

Seroprevalence of SARS-CoV-2 antibodies in patients with autoimmune inflammatory rheumatic diseases

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Abstract

Objective

To assess the prevalence of anti-SARS-CoV-2 antibodies in autoimmune inflammatory rheumatic disease (AIIRD) patients, and to define clinical factors associated with seropositivity.

Methods

A cross sectional study was conducted at a tertiary rheumatology department in Israel. Consecutive patients completed a questionnaire and were tested for SARS-CoV-2 anti-nucleoprotein IgG (N-IgG). If this was positive, an anti-S1/S2 spike IgG (S-IgG) test was done. If both were positive, the patient was considered seropositive. Seropositive patients were retested after 3 months.

Results

The study included 572 AIIRD patients. Thirty patients were found seropositive, for a seroprevalence of 5.24%. The seropositive rate was significantly lower for patients treated with immunosuppressive medications (3.55%, $p \leq 0.01$), and specifically for patients treated with biologic disease-modifying anti-rheumatic drugs (bDMARDs) (2.7%, $p \leq 0.05$). These associations remained significant in the multivariate regressions adjusting for age, sex and exposure to a known COVID-19 patient. A second serology test 3 months later was collected in 21 of the 30 seropositive patients. In a mean \pm standard deviation (SD) of 166.63 ± 40.76 days between PCR and second serology, 85% were still positive for N-IgG, and 100% were still positive for S-IgG, with a higher mean \pm SD titre compared to the first S-IgG (166.77 ± 108.77 vs. 132.44 ± 91.18 , respectively, $p \leq 0.05$).

Conclusion

Humoral response to SARS-CoV-2 in AIIRD patients may be affected by immunosuppressive treatment, especially bDMARDs. In patients with AIIRD, titres of SARS-CoV-2 IgG antibodies, especially N-IgG antibodies, fade with time, while S-IgG antibodies persist.

Key words

seroepidemiologic study, SARS-CoV-2, immunosuppressive agents, rheumatic disease, anti-rheumatic agents

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Introduction

Since December 2019 the world has been struggling with coronavirus disease-19 (COVID-19) (1). Patients with autoimmune inflammatory rheumatic diseases (AIIRD) may be subject to an increased incidence of infectious diseases, often carrying a worse prognosis (2). Immune responses in AIIRD patients may be attenuated and affected by immunosuppressive treatments (3). An extensive amount of knowledge regarding the relationship between AIIRD and COVID-19 has been gathered, but questions still remain unanswered (4).

It is yet unclear whether contraction of COVID-19 is more prevalent among AIIRD patients compared to the general population (5-12). The prognosis of COVID-19 in AIIRD patients is dependent on comorbidities recognised as classical COVID-19 risk factors as well as prednisone dosage, and possibly specific rheumatic diseases, such as SLE (11-20). Data on the effect of immunosuppressive treatment on mounting of antibodies against SARS-CoV-2 in AIIRD patients is limited.

Antibodies against SARS-CoV-2 are detected in COVID-19 patients within 11–14 days following disease onset (21-24). Antibody titres tend to increase up to 3 weeks post infection (23, 25, 26) and to fade over time, depending on the method of antibody testing employed (25-27). Most studies show that SARS-CoV-2 induces a classic pattern of immunoglobulin (Ig) responses with IgM appearing first and IgA following shortly after, then both decline, while the IgG isotype remain detectable for a longer period of time (28). Antibody titres seem to correlate with the severity of COVID-19 (21, 24, 29). Anti-spike or anti-nucleocapsid SARS-CoV-2 IgG antibodies confer a significantly reduced risk of recurrent infection with the virus (30).

