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Timing of rituximab and immunoglobulin level influence the risk of death for COVID-19 in ANCA-associated vasculitis

Rheumatology key message

- Immunoglobulins, timing and SARS-CoV-2 vaccination should be carefully considered during maintenance with RTX in AAV.

Dear Editor, since rituximab (RTX) primarily interferes with the humoral response, some reports have already highlighted the risk of its use facilitating severe consequences in SARS-CoV-2 infection [1–4]. The latest data coming from the COVID-19 Global Rheumatology Alliance (C19-GRA) physician-reported registry reported the strongest association of RTX with the worst outcomes in rheumatic patients getting SARS-CoV-2 infection [5]. Yet, patients carrying systemic vasculitis or SLE may be at a higher risk of hospitalization from COVID-19 [6]. While the registry collected a large amount of clinical data, unfortunately, the C19-GRA physician-reported registry did not capture the exact timing of infection after RTX administration, the possible role of concurrent glucocorticoids and previous immunosuppression, or, finally, the level of baseline immunoglobulins.

RTX became a licenced therapy for remission induction of ANCA-associated vasculitis (AAV) in 2011, and it has recently been proposed as a treatment option in remission maintenance [7]. Importantly, RTX or CYC are the drugs of choice as induction therapy in severe or life-threatening AAV [7]. Recently, baseline low immunoglobulin levels have been listed among the main risk factors for serious infections under RTX in AAV [8].

From February to December 2020, we evaluated 100 patients (53 females; 47 males) with the diagnosis of granulomatosis with polyangiitis (56%), granulomatosis eosinophilic with polyangiitis (31%), or microscopic polyangiitis (MPA) (13%). SARS-CoV-2 infection was diagnosed in 2 cases (2%) by nose–pharyngeal (NP) swab. Notably, the incidence of SARS-CoV-2 infection in the general population of the same geographical area was 6.3% (29 680 cases/466 700 inhabitants). In that period, RTX was employed as maintenance treatment in 15 patients with AAV. Low doses of glucocorticoids were concomitantly taken by 6 out of the 15 patients ($\leq$ 5 mg/day of prednisone equivalent). Both the two cases of SARS-CoV-2 infection were undergoing RTX as remission maintenance.

Patient 1 (a 73 year-old woman), with ANCA-PR3 positive granulomatosis with polyangiitis was treated with RTX as remission induction and subsequently she was undergoing maintenance therapy with RTX since October 2017. Previously, cyclophosphamide (cumulative dose of 12 g) had failed as induction (from September 2016 to September 2017). Last RTX infusion (500 mg fixed six-month dose) was on November 9, 2020, and, at the time of infusion, she was in remission (BVASv3 0, ANCA-PR3 + 0 UA/ml), while taking 2.5 mg/day of prednisone equivalent. IgG level was 456 mg/dl just before RTX last infusion. COVID-19 was diagnosed by NP swab on December 24, 2020 (45 days after RTX infusion). At that time, she was B-depleted (CD19 + 0%), and IgG level was 455 mg/dl. COVID-19 rapidly evolved into severe respiratory failure. On January 10, 2021, she was admitted to the intensive care unit and received glucocorticoids, piperacillin/tazobactam, enoxaparin, and oxygen therapy. NP swab persisted positive and no anti-SARS-CoV-2 IgM or IgG production above the cut-off (cut-off value 10 AU/ml) was observed. Finally, she died on January 17, 2021, 25 days after COVID-19 diagnosis.

Patient 2 (a 74-year-old woman) affected by ANCA-MPO positive MPA, was maintaining remission with RTX since December 2019, after induction with RTX occurred in June 2019. Previously, CYC (cumulative dose of 9 g) was employed as induction (from April 2016 to January 2017) followed by azathioprine, which was suspended due to disease relapse. Last RTX infusion (500 mg fixed six-month dose) was given on August 17, 2020. At the time of infusion, she was in remission (BVASv3 0, ANCA-MPO+ 12 UA/ml), while taking 5 mg/day of prednisone equivalent. NP swab was done on November 25, 2020 (100 days after RTX infusion) because of a close contact with a COVID-19 positive case. Anyway, she never developed symptoms of COVID-19. At the time of the first positive NP swab, she was B-depleted (CD19 + 0%), and IgG level was 866 mg/dl. The NP swab became negative on January 27, and only anti-SARS-CoV-2 IgG antibodies at low level (39 AU/ml, cut-off value 10 AU/ml) were detected.

