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Antibody development after COVID-19 vaccination in patients with autoimmune diseases in the Netherlands: a substudy of data from two prospective cohort studies

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Lancet Rheumatol 2021; 3: e778–88

Published Online August 6, 2021 https://doi.org/10.1016/S2665-9913(21)00222-8

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Summary

Background Data are scarce on immunogenicity of COVID-19 vaccines in patients with autoimmune diseases, who are often treated with immunosuppressive drugs. We aimed to investigate the effect of different immunosuppressive drugs on antibody development after COVID-19 vaccination in patients with autoimmune diseases.

Methods In this study, we used serum samples collected from patients with autoimmune diseases and healthy controls who were included in two ongoing prospective cohort studies in the Netherlands. Participants were eligible for inclusion in this substudy if they had been vaccinated with any COVID-19 vaccine via the Dutch national vaccine programme, which at the time was prioritising vaccination of older individuals. Samples were collected after the first or second COVID-19 vaccination. No serial samples were collected. Seroconversion rates and IgG antibody titres against the receptor-binding domain of the SARS-CoV-2 spike protein were measured. Logistic and linear regression analyses were used to investigate the association between medication use at the time of vaccination and at least until sampling, seroconversion rates, and IgG antibody titres. The studies from which data were collected are registered on the Netherlands Trial Register, Trial ID NL8513, and ClinicalTrials.org, NCT04498286.

Findings Between April 26, 2020, and March 1, 2021, 3682 patients with rheumatic diseases, 546 patients with multiple sclerosis, and 1147 healthy controls were recruited to participate in the two prospective cohort studies. Samples were collected from patients with autoimmune diseases (n=632) and healthy controls (n=289) after their first (507 patients and 239 controls) or second (125 patients and 50 controls) COVID-19 vaccination. The mean age of both patients and controls was 63 years (SD 11), and 423 (67%) of 632 patients with autoimmune diseases and 195 (67%) of 289 controls were female. Among participants without previous SARS-CoV-2 infection, seroconversion after first vaccination were significantly lower in patients than in controls (210 [49%] of 432 patients *vs* 154 [73%] of 210 controls; adjusted odds ratio 0·33 [95% CI 0·23–0·48]; p<0·0001), mainly due to lower seroconversion in patients treated with methotrexate or anti-CD20 therapies. After the second vaccination, seroconversion exceeded 80% in all patient treatment subgroups, except among those treated with anti-CD20 therapies (three [43%] of seven patients). We observed no difference in seroconversion and IgG antibody titres between patients with a previous SARS-CoV-2 infection who had received a single vaccine dose (72 [96%] of 75 patients, median IgG titre 127 AU/mL [IQR 27–300]) and patients without a previous SARS-CoV-2 infection who had received two vaccine doses (97 [92%] of 106 patients, median IgG titre 49 AU/mL [17–134]).

Interpretation Our data suggest that seroconversion after a first COVID-19 vaccination is delayed in older patients on specific immunosuppressive drugs, but that second or repeated exposure to SARS-CoV-2, either via infection or vaccination, improves humoral immunity in patients treated with immunosuppressive drugs. Therefore, delayed second dosing of COVID-19 vaccines should be avoided in patients receiving immunosuppressive drugs. Future studies that include younger patients need to be done to confirm the generalisability of our results.

Funding ZonMw, Reade Foundation, and MS Center Amsterdam.

Introduction

The relevance of vaccination against COVID-19 for patients with autoimmune diseases is emphasised by studies suggesting that this patient population is at increased risk of developing severe COVID-19.[1] However, the induction of protective immunity after COVID-19 vaccination might be reduced in patients with autoimmune diseases due to treatment with immunosuppressive medication.[2] Effects of immunosuppressive treatment on immunogenicity of vaccines might depend on the drug and vaccine type, and potentially the autoimmune disease type.[3–6] For example, results of a meta-analysis by Pugès and colleagues indicate that seroconversion rates after influenza

Research in context

Evidence before this study

We searched PubMed and Google Scholar on June 9, 2021, for studies published since January, 2020, in English that describe the development of humoral immunity after COVID-19 vaccination in patients with autoimmune diseases, using the terms "autoimmune diseases", "rheumatic diseases", "antirheumatic agents", "immunosuppressive agents", "vaccination", "antibodies", "humoral immunity", and variations on these. Data from previous studies suggest that treatment with methotrexate, glucocorticoids, TNF inhibitors, and anti-CD20 therapies impair the development of humoral immunity after the first dose of COVID-19 vaccines, while a second dose or a history of infection with SARS-CoV-2 before vaccination led to similar seroconversion rates in patients with autoimmune diseases treated with TNF inhibitors compared with healthy controls. Whether or not a second COVID-19 vaccination will have similar effects in patients treated with methotrexate, prednisone, TNF inhibitors, or anti-CD20 therapies is still unknown.

Added value of this study

To our knowledge, this is the first study to compare seroconversion after first and second COVID-19 vaccinations between patients with autoimmune diseases on various common treatment regimens and healthy controls. We compared SARS-CoV-2 IgG antibody development after first and second COVID-19 vaccinations between patients with autoimmune diseases and healthy controls with and without a previous SARS-CoV-2 infection. We found that treatment with methotrexate or anti-CD20 therapies significantly reduces seroconversion rates after first COVID-19 vaccination compared with healthy controls. However, seroconversion rates were similar for patients and controls who received two COVID-19 vaccinations and who had been infected with SARS-CoV-2 before vaccination, with the exception of patients on anti-CD20 therapies. Therefore, our data suggest that repeated exposure to SARS-CoV-2, either via infection or vaccination, is important to improve the development of humoral immunity against SARS-CoV-2 in patients receiving immunosuppressive treatment.

Implications of all the available evidence

Our data will help formulate recommendations on COVID-19 vaccinations in patients with autoimmune diseases. Physicians who prescribe immunosuppressive drugs to patients with autoimmune diseases should be aware that the development of humoral immunity after a first COVID-19 vaccination might be impaired in their patients, especially in those receiving methotrexate or anti-CD20 therapies, so delayed second dosing of COVID-19 vaccinations should be avoided. At the same time, physicians should be cautious when considering discontinuation of immunosuppressive therapies in their patients around the time of vaccination, especially because previous studies have found associations between high disease activity and severe COVID-19 disease manifestations.