The estimation of COVID-19 prevalence in the general population differs based on the method of assessment. Seroprevalence studies measuring serum anti-SARS-CoV-2 Ig yielded a significantly higher COVID-19 prevalence than screening with SARS-CoV-2 polymerase chain reaction (PCR) (23, 31, 32). Data regarding the humoral

response to COVID-19 and seroprevalence of SARS-CoV-2 in AIIRD is scarce. During the first wave of SARS-CoV-2 in Israel, we have reported a PCR-based prevalence of 0.22% in AIIRD patients under care at a tertiary rheumatology clinic which was similar to the prevalence in the general population (33). In the same study, the seroprevalence in those AIIRD patients was 2.07% which was 10 times higher than the PCR-based prevalence (33), suggesting a high prevalence of asymptomatic or non-diagnosed cases of COVID-19. D'Silva *et al.* (34) reported that 10 out of 13 (77%) AIIRD COVID-19 PCR positive patients had anti SARS-CoV-2 antibodies.

The goals of the present study were to assess the prevalence of anti-SARS-CoV-2 nucleoprotein and S1/S2 spike antibodies in AIIRD patients, to assess the seroconversion rate in PCR-positive AIIRD patients and the persistence of antibodies over time. In addition, we aimed to define clinical factors associated with seropositivity.

Patients and methods

This cross-sectional study was conducted at the department of rheumatology of the Tel Aviv Sourasky Medical Center, a university tertiary centre in Israel, from September 2020 to March 2021. The study was approved by the institutional ethical board (TLV-0526-20).

Endpoints of the study

The primary endpoint of the study was to evaluate the seroprevalence of antibodies against SARS-CoV-2 in a population of patients with AIIRD.

Secondary endpoints

1. To characterise the clinical factors associated with seropositivity;
2. To monitor lasting antibody positivity overtime;
3. To assess the seroconversion rate and clinical factors associated with seroconversion in patients with COVID-19 infection confirmed by positive a SARS-CoV-2 PCR swab test.

Study population

Consecutive patients, 18 years of age or older, were recruited into the study

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Competing interests: none declared.

after obtaining a written informed consent, according to the following inclusion criteria: rheumatoid arthritis (RA) fulfilling ACR/EULAR 2010 classification criteria (35); psoriatic arthritis (PsA) fulfilling Classification Criteria for Psoriatic Arthritis (36); axial spondyloarthritis (axSpA) fulfilling ASAS classification criteria (37), SLE fulfilling 1997 ACR (38) or 2012 SLICC criteria (39), systemic vasculitis: large-vessel vasculitis (LVV), antineutrophil cytoplasmic antibody associated vasculitis (AAV), including granulomatosis with polyangiitis (GPA), microscopic polyangiitis and eosinophilic GPA fulfilling Chapel Hill Consensus Conference definitions (40).

Patients vaccinated against SARS-CoV-2 prior to the study were excluded.

Study design

At baseline, the participating patients completed a questionnaire including demographics, comorbidities, current medications and dosages, including glucocorticoids (GC) disease-modifying anti-rheumatic drugs (DMARDs), exposure to COVID-19 patients, suggestive COVID-19 symptoms, SARS-CoV-2 PCR test results, COVID-19 related hospitalisations and recovery (see the online Supplementary file for the detailed questionnaire).

Evaluation of antibodies against SARS-CoV-2

All patients were tested for SARS-CoV-2 antibodies. A two-stage antibody testing was performed in order to increase the specificity. First, an Abbott Architect assay for SARS-CoV-2 nucleoprotein IgG (N-IgG) was performed. This is a qualitative chemiluminescent microparticle immunoassay, reporting results as positive or negative. If the result was positive, a second LIAISON DiaSorin assay against the S1/S2 spike antigen (S-IgG) (considered a neutralising antibody) was performed as a confirmatory test (28, 41-43). A value above 15 binding antibody units was considered as positive, according to the manufacturer's instructions. A patient was considered to be seropositive if both assays were positive. Patients tested positive for SARS-CoV-2 IgG

