









BRIEF REPORT

Impact of Cytokine Inhibitor Therapy on the Prevalence, Seroconversion Rate, and Longevity of the Humoral Immune Response Against SARS-CoV-2 in an Unvaccinated Cohort

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Objective. To investigate the impact of biologic disease-modifying antirheumatic drug (bDMARD) treatment on the prevalence, seroconversion rate, and longevity of the humoral immune response against SARS-CoV-2 in patients with immune-mediated inflammatory diseases (IMIDs).

Methods. Anti-SARS-CoV-2 IgG antibodies were measured in a prospective cohort of health care professional controls and non-health care controls and IMID patients receiving no treatment or receiving treatment with conventional or biologic DMARDs during the first and second COVID-19 waves. Regression models adjusting for age, sex, sampling time, and exposure risk behavior were used to calculate relative risks (RRs) of seropositivity. Seroconversion rates were assessed in participants with polymerase chain reaction (PCR)-positive SARS-CoV-2 infection. Antibody response longevity was evaluated by reassessing participants who tested positive during the first wave.

Results. In this study, 4,508 participants (2,869 IMID patients and 1,639 controls) were analyzed. The unadjusted RR (0.44 [95% confidence interval (95% CI) 0.31–0.62]) and adjusted RR (0.50 [95% CI 0.34–0.73]) for SARS-CoV-2 IgG antibodies were significantly lower in IMID patients treated with bDMARDs compared to non-health care controls ($P < 0.001$), primarily driven by treatment with tumor necrosis factor inhibitors, interleukin-17 (IL-17) inhibitors, and IL-23 inhibitors. Adjusted RRs for untreated IMID patients (1.12 [95% CI 0.75–1.67]) and IMID patients receiving conventional synthetic DMARDs (0.70 [95% CI 0.45–1.08]) were not significantly different from non-health care controls. Lack of seroconversion in PCR-positive participants was more common among bDMARD-treated patients (38.7%) than in non-health care controls (16%). Overall, 44% of positive participants lost SARS-CoV-2 antibodies by follow-up, with higher rates in IMID patients treated with bDMARDs (RR 2.86 [95% CI 1.43–5.74]).

Conclusion. IMID patients treated with bDMARDs have a lower prevalence of SARS-CoV-2 antibodies, seroconvert less frequently after SARS-CoV-2 infection, and may exhibit a reduced longevity of their humoral immune response.

INTRODUCTION

SARS-CoV-2 poses a considerable threat to patients with immune-mediated inflammatory diseases (IMIDs). Due to their immune dysfunction, the consequence of immunomodulatory

treatment, and the large burden of comorbidities, IMID patients are of particular interest in the current COVID-19 pandemic (1). Initially, there were concerns that IMID patients, particularly those receiving cytokine inhibitors, may be at an increased susceptibility for SARS-CoV-2 infection and may develop a more severe

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disease course if infected. However, more recent data suggest that IMiD patients, especially those treated with cytokine inhibitors, are not at increased risk for severe COVID-19 (2).

SARS-CoV-2 encounters a different immune system in IMiD patients treated with cytokine inhibitors. Respective drugs target key mediators that mount adaptive immune responses to infections, such as interleukin-23 (IL-23) and IL-17, but also those with inflammatory effector function, such as tumor necrosis factor (TNF) and IL-6 (3). Therefore, the immune response against SARS-CoV-2 may be altered in IMiD patients. This situation may have advantages, as impaired inflammatory responses could explain the observed milder course of COVID-19 in patients treated with cytokine inhibitors (2,4,5). Alternatively, cytokine inhibitors may influence the mounting of a protective immunity against the virus.

