Concerns and opportunities related to discontinuation of treatment in rheumatoid arthritis

Ouwerkerk, L. van


8

Presence of SARS-CoV-2 antibodies in patients with COVID-19 like symptoms from the IENIMINI cohort

L van Ouwerkerk, D van der Woude, T Rispens, CF Allaart, TWJ Huizinga

Published: Scandinavian Journal of Rheumatology. 2022 Jul 14;1-4.

ABSTRACT

OBJECTIVES: To evaluate the relation between reported COVID-19 like symptoms and presence of SARS-CoV-2 antibodies in patients with an immune mediated inflammatory disorder or post solid organ transplantation (IMIDT) with and without immunosuppressive medication (imed) and controls.

METHODS: The IENIMINI cohort was a prospective cohort study set up in the Netherlands in march 2020, with 2-monthly (paper) or weekly (online) questionnaires about COVID-19 like symptoms. Participants from this cohort who reported these symptoms between March 2020 and November 2020 were approached for this sub study. SARS-CoV-2 antibodies were tested using a total antibody assay.

RESULTS: Of the 1203 participants approached, 629 agreed to participate and were sent a finger prick test. 565 participants collected a capillary blood sample of which 562 were usable. Analysis showed that 57/202(28.2%) of the tested IMIDT group with imed, 48/163(29.4%) of the IMIDT group without imed and 69/197(35.0%) of the control group tested positive for SARS-CoV-2 antibodies. Seroprevalence of SARS-CoV-2 antibodies between males/females, biological disease-modifying antirheumatic drug (DMARD) user or not, or having had a serious disease period (defined as episode with dyspnea and fever) or not, were not statistically different between the three groups.

CONCLUSIONS: Approximately 30% of patients who had reported COVID-19 like symptoms had SARS-CoV-2 antibodies. The seroprevalence for SARS-CoV-2 antibodies after reported COVID-19 like symptoms was similar in IMIDT patients with and without imed compared to controls.

Introduction

During the first wave of the pandemic there appeared to be no increased risk for COVID-19 disease in patients with autoimmune diseases.(1-4) However, generally more aware of infectious risks, these patients may have taken more extreme caution than the general population.(5) In addition, in the initial (retrospective) registries mild infections may have been overlooked. Such bias might have been avoided by the IENIMINI study, a prospective registration of symptoms in both patients with an autoimmune or autoinflammatory disease or who had had an organ transplantation (IMIDT) with or without immunosuppressive medication (imeds) and a representative comparative group.(1) With the ongoing SARS-CoV-2 pandemic there are concerns that patients with an IMIDT with or without imeds may not develop sufficient protective antibodies after infection or vaccination.(6,7) Possibly causing less protection against (severe) illness after re-infection. We compared the seroprevalence of SARS-CoV-2 antibodies between such patients, with or without imeds and controls from the general population.

Methods

We included patients and controls from the IENIMINI cohort study who in that study had reported to have COVID-19 like symptoms (CLS). The IENIMINI cohort was set up in March 2020 with as main objective to prospectively register CLS in IMIDT patients with or without imeds and in controls without such disease or medication. Patient and control selection is described elsewhere.(1)

Participants of the IENIMINI cohort who reported to have CLS at least once between March 2020 and November 2020 were invited by mail to participate in this SARS-CoV-2 antibody sub study. They were instructed that they could not participate if they already had been vaccinated. Those who signed informed consent were sent a finger prick test kit. Participants conducted the finger prick test themselves and sent the samples to Sanquin, the analyzing partner of this study. Samples were collected between April and June 2021. The serological bridging assay for the detection of antibodies against the receptor-binding domain of the spike protein of SARS-CoV-2 (IgG, IgA and IgM) used in this study was developed by Sanquin and has a sensitivity of 98.1% and a specificity of 99.5%.(8) The cut-off for the normalized optical density was 0.10 and samples close to this cut-off were measured twice to confirm the result.

Since the IENIMINI cohort is an explorative cohort, no adjustments on multiple testing have been made. Descriptive statistics were used and to test for statistical significance chi-square tests were done. Statistical analysis were performed by Stata SE version 16 (StataCorp LP).

Results

Of the 3172 participants of the IENIMINI cohort, 1203 reported to have had at least one disease episode between March 2020 and November 2020. These 1203 participants were approached for this finger prick sub study. Of these, 629 sent in a signed informed consent form and ultimately, 565 sent in a sample to be tested. Baseline characteristics of the 629 participants who signed informed consent and of the 574 who were approached but did not participate were similar (supplementary table 1). Three patients were excluded from analysis because they patients appeared to be already vaccinated at the time the finger prick test was done. This resulted in 562 samples available for analysis (supplementary figure 1). Baseline demographic characteristics of the participants were similar between the groups except for more self-reported heart and lung disease and diabetes mellitus in the IMIDT groups (table 1).