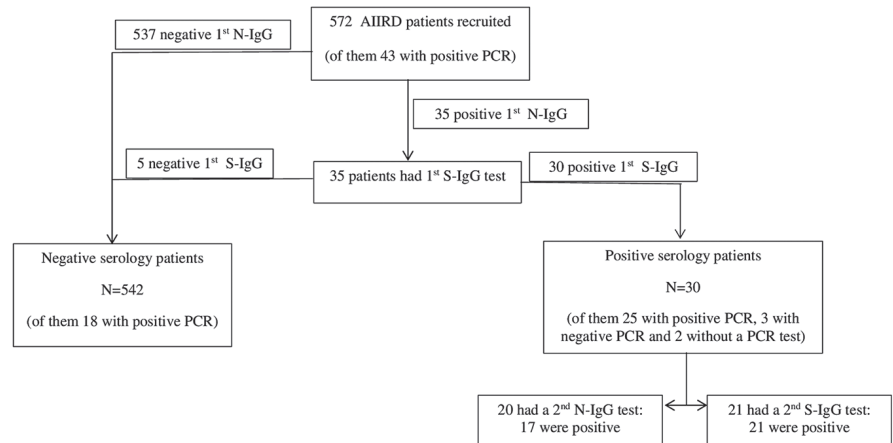


Fig. 1. Disposition of the study participants.

AIIRD: autoimmune inflammatory disease; PCR: polymerase chain reaction; N-IgG: anti-nucleoprotein immunoglobulin G; S-IgG: anti-spike S1/S2 immunoglobulin G.

were retested 3 months after the 1st test for both N-IgG and S-IgG, unless they were vaccinated against SARS-CoV-2, in which case they were excluded from further testing.

Statistical analysis

Patients were grouped according to the AIIRD diagnosis, immunosuppressive medications, known exposure to a COVID-19 patient or positive SARS-CoV-2-PCR. Seroprevalence rates were compared between the groups. Medication groups were defined as follows:

Conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) included: methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, azathioprine, mycophenolate mofetil.

Biologic (b)DMARDs included: tumour necrosis factor inhibitors (TNFi), interleukin (IL)-1 inhibitors, IL-6 inhibitors, IL-17 inhibitors, IL-12/23 inhibitor, anti-CD20 antibody and abatacept.

Targeted synthetic (ts)DMARDs included: Janus kinase inhibitors and apremilast.

Total immunosuppressive treatment included GCs, csDMARDs, bDMARDs and tsDMARDs.

Differences in continuous variables were tested for significance using independent sample t-test. Differences in categorical variables were tested for significance using the Fisher exact test. Change within subject in serology was tested for significance using the dependent sample t-test.

Logistic regressions were applied to test for the relationship between medications and positive serology. The models were adjusted for age, sex and exposure to COVID-19.

All tests applied were two-tailed, and a *p*-value of 5% or less was considered statistically significant. The data was analysed using R v. 4.0.3 (R Development Core Team, Vienna, Austria).

Results

The study included 572 AIIRD patients (232 RA, 149 PsA, 88 SLE, 57 vasculitides, 41 SpA, 5 other CTD), of them 30 patients were seropositive for SARS-CoV-2 IgG antibodies, corresponding to a seroprevalence rate of 5.24% (Fig. 1; Table I). Of the 30 seropositive patients, 25 had a known history of a confirmed SARS-CoV-2 PCR swab test. The remaining 5 patients were all female, with a known exposure to a COVID-19 confirmed case in three of them. Subsequent SARS-CoV-2 PCR testing was negative in these patients.

Clinical factors associated with seropositivity

Seropositivity tended to be associated with a higher BMI (BMI of 28.3 ± 5.35 in seropositive patients vs. 26.45 ± 5.29 in seronegative, *p*=0.06) and with the presence of a hypercoagulable state (seroprevalence in patients with antiphospholipid antibodies was 8.33%, seroprevalence in patients with other hypercoagulable conditions was 25%, versus 4.54% in patients without any

Table I. Demographic and clinical characteristics of patients with negative and positive SARS-CoV-2 IgG, and in the subgroup with positive SARS-CoV-2 PCR test.