SARS-CoV-2 triggers the formation of specific antibodies, which are related to the severity of the infection (6). IMiD patients, especially those treated with cytokine inhibitors, may have an altered prevalence, seroconversion rate, and longevity of the anti-SARS-CoV-2 immune response. Large studies assessing these parameters in IMiD patients are lacking to date. It has previously been shown that the majority of IMiD patients are capable of developing protective immunity after SARS-CoV-2 infection (7,8) as well as after messenger RNA vaccination (9,10). However, a study conducted during the first wave of the COVID-19 pandemic showed that the prevalence of anti-SARS-CoV-2 antibody positivity was significantly lower in IMiD patients treated with cytokine inhibitors compared to patients receiving no such treatments and compared to healthy controls (11). This finding suggests that anticytokine treatment may dampen the adaptive immune responses to SARS-CoV-2 vaccines, which has been described for conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), such as methotrexate (12), but that could not yet be confirmed for biologic DMARDs (bDMARDs) (i.e., cytokine inhibitors) (13,14). Furthermore, studies on the humoral response to SARS-CoV-2 and other coronaviruses in healthy individuals indicated that humoral immunity is not permanent but declines over time, rendering individuals susceptible for reinfection with coronaviruses (15).

Based on these data, we investigated whether IMiD patients and healthy controls differ in their humoral immune

response to SARS-CoV-2 infection and especially if individual cytokine inhibitors may affect this process. In order to test the influence of individual cytokine inhibitors on the prevalence of SARS-CoV-2 infection, large and well-controlled data sets that allow for adjustment for social exposure are needed. Furthermore, information on polymerase chain reaction-confirmed SARS-CoV-2 infection helps to test for true seroconversion rates, while prospectively collected longitudinal data allow testing for the longevity of humoral immune responses in IMiD patients and controls. To address these points, we analyzed a large prospective cohort of IMiD patients and controls and investigated the prevalence, seroconversion rate, and longevity of humoral SARS-CoV-2 immune responses in IMiD patients and healthy controls.

PATIENTS AND METHODS

Participants. IMiD patients and healthy controls were recruited from a large longitudinal COVID-19 study at the Deutsche Zentrum fuer Immuntherapie, which was initiated in February 2020 and monitors respiratory infections including COVID-19, anti-SARS-CoV-2 antibody responses, and social exposure. Exact details of the recruitment have been described elsewhere (11). The study had 2 sample collection waves (i.e., from March 1, 2020 to June 1, 2020 during the first wave of COVID-19 and from December 1, 2020 to March 1, 2021 during the second wave). For the cross-sectional analysis, we included all subjects who provided samples during the second wave of sample collection. For the longitudinal analysis, participants were included if they had a positive anti-SARS-CoV-2 antibody test in the first wave and were also evaluated in the second wave of the sample collection. Accordingly, patients who had already been enrolled in a first cross-sectional analysis (11) were included in the cross-sectional analysis performed for the second wave and the longitudinal analysis.

Briefly, the study recruited IMiD patients receiving either no treatment or treatment with csDMARDs, bDMARDs, or targeted synthetic DMARDs (tsDMARDs). In addition, 2 healthy control groups were recruited: non-health care controls from the general population as well as health care professionals (physicians, nurses, and technicians). Healthy controls did not have any IMiDs. Subjects who already had received a SARS-CoV-2 vaccination

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Table 1. Baseline characteristics of the study subjects*

