Onset of rheumatoid arthritis after COVID-19: coincidence or connected?

Derksen, V.F.A.M.; Kissel, T.; Lamers-Karnebeek, F.B.G.; Bijl, A.E. van der; Venhuizen, A.C.; Huizinga, T.W.J.; ... ; Woude, D. van der

The onset of rheumatoid arthritis after COVID-19 – coincidence or connected?

Authors: V.F.A.M. Derksen MD (1), T. Kissel MSc (1), F.B.G. Lamers – Karnebeek MD (2), A.E. van der Bijl MD PhD (3), A.C. Venhuizen MD (4), prof T.W.J. Huizinga MD PhD (1), prof R.E.M. Toes PhD (1), A.H.E. Roukens MD PhD (5), D. van der Woude MD PhD (1)

Affiliations:

(1) Leiden University Medical Center, department of Rheumatology, Leiden, the Netherlands
(2) Hospital Bernhoven, department of Rheumatology, Uden, the Netherlands
(3) Isala Hospitals, department of Rheumatology, Zwolle, the Netherlands
(4) Hospital Rivierenland, department of Rheumatology, Tiel, the Netherlands
(5) Leiden University Medical Center, department of Infectious Diseases, Leiden, the Netherlands

Address for correspondence:

Veerle Derksen MD

Leiden University Medical Center, Department of Rheumatology, C1-R-041

Albinusdreef 2, PO Box 9600, 2300 RC Leiden, the Netherlands

Phone: +31-715263598

E-mail: v.f.a.m.derksen@lumc.nl

Wordcount: 651

Figures: 1

Supplementary file: 1

COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), can lead to severe inflammation and has been suggested to induce autoimmune phenomena. Multiple studies have reported autoantibodies in patients with COVID-19, particularly anti-cardiolipin, anti-β2 glycoprotein I and anti-nuclear antibodies.[1, 2] Anti-citrullinated protein antibodies (ACPA) and flaring of rheumatoid arthritis (RA) after SARS-Cov-2 infection have also been described.[1, 3] However, it is unclear how often ACPA occur after COVID-19 and whether they differ from ACPA normally found in RA patients.

We have therefore performed a detailed investigation into ACPA-positivity after COVID-19. To determine the seroprevalence of ACPA after COVID-19, ACPA was measured using routine tests or in-house enzyme-linked immunosorbent assay (ELISA) in 61 patients visiting the post-COVID outpatient clinic of the LUMC 5 weeks after hospitalization. None of the patients tested positive for ACPA, except two patients previously diagnosed with ACPA-positive RA. Thus, we could not observe an increase in ACPA-positivity after COVID-19.

Furthermore, we identified five patients across various Dutch rheumatology clinics presenting with polyarthritis compatible with RA after SARS-CoV-2 infection. To study the impact of COVID-19 on disease presentation, we closely examined their clinical phenotype and autoantibody characteristics (Supplementary table S1). All had suffered from moderate to severe COVID-19. On average, joint complaints started 6.6 weeks after infection, although two patients reported symptoms before infection. 4/5 patients fulfilled the ACR 2010 criteria for RA. Three patients were phenotypically very similar to regular new-onset RA patients. Patient 3 had a history of seronegative RA and had been in DMARD-free remission for 5 years. She flared 6 weeks after SARS-CoV-2 infection. Patient 2 had a remarkably different presentation. He was admitted with acute polyarthritis and high inflammatory markers 6 weeks after COVID-19. Pneumonia with reactive polyarthritis or septic polyarthritis were considered and treatment was started accordingly. ACPA-level was low positive. The patient died unexpectedly after two days and autopsy revealed dilating myocarditis of unclear underlying cause. No causative pathogen, nor compelling evidence of autoimmunity, could be identified.

Previous studies have shown that RA-patients are most often either seronegative or triple-positive for rheumatoid factor, ACPA and anti-carbamylated protein antibodies. ACPA IgM and IgA are most frequently found within patients positive for ACPA IgG.[4] Autoantibody measurements on sera of the post-COVID polyarthritis patients using in-house ELISA's,[4] revealed patterns very similar to RA (figure 1A) with two patients being completely seronegative, and three patients positive for a range of autoantibodies at presentation. Sera prior to presentation to the rheumatologist are not available.