	Total population (n=572)			Positive SARS-CoV-2-PCR population (n=43)		
	Negative serology (n=542)	Positive serology (n=30)	p-value	Negative serology (n=18)	Positive serology (n=25)	p-value
Female n (%)	365 (93.59)	25 (6.41)	NS	14 (41.18)	20 (58.82)	NS
Age median (range)	57 (18-95)	53.5 (22-82)	NS	47.5 (25-76)	53 (22-82)	NS
BMI mean±STD (95%CI)*	26.45±5.29 (25.99-26.9)	28.3±5.35 (26.31-30.3)	0.063	25.47±5.33 (21.81-28.12)	28.17±5.49 (25.9-30.43)	NS
No. of comorbidities median (range)	0.5 (0-7)	1 (0-5)	NS	0 (0-3)	1 (0-5)	NS
Malignancy ever n (%)	43 (97.73)	1 (2.27)	NS	2 (66.67)	1 (33.33)	NS
Ever smoker n (%)**	221 (96.51)	8 (3.49)	NS	2 (22.22)	7 (77.78)	NS
Hypercoagulability n (%)†						
None	505 (95.46)	24 (4.54)	≤0.05	13 (40.62)	19 (59.38)	NS
APLA	22 (91.67)	2 (8.33)		1 (33.33)	2 (66.67)	
Other hypercoagulability	6 (75)	2 (25)		0	2 (100)	
AIIRD diagnosis n (%)						
RA	222 (95.69)	10 (4.31)	NS	4 (33.33)	8 (66.67)	NS
PsA	141 (94.63)	8 (5.37)		2 (25)	6 (75)	
SLE	80 (91.95)	8 (9.09)		3 (27.27)	8 (72.73)	
Vasculitides	55 (96.49)	2 (3.51)		4 (66.67)	2 (33.33)	
SpA	39 (95.12)	2 (4.88)		3 (75)	1 (25)	
CTD	5 (100)	0 (0)		2 (100)	0	
AIIRD treatments n (%)						
Total immunosuppression	407 (96.45)	15 (3.55)	0.0046	13 (48.15)	14 (51.85)	NS
GC	118 (96.72)	4 (3.28)	NS	7 (63.64)	4 (36.36)	NS
csDMARDS	262 (94.76)	14 (5.07)	NS	9 (39.13)	14 (60.87)	NS
bDMARDS	252 (97.3)	7 (2.7)	0.014	9 (56.25)	7 (43.75)	NS
Anti CD-20	36 (100)	0 (0)	NS	1 (100)	0	NS
Exposure to COVID-19 known case n (%)	77 (73.33)	28 (26.67)	<0.0001	15 (37.5)	25 (62.5)	0.066
Hospitalisation n (%)	5 (50)	5 (50)	0.0001	5 (50)	5 (50)	NS
Days from positive PCR to serology testing mean ± SD (95%CI)††	NA	NA		129.61±79.43 (90.11-169.11)	84±59.25 (58.98-109.02)	0.039
Days from positive PCR to recovery mean ± SD (95%CI)††	NA	NA		16.21±14.46 (7.87-24.56)	18.46±14.11 (12.5-24.42)	NS

* n=553, of them 523 in the negative serology group, and 30 in the positive serology group

** n=559, of them 530 in the negative serology group, and 29 in the positive serology group. Total number in negative serology, positive PCR patients is 17, and in positive serology, positive PCR is 24

† n=561, of them 533 in the negative serology group, and 28 in the positive serology group.

†† n=42, of them 18 in the positive PCR negative serology group, and 24 in the positive PCR positive serology group

SARS-CoV-2: severe acute respiratory syndrome-coronavirus-2; IgG: immunoglobulin G; PCR: polymerase chain reaction; n: number; NS: non-significant; 95%CI: 95% confidence interval; BMI: body mass index (kg/m²); STD: standard deviation; APLA: antiphospholipid antibodies; AIIRD: autoimmune inflammatory rheumatic disease; RA: rheumatoid arthritis; PsA: psoriatic arthritis; SLE: systemic lupus erythematosus; SpA: spondyloarthritis; CTD: other connective tissue diseases; GC: glucocorticoids; csDMARDS: conventional synthetic disease-modifying anti-rheumatic drugs; bDMARDS: biologic disease-modifying anti-rheumatic drugs; NA: not applicable.**Table II.** Titres of Diasorin anti S1/S2-IgG in seropositive patients.