	IMID (n = 2,869)	Health care professional controls (n = 455)	Non-health care controls (n = 1,184)	Overall (n = 4,508)
Age, mean \pm SD years	55.1 \pm 15.2	40.0 \pm 12.9	43.5 \pm 14.7	50.5 \pm 16.1
Sex				
Male	1,180 (41.1)	133 (29.2)	820 (69.3)	2,133 (47.3)
Female	1,687 (58.8)	321 (70.5)	362 (30.6)	2,370 (52.6)
Smoking status				
Current	508 (17.7)	59 (13.0)	197 (16.6)	764 (16.9)
Past	738 (25.7)	70 (15.4)	219 (18.5)	1,027 (22.8)
Never	1,339 (46.7)	301 (66.2)	690 (58.3)	2,330 (51.7)
Missing	284 (9.9)	25 (5.5)	78 (6.6)	387 (8.6)
BMI, mean \pm SD kg/m ²	27.3 \pm 5.9	24.0 \pm 4.3	26.6 \pm 4.9	26.8 \pm 5.6
Diagnosis				
No IMID	-	455 (100.0)	1,184 (100.0)	1,639 (36.4)
RA	979 (34.1)	-	-	979 (21.7)
SpAt	794 (27.7)	-	-	794 (17.6)
CTD	307 (10.7)	-	-	307 (6.8)
IBD	223 (7.8)	-	-	223 (4.9)
Other†	207 (7.2)	-	-	207 (4.6)
Systemic vasculitis	180 (6.3)	-	-	180 (4.0)
Psoriasis	136 (4.7)	-	-	136 (3.0)
Autoinflammatory disease	43 (1.5)	-	-	43 (1.0)
Comorbidities				
Diabetes mellitus	271 (9.5)	5 (1.1)	33 (2.9)	309 (7.0)
Hypertension	1,094 (38.4)	27 (6.2)	184 (16.3)	1,305 (29.6)
Ischemic heart disease	71 (2.5)	-	6 (0.5)	77 (1.7)
DVT	54 (1.9)	1 (0.2)	8 (0.7)	63 (1.4)
Cancer	231 (8.1)	12 (2.7)	46 (4.1)	289 (6.5)
Lung disease	252 (8.8)	24 (5.5)	44 (3.9)	320 (7.3)
Treatment				
bDMARDs	1,344 (46.8)	-	-	1,344 (29.8)
csDMARDs	742 (25.9)	-	-	742 (16.5)
tsDMARDs	176 (6.1)	-	-	176 (3.9)
Blockade type				
TNFi	666 (23.2)	-	-	666 (14.8)
IL-17 inhibitors	202 (7.0)	-	-	202 (4.5)
IL-12/23 inhibitors	117 (4.1)	-	-	117 (2.6)
IL-6 inhibitors	109 (3.8)	-	-	109 (2.4)
CD20 depletion	101 (3.5)	-	-	101 (2.2)
IL-23 inhibitors	47 (1.6)	-	-	47 (1.0)
CD80/86 inhibitors	35 (1.2)	-	-	35 (0.8)
Integrin α 4 β 7	27 (0.9)	-	-	27 (0.6)
Other‡	40 (1.4)	-	-	40 (0.9)
PCR test results				
Total tested	1,109 (38.7)	273 (60.0)	575 (48.6)	1,957 (43.4)
Positive¶	57 (5.1)	45 (16.5)	50 (8.7)	152 (7.8)
Negative¶	1,040 (93.8)	227 (83.2)	523 (91.0)	1,790 (91.5)
Risk behavior				
Home office	1,120 (39.0)	26 (5.7)	370 (31.2)	1,516 (33.6)
Contact with infected	262 (9.1)	199 (43.7)	231 (19.5)	692 (15.4)
Visit to risk area	87 (3.0)	62 (13.6)	73 (6.2)	222 (4.9)
Social distancing	2,244 (78.2)	391 (85.9)	1,020 (86.1)	3,655 (81.1)

* Except where indicated otherwise, values are the number (%) of subjects. IMID = immune-mediated inflammatory disease; BMI = body mass index; RA = rheumatoid arthritis; SpA = spondyloarthritis; CTD = connective tissue disease; IBD = inflammatory bowel disease; DVT = deep vein thrombosis; bDMARDs = biologic disease-modifying antirheumatic drugs; csDMARDs = conventional synthetic DMARDs; tsDMARDs = targeted synthetic DMARDs; TNFi = tumor necrosis factor inhibitors; PCR = polymerase chain reaction.

† Including psoriatic arthritis.

