

Increased risk for severe COVID-19 in patients with inflammatory rheumatic diseases treated with rituximab

It is currently unknown whether immunosuppressive and/or immunomodulating agents such as biological disease-modifying antirheumatic drugs (bDMARDs) affect the rate and the outcome of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections of patients with inflammatory rheumatic diseases (IRDs). While several national authorities have defined patients under immunosuppressive therapy as at risk for severe COVID-19,¹ accumulating data from individual cases and also from case series, such as a series from Italy published in the *Annals of the Rheumatic Diseases* by Monti *et al*² and a report about patients with immune-mediated inflammatory diseases from New York,³ suggest that baseline use of bDMARDs is not associated with worse COVID-19 outcome. Although the idea of a potentially protective effect of bDMARDs in COVID-19 is intriguing, we feel that extrapolation of these initial data is dangerous and potentially harmful. In particular, some caution may have to be applied when employing rituximab (RTX), a B-cell depleting bDMARD, in patients with immune-mediated disease. This notion may be illustrated by the following observations:


We recently lost two patients with rheumatoid arthritis (RA) treated with RTX to lethal COVID-19. The first patient, a 71-year-old man with rheumatoid factor positive, erosive RA and a history of mild chronic obstructive pulmonary disease was admitted to the hospital with symptoms of severe COVID-19. His RA was well controlled by RTX (2×1000 mg within 14 days every 6 months since 2015) in combination with methotrexate (MTX) 15 mg subcutaneously per week and he has been off daily glucocorticoids since 2017. RTX was well tolerated, no increased infection rate was noted and serum IgG was always within normal limits. As required by label, RTX was always administered with premedication including 50 mg prednisolone. Two weeks after the second RTX infusion in March 2020, the patient presented with a 2-day history of fever (up to 39.5°C), cough and chest pain. SARS-CoV-2 was proven and bilateral COVID-19 pneumonia was diagnosed by clinical examination and chest X-ray. Due to rapidly increasing dyspnoea and renal failure, the patient was transferred to the intensive care unit. Despite antibiotic treatment (piperacillin/tazobactam, followed by meropenem) and nasal high flow therapy, no improvement of the respiratory condition could be achieved. CT scan at that time showed bilateral pneumonia and reticular densifications. Invasive ventilation and increasing inotropic support were subsequently required due to further deterioration. Continuous veno-venous haemofiltration dialysis with cytosorb therapy was initiated. Despite all efforts, the patient died 12 days after admission in multiorgan failure.

The second patient, an 80-year-old woman with erosive RA and a history of mild hypertension and osteoporosis was started on treatment with RTX (2×1000 mg within 14 days) 6 months ago in combination with MTX 10 mg subcutaneously per week and 5 mg/day prednisolone. Her serum IgG was within normal limits. The patient presented to the hospital with sudden onset of fever (up to 39.5°C), dry cough, fatigue and dizziness. SARS-CoV-2 was proven and the patient rapidly deteriorated, requiring invasive ventilation. She developed acute respiratory distress syndrome and passed away despite intensive efforts 17 days after admission in multiorgan failure.

Sustained treatment of IRD with RTX is associated with a decrease in serum IgG and with an increased incidence of certain

viral infections. However, COVID-19 has a mild clinically course in patients with agammaglobulinaemia,⁴ suggesting that protection from severe COVID-19 may be rather independent of serum IgG. In this regard, our patients' serum IgG always was within normal limits. The lesson from our patients may rather argue that they might have been severely immunocompromised by the depletion of B cells and the application of prednisolone (as part of the premedication in patient 1 and as part of the daily treatment in patient 2). Supportive of this assumption is the aggressive course of COVID-19 in patients with common variable immunodeficiency⁴ and the recent observation that glucocorticoids may impose a risk for requiring hospitalisation in patients with IRD infected with SARS-CoV-2.³

Our patients are not the unfortunate exceptions in that a substantial proportion of patients with IRD treated with RTX require hospitalisation when infected with SARS-CoV-2 (eg, 67% of the patients in the National Registry for patients with IRD infected with SARS-CoV-2 in Germany) (Hasseli *et al*, submitted for publication, 2020). Although successful treatment of granulomatosis with polyangiitis in a patient with COVID-19 with RTX has been reported,⁵ RTX may need to be applied with particular caution in patients with IRD. Consequences for future management of patients with RTX therapy could be to perform a SARS-CoV-2 test before applying RTX, to consider reducing the dose of glucocorticoids during application of RTX (despite the requirement noted in the label) and to instruct the patient to strictly follow the measures in place to avoid contact for several days following RTX application.¹ The fatal outcome of COVID-19 in our patient illustrates the need to be extremely vigilant for the potential of complications associated with immunosuppressive therapy in patients with immune-mediated diseases.

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