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vaccination, but not pneumococcal vaccination, are lower in patients with systemic lupus erythematosus than in healthy controls.[6] By contrast, others have found diminished seroconversion after pneumococcal vaccination in patients with rheumatoid arthritis treated with methotrexate compared with healthy controls or patients treated with TNF inhibitors,[7,8] whereas findings from studies reporting the effects of methotrexate on seroconversion rates after influenza vaccination have been inconsistent.[9–12]

Data on immunogenicity of COVID-19 vaccines in patients with autoimmune diseases are still scarce because these individuals were largely excluded from the original vaccine trials. Data suggest that TNF inhibitors, glucocorticoids, methotrexate, and anti-CD20 therapies reduce the immunogenicity of COVID-19 vaccines.[13–15] However, the clinical implications of these findings remain to be established, because low seroconversion after the first dose of vaccine does not necessarily indicate that no immune response has been generated. For example, Kennedy and colleagues found that seroconversion after the first dose of COVID-19 vaccine was lower in patients with inflammatory bowel disease treated with the TNF inhibitor infliximab than in controls with inflammatory bowel disease who had been treated with vedolizumab, whereas seroconversion after the second dose of COVID-19 vaccine was comparable, suggesting that the immune response to COVID-19 vaccines might have been delayed rather than impaired in these patients.[14] Whether or not the second dose of vaccine will have similar effects in patients treated with methotrexate, glucocorticoids, TNF inhibitors, or anti-CD20 therapies is still unknown. Hence, no consensus exists as to whether specific treatments should be delayed or temporarily stopped around the time of receiving a COVID-19 vaccination, and whether specific patient groups would benefit from a booster vaccination. We assessed humoral immune responses after COVID-19 vaccinations in a population of patients with various autoimmune diseases with or without a previous SARS-CoV-2 infection, and compared the results to healthy controls.

Methods

Study design and participants

In this study, we collected data from participants enrolled in two prospective cohort studies that have the primary objective to study seroprevalence of SARS-CoV-2 antibodies and COVID-19-related disease severity in patients with autoimmune diseases. In the first study (Netherlands Trial Register, Trial ID NL8513), all adult patients (aged ≥18 years) with chronic inflammatory diseases from the Amsterdam Rheumatology and

Immunology Center in Amsterdam, The Netherlands, were invited to participate between April 26, 2020, and March 1, 2021. All patients were asked (but not obliged) to recruit their own control participant of the same sex, of comparable age (difference of <5 years), and without a chronic inflammatory disease. In the second study (NCT04498286), adult patients (aged ≥18 years) with multiple sclerosis from the MS Center Amsterdam in Amsterdam, the Netherlands, were invited to participate between July 31 and Dec 18, 2020.[16]

Between April 1 and June 26, 2021, all participants enrolled in the two prospective cohort studies received a questionnaire including questions on COVID-19 vaccination status. All participants vaccinated with any vaccine included in the Dutch national vaccine programme were eligible for inclusion in this substudy. Older people were prioritised for vaccination by the Dutch national vaccination programme at this time,[17] and so for this substudy the majority of patients and controls are older than 60 years.

The research protocols for both these studies were approved by the medical ethical committee of the VU University Medical Center (registration numbers 2020.169 and 2020.370). All participants gave written informed consent.

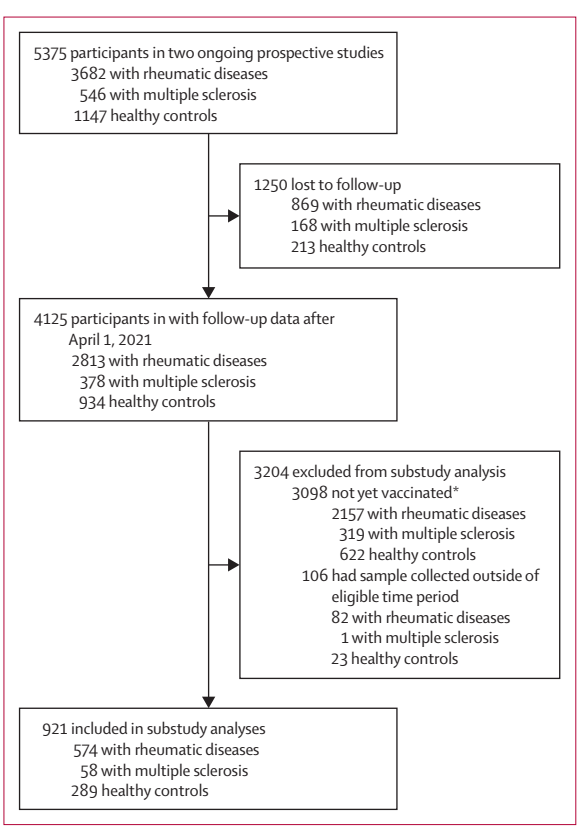

Figure 1: **Selection of participants from prospective cohort studies for inclusion in this study**

*These participants were invited for a national vaccine trial of the Target-to-B (T2B) Consortium when they fulfilled inclusion criteria for the trial.

Procedures

Demographic and clinical data were collected via online questionnaires that were distributed by email. Questionnaires were sent at baseline and up to three times during follow-up. Demographic data were only collected at baseline and included age, sex, height, weight, smoking status, autoimmune disease type, and educational level. At baseline and during follow-up, participants reported their disease activity, medication use, and COVID-19-related clinical characteristics. Autoimmune disease activity was only assessed for patients with rheumatoid arthritis, using the Multi-Dimensional Health Assessment Questionnaire (including Routine Assessment of Patient Index Data 3 known as RAPID-3] and Health Assessment Questionnaire 2 [known as HAQ2]), and with ankylosing spondylitis, using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI); these data are to be reported elsewhere. COVID-19-related characteristics included information on symptomology (cough, dyspnoea, fever, loss of taste or smell, malaise, fatigue, headache, vomiting, and diarrhoea), physical distancing measures (no measures at all, only hygiene measures, hygiene measures and physical distancing, all aforementioned measures and staying indoors as much as possible, or total isolation), PCR test results, admissions to hospital, and, from April 26, 2021, information on COVID-19 vaccinations (vaccination dates, vaccine type, and adverse events). Data on vaccine-induced adverse events have been reported elsewhere.[18]

The Dutch national vaccination programme included four COVID-19 vaccine types: ChAdOx1 nCoV-19 (AstraZeneca), BNT162b2 (tozinameran; Pfizer-BioNtech), CX-024414 (elasomeran; Moderna), and Ad.26.COV2.S (Janssen). Vaccination schemes of ChAdOx1 nCoV-19, BNT162b2, and CX-024414 included two doses of vaccine, whereas Ad.26.COV2.S only included a single vaccination. Time intervals between first and second doses varied between January and June, 2021, but at the start of the vaccination programme the time interval between first and second dose was 12 weeks for ChAdOx1 nCoV-19, 6 weeks for BNT162b2, and 4 weeks for CX-024414.[19] Each participant provided one post-vaccination sample, after either the first or second dose of vaccine. To assess seroprevalence after the first vaccine dose, samples were collected from 14 days after the first dose until 3 days after a second dose. To assess seroprevalence after two doses of COVID-19 vaccine, sampling took place at least 7 days after the second dose.