‡ Including autoimmune hepatitis, uveitis, eosinophilic fasciitis, IgG4 disease, juvenile idiopathic arthritis, polymyalgia rheumatica, recurrent polychondritis, sarcoidosis, and undifferentiated arthritis.

§ Including neutralizing antibodies against interleukin-1 (IL-1), IL-4, IL-5, and B lymphocyte stimulator.

¶ Percentages among subjects tested.

were excluded from the study. In all participants, a structured questionnaire was used to collect data on age, sex, body mass index, and risk factors for severe COVID-19 (smoking status, arterial hypertension, diabetes mellitus, and chronic lung diseases). Recent history of COVID-19-related symptoms was also recorded. Data about exposure risk-related behavior, including compliance with social distancing, avoidance of the workplace, contact with infected individuals, and travel to respective risk areas designated by the German federal government agency for disease control and prevention (the Robert Koch Institute [RKI]) at the time of data collection were documented. In addition, the results from all the conducted mucosal swabs for SARS-CoV-2 PCR testing were documented, as reported by participants. Ethical approval (no. 157_20 B) to conduct this analysis was granted by the institutional review board of the University Clinic of Erlangen. Written informed consent was obtained from all study participants.

Anti-SARS-CoV-2 antibody testing. IgG antibodies against the S1 domain of the spike protein of SARS-CoV-2 were tested by enzyme-linked immunosorbent assay (recent CE version [April 2020]) (Euroimmun) using the Euroimmun Analyzer I platform and according to manufacturer protocols. Optical density (OD) was determined at 450 nm with reference wavelength at 630 nm. A cutoff of ≥ 0.8 (OD at 450 nm) was considered as positive. Assays were performed according to the guidelines of the German Medical Association (RiliBAK) with stipulated internal and external quality controls.

Statistical analysis. Participant characteristics are described using the mean \pm SD, median and interquartile range (IQR), and percentages, as appropriate. We calculated the crude proportions of seropositivity for anti-SARS-CoV-2 IgG (≥ 0.8 , OD at 450 nm) and estimated exact 95% confidence intervals (95% CIs) based on the binomial distribution for each study group. Relative risks (RRs) of seropositivity in study groups were estimated using a Poisson regression model with robust sandwich SEs using the non-health care control group as the reference. This method enables estimation of adjusted RRs; therefore, in addition to crude RRs, we estimated RRs adjusted for age, sex, sampling time, and participant-reported exposure risk behavior (16). Adjustment for sampling time was achieved using the mean cumulative incidences of COVID-19 in the administrative districts of Erlangen and Erlangen-Höchstadt per 100,000 population as reported by the RKI for the date of serum sampling, to approximate the overall risk of exposure to SARS-CoV-2. Case count data was acquired from the RKI using the R package covid19germany (version 0.0.2; <https://github.com/nevrome/covid19germany>).

Exposure risk behavior was included in models as a count of favorable responses to 4 questions about compliance with social distancing, avoidance of the workplace, contact with infected individuals, and travel to risk areas. Finally, we used a similar

regression to estimate the RR of losing naturally acquired SARS-CoV-2 spike IgG antibodies among initially seropositive participants during follow-up, in which we adjusted for age, sex, OD value at baseline, and number of days between baseline and follow-up samples. We used R version 4.0.1 for the analyses. Two-sided *P* values less than 0.05 or 95% CIs for RRs excluding unity were considered significant.