Table 1. Baseline characteristics

	Controls N=197	**IMIDT without imed N=163**	**IMIDT with imed N=202**
Age (years, mean (SD))	55.0 (12.8)	54.4 (14.2)	54.8 (14.0)
Female N (%)	145 (74)	108 (66)	127 (63)
BMI kg/m2, mean (SD)	25.6 (4.1)	25.6 (5.0)	26.1 (5.2)
Daily alcohol use N (%)	90 (48.9)	63 (44.0)	81 (40.5)
Current smokers N (%)	24 (12.8)	12 (8.2)	12 (6.0)
Self-reported heart disease N (%)	25 (13.6)	29 (20.7)	48 (23.9)
Self-reported lung disease N (%)	57 (31.0)	73 (52.1)	91 (45.5)
Self-reported diabetes mellitus N (%)	8 (4.4)	8 (5.8)	20 (10.1)

Abbreviations: BMI=Body Mass Index; N=number; SD= standard deviation; imed=immunosuppressive medication; IMIDT= with immune mediated inflammatory disorders or transplant organ

Of all tested samples, 31.0% were positive for SARS-CoV-2 antibodies. This result was similar across the 3 groups (35.0% in the controls, 29.4% in the IMIDT group without imed and 28.2% in the IMIDT group with imed, p-value=0.300) (table 2). Seropositivity was similar in female (31.3%) and male (30.2%) participants, without major differences across the 3 groups (supplementary table 2). Also, there was no significant difference in seropositivity between patients who reported more severe symptoms (defined as a disease episode with both dyspnea and fever) and who reported milder symptoms (33.9% and 31.2%, respectively, p=0.681). Small number of hospital admissions (N=18) did not allow meaningful analysis of this outcome.

Table 2. Antibody test results

	IMIDT with imed N=202		**IMIDT without imed N=163**	**Controls N=197**
SARS-CoV-2 positive N(%)	57 (28)		48 (29)	69 (35)
	GC use	-	-	
	Yes 72	No 130		
SARS-CoV-2 positive N(%)	23 (32)	34 (26)	-	-
	bDMARD use	-	-	
	Yes 56	No 146		
SARS-CoV-2 positive N(%)	15 (27)	42 (29)	-	-
	TNF inhibitor use	-	-	
	Yes 40	No 162		
SARS-CoV-2 positive N(%)	8 (20)	49 (30)	-	-
	RTX or Cyc use	-	-	
	Yes 8	No 194		
SARS-CoV-2 positive N(%)	5 (63)	52 (27)	-	-

Abbreviations: bDMARD=biological disease modifying antirheumatic drug; Cyc=cyclophosphamide; GC=glucocorticoids (mono or combination therapy); imed=immunosuppressive medication; IMIDT= with immune mediated inflammatory disorders or transplant organ; N=number; RTX=rituximab; TNF=tumor necrosis factor

Of the 202 IMIDT with imed participants, 72 (35.6%) used glucocorticosteroids (GC), either as mono-therapy or in combination with other imed (supplementary table 3). 31.9% of GC users tested positive for SARS-CoV-2 antibodies compared to 26.2% of non-GC users (p=0.381). Seropositivity was similar between patients who used or did not use a biological Disease Modifying Antirheumatic Drug (bDMARD), either as mono-therapy of in combination with other imed (26.8% and 28.8% respectively, p=0.779) and more specifically between TNF inhibitor users and patients on other imeds (20.0% vs 30.3%, p-value 0.197). Only 8 patients used either rituximab or cyclophosphamide. Five of these (62.5%) tested positive for SARS-CoV-2 antibodies, compared to 52 (26.8%) of the patients on other imed (p-value 0.028).

Discussion

We evaluated the prevalence of SARS-CoV-2 antibodies in patients in our IENIMINI cohort who had reported COVID-19 like symptoms. We found overall seropositivity in 31.0%, with similar percentages in patients with an IMIDT with and without imed and in controls.

The findings in this cohort provide a positive view on antibody formation after experiencing CLS within IMIDT patients with or without imed. The 31.0% seropositivity is much higher than previously reported in similar patient groups and healthy controls. A cohort study in patients with immune-mediated inflammatory diseases (IMID) treated with cytokine inhibitors showed a lower prevalence of SARS-CoV-2 IgG (0.75%) compared to a combined cohort of healthy participants and firefighters (2.27%).(9) In contrast to our study, they included individuals regardless of whether they had had symptoms. Moreover, only IgG was tested which could have led to missing cases who had been recently ill and in whom IgG had not been produced yet. Also, the study was conducted earlier (first half year of 2020) than ours (first quarter of 2021) which also could have led to the difference in seroprevalence.