Timing of RTX and IgG levels were quite different between the two cases (Fig. 1), and may have conditioned the final outcome greatly. SARS-CoV-2 viral load was not available for these cases, but it could be of importance for the outcome of patients undergoing RTX who develop COVID-19. Importantly, while AAV patients do not appear at higher risk of COVID-19 than the general population, those patients undergoing anti-CD20 therapy could be at higher risk of developing critically ill COVID-19. Thus, patients needing RTX require prioritization for SARS-CoV-2 vaccination.

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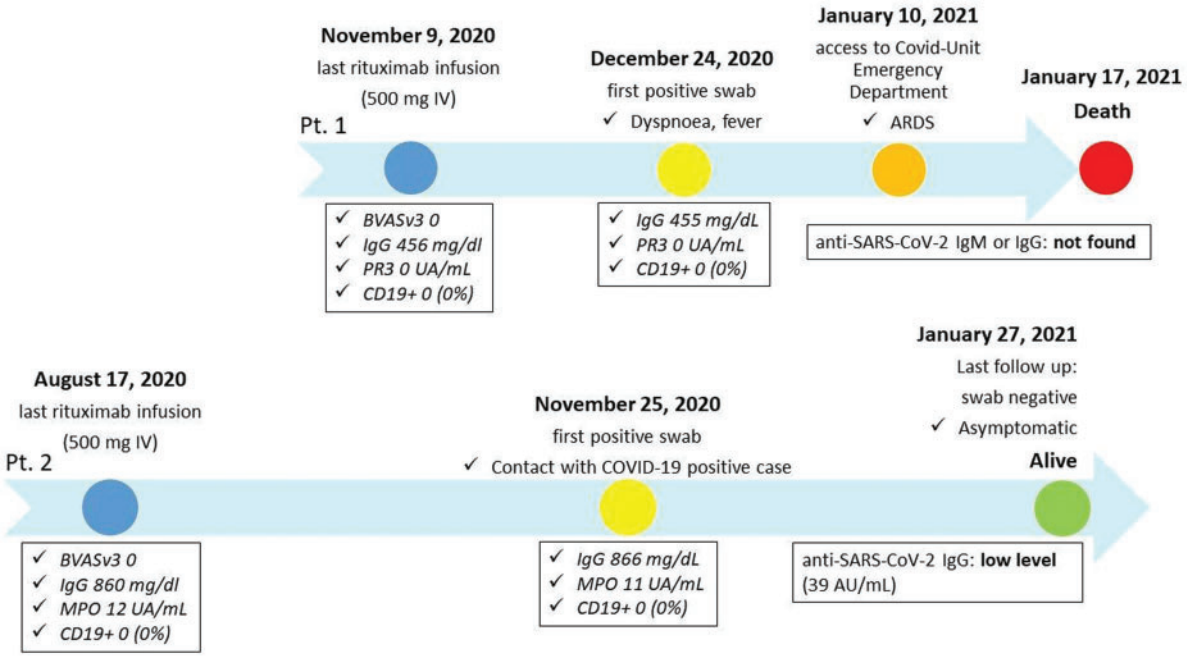
Fig. 1 Summary of the course of COVID-19 in the two AAV cases



AAV: ANCA-associated vasculitis; ARDS: acute respiratory distress syndrome; Pt.: patient.

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Data availability statement

All data relevant to the study are included in the article. No additional data are available.

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References

1 Tepasse P-R, Hafezi W, Lutz M *et al.* Persisting SARS-CoV-2 viraemia after rituximab therapy: two cases with fatal outcome and a review of the literature. Br J Haematol 2020;190:185–8.

2 Kant S, Morris A, Ravi S *et al.* The impact of COVID-19 pandemic on patients with ANCA associated vasculitis. J Nephrol 2020;34:185–6.

3 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.

4 Schulze-Koops H, Krueger K, Vallbracht I, Hasseli R, Skapenko A. Increased risk for severe COVID-19 in patients with inflammatory rheumatic diseases treated with rituximab. Ann Rheum Dis 2020; Advance Access published 26 June 2020. doi: 10.1136/annrheumdis-2020-218075

5 Strangfeld A, Schäfer M, Gianfrancesco MA *et al.* Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis 2021; Advance Access published 27 January 2021. doi: 10.1136/annrheumdis-2020-219498

6 Gianfrancesco M, Hyrich KL, Al-Adely S *et al.* Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis 2020;79:859–66.

7 Ntatsaki E, Carruthers D, Chakravarty K *et al.* BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis. Rheumatology (Oxford) 2014;53:2306–09.

8 McClure ME, Zhu Y, Smith RM *et al.* Long-term maintenance rituximab for ANCA-associated vasculitis: relapse and infection prediction models. Rheumatology (Oxford) 2021;60:1491–501.