RESULTS

Patient characteristics. A total of 4,508 participants provided samples for SARS-CoV-2 spike protein S1 IgG antibody analysis between December, 2020 and March, 2021 (Table 1). Of these subjects, 2,869 were patients with IMIDs and 1,639 were healthy controls (455 health care professional controls and 1,184 non-health care controls). The most common IMIDs in the cohort were rheumatoid arthritis ($n = 979$), spondyloarthritis (SpA; $n = 794$, including psoriatic arthritis), connective tissue diseases ($n = 307$), and inflammatory bowel disease ($n = 223$). Among patients with IMIDs, 1,344 (47%) were treated with bDMARDs, 742 (26%) with csDMARDs, and 176 (6%) with tsDMARDs. Among bDMARDs, TNF inhibitors ($n = 666$), IL-17 inhibitors ($n = 202$), IL-23 inhibitors ($n = 117$), IL-6 inhibitors ($n = 109$), and B cell-depleting agents ($n = 109$) were the most frequently used drugs. Of those receiving bDMARDs, 394 patients (29%) were receiving combination treatment with csDMARDs. Overall, 1,957 participants (43%) had a history of a SARS-CoV-2 PCR test, with 152 participants (8%) having had a positive PCR test.

Seroprevalence of anti-SARS-CoV-2 antibodies in IMID patients and controls. Among the 4,508 participants, 256 (5.7%) had SARS-CoV-2 spike protein S1 IgG antibodies. Similar crude prevalence rates of humoral immune responses against SARS-CoV-2 occurred in healthy non-health care controls (84 of 1,184; 7.1%) and IMID patients without DMARD treatment (42 of 607; 6.9%). In contrast, IMID patients treated with bDMARDs (42 of 1,344; 3.1%) or csDMARDs (29 of 742; 3.9%) showed the lowest point prevalence estimate for anti-SARS-CoV-2 antibodies. Health care professional controls had a substantially higher prevalence (51 of 455; 11.2%) of anti-SARS-CoV-2 antibodies. Crude seroprevalence rates and the corresponding 95% CIs are summarized in Table 2.

Unadjusted RRs for SARS-CoV-2 IgG antibodies were significantly lower in IMID patients treated with bDMARDs (RR 0.44 [95% CI 0.31–0.62]) ($P < 0.001$) compared to non-health care controls (Table 2). These differences between healthy non-health care controls and bDMARD-treated IMID patients remained significant after adjusting for age, sex, sampling time, and participant-reported exposure risk behavior (RR 0.50 [95% CI 0.34–0.73]) ($P < 0.001$). Furthermore, the adjusted RR was numerically lower when bDMARDs were combined with csDMARDs (adjusted RR

Table 2. Unadjusted and adjusted relative risks (RRs) for SARS-CoV-2 spike IgG antibodies in IMID patients compared to non-health care controls*

Group	Total no.	No. of positive subjects	Prevalence, % (95% CI)	Unadjusted RR (95% CI)	Crude <i>P</i>	Adjusted RR (95% CI)†	Adjusted <i>P</i>
Controls							
Non-health care professionals	1,184	84	7.09 (5.70–8.71)	1 (reference)	–	1 (reference)	–
Health care professionals	455	51	11.21 (8.46–14.47)	1.58 (1.14–2.20)	0.007	1.77 (1.19–2.64)	0.005
IMID patients							
bDMARD-treated	1,344	42	3.12 (2.26–4.20)	0.44 (0.31–0.63)	<0.001	0.50 (0.34–0.73)	<0.001
csDMARD-treated	742	29	3.91 (2.63–5.57)	0.55 (0.36–0.83)	0.005	0.70 (0.45–1.08)	0.107
tsDMARD-treated	176	8	4.55 (1.98–8.76)	0.64 (0.32–1.30)	0.218	0.82 (0.39–1.72)	0.607
Untreated	607	42	6.92 (5.03–9.24)	0.98 (0.68–1.39)	0.891	1.12 (0.75–1.67)	0.591

* 95% CI = 95% confidence interval (see Table 1 for other definitions).

† Adjusted using Poisson regression for age, sex, sampling time, and participant-reported exposure risk behavior. Non-health care controls are the reference group.

0.34 [95% CI 0.16–0.71]) as opposed to bDMARD monotherapy (adjusted RR 0.55 [95% CI 0.37–0.82]), whereas a formal interaction was not detected (*P* for interaction = 0.45).

