

**Title:** Timing of Rituximab and immunoglobulin level influence the risk of death for COVID-19 in ANCA-associated vasculitis

**Authors:** Luca Quartuccio, Elena Treppo, Marco Binutti, Giulia Del Frate, Salvatore De Vita

**Affiliation:**

Rheumatology Clinic ASUFC, Department of Medicine (DAME), University of Udine, Udine, Italy

**Corresponding author:**

Luca Quartuccio, M.D., Ph.D.

Rheumatology Clinic, Department of Medicine (DAME) University of Udine, ASUFC, Udine, Italy

Email to [luca.quartuccio@uniud.it](mailto:luca.quartuccio@uniud.it)

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Dear Editor,

Since RTX primarily interferes with the humoral response, some reports have already highlighted the risk of facilitating severe consequences in SARS-CoV-2 infection by RTX (1–4). The latest data coming from the COVID-19 Global Rheumatology Alliance (C19-GRA) physician-reported registry reported the strongest association of rituximab (RTX) with the worst outcomes in rheumatic patients getting SARS-CoV-2 infection (5). Yet, patients carrying systemic vasculitis or systemic lupus erythematosus may be at higher risk of hospitalisation due to 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, and, finally, the level of baseline immunoglobulins.

RTX became a licenced therapy for remission induction of ANCA-associated vasculitis (AAV) in 2011, and it has been recently proposed even as a treatment option in remission maintenance (7). Importantly, RTX or cyclophosphamide 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 (GPA) (56%), granulomatosis eosinophilic with polyangiitis (EGPA) (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% (29680 cases/466700 inhabitants). In that period, RTX was employed as maintenance in 15 patients with AAV. Low doses of glucocorticoids were concomitantly taking by 6 out of 15 ( $\leq 5$  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 GPA 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 grams) 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, cyclophosphamide (cumulative dose of 9 grams) 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 (Figure 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.

### **Competing interests**

There are no competing interests for any author

### **Contributorship**

Conceptualization, Luca Quartuccio; Data curation, Elena Treppo; Investigation, Luca Quartuccio, Elena Treppo, Marco Binutti, Giulia Del Frate; Methodology, Luca Quartuccio, Elena Treppo; Project administration, Luca Quartuccio; Supervision, Luca Quartuccio, Salvatore De Vita; Validation, Luca Quartuccio, Elena Treppo; Writing – original draft, Luca Quartuccio, Elena Treppo; Writing – review & editing, Luca Quartuccio, Elena Treppo, Marco Binutti, Giulia Del Frate, Salvatore De Vita.

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### **Ethical approval information**

The study was conducted in accordance with the ethical principles of the Helsinki Declaration, and approved by the local Ethics Committee (ID number CEUR-2020-Os-129).