Among our participants, there appeared to be no association between having had a more severe disease episode(s) or having had only mild complaints. Furthermore, different groups of immunosuppressive medication which can alter antibody production after infection were not associated with differences in antibody prevalence compared to other imed users, except for the rituximab or cyclophosphamide users. Remarkably, despite the B-cell depleting properties of these medications, in this very small group (8 patients) we found a higher antibody positivity than among users of other imeds. Their reported symptoms and number of episodes were comparable to those reported by non-rituximab/cyclophosphamide users (resp. 16.7 vs 10.8% of symptoms included both dyspnea and fever, p=0.648 and resp. 6.1% vs 8.3% of patients reported ≥1 episode of CLS, p=0.107). Previous research has shown that patients with IMIDT and/or use of imeds are following COVID-19 preventive measures more strictly because they know they are a risk group for infections.(5) This extra caution may have led to staying more indoors by these patients compared to healthy controls. However, rituximab and cyclophosphamide are both administered intravenously which requires hospital visits and potentially more laboratory checks, possibly causing an extra risk of COVID-19 exposure, to which they also may have been more vulnerable.

By using the IENIMINI cohort we were one of the few studies to date to be able to select IMIDT patients and controls who prospectively had reported COVID-19 like symptoms, ranging from mild (e.g. resembling a common cold) to more severe (including dyspnea and fever). The prevalence of SARS-CoV-2

antibodies in our cohort can therefore be a realistic reflection of the SARS-CoV-2 antibody prevalence in controls and patients with IMIDT in the Netherlands who experienced CLS. However, although the antibody screentest has been validated by Sanquin, we cannot completely rule out the possibility of cross-reacting antibodies raised by endemic coronavirus infections, causing false positive results.(10) We also cannot rule out the possibility that more IENIMINI participants were infected but remained asymptomatic and were not selected for this sub-study. Nor can we speculate on the percentage of patients who were infected, were asymptomatic, but due to their illness and/or medication did not (or no longer) have detectable SARS-CoV-2 antibodies. Our test method does also not provide antibody titers/levels. With the ongoing pandemic again it becomes apparent that also patients with antibodies can fall ill, although rarely as serious as patients without antibodies.(11) It is possible that antibody titers play a role in susceptibility for (re)infection. Thus, without information on antibody titers, finding a high seroprevalence among our patients is only partly reassuring. As our IENIMINI cohort study period covers the first months of the pandemic with questionnaires when routine testing was not available, we cannot match symptoms and/or serology outcomes with PCR test results or disease episodes, nor can we report about the median time between infection and antibody presence. The cross-sectional design of this study makes it impossible to speculate on how long antibodies against SARS-CoV-2 remain. A review on IgM and IgG response after SARS-CoV-2 infection reports that IgG can last for six to eight months.(12) However, this review was not focused on IMIDT patients and included only one study about patients who had a kidney transplantation. Further research is needed to learn more about the efficacy and lasting presence of SARS-CoV-2 antibodies in patients with IMIDT after reporting COVID-19 like symptoms or vaccination.

In conclusion, in patients with an IMIDT with or without imed and controls after reporting COVID-19- like symptoms we found a similar prevalence of SARS-CoV-2 antibodies.

References

1. van Ouwerkerk L et al. Prospective study into COVID-19-like symptoms in patients with and without immune mediated inflammatory diseases or immunomodulating drugs. Ann Rheum Dis. 2021
2. Conticini E, et al. COVID-19 pneumonia in a large cohort of patients treated with biological and targeted synthetic antirheumatic drugs. Ann Rheum Dis. 2020
3. Fredi M et al. COVID-19 in patients with rheumatic diseases in northern Italy: a Single centre observational and case-control study. Lancet Rheumatol. 2020
4. Moiseev S et al. Rheumatic diseases in intensive care unit patients with COVID-19. Ann Rheum Dis. 2020
5. Hooijberg F et al. Patients with rheumatic diseases adhere to COVID-19 isolation measures more strictly than the general population. Lancet Rheumatol. 2020
6. Fagni F et al. COVID-19 and immune-mediated inflammatory diseases: effect of Disease and treatment on COVID-19 outcomes and vaccine responses. Lancet Rheumatol. 2021
7. Friedman MA et al. Impact of disease-modifying antirheumatic drugs on vaccine immunogenicity in patients with inflammatory rheumatic and musculoskeletal diseases. Ann Rheum Dis. 2021
8. Vogelzang EH et al. Development of a SARS-CoV-2 total antibody assay and the Dynamics of antibody response over time in hospitalized and non-hospitalized patients with COVID 19. J Immunol. 2020
9. Simon D et al. Patients with immune-mediated inflammatory diseases receiving cytokine inhibitors have lowprevalence of SARS-CoV-2 seroconversion. Nat Commun. 2020
10. Sjöwall J et al. SARS-CoV-2 Antibody Isotypes in Systemic Lupus Erythematosus Patients Prior to Vaccination: Associations With Disease Activity, Antinuclear Antibodies, and Immunomodulatory Drugs During the First Year of the Pandemic. Front Immunol. 2021
11. Cook C et al. Clinical characteristics and outcomes of COVID-19 breakthrough infections among vaccinated patients with systemic autoimmune rheumatic diseases. Ann Rheum Dis. 2022
12. Knies A et al. Persistence of humoral response upon SARS-CoV-2 infection. Rev Med virol. 2021