ORIGINAL RESEARCH

Humoral and cellular SARS-CoV-2 vaccine responses in patients with giant cell arteritis and polymyalgia rheumatica

Yannick van Sleen [ID],[1] Kornelis S M van der Geest [ID],[1] Rosanne D Reitsema,[1] Idil Esen,[1] Janneke H Terpstra,[1] Elisabeth Raveling-Eelsing,[1] Marieke van der Heiden,[2] Thomas Lieber,[3] Annemarie M Buisman,[4] Debbie van Baarle,[2] Maria Sandovici,[1] Elisabeth Brouwer [ID] [1]

ABSTRACT

Objectives Giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) are overlapping autoinflammatory diseases affecting people over 50 years. The diseases are treated with immunosuppressive drugs such as prednisolone, methotrexate, leflunomide and tocilizumab. In this study, we assessed the immunogenicity and safety of SARS-CoV-2 vaccinations in these diseases (based on humoral and cellular immunity).

Methods Patients (n=45 GCA, n=33 PMR) visited the outpatient clinic twice: pre-vaccination and 4 weeks after the second dose (BNT162b2 or ChAdOx1 vaccine). Patients with previous SARS-CoV-2 infection were excluded. In both pre-vaccination and post-vaccination samples, anti-Spike antibody concentrations were assessed and compared with age-, sex- and vaccine-matched control groups (n=98). In addition, the frequency of SARS-CoV-2 Spike-specific T-cells was assessed by IFN-γ ELIspot assay, and side effects and disease activity were recorded.

Results GCA/PMR patients did not have reduced antibody concentrations compared with controls. However, linear regression analysis revealed a significant association of methotrexate and >10 mg/day prednisolone use with lower antibody concentrations in GCA/PMR patients. Evidence of cellular immunity, as assessed by ELIspot assay, was found in 67% of GCA/PMR patients. Patients using >10 mg/day prednisolone had reduced cellular immunity. Importantly, vaccination did not lead to significant side effects or changes in disease activity.

Conclusions SARS-CoV-2 vaccination was safe for GCA/ PMR patients and immunogenicity was comparable to other older individuals. However, patients using methotrexate and particularly >10 mg/day prednisolone did show lower vaccine responses, which corroborates findings in other autoinflammatory patient populations. These patients may therefore be at higher risk of (potentially even severe) breakthrough SARS-CoV-2 infection.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) patients have a substantially higher risk for severe infections, likely due to the immunosuppressive treatment. Systematic literature reviews have pointed out that immunosuppressive therapy such as glucocorticoids could hamper humoral SARS-CoV-2 vaccine responses, although less is known on cellular immunity.

WHAT THIS STUDY ADDS

⇒ Humoral and cellular immune responses after SARS-CoV-2 vaccination in GCA and PMR are comparable to those in age-matched controls from the 2021 Dutch vaccination programme. However, methotrexate and particularly high-dose prednisolone treatment are associated with lower vaccine immunogenicity. Importantly, SARS-CoV-2 vaccination is safe for GCA/PMR patients in terms of side effects and disease activity.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study stresses the importance of booster vaccinations in GCA/PMR patients using methotrexate or high-dose glucocorticoids.

INTRODUCTION

Giant cell arteritis (GCA) is a seriously debilitating vasculitis affecting people over 50 years old.[1] GCA commonly overlaps with polymyalgia rheumatica (PMR), an inflammatory disease affecting the shoulders and hips. Glucocorticoids have remained the cornerstone of treatment in GCA and PMR.[2] Long-term glucocorticoid treatment, however, is accompanied by side effects, and relapses during glucocorticoid treatment are common.[3 4] The effects of glucocorticoid-mediated immunosuppression are pleiotropic and not yet completely understood.[5] Glucocorticoid-sparing therapies, such as

methotrexate (MTX), tocilizumab (TCZ) and to some extent leflunomide (LEF), are increasingly used in the management of GCA/PMR.[6–8]