Unadjusted RRs for SARS-CoV-2 IgG antibodies were also significantly lower in IMID patients treated with csDMARDs (RR 0.55 [95% CI 0.36–0.83]) (*P* = 0.005), but after adjusting for age, sex, sampling time, and participant-reported exposure risk behavior, the point estimate shifted toward unity (RR 0.70 [95% CI 0.45–1.08]) (*P* = 0.107). Furthermore, in untreated IMID patients, there was no RR difference for developing SARS-CoV-2 IgG antibodies (RR 1.12 [95% CI 0.75–1.67]) (*P* = 0.591). As expected, the unadjusted and adjusted RRs for SARS-CoV-2 IgG antibodies were significantly higher in health care professional controls than in non-health care controls.

Seroprevalence according to diagnosis and type of treatment. In further analyses, we explored whether individual IMID groups and types of treatments influenced the RR of SARS-CoV-2 IgG antibody development. In the analyses for diagnoses, point estimates for the RR of antibody development were below unity with considerable lack of precision (Figure 1A). Patients with SpA and psoriasis showed the highest and lowest point estimates respectively, but none of them were significant. In contrast, 3 particular types of cytokine inhibitors seemed to drive the overall negative association with bDMARD treatment and antibody development. These included TNF inhibitors (adjusted RR 0.60 [95% CI 0.38–0.94]), IL-17 inhibitors (adjusted RR 0.40 [95% CI 0.16–0.98]), and IL-23 inhibitors (adjusted RR 0.28 [95% CI 0.09–0.89]) (Figure 1B).

Seroconversion in the subset of patients with positive SARS-CoV-2 PCR test results. A total of 152 among the 1,109 tested participants had a history of positive SARS-CoV-2 PCR test. When these individuals were analyzed for SARS-CoV-2 IgG antibodies, we could observe that most but not all developed antibodies (120 of 152; 78%). Notably, seroconversion rates were dependent on treatment. Therefore, lack of

seroconversion was found in only 16% and 15.5% in non-health care and health care controls, respectively. Additionally, only 13.3% of untreated IMID patients did not seroconvert. In contrast, the likelihood of a lack of seroconversion was numerically higher in IMID patients treated with csDMARDs (27.3%) and those receiving either bDMARDs or tsDMARDs (38.7%) (Supplementary Figure 1, available on the *Arthritis & Rheumatology* website at <https://onlinelibrary.wiley.com/doi/10.1002/art.42035>). Of note, the time period between positive PCR tests and analysis of antibody levels was not different between IMID patients treated with bDMARDs (median 49.5 days [IQR 35.5–82.0]), IMID patients treated with csDMARDs (median 52.0 days [IQR 46.5–75.5]), and controls (median 59.0 days [IQR 35.0–282.0]).

Longevity of the humoral immune response to SARS-CoV-2. Among the 4,508 participants, 1,812 (40.2%) had previously donated a blood sample between March 1 and June 1, 2020. The median time interval between first-wave and second-wave samples was 270 days (IQR 261–281). Among participants with available longitudinal data, there were 48 seropositive participants (2.6%) in the first wave and 81 seropositive participants (4.5%) in the second wave, which is depicted in the spaghetti plot in Supplementary Figure 2 (<https://onlinelibrary.wiley.com/doi/10.1002/art.42035>) and reflects the impact of the second SARS-CoV-2 wave in autumn/winter 2020. Conversely, we observed uniformly decreasing antibody levels over time among initially seropositive participants. Among 48 participants who were initially positive, 21 tested negative during the second wave, indicating a high proportion of loss (43.8%) in SARS-CoV-2 infection-induced antibodies over a 9-month period. The number and proportion of participants losing initial antibodies per study group are summarized in Supplementary Table 1 (<https://onlinelibrary.wiley.com/doi/10.1002/art.42035>). Of note, all 4 participants receiving bDMARDs (all anticytokine treatments) lost the initial antibody response in the second wave, corresponding to an adjusted RR of 2.86 (95% CI 1.43–5.74) compared to non-health care controls.