Serum samples were collected via regular blood withdrawal at the local research institutes or via a finger prick at home before and after receiving a COVID-19 vaccination. Pre-vaccination serum samples were collected between April 26, 2020, and March 31, 2021, and post-vaccination serum samples were collected between April 1 and June 26, 2021. Analyses were done at Sanquin (Amsterdam, the Nerthlands). Pre-vaccination serum samples were analysed for the presence of SARS-CoV-2 specific antibodies with a receptor-binding domain

	Patients with autoimmune diseases			Healthy controls (n=289)
	All patients (n=632)	Not on immunosuppressive treatment (n=125)	On methotrexate (n=223)	
Demographic characteristics				
Age, years	63 (11)	64 (11)	65 (10)	63 (11)
Sex				
Female	423 (67%)	82 (66%)	153 (69%)	195 (67%)
Male	209 (33%)	43 (34%)	70 (31%)	94 (33%)
Body-mass index, kg/m²	26 (5)	26 (5)	26 (4)	25 (4)
Coexisting conditions				
Chronic pulmonary disease	88 (14%)	19 (15%)	29 (13%)	21 (7%)
Cardiovascular disease	83 (13%)	21 (17%)	24 (11%)	30 (10%)
Diabetes	35 (6%)	6 (5%)	15 (7%)	16 (6%)
Obesity	109 (17%)	23 (18%)	42 (19%)	29 (10%)
Clinical characteristics				
Autoimmune disease type*				
Rheumatoid arthritis	260 (41%)	21 (17%)	165 (74%)	NA
Psoriatic arthritis	68 (11%)	5 (4%)	39 (17%)	NA
Ankylosing spondylitis	68 (11%)	20 (16%)	4 (2%)	NA
Axial or peripheral spondyloarthritis	6 (1%)	0	0	NA
Juvenile idiopathic arthritis	8 (1%)	0	3 (1%)	NA
Systemic lupus erythematosus	33 (5%)	9 (7%)	2 (1%)	NA
Vasculitis	11 (2%)	3 (2%)	0	NA
Polymyalgia rheumatica	37 (6%)	5 (4%)	4 (2%)	NA
Sjögren's syndrome	33 (5%)	10 (8%)	5 (2%)	NA
Other rheumatic diseases†	103 (16%)	46 (37%)	17 (8%)	NA
Multiple sclerosis	58 (9%)	13 (10%)	0	NA
Immunosuppressive medication*				
No immunosuppressive medication	125 (20%)	125 (100%)	NA	NA
Conventional synthetic DMARDs	316 (50%)	NA	223 (100%)	NA
Methotrexate	223 (35%)	NA	223 (100%)	NA
≥15 mg	120 (19%)	NA	120 (54%)	NA
<15 mg	103 (16%)	NA	103 (46%)	NA
Monotherapy	87 (14%)	NA	87 (39%)	NA
Other‡	93 (15%)	NA	0	NA
Biologicals	202 (32%)	NA	77 (35%)	NA
TNF inhibitor	141 (22%)	NA	61 (27%)	NA
Monotherapy	61 (10%)	NA	0	NA
Anti-CD20 therapy	27 (4%)	NA	6 (3%)	NA
Other	34 (5%)	NA	9 (4%)	NA
Immunomodulatory multiple sclerosis therapies	25 (4%)	NA	0	NA
Interferon beta	4 (1%)	NA	0	NA
Other	21 (3%)	NA	0	NA
Prednisone	109 (17%)	NA	36 (16%)	0
Dose, mg	7 (5)	NA	5 (3)	NA
Monotherapy	32 (5%)	NA	0	0
SARS-CoV-2 infection				
Confirmed diagnosis of SARS-CoV-2 infection	94 (15%)	22 (18%)	33 (15%)	39 (13%)
Serological confirmed diagnosis§	72 (11%)	17 (14%)	24 (11%)	28 (10%)
PCR confirmed diagnosis	52 (8%)	14 (11%)	19 (9%)	25 (9%)

(Table 1 continues on next page)

	Patients with autoimmune diseases			Healthy controls (n=289)
	All patients (n=632)	Not on immunosuppressive treatment (n=125)	On methotrexate (n=223)	
(Continued from previous page)				
COVID-19 vaccination				
Vaccine type				
ChAdOx1 nCoV-19 (AstraZeneca)	343 (54%)	67 (54%)	124 (56%)	171 (59%)
BNT162b2 (Pfizer-BioNtech)	241 (38%)	48 (38%)	91 (41%)	108 (37%)
CX-024414 (Moderna)	48 (8%)	10 (8%)	8 (4%)	7 (2%)
Ad.26.COV2.S (Janssen)	0	0	0	3 (1%)
Serum sample acquired after the first vaccination	507 (80%)	96 (77%)	192 (86%)	239 (83%)
Time between vaccination and sampling, days	34 (31–38)	34 (32–38)	34 (31–37)	36 (34–41)
Serum sample acquired after the second vaccination	125 (20%)	29 (23%)	31 (14%)	50 (17%)
Time between vaccination and sampling, days	38 (30–61)	31 (20–44)	36 (30–75)	42 (35–85)

Data are mean (SD), median (IQR), or n (%). Other biologicals were tocilizumab, natalizumab, secukinumab, ustekinumab, ixekizumab, and abatacept; other conventional synthetic DMARDs were sulfasalazine, hydroxychloroquine, leflunomide, azathioprine, and ciclosporin; and other immunomodulatory multiple sclerosis therapies were fingolimod, stem-cell transplantation, and fampridine. DMARDs=disease modifying anti-rheumatic drugs. NA=not applicable. *One person can be diagnosed with more than one autoimmune disease type and receive more than one immunosuppressive drug. †Other rheumatic diseases included mixed connective tissue disease, sarcoidosis, systemic sclerosis and myositis. ‡Other conventional synthetic DMARDs included hydroxychloroquine, sulfasalazine, leflunomide and azathioprine. §Measured with a total receptor-binding domain-antibody bridging ELISA.