	1 st serology mean ± SD, (n)	2 nd serology mean ± SD, (n)	Change mean ± SD, (n)	p-value
All seropositive patients	132.44±91.18 (30)	166.77±108.77 (21)	57.01±112.24 (21)	0.0305
PCR positive seropositive	133.48±85.52 (25)	172.31±113.99 (18)	55.06±114.94 (18)	0.058

IgG: immunoglobulin G; SD: standard deviation; n: number; PCR: polymerase chain reaction.

hypercoagulability, $p \leq 0.05$, see Table I). The seropositive rate was lower in patients treated with immunosuppressive medications (3.55% vs. 10% for patients not taking immunosuppressive

medications, $p \leq 0.01$), and specifically in patients treated with bDMARDS (2.7% vs. 7.35% for patients not taking bDMARDS, $p \leq 0.05$) (Table I). All 36 patients treated with anti-CD20 bio-

logics were seronegative, including one patient with previous COVID-19 confirmed by PCR testing, although this did not reach statistical significance.

Seropositivity was higher in patients with known exposure to a COVID-19 case and in patients hospitalised for COVID-19 (Table I).

In a multivariate regression analysis adjusting for age, sex and exposure to a known COVID-19 patient, immunosuppressive treatments and bDMARD treatment were significantly associated with a lower likelihood of developing

Table III. Prevalence of COVID-19 by SARS-CoV-2 PCR according to AIIRD diagnosis and immunomodulatory medications.

	Negative PCR, n (%)	Positive PCR, n (%)	p-value
AIIRD diagnosis n, (% of total in diagnosis)			
Rheumatoid arthritis n=95 (40.95)	83 (87.37)	12 (12.63)	0.0259
Psoriatic arthritis n=68 (45.64)	60 (88.24)	8 (11.76)	
Systemic lupus erythematosus n=37 (40.91)	26 (70.27)	11 (29.73)	
Vasculitides n=20 (35.09)	14 (70)	6 (30)	
Spondyloarthritis n=19 (46.34)	15 (78.95)	4 (21.05)	
Connective tissue diseases n=4 (80)	2 (50)	2 (50)	
Total n=243 (42.48)	200 (82.3)	43 (17.7)	
Immunomodulatory tx n, (% of total in tx)			
Total immunosuppression n= 179 (42.42)	152 (84.92)	27 (15.08)	0.087
GC n=54 (44.26)	43 (79.63)	11 (20.37)	
csDMARDS n=110 (39.86)	87 (79.09)	23 (20.91)	
bDMARDS n=114 (44.02)	98 (85.96)	16 (14.04)	
Anti CD-20 n=17 (47.22)	16 (94.12)	1 (5.88)	

COVID-19: coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome-coronavirus-2; PCR: polymerase chain reaction; AIIRD: autoimmune inflammatory rheumatic disease; n: number; tx: treatment; GC: glucocorticoids; csDMARDS: conventional synthetic disease-modifying anti-rheumatic drugs; bDMARDS: biologic disease-modifying anti-rheumatic drugs.

anti-SARS-CoV-2 antibodies (or seropositivity) (odds ratio (OR) - 0.31, $p=0.009$); OR 0.33, $p=0.026$, respectively). Exposure to a known COVID-19 patient was significantly associated with seropositivity (OR 88.23, $p<0.0001$). GC, csDMARDS and anti-CD20 were not significantly associated with SARS-CoV-2 serology.

Results of anti-SARS-CoV-2 antibody retesting after 3 months

We collected a second serology test 3 months later in 21 of the 30 seropositive patients. Six patients had received the BNT162b2 vaccine during this

period and were not re-tested; 3 patients declined a second blood test and in one patient only a S-IgG second test was performed.