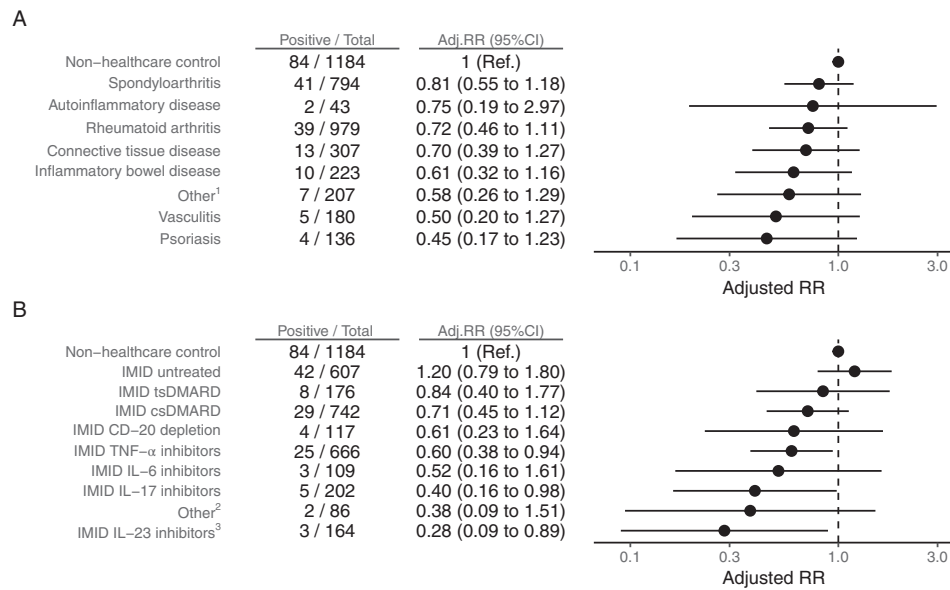


Figure 1. Relative risk (RR) of SARS-CoV-2 IgG antibody prevalence according to type of disease and type of treatment. **A**, RRs with 95% confidence intervals (95% CIs) of positive IgG antibodies against SARS-CoV-2 according to type of disease, compared to non-health care controls as the reference (Ref.). **B**, RRs with 95% CIs of positive IgG antibodies against SARS-CoV-2 according to type of treatment, compared to non-health care controls as the reference. ¹ Other diagnoses include autoimmune hepatitis, uveitis, eosinophilic fasciitis, IgG4 disease, juvenile idiopathic arthritis, polymyalgia rheumatica, recurrent polychondritis, sarcoidosis, and undifferentiated arthritis. ² Other types of blockades include neutralizing antibodies against interleukin-1 (IL-1), IL-4, IL-5, and B lymphocyte stimulator. ³ IL-23 inhibitors include IL-12/23 inhibitors as well as IL-23 inhibitors. IMID = immune-mediated inflammatory disease; tsDMARD = targeted synthetic disease-modifying antirheumatic drug; bDMARD = biologic DMARD; csDMARD = conventional synthetic DMARD; TNF = tumor necrosis factor.

DISCUSSION

This large prospective cohort study shows that IMID patients receiving bDMARDs, most of them treated with cytokine inhibitors, have lower seroprevalence rates for SARS-CoV-2 infection than healthy controls. This “protective” effect in bDMARD-treated IMID patients remained robust after adjustment for age, sex, and participant-reported exposure risk behavior and was not observed in IMID patients receiving no treatment or conventional drug treatment. The data support the concept that IMID patients treated with bDMARDs are not at particular risk during the SARS-CoV-2 pandemic, supporting statements in favor of the continuation of treatment. One exception is B cell-depleting treatment, which shows more severe courses of COVID-19 (17,18).