Table 1: **Characteristics of patients with autoimmune diseases and healthy controls who have been vaccinated against COVID-19**

(RBD)-antibody bridging ELISA (in-house) with a 98·1% sensitivity and a 99·5% specificity.[20] In post-vaccination serum samples, levels of IgG antibodies against the RBD protein of the SARS-CoV-2 spike protein were quantified as described previously.[21] Signals were compared with a serially diluted calibrator (assigned a value of 100 arbitrary units [AU] per mL) consisting of pooled convalescent plasma that was included on each plate. Anti-RBD IgG titres were expressed as AU/mL. A cutoff of 4 AU/mL represents 99% specificity in pre-outbreak serum samples (ie, collected before December, 2019);[21] seroconversion after vaccination was based on this cutoff. Neutralisation assays are considered to be more biologically relevant compared with total antibody assays, but we previously found high correlations between both assays.[21]

Confirmed COVID-19 cases were defined as participants who reported a positive PCR test to SARS-CoV-2 at any time during follow-up, but before collection of post-vaccination serum samples and participants in whom SARS-CoV-2 specific antibodies were detected in pre-vaccination serum samples.

Outcomes

The primary outcome was humoral immunity to the RBD protein of the SARS-CoV-2 spike protein after COVID-19 vaccination. The primary objective of this study was to assess the effect of different immunosuppressive drugs on seroconversion rates and the magnitude of IgG antibody titres after COVID-19 vaccinations in participants with and without a previous SARS-CoV-2 infection. Treatment groups were divided into methotrexate (further stratified to all methotrexate users [monotherapy and combination therapy], dose of ≥15 mg [monotherapy and combination therapy], dose of <15 mg [monotherapy and combination therapy], and monotherapy only), monotherapy with TNF inhibitors, anti-CD20 therapy (monotherapy and combination therapy), and monotherapy with prednisone. Methotrexate combination therapy could include any additional immunosuppressive drug or drugs other than anti-CD20 therapies. Anti-CD20 combination therapy could include any additional immunosuppressive drugs, including methotrexate. Other objectives were to explore whether seroconversion rates and the magnitude of IgG antibody titres after COVID-19 vaccinations differed between autoimmune disease types, and whether vaccine type affects seroconversion rates after first COVID-19 vaccination. Treatment groups were based on medication use at the time of vaccination.

Statistical analysis

Participants were included in these analyses if they had blood drawn within the above described timeframe (ie, up until June 26, 2021) and completed the questionnaires on COVID-19 vaccinations before June 1, 2021. We present baseline characteristics and serological results as mean (SD), median (IQR), or frequencies and proportions depending on the type and distribution of the data. Additionally, we present titres of IgG antibodies in scatter plots stratified for defined treatment groups and by previous SARS-CoV-2 positivity.

We did univariable and multivariable logistic regression analyses to compare seroconversion rates after a first COVID-19 vaccination between patients and healthy

controls in participants without previous SARS-CoV-2 infection. In additional analyses, we compared defined treatment groups against healthy controls. A priori, we adjusted multivariable analyses for sex, age, and vaccine type. We investigated effect modification for age (stratified to participants aged ≤55 years *vs* >55 years, in line with BNT162b2 and ChAdOx1 nCoV-19 phase 3 vaccine trials[22]) and sex, but only in the analyses that included all patients (regardless of their treatment group) and controls. p values of less than 0·10 were determined to be significant in these interaction analyses.

We did univariable and multivariable linear regression analyses to compare the magnitude of IgG antibody titres after first and second COVID-19 vaccinations between patients and healthy controls in both participants with and without previous SARS-CoV-2 infection. In additional analyses we compared defined treatment groups against healthy controls. IgG antibody titre data did not follow a normal distribution, so we transformed these data logarithmically before analyses. We only did these analyses for treatment groups in which a normal distribution of IgG antibody titres was obtained after transformation. Again, we adjusted multivariable analyses for sex, age, and vaccine type. For presentation in tables, data were back-transformed.

Seroconversion rates and IgG antibody titers stratified for defined treatment groups were separately described for patients with rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, and multiple sclerosis.

Finally, we did exploratory multivariable logistic and linear regression analyses to compare seroconversion rates and the magnitude of IgG titres between first ChAdOx1 nCoV-19 and BNT162b2 vaccinations. A priori, these analyses were adjusted for sex, age, having an autoimmune disease, treatment with anti-CD20, and treatment with methotrexate. We used the Benjamini-Hochberg method to correct for multiple tests to ensure a family-wise false discovery rate of 5%.[23]

We did all statistical analyses using SPSS (version 27.0). We created scatter plots of IgG antibody titres in GraphPad Prism (version 6.0).

Role of the funding source

The funders of this study had no role in the study design, data collection, data analysis, data interpretation, or in the writing of the report.

Results

Between April 26, 2020, and March 1, 2021, 3682 patients with rheumatic diseases, 546 patients with multiple sclerosis, and 1147 healthy controls were recruited to participate in the two prospective cohort studies. Serum samples after one or two doses of COVID-19 vaccine and completed questionnaires on COVID-19 vaccinations were collected for 632 patients (574 patients with rheumatic diseases and 58 patients with multiple sclerosis) and 289 healthy controls, who were included for analyses (figure 1).