The mean \pm SD time which elapsed between the 2nd serologic test and the SARS-CoV-2 PCR test was 166.63 \pm 40.76 days.

Of the 20 patients tested for anti-N-IgG-17 (85%) remained positive after 3 months. All patients tested for a second S- IgG had a positive result on repeat testing, with a higher mean titre compared to the first S-IgG test (166.77 \pm 108.77 vs. 132.44 \pm 91.18 respectively, $p\leq 0.05$, Table II).

Seroconversion among patients with COVID-19 infection confirmed by a positive SARS-CoV-2 PCR swab test

Forty-three patients had a history of a confirmed SARS-CoV-2 PCR swab test (prevalence of 7.52 %), of whom 18 (41.86%) were negative for SARS-CoV-2 IgGs (Tables I and III).

Within the positive PCR group, the only factor correlating with seroconversion was the interval between the confirmed PCR and the serology test. Seropositivity was significantly associated with a shorter interval, with a mean \pm SD (95%CI) of 75.57 \pm 40.44 days (57.17–93.98) in the PCR positive/serology positive patients vs. 129.61 \pm 79.43 days (90.11–169.11) ($p\leq 0.05$) in PCR positive/serology negative patients (Fig. 2). None of the demographic or clinical characteristics were significantly associated with seropositivity (Table I). The median (range) number of COVID-19 symptoms (0 (0–4) and 0 (0–5), respectively, $p=0.17$), as well as the rate of hospitalisation did not differ between PCR positive, seropositive and seronegative patients.

Discussion

In this study we have shown that the seroprevalence of SARS-CoV-2 IgG among the AIIRD population is 5.24%. This is more than double our previous estimation of 2.07% in the same patient population which we have studied after the first wave of the pandemic in Israel (33). In a recent meta-analysis, the estimated global seroprevalence of SARS-CoV-2 antibodies in August 2020 was 3.38% (27). Unfortunately, we do not have data on the SARS-CoV-2 seroprevalence in the general population in Israel.

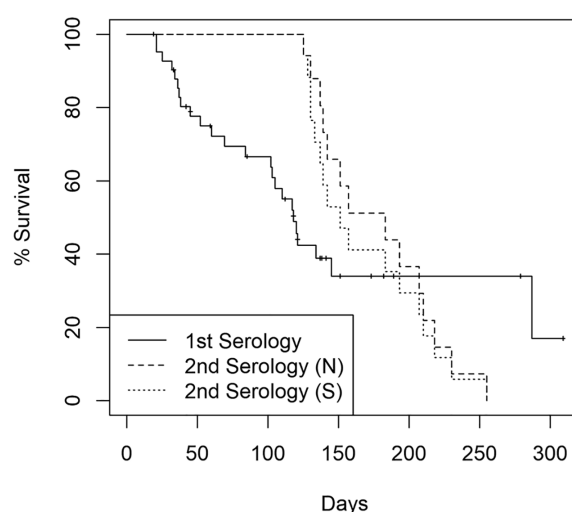
Seroprevalence was lower for medically immunosuppressed patients, especially in patients treated with bDMARDS, in accordance with recent publications in patients treated with anti-cytokine biologics (42, 44).

The lower prevalence of seropositivity among bDMARD treated AIIRD patients may have several explanations. First, it may reflect the fact that these patients were more adherent to social distancing and other COVID-19 pre-

Fig. 2. Kaplan-Meier plot of SARS-CoV-2 antibodies survival in days from SARS-CoV-2 PCR test.

1st serology includes both positive anti nucleocapsid and anti spike S1/S2 antibodies.
2nd serology (N) is the second anti nucleocapsid antibody.
2nd serology (S) is the second anti spike S1/S2 antibody.
SARS-CoV-2: severe acute respiratory syndrome-2;
PCR: polymerase chain reaction.