GCA and PMR patients have a substantially higher risk for infections. The incidence of severe infections, including those of the urinary tract and respiratory system, is substantially higher in GCA and PMR patients compared with the background population.[9–12] Also mortality due to infections is significantly increased in GCA/PMR patients compared with the general population.[10] Various factors may contribute to the increased susceptibility for infections in GCA/PMR patients: age, use of immunosuppressive drugs, comorbidities associated with immunosuppressive treatment and GCA/PMR disease activity.[13] The same factors could potentially contribute to an increased risk of severe SARS-CoV-2 infection. Recent systematic literature reviews have concluded that in general patients with rheumatic diseases are not at a higher risk for severe SARS-CoV-2, but did find strong evidence that glucocorticoids, and particularly a daily dose of >10 mg, are associated with more severe SARS-CoV-2 infections, including death.[14 15] However, the most recent European Alliance of Associations for Rheumatology (EULAR) guidelines argue against discontinuation of glucocorticoid treatment.[16]

Vaccination is therefore critical for preventing severe SARS-CoV-2 infections in GCA and PMR patients. EULAR guidelines recommend vaccination of these patients, however, detailed information on how these patients respond to vaccination, with regard to their cellular and humoral immune responses, is lacking.[17 18] A systematic literature review concluded that antibody responses are typically lower in patients with rheumatic diseases, and that there is a relation with glucocorticoid use.[15 16] However, effects of immunosuppressive therapies used in GCA/PMR patients on vaccine response are less well known.[16] In particular, the influence of prednisolone on vaccine immunogenicity may be hard to study, as this drug is not used as monotherapy in most other diseases. Finally, age may also be a risk factor for a decreased vaccine immunogenicity in these ageing-associated diseases.

The main objective of this study is to assess the immunogenicity of the SARS-CoV-2 vaccinations in patients with GCA/PMR, as determined by humoral and cellular immune responses. We also evaluated the prevalence of side effects of SARS-CoV-2 vaccinations in this patient population and assessed whether vaccination increases GCA/PMR relapses.

PATIENTS AND METHODS
Patient description
Participants, all >50 years of age, were selected from patients enrolled in our longitudinal GPS (GCA, PMR, SENEX) cohort (online supplemental data S1). Patients were excluded in case of evidence of SARS-CoV-2 infection, a divergent vaccination strategy and use of immunosuppressive medication other than prednisolone, MTX,

LEF or TCZ (see online supplemental figure S1 for a flow diagram). The disease status of each patient was assessed pre-vaccination and post-vaccination. Active disease was defined as the presence of symptoms attributable to active GCA/PMR, encompassing minor/major relapses and refractory disease, otherwise patients were considered to be in remission.[19] For patients in active disease, treatment was intensified or at least not tapered further.

Patients were treated according to the BSR guidelines for GCA and PMR.[20 21] In short, patients started with glucocorticoid (i.e. prednisolone) treatment (40–60 mg/day for GCA, 15–20 mg/day for PMR) which was tapered until treatment-free remission was achieved. In case of a relapse, the prednisolone dose was increased and/or MTX or LEF was added to the treatment regimen. A subset of relapsing GCA patients received TCZ treatment. Patients using other immunomodulatory drugs such as rituximab were excluded.

As a comparison, we included an age- and sex-matched control group, part of a subcohort of the Doetinchem Cohort Study,[22 23] in which 1270 persons participated in the investigations of SARS-CoV-2 vaccine responses (VIDO), NL76551.041.21. As a comparison for patients vaccinated with either BNT162b2 (BioNTech/Pfizer) or ChAdOx1 (AstraZeneca), equal numbers of VIDO participants per stratum were selected. In addition, data on vaccination side effects from age- and sex-matched controls, four controls per included patient, was extracted by the Pharmacovigilance Centre Lareb.

Sampling
We assessed immune responses to SARS-CoV-2 vaccines that are part of the 2021 Dutch vaccination programme. Participants were requested to visit the outpatient clinic twice: pre-vaccination and post-vaccination. We aimed to schedule the pre-vaccination visits within four months prior to the first vaccination and post-vaccination visits ±28 days after the second vaccination. During the post-vaccination visits, patients filled in questionnaires on vaccination side effects. At each visit, serum and peripheral blood mononuclear cells (PBMCs) were collected and stored until further use.

Antibody responses
In both pre-vaccination and post-vaccination samples of patients and controls, antibodies against the Spike protein S1 and nucleocapsid protein of SARS-CoV-2 were assessed. This analysis was performed by a multiplex bead-based Immuno assay at the National Institute for Public Health and the Environment (RIVM) (see online supplemental data S2).[24] This method is highly validated with an internal WHO standard. Patients with a previous SARS-CoV-2 infection were excluded from the main analysis.