	After first vaccination		After second vaccination	
	Seroconverted	IgG titre, AU/mL	Seroconverted	IgG titre, AU/mL
Without previous SARS-CoV-2 infection				
Healthy controls	154/210 (73%)	8·1 (3·8–21·5)	38/40 (95%)	86·7 (44·6–205·0)
All patients	210/432 (49%)	3·9 (1·0–11·0)	97/106 (92%)	48·6 (16·7–134·0)
No immunosuppressive therapy	52/77 (68%)	9·5 (2·9–27·1)	23/26 (88%)	102·4 (26·2–274·0)
Prednisone monotherapy	14/22 (64%)	5·4 (2·4–16·0)	4/5 (80%)	78·1 (23·8–152·0)
TNF inhibitor monotherapy	24/36 (67%)	6·7 (2·8–13·9)	14/14 (100%)	85·8 (35·3–166·3)
Methotrexate				
All methotrexate*	43/144 (30%)	1·4 (0·5–5·3)	17/18 (94%)	41·0 (10·2–85·1)
≥15 mg	16/72 (22%)	1·1 (0·5–3·6)	9/10 (90%)	40·0 (9·9–112·0)
<15 mg	27/72 (38%)	1·8 (0·9–5·9)	8/8 (100%)	41·0 (8·4–74·2)
Monotherapy	26/71 (37%)	1·7 (0·7–6·0)	5/5 (100%)	38·5 (16·8–104·8)
Anti-TNF therapy and methotrexate	14/42 (33%)	1·7 (1·0–11·1)	8/9 (89%)	15·9 (8·8–119·5)
Anti-CD20 therapy	1/18 (6%)	0·6 (0·5–0·9)	3/7 (43%)	2·0 (0·5–28·3)
With previous SARS-CoV-2 infection				
Healthy controls	28/29 (97%)	145·0 (87·2–275·0)	9/10 (90%)	114·0 (62·2–252·8)
All patients	72/75 (96%)	127·0 (27·3–300·0)	17/19 (89%)	82·3 (31·0–270·0)
No immunosuppressive therapy	19/19 (100%)	140·0 (37·6–277·0)	3/3 (100%)	306·0 (NA)
Prednisone monotherapy	4/4 (100%)	195·5 (81·0–365·3)	1/1 (100%)	106·0 (NA)
Anti-TNF monotherapy	8/8 (100%)	32·4 (9·8–248·2)	3/3 (100%)	77·5 (NA)
Methotrexate				
All methotrexate*	22/23 (96%)	143·0 (32·8–300·0)	7/9 (78%)	57·7 (8·6–273·5)
≥15 mg	11/11 (100%)	180·0 (32·8–300·0)	6/7 (86%)	82·3 (16·4–300·0)
<15 mg	11/12 (92%)	126·0 (41·4–294·3)	1/2 (50%)	29·2 (NA)
Monotherapy	6/7 (86%)	142·0 (32·6–291·0)	2/4 (50%)	10·2 (0·7–190·2)
Anti-TNF and methotrexate	8/8 (100%)	129·0 (46·0–299·8)	2/2 (100%)	49·4 (NA)
Anti-CD20 therapy	0/1 (0%)	1·2 (NA)	1/1 (100%)	45·4 (NA)

Data are n (%) or median (IQR). IgG titre data are provided to one decimal place. NA=not applicable. *Patients treated with anti-CD20 therapies were excluded from this subgroup.

Table 2: **Seroconversion of SARS-CoV-2 IgG antibodies following vaccination in participants without and with previous SARS-CoV-2 infection**

Baseline characteristics of all patients with autoimmune diseases, patients not treated with immunosuppressive drugs, patients treated with methotrexate, and healthy controls are shown in table 1. The mean age for both patients and controls was 63 years (SD 11), and most participants were female: 423 (67%) of 632 patients with autoimmune diseases and 195 (67%) of 289 controls. Age and sex distributions were similar across different treatment groups (table 1; appendix p 1). 507 (80%) of 632 patients were receiving immunosuppressive treatment. Patients were most frequently being treated with methotrexate (223 [35%] of 632; 87 [14%] on monotherapy), TNF inhibitors (141 [22%] of 632; 61 [10%] on monotherapy; including adalimumab [any n=46; monotherapy n=13], etanercept [any n=64; monotherapy

See Online for appendix

	Crude model		Adjusted model	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Healthy controls	1·0 (ref)	..	1·0 (ref)	..
All patients	0·34 (0·24–0·49)	<0·0001*	0·33 (0·23–0·48)	<0·0001*
No immunosuppressive therapy	0·76 (0·43–1·3)	0·33	0·72 (0·40–1·3)	0·27
Prednisone monotherapy	0·64 (0·25–1·6)	0·34	0·65 (0·24–1·7)	0·39
TNF inhibitor monotherapy	0·73 (0·34–1·6)	0·41	0·57 (0·25–1·3)	0·18
Methotrexate				
All methotrexate†	0·16 (0·10–0·25)	<0·0001*	0·15 (0·094–0·25)	0·0001*
≥15 mg	0·10 (0·055–0·20)	<0·0001*	0·10 (0·051–0·19)	0·0001*
<15 mg	0·22 (0·12–0·39)	<0·0001*	0·20 (0·11–0·37)	0·0001*
Concomitant therapy				
Monotherapy	0·21 (0·12–0·37)	<0·0001*	0·20 (0·11–0·37)	0·0001*
Anti-TNF therapy and methotrexate	0·15 (0·068–0·34)	<0·0001*	0·14 (0·062–0·32)	0·0001*
Anti-CD20 therapy	0·021 (0·0027–0·16)	<0·0001*	0·014 (0·0015–0·14)	0·0001*

Data are odds ratios with 95% CIs in parentheses, and p values. Adjusted odds ratios are adjusted for age, sex, and vaccine type. Data are presented to two significant figures or three decimal places. *Below the Benjamini threshold. †Patients treated with anti-CD20 therapies were excluded from this subgroup.

Table 3: **Likelihood of seroconversion after the first COVID-19 vaccination in patients with autoimmune diseases compared with healthy controls, in participants without a previous SARS-CoV-2 infection**

n=26], certolizumab pegol [any n=12; monotherapy n=9], golimumab [any n=9; monotherapy n=8], or infliximab [any n=10; monotherapy n=5]), or both in combination (61 [10%] of 632). Additionally, 109 (17%) of 623 patients were treated with prednisone (32 [5%] on monotherapy). Finally, 27 (4%) of 632 patients were being treated with anti-CD20 therapies (rituximab for patients with rheumatic disease [n=13] or ocrelizumab for patients with multiple sclerosis [n=14]).

Pre-vaccination serum samples were obtained for 507 (80%) of 632 patients and 252 (87%) of 289 controls. Diagnosis of COVID-19 (via PCR or serology, or both) was confirmed in 94 (15%) of 632 patients, and 39 (13%) of 289 controls (table 1). ChAdOx1 nCoV-19 and BNT162b2 were the most common vaccines in both patients and controls. Most patients and controls were vaccinated only once at the time of blood sampling: 507 (80%) of 632 patients and 239 (83%) of 289 controls. For participants who were sampled after their first dose, the median number of days between vaccination and sampling was 34 days (IQR 31–38) for patients and 36 days (34–41) for controls. For participants who were sampled after their second dose, the median number of days between the second vaccination and sampling was 38 days (31–61) for patients and 42 days (35–85) for controls (table 1). Distribution of age, sex, and comorbidities were comparable for participants who had received a single vaccination and participants who had received two vaccinations at the time of sampling (appendix p 2).

