | 4 |
| Concomitant steroids | – | Yes |
| Concomitant treatments | – | – |
| COVID-19 outcome | Recovery | Death |

During the Italian lockdown (March-May 2020), six of the ten rheumatology departments involved in our study decided to postpone non-urgent infusions in order to avoid exposing patients to hospital or care facility risks, but five departments had to treat 17 new patients with active disease (five with severe active RA, three with IgG4-related disease, three with granulomatosis and polyangiitis, two with scleroderma-related interstitial lung disease, two with myositis, one with severe scleroderma-related arthritis, and one with cryoglobulinaemic vasculitis).

Analysis of the two patients undergoing chronic RTX treatment who developed COVID-19 showed that one (a 55-year-old female who had been affected by RA and HCV-related cryoglobulinaemia for 10 years) was hospitalised but recovered without sequelae after ten days, and the other (a 32-year-old female who had been affected by scleroderma-related interstitial lung disease for eight years) died of COVID-19 induced pneumonia (Table I).

Although the limited data currently available prevents us from drawing any definite conclusions, the long-lasting effects of RTX on B cells certainly deserve further investigation in larger patient cohorts in order to improve our understanding of the reaction of a suppressed immune system during the infectious phase of SARS-COV-2 virus and its ability to develop a long-term immunological memory.

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### References

1. Sarzi-Puttini P, Marotto D, Caporali R *et al*.: Prevalence of COVID infections in a population of rheumatic patients from Lombardy and Marche treated with biological drugs or small molecules: A multicentre retrospective study. *J Autoimmun* 2021; 116: 102545.
2. Cohen MD, Keystone E: Rituximab for rheumatoid arthritis. *Rheumatol Ther* 2015; 2: 99-111.
3. Di Mauro G, Scavone C, Rafaniello C, Rossi F, Capuano A: SARS-Cov-2 infection: Response of human immune system and possible implications for rapid testing and treatment. *Int Immunopharmacol* 2020; 84: 106519.
4. Landewé RB, Machado PM, Kroon F *et al*.: EULAR provisional recommendations for the management of rheumatic and musculoskeletal diseases in the context of SARS-CoV-2. *Ann Rheum Dis* 2020; 79: 851-8.
5. Ferro F, Elefante E, Baldini C *et al*.: COVID-19: the new challenge for rheumatologists. *Clin Exp Rheumatol* 2020; 38: 175-80.
6. Ferro F, Elefante E, Puxeddu I *et al*.: COVID-19: the new challenge for rheumatologists. First update. *Clin Exp Rheumatol* 2020; 38: 373-82.
7. Sarzi-Puttini P, Marotto D, Antivalle M *et al*.: How to handle patients with autoimmune rheumatic and inflammatory bowel diseases in the COVID-19 era: An expert opinion. *Autoimmun Rev* 2020; 19:102574.
8. Schulze-Koops H, Krüger K, Vallbracht I *et al*.: Increased risk for severe COVID-19 in patients with inflammatory rheumatic diseases treated with rituximab. *Ann Rheum Dis* 2020 Aug 4 [Online ahead of print].