A unique feature of ACPA IgG in RA patients is that they harbour glycans not only in their Fc-part, but also in their variable domains (V-domains)[5]. We analysed the ACPA IgG V-domain glycosylation profiles of the above-mentioned 3 ACPA-positive post-COVID patients and established RA patients (Supplementary table S1) using UHPLC.[5] In all post-COVID samples, the percentage of ACPA V-domain glycosylation was increased compared to total IgG (figure 1B), similar to regular RA. Inflammatory conditions, among which COVID-19, can induces changes in the composition of antibody Fc-glycans[6]. A detailed examination of the specific ACPA IgG V-domain glycan traits revealed a significant decrease in bisecting N-Acetylglucosamine containing moieties (G2FBS1, G2FBS2) after COVID-19 (figure 1C), comparable to patterns described for total IgG Fc-glycosylation post-COVID.[6] The biological causes and consequences of these glycosylation changes currently remain unclear.

Limitations of this study include the small sample size and limited follow-up duration after COVID-19. Although autoantibody responses can develop rapidly after (SARS-Cov-2) infections, replication in a larger cohort with a longer follow-up would be valuable. Furthermore, part of the samples were measured on in-house instead of commercial tests. However, the characteristics of these assays appear very comparable based on previous experience.

In conclusion, we found that the seroprevalence of ACPA is not increased after COVID-infection and that patients presenting with polyarthritis post-COVID resemble regular RA patients, both regarding clinical phenotype and autoantibody characteristics. Based on these data, it appears that RA post-COVID may be coincidence rather than connected.

Figure legend: Figure 1. A Auto-antibody measurements using in-house ELISA's: Rheumatoid factor (RF), anti-citrullinated protein antibody (ACPA) and anti-carbamylated protein antibody (anti-CarP) isotype levels per patient. White – seronegative, Gradient light to dark blue – low to highest levels, normalized against maximum detection limit ELISA per antibody isotype. B Percentage of variable domain glycosylation (mean, SD). Average value of duplicates plotted. V- domain glycosylation in ACPA IgG post-COVID is significantly increased compared to total IgG ($p<0.05$;Mann-Whitney U test), no significant difference between ACPA IgG V-domain glycosylation post-COVID and in regular RA (disease characteristics in supplementary table S1). C Percentage of specific glycan traits of all ACPA IgG V-domain glycans (mean, SD). Average value of duplicates plotted. Glycan trait G2FS2 without bisecting N-Acetylglucosamine is significantly increased, while G2FBS1, a glycan traits with bisecting N-Acetylglucosamine is significantly decreased post-COVID-19 ($p<0.05$; Mann-Whitney U test). Blue square – N-Acetylglucosamine (B when bisecting), green circle – mannose, red triangle – Fucose (F), yellow circle – galactose (G), purple diamond – sialic acid (S).

Statements

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Data Availability Statement All glycan analysis data are available upon reasonable request.

Funding The authors did not receive specific funding for this research.

Competing interests None declared.

Patient consent for publication Patients did not object to the use of their anonymized data.

Contributorship statement: VD, TH, RT and DvdW designed the study. FLK, AvdB, AV and AR collected the patient data and materials. VD and TK performed the experiments. VD, TK and DvdW analysed the data. VD drafted the manuscript. All authors revised the manuscript critically and gave approval of the version to be published.

References

1. Vlachoyiannopoulos PG, Magira E, Alexopoulos H, et al. Autoantibodies related to systemic autoimmune rheumatic diseases in severely ill patients with COVID-19. *Ann Rheum Dis*, 2020;79(12):1661-3. doi: 10.1136/annrheumdis-2020-218009
2. Borghi MO, Beltagy A, Garrafa E,et al. Anti-Phospholipid Antibodies in COVID-19 Are Different From Those Detectable in the Anti-Phospholipid Syndrome. *Front Immunol*, 2020; 11:584241. doi: 10.3389/fimmu.2020.584241
3. Perrot, L, Hemon M, Busnel JM, et al. First flare of ACPA-positive rheumatoid arthritis after SARS-CoV-2 infection. *Lancet Rheumatol* 2021;3(1):E6-E8. doi:https://doi.org/10.1016/S2665-9913(20)30396-9
4. De Moel EC, Derksen VFAM, Stoeken G, et al. Baseline autoantibody profile in rheumatoid arthritis is associated with early treatment response but not long-term outcomes. *Arthritis Res Ther*, 2018;20(1):33. doi: 10.1186/s13075-018-1520-4
5. Kissel T, Van Schie KA, Hafkenscheid L, et al. On the presence of HLA-SE alleles and ACPA-IgG variable domain glycosylation in the phase preceding the development of rheumatoid arthritis. *Ann Rheum Dis*, 2019;78(12):1616-20. doi:10.1136/annrheumdis-2019-215698.
6. Larsen MD, De Graaf EL, Sonneveld ME, et al. Afucosylated IgG characterizes enveloped viral responses and correlates with COVID-19 severity. *Science*, 2020;eabc8378. doi: 10.1126/science.abc8378