In participants who had not been previously infected with SARS-CoV-2, the seroprevalence of IgG SARS-CoV-2 antibodies in patients with autoimmune diseases after their first COVID-19 vaccination was 49% (210 of 432) compared with 73% (154 of 210) in healthy controls (adjusted odds ratio 0·33 [95% CI 0·23–0·48]; p<0·0001; tables 2, 3). Patients treated with methotrexate and anti-CD20 therapies had significantly lower seroconversion rates than healthy controls, but patients on TNF inhibitors or prednisone monotherapy and patients not on immunosuppressive therapy did not, although seroconversion rates were numerically lower in all these groups than among healthy controls (tables 2, 3). Patients with autoimmune disease had lower median IgG titres than did controls. Additional analyses stratified by treatment group showed a significant effect of methotrexate therapy (0·15 [0·094–0·25]; p<0·0001), and anti-CD20 therapy (0·014 [0·002–0·14]; p<0·0001), on IgG titres that was not present with TNF inhibitors or prednisone monotherapy (figure 2 and tables 2, 3, 4).

After a second COVID-19 vaccination, seroconversion was seen in the majority of patients and controls without previous SARS-CoV-2 infection (table 2). Seroconversion rates were similar across all predefined treatment groups, except for patients on anti-CD20 therapies, of whom only three (43%) of seven were seropositive.

Seroconversion rates and the magnitude of IgG antibody titres in participants with a previous infection with SARS-CoV-2 infection are shown in table 2 and figure 2. After first vaccination, seropositivity was seen in 28 (97%) of 29 healthy controls and 72 (96%) of 75 patients. The three patients in whom seropositivity was not seen were being treated with methotrexate monotherapy (dose <15 mg), rituximab and methotrexate (dose ≥15 mg), and 4-aminopyridine monotherapy. Magnitudes of IgG antibody titres were not significantly different for patients and controls, which was consistent across different treatment groups (table 2). Additionally, seroconversion rates and magnitudes of IgG antibody titres were similar in participants with previous SARS-CoV-2 infection after the first COVID-19 vaccination and participants without previous SARS-CoV-2 infection after their second COVID-19 vaccination (table 2).

Descriptive results on seroconversion, stratified for patients with rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, and multiple sclerosis are shown in the appendix (p 4). Seroconversion rates and the magnitude of IgG antibody titres after the first and second COVID-19 vaccination were similar across these autoimmune disease types in patients who were not on immunosuppressive drugs. Seroconversion was seen in eight (73%) of 11 patients with rheumatoid arthritis, ten (77%) of 13 patients with ankylosing spondylitis, five (83%) of six patients with systemic lupus erythematosus, and eight (73%) of 11 patients with multiple sclerosis.

Via multivariable logistic regression analyses we found that the likelihood of seroconversion after the first vaccination was similar for ChAdOx1 nCoV-19 and

BNT162b2: the odds ratio for seroconversion for BNT162b2 compared with ChAdOx1 nCoV-19 was 1·33 (95% CI 0·69–2·55; p=0·39). Additionally, the size of IgG titres in participants who had been vaccinated with BNT162b2 were similar to those of participants vaccinated with ChAdOx1 nCoV-19 (odds ratio for seroconversion after first vaccine 1·26 [0·79–2·00; p=0·33]).

Discussion

We found that, among participants without previous SARS-CoV-2 infection, seroconversion rates after first COVID-19 vaccination in patients with autoimmune diseases treated with methotrexate or anti-CD20 therapies, but not prednisone or TNF inhibitors, were lower than those of patients not on immunosuppressive medication and healthy controls. However, most patients who received two doses of COVID-19 vaccine were seropositive, and seroconversion rates were similar for patients across all different treatment regimens to controls, except those on anti-CD20 therapies. Additionally, in patients with a previous SARS-CoV-2 infection who received a single dose of COVID-19 vaccine, seroconversion rates were similar to patients without previous SARS-CoV-2 infection who received two doses of vaccine. Finally, differences in seroconversion rates and antibody titres were similar across autoimmune disease types and the two main vaccine types, suggesting that treatment with immunosuppressive medication, rather than the underlying autoimmune disease, is the main factor that influences immunogenicity of vaccines.

Data on the development of humoral immunity in patients with autoimmune diseases after COVID-19 vaccination are still scarce, but first results have now been published. A large UK cohort study in patients with inflammatory bowel disease compared seroconversion rates after COVID-19 vaccination between patients treated with infliximab (TNF inhibitor) and vedolizumab (a gut-selective anti-integrin $\alpha_4\beta$ monoclonal antibody).[14] In line with our results, they observed similar seroconversion rates in patients with previous SARS-CoV-2 infection who received a single dose of COVID-19 vaccine and patients without previous SARS-CoV-2 infection who received two dose of COVID-19 vaccine. However, lower IgG titres in patients without previous SARS-CoV-2 infection after a single COVID-19 vaccine were observed than among similar patients in our cohort. A second study by Haberman and colleagues[24] assessed IgG antibody development in patients treated with methotrexate, and observed lower seroconversion rates after the second BNT162b2 dose in patients than in healthy controls.[24] This discrepancy with the results of our study might be explained by the difference in time intervals between receiving the second vaccine dose and sampling; serum samples in the study by Haberman and colleagues were collected 7 days after the second dose, while the median time between vaccination and sampling in our patient cohort was 38 days. These data suggest that methotrexate might delay rather than impair the development of humoral immunity in patients with autoimmune diseases or that methotrexate affects short-lived antibody formation, whereas long-lived antibody formation might be less affected. A third study by Geisen and colleagues[25] assessed seroconversion after two doses of mRNA-based