Positive Serology Survival Kaplan-Meier Plot



ventive measures, reducing exposure to SARS-CoV-2 (4). Secondly, cytokine inhibitors may have a protective effect on the severity of COVID-19. Simon *et al.* (42) have shown that seroprevalence of anti-SARS-CoV-2 antibodies is lower in patients treated with cytokine inhibitors compared to those treated with csDMARDs and healthy controls, and suggested that cytokine inhibitors may have a protective effect against COVID-19 infection. However, the fact that in our cohort the rate of positive SARS-CoV-2 by PCR was similar in patients treated with bDMARDs in comparison with patients not treated with bDMARDs (Table III) does not support this explanation. Several studies have shown that patients with mild COVID-19 tend to have lower titres of SARS-CoV-2 antibodies (21, 24, 27). This is also in accordance with our observation of increased seropositivity among patients with a high BMI, a known risk factor of COVID-19 severity.

An alternative explanation may be that bDMARDs may prevent a robust humoral response although data on the effect of bDMARDs on antibody response to infections is scarce. This may be more relevant for bDMARDs based on cellular-inhibition, such as CD20 depleting therapies and abatacept (45–48), although in inflammatory bowel disease patients treated with TNFi, seroprevalence and SARS-CoV-2 anti-nucleocapsid antibody titres were significantly lower compared to those treated with vedolizumab (44).

In the patients with positive SARS-CoV-2 PCR, only 58.14% had detectable anti-SARS-CoV-2 antibodies. This figure is lower than the estimate of D'Silva *et al.* of 77% (34). The only significant factor that predicted seropositivity in this group was the time which elapsed between clinical COVID-19 as confirmed by PCR and serology testing, suggesting a fading of antibody levels with time. On the other hand, in patients tested twice, at an interval of 3 months, 15% “lost” their N-IgG while preserving S-IgG, with the titre of S-IgG even increasing over time. The interval between PCR and serology testing may be more relevant for N-IgG than S-IgG. The two-

stage antibody testing performed in our study, in all 572 participants on the first serologic test may have missed patients with positive S-IgG and classified them as “negative”. Similar results have been observed in health care workers, with N-IgG antibodies having a mean half-life of 85 days, and fast waning of antibodies in young adults and asymptomatic subjects (49). Bolotin *et al.* (5) also showed in the general population of Ontario, that N-IgG titres declined, while S-IgG persisted longer. Most studies in COVID-19 patients demonstrated that in general SARS-CoV-2 IgG antibodies remained detectable for 2–5 months, whereas neutralising antibodies, like the anti-S-IgG antibodies, may persist for up to 6 months (28).

This study has several strengths. This is the first study to assess the seroprevalence of SARS-CoV-2 in a relatively large population of representative AIIRD patients treated with a variety of immunomodulatory drugs. We increased the specificity of serologic testing by using two antibodies with different antigen targets. This is also one of few studies examining the seropositivity over time and showing that S-IgG may remain detectable for a long period of time after exposure to SARS-CoV-2, even in immunosuppressed AIIRD patients.

The main limitations of our study are the lack of a control group from the general population, allowing a comparison of the seroprevalence rate. Without a general population control group, we could analyse the impact of immunosuppression within a population of patients with AIIRD themselves. Second, the PCR positive group was relatively small and not powered to assess the effect of specific medications on seropositivity, such as methotrexate, mycophenolate mofetil, anti-CD20, abatacept, and glucocorticoids.

In conclusion, the prevalence of SARS-CoV-2 IgG antibodies was 5.24% in a population of AIIRD patients from a single large tertiary medical center in Israel. SARS-CoV-2 seroprevalence was lower among AIIRD patients on immunosuppressive treatment, especially biologics, including patients with a confirmed history of positive SARS-

CoV-2 by PCR. Similarly to individuals without AIIRD, titres of SARS-CoV-2 IgG antibodies, especially anti-nucleoprotein IgG antibodies, faded with time, while anti-S-IgG antibodies persisted.

The significance of the lack of production of SARS-CoV-2 antibodies in a substantial proportion of COVID-19 PCR positive patients remains to be elucidated.

Larger studies are needed to confirm the potential effect of immunosuppressive medication on the antibody response in AIIRD patients.

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