Based on the mere size of the cohort (>1,300 patients treated with bDMARDs and tsDMARDs) this study also allowed for assessment of the influence of different agents, in particular cytokine inhibitors, on the SARS-CoV-2 immune response. Hence, IL-23 inhibitors, IL-17 inhibitors, and TNF inhibitors were associated with significantly lower seroconversion rates. These cytokines are released upon SARS-CoV-2-induced alveolar tissue damage, mount systemic adaptive immunity to the virus, and trigger inflammation and tissue damage (19). Therefore, SARS-CoV-2 infection may not be able to induce full-blown

inflammation and adaptive immune responses in hosts, in whom these mediators are neutralized by respective drugs. Targeted inhibition of these cytokines may thus not only mitigate the risk for severe COVID-19, as previously shown (2,4,5), but also attenuate the formation of anti-SARS-CoV-2 antibodies. This concept is supported by the observation that among participants with a history of SARS-CoV-2 PCR positivity, those treated with cytokine inhibitors had the lowest seroconversion rates. Supporting this notion, the time period between positive PCR tests and analysis of antibody levels was not different between IMID patients and controls.

The prospective part of this study, in which participants who were assessed in the first COVID-19 wave were reassessed during the second wave, provided insights into the persistence of the humoral response in IMID patients after SARS-CoV-2 infection. It is known from previous work that the level of humoral response corresponds with protection from COVID-19 (20). Notably, 44% of the participants lost protective SARS-CoV-2 antibody responses between the 2 sampling periods. An increased tendency toward losing protective anti-SARS-CoV-2 IgG responses was noted in initially seropositive IMID patients receiving stable anticytokine treatment. Although observed in a very small subset of patients, it is important that this finding also aligns with a lower rate of seroconversion in bDMARD-treated patients with PCR-confirmed SARS-CoV-2 infection. Consequently, protective

humoral responses against SARS-CoV-2 seem to be comparatively short-lived in IMID patients, potentially putting patients at risk for reinfection earlier and identifying a need for booster vaccination.

Our study has some limitations. IMID patients who were receiving bDMARDs not blocking cytokines, i.e., those affecting B/T lymphocytes and cell migration, constituted a minority of our study population, and thus, the analyses had less power for these subgroups in comparison to those receiving cytokine-blocking bDMARDs. Furthermore, we were able to longitudinally assess only a limited number of participants who showed positive antibodies in the first wave, among whom only a few were receiving bDMARD treatment. Therefore, the risk of losing antibodies over time needs to be confirmed in a larger group of seropositive patients. Another limitation is that the PCR test results were participant-reported and therefore potentially subject to reporting error; however, we expect such error to be evenly distributed and only bias the findings toward the null. Nonetheless, we observed a lower proportion of seroconversion among PCR-positive IMID patients who received bDMARDs. Finally, our study did not analyze the clinical manifestations in patients who were PCR-positive. However, very few study participants reported to have been hospitalized due to COVID-19. This is consistent with reported hospitalization rates for SARS-CoV-2 infection ranging between 0.06% and 1.5% (21) and reflects that studies on hospitalization rates require cohorts of infected patients, as has been done previously (17,18).

In conclusion, these data show that IMID patients receiving bDMARDs, i.e., those receiving cytokine inhibitors, have a lower prevalence rate of SARS-CoV-2 seropositivity, exhibit a blunted seroconversion rate, and lose their anti-SARS-CoV-2 antibodies faster than healthy controls or IMID patients not receiving bDMARDs. While it is highly unlikely that cytokine inhibitors lower the susceptibility to SARS-CoV-2 infection, it seems that they mitigate the overshooting inflammatory response to the virus and, consequently, the severity of SARS-CoV-2 infection. While this effect appears to be an advantage in the case of SARS-CoV-2 infection, it presents some challenges in maintaining protective immunity against the virus.

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AUTHOR CONTRIBUTIONS

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