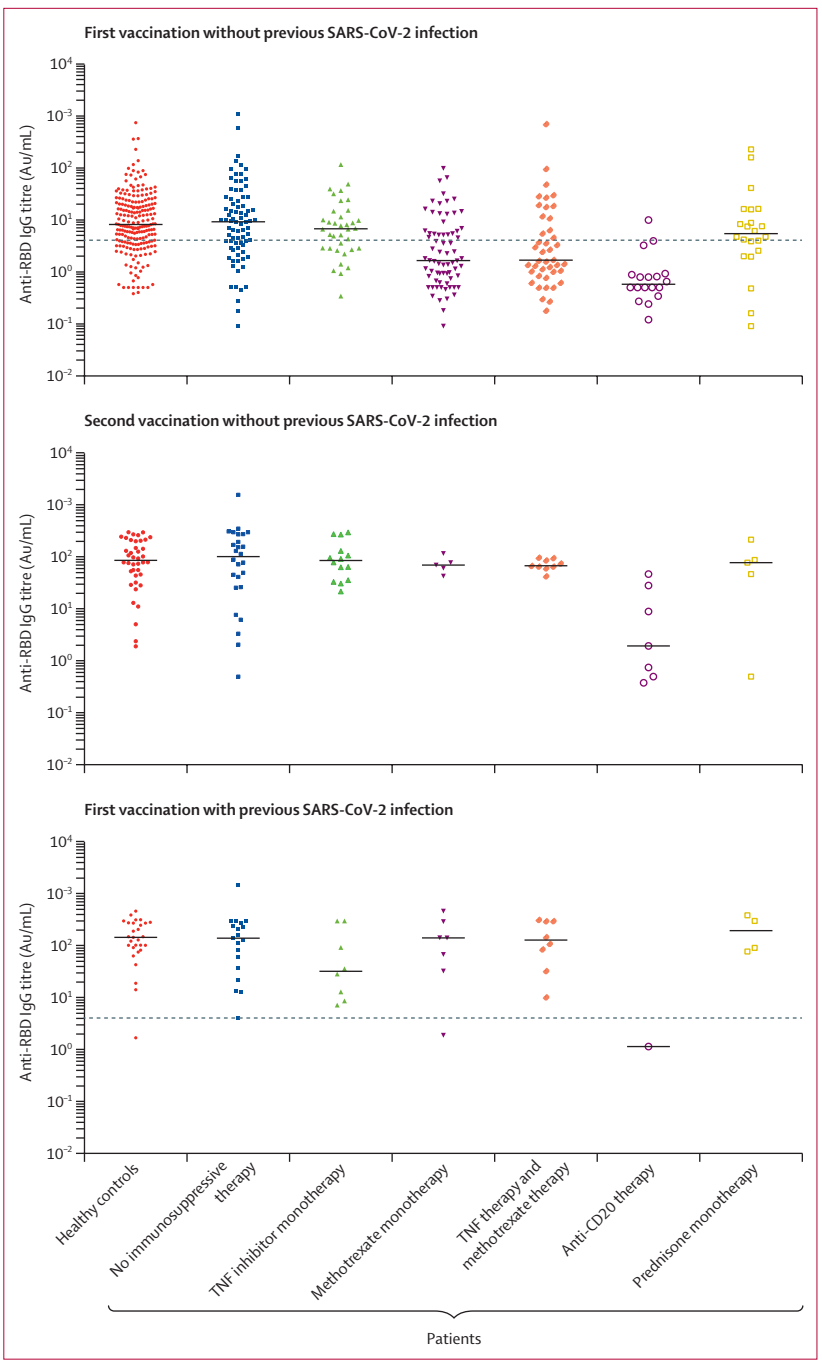

Figure 2: **Anti-SARS-CoV-2 IgG antibody concentrations after COVID-19 vaccination**
Each datapoint is a participant, and the solid horizontal lines show the group median.

	Crude model			Adjusted model		
	β	Ratio (95% CI)	p value	β	Ratio (95% CI)	p value
SARS-CoV-2 negative, after first COVID-19 vaccination						
Healthy controls	0·00	1·00 (ref)	..	0·00	1·00 (ref)	..
All patients	–0·84	0·43 (0·33 to 0·56)	<0·0001*	–0·95	0·39 (0·37 to 0·54)	<0·0001*
No immunosuppressive therapy	–0·016	0·98 (0·67 to 1·4)	0·94	0·14	1·2 (0·71 to 1·7)	0·56
TNF inhibitor monotherapy	–0·31	0·73 (0·46 to 1·2)	0·19	–0·49	0·61 (0·33 to 1·2)	0·13
All methotrexate†	–1·5	0·22 (0·16 to 0·29)	0·0001*	–1·5	0·22 (0·16 to 0·31)	<0·0001*
SARS-CoV-2 negative, after second COVID-19 vaccination						
Healthy controls	0·00	1·00 (ref)	..	0·00	1·00 (ref)	..
All patients	–0·59	0·55 (0·31 to 0·99)	0·045	–0·67	0·51 (0·26 to 1·0)	0·051
No immunosuppressive therapy	–0·11	0·90 (0·42 to 1·9)	0·77	–0·065	0·94 (0·36 to 2·4)	0·89
TNF inhibitor monotherapy	0·16	1·2 (0·57 to 2·4)	0·67	–0·099	0·91 (0·34 to 2·4)	0·84
All methotrexate†	–0·86	0·43 (0·21 to 0·88)	0·022	–0·72	0·49 (0·20 to 1·2)	0·12
SARS-CoV-2 positive, after first COVID-19 vaccination						
Healthy controls	0·00	1·00 (ref)	..	0·00	1·00 (ref)	..
All patients	–0·37	0·69 (0·37 to 1·3)	0·26	–0·76	0·47 (0·16 to 1·3)	0·15
No immunosuppressive therapy	–0·16	0·85 (0·40 to 1·8)	0·68	–0·25	0·78 (0·18 to 3·4)	0·73
TNF inhibitor monotherapy	–1·1	0·34 (0·13 to 0·93)	0·036	–1·2	0·32 (0·058 to 1·7)	0·17
All methotrexate†	–0·21	0·81 (0·39 to 1·7)	0·57	–1·0	0·36 (0·087 to 1·4)	0·17

Data are βs, back-transformed ratios with corresponding 95% CIs in parentheses, and p values. Ratios in the adjusted models are adjusted for age, sex, and vaccine type. Data are presented to two significant figures. *Below Benjamini threshold. †Patients treated with anti-CD20 therapies were excluded from this subgroup.

Table 4: **Linear regression comparing SARS-CoV-2 IgG titres between patients and controls stratified by previous SARS-CoV-2 infection, number of vaccinations, and treatment groups**

vaccines in patients with various chronic inflammatory diseases and healthy controls. Similar to our findings, they observed a pronounced reduction in seroconversion rates and IgG antibody titres in patients treated with anti-CD20 therapies compared with healthy controls. They also observed attenuated IgG antibody titres in patients treated with prednisone, which is in contrast with our results. This finding might be because patients in Geisen and colleagues' study received other immunosuppressive drugs in addition to prednisone whereas we assessed patients on prednisone monotherapy.