### **Data sharing statement**

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

## **Key message**

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

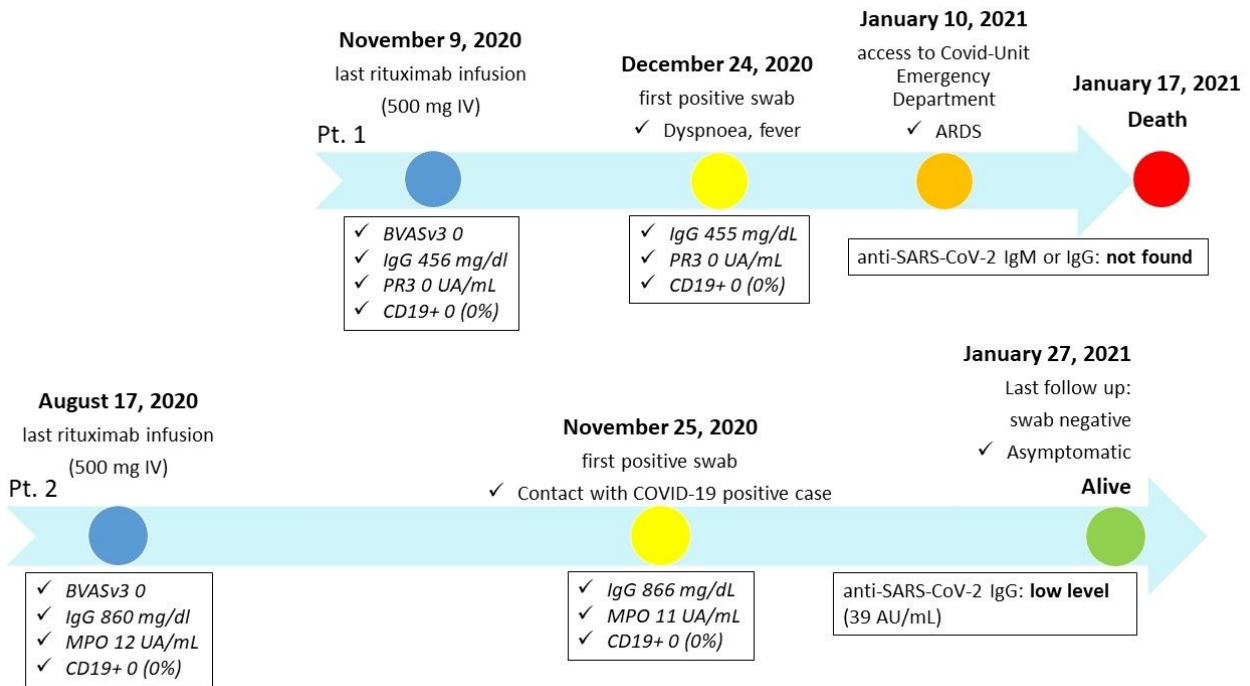
## **References**

1. Tepas P-R, Hafezi W, Lutz M, Kühn J, Wilms C, Wiewrodt R, 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(2):185–8.
2. Kant S, Morris A, Ravi S, Floyd L, Gapud E, Antichos B, et al. The impact of COVID-19 pandemic on patients with ANCA associated vasculitis. *J Nephrol.* 2020 Oct 8:1–6. doi: 10.1007/s40620-020-00881-3.
3. Guilpain P, Le Bihan C, Foulongne V, Taourel P, Pansu N, Maria ATJ, 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(1):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 Jun 26:annrheumdis-2020-218075. doi: 10.1136/annrheumdis-2020-218075.
5. Strangfeld A, Schäfer M, Gianfrancesco MA, Lawson-Tovey S, Liew JW, Ljung L, 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 Jan 27:annrheumdis-2020-219498. doi: 10.1136/annrheumdis-2020-219498.
6. Gianfrancesco M, Hyrich KL, Al-Adely S, Carmona L, Danila MI, Gossec L, 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(7):859-866. doi: 10.1136/annrheumdis-2020-217871.

7. Ntatsaki E, Carruthers D, Chakravarty K, D'Cruz D, Harper L, Jayne D, et al. BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis. *Rheumatology (Oxford)*. 2014;53(12):2306–2309.6.
8. McClure ME, Zhu Y, Smith RM, Gopaluni S, Tieu J, Pope T, et al. Long-term maintenance rituximab for ANCA-associated vasculitis: relapse and infection prediction models. *Rheumatology (Oxford)*. 2020 Nov 3:keaa541. doi: 10.1093/rheumatology/keaa541

**Legend to the Figure.**

**Figure 1.** Summary of the course of COVID-19 in the two AAV cases. ARDS, acute respiratory distress syndrome.



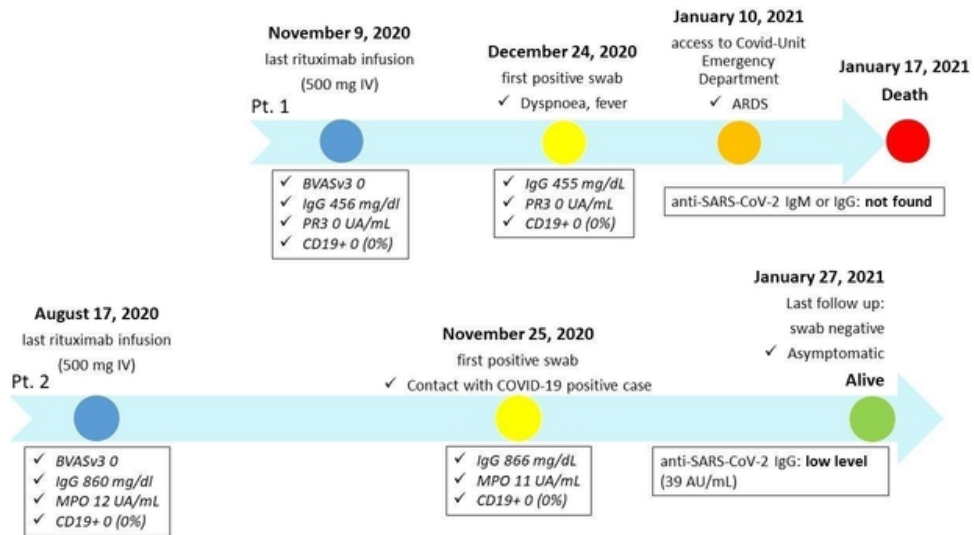


Figure 1. Summary of the course of COVID-19 in the two AAV cases. ARDS, acute respiratory distress syndrome.

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