Previous studies that compared the magnitude of IgG antibody titres after influenza vaccination in patients who continued or discontinued treatment with methotrexate showed favourable effects of treatment discontinuation up to 2 weeks after vaccination on antibody titres with minimal risk of disease flares.[26] However, previous studies have found that not only humoral immunity, but also cellular immunity is important for protection against SARS-CoV-2.[27] Therefore, the extent to which reduced IgG antibody titres after COVID-19 vaccinations in patients treated with methotrexate (or anti-CD20 therapies) will also result in reduced protection against severe COVID-19 illness is difficult to predict. Therefore, especially because high rheumatic disease activity is associated with a worse disease outcome of COVID-19,[28] discontinuation of methotrexate treatment at the time of vaccination should be considered with caution in patients with autoimmune diseases. Considerations about introduction of an additional booster vaccine might be worthwhile to discuss and incorporate into future clinical explorations.

Our study has several strengths. First, to our knowledge, this is the first study to compare seroconversion after first and second COVID-19 vaccinations between patients with autoimmune diseases on various common treatment regimens and healthy controls. This is important, because to date, the ability to compare results of different studies that assess immunogenicity of COVID-19 vaccines is restricted due to differences in the applied serological assays and thresholds of seroconversion between studies. Second, our heterogeneous patient population, who had a broad range of autoimmune disease types, enhances the generalisability of our results and distinguishes our findings from previous studies that have often only included patients with a single autoimmune disease type. Third, we compared seroconversion rates between the two most commonly used vaccine types, which further improves the generalisability of our results. Fourth, our patient population mainly consisted of older people, because these individuals comprised the first group that was invited for COVID-19 vaccination in the Netherlands. Older age is a known risk factor for severe COVID-19 outcomes,[28] but also for attenuated response to vaccination.[29] Therefore, although the inclusion of mainly older patients might minimise the generalisability of our results, they translate well to

patients for whom protection against SARS-CoV-2 is most relevant.

Our study also has several limitations. First, the sample size of some patient groups was small, notably for patients on anti-CD20 therapy and prednisone monotherapy. Second, we had no data on the timing of anti-CD20 therapy administration before vaccination. Third, few participants were vaccinated with CX_022414 or Ad.26.COV2.S and only a small number of participants included in our analysis had received a second dose of ChAdOx1 nCoV-19 beacsue of the longer interval between the first and second vaccine dose of ChAd_x1 nCoV-19 than for BNT62b2 and CX-024414. This might reduce the generalisability of our results, because immunogenicity might differ between vaccines, even between vaccines with the same working mechanism. However, because we found no difference in seroconversion rates and antibody titres between ChAdOx1 nCoV-19 and BNT62b2 after a single dose (vaccines with different working mechanisms), our data suggest that the effect of vaccine type on immunogenicity might be negligible.. Fourth, no longitudinal data on antibody development after first and second COVID-19 vaccinations were available, so responses to first and second doses cannot be compared on an individual patient level. However, we attempted to correct for this limitation by adjusting for a set of variables known to affect immunogenicity (age, sex, and vaccine type).[29,30] Finally, because a cutoff value for SARS-CoV-2 IgG antibody titres that defines clinical immunity has not been established, the cutoff values we used are based on the specificity and sensitivity of the assay, and represent primarily a measurable humoral immune response. Therefore, because the number of participants and duration of follow-up after receiving their vaccination or vaccinations (1–5 months) are insufficient to correlate antibody titres to clinical protection against SARS-CoV-2, our results should be interpreted with caution.

Our data will help formulate recommendations on vaccination against COVID-19 in patients with autoimmune diseases. We found that in older patients with autoimmune diseases, treatment with immunosuppressive drugs (especially methotrexate and anti-CD20 therapies) rather than the underlying autoimmune disease is the main factor that can reduce seroconversion rates after a first COVID-19 vaccination. Additionally, we found that a single dose of vaccine in patients with a previous SARS-CoV-2 infection or a second dose of vaccine in patients without previous infection led to seroconversion in the vast majority of patients on any immunosuppressive treatment, with the exception of patients on anti-CD20 therapies. Therefore, delayed second dosing of COVID-19 vaccines should be avoided in patients on immunosuppressive treatment regimens.

Contributors

LB wrote the manuscript. LB and FH did the statistical analyses. MS, OC, SK, and TR did the serological assays to measure SARS-CoV-2 antibody response. MS, FH, YRB, ZLEvK, LYK, KPJvD, EWS, EHV, OC, SK, GV, AEV, LW, FE, RvV, TWK, SMvH, SWT, JK, MB, MTN, TR, and GW helped revise the manuscript for important intellectual content. GW supervised the manuscript. LB and FH had access to and verified the underlying data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

JK reports grants from Biogen Idec, Novatis, TEVA, Bayer Schering Pharma, GlaxoSmithKline, Merck Serono, Genzyme, and Roche outside of the submitted work. All other authors declare no competing interests.

Data sharing

We intend to share de-identified participant level data on request after we have published all data on our predefined research objectives. Researchers that are interested in doing additional analyses using these data can contact the corresponding author. Data can only be used for scientific research without conflict of interests. After data collection has been completed and data on our predefined research objectives has been published, there will be no end date before which researchers can request access to the data. Additional documents that will be made available on request are the protocol (including all amendments), and informed consent forms.

Acknowledgments

TR reports grants from ZonMw during the conduct of the study. GW reports grants from ZonMw and Reade foundation during the conduct of the study. We thank Sanquin Diagnostic services (Amsterdam, Netherlands) for their support in logistics of the study design, especially Floris Loeff, Annick de Vries, and Fabiënne Langedijk. We also thank the Nationaal Screeningslaboratorium Sanquin for processing the finger prick envelopes, especially Chaya Badal, Jim Keijser, Kristine Khamis, Judith Borst, Mark Hogenboom, Rogier Gorter, and Mariëlle van Rijswijk). We also acknowledge the support of our colleagues in the Dutch Target to B! Consortium on COVID-19 in Autoimmune Diseases. Trial ID NL8513 received funding of ZonMw and Reade Foundation. The Dutch MS Research Foundation funded the study of the MS Center Amsterdam (grant 20-005 PP).

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