Cellular responses
The frequency of SARS-CoV-2 Spike-specific T-cells was assessed by an IFN-γ ELISpot assay with pre-vaccination and post-vaccination PBMC samples. For the protocol details, see online supplemental data S3 and online supplemental

Table 1 Characteristics of GCA and PMR patients included in the main analyses and that of age- and sex-matched controls

	Total	GCA	PMR	Controls
N	78	45	33	88
Pre-vaccination visit included, n	66	38	28	88
Age, years (mean (SD))	73 (8)	72 (8)	73 (9)	70
Sex, % female	62	73	45	61
Diagnosis				
TAB positive/performed	NA	15/22	0/4	NA
PET-CT for large-vessel GCA positive/performed	NA	29/37	0/25	NA
PET-CT for PMR positive/performed	NA	18/37	25/25	NA
ACR 1990 criteria for GCA, % positive	NA	58	NA	NA
ACR/EULAR 2012 criteria for PMR, % positive	NA	NA	91	NA
Time since diagnosis, months (mean)	51	55	45	NA
Medication at first vaccination				
Prednisolone, n (%)	37 (47)	17 (38)	20 (61)	NA
Prednisolone, daily dose in mg (mean (SD))	9.6 (9)	13.1 (7)	6.6 (9)	NA
Glucocorticoids, cumulative dose in mg (mean (SD))	8233 (6971)	9496 (6269)	6535 (7819)	NA
Methotrexate, n (%)	26 (33)	20 (44)	6 (18)	NA
Methotrexate, weekly dose in mg (mean (SD))	15.8 (4)	15.5 (4)	16.7 (2)	NA
Leflunomide, n (%)	4 (5)	2 (4)	2 (6)	NA
Tocilizumab, n (%)	6 (8)	6 (13)	0 (0)	NA
Treatment-free remission, n (%)	19 (24)	11 (24)	8 (24)	NA
Vaccination				
Bnt162b2/ChAdOx1	67/11	38/7	29/4	70/18
Post-vaccination visit, days after second vaccination (average, (range))	28 (19–38)	28 (19–38)	28 (20–36)	28 (21–35)

Glucocorticoids include prednisolone and methylprednisolone. Shortest time since diagnosis was 28 days for GCA and 42 days for PMR.
EULAR, European Alliance of Associations for Rheumatology; GCA, giant cell arteritis; NA, not applicable; PET-CT, positron emission tomography CT; PMR, polymyalgia rheumatica; TAB, temporal artery biopsy.

figure S2. The Spike-specific T-cell response was calculated by subtracting the average spot-forming cell (SFC) count of the negative control from the SFC count of the summed averages of the Spike1 and Spike2 SFC counts.

Statistics

Group differences were compared using non-parametric testing with the Mann-Whitney U test, the Fisher's exact test or the Kruskal Wallis test followed by Dunn's post hoc test. Correlations were assessed using Spearman's rank correlation coefficient. Multiple linear regression and binary logistic regression analysis were performed with backward exclusion of predicting variables (see online supplemental data S4 for details). Data were analysed with IBM SPSS Statistics V.27 and Graphpad Prism V.7.02 software.

RESULTS

Patient characteristics

In total, 90 patients participated in this study, of which, after exclusion, 78 remained for the main analysis (online supplemental figure S1). Patient characteristics are displayed in table 1 and online supplemental table S1 (laboratory data). Almost half of the patients were using prednisolone at the time of the first vaccination,

PMR patients more often than GCA patients. However, GCA patients using prednisolone were on average on a higher daily and cumulative dose. MTX, LEF and TCZ were used as a therapy added to prednisolone treatment or as a monotherapy.

Spike-protein antibody concentrations in GCA/PMR patients and controls

SARS-CoV-2-binding antibody concentrations in GCA/PMR patients receiving the BNT162b2 or the ChAdOx1 vaccine were not significantly different from age- and sex-matched controls (figure 1A). We observed no significant differences between patients with a diagnosis of GCA or PMR (figure 1B). We next investigated whether antibody concentrations were reduced in older patients, but found no association with age nor sex in GCA/PMR patients (online supplemental figure S3). Antibody concentrations were not associated with time between second vaccination and the post-vaccination visit, nor with the time between the first and second vaccination (online supplemental figure S3). In the patients that were not excluded, the nucleocapsid antibody concentrations were not increased post-vaccination, when compared with the pre-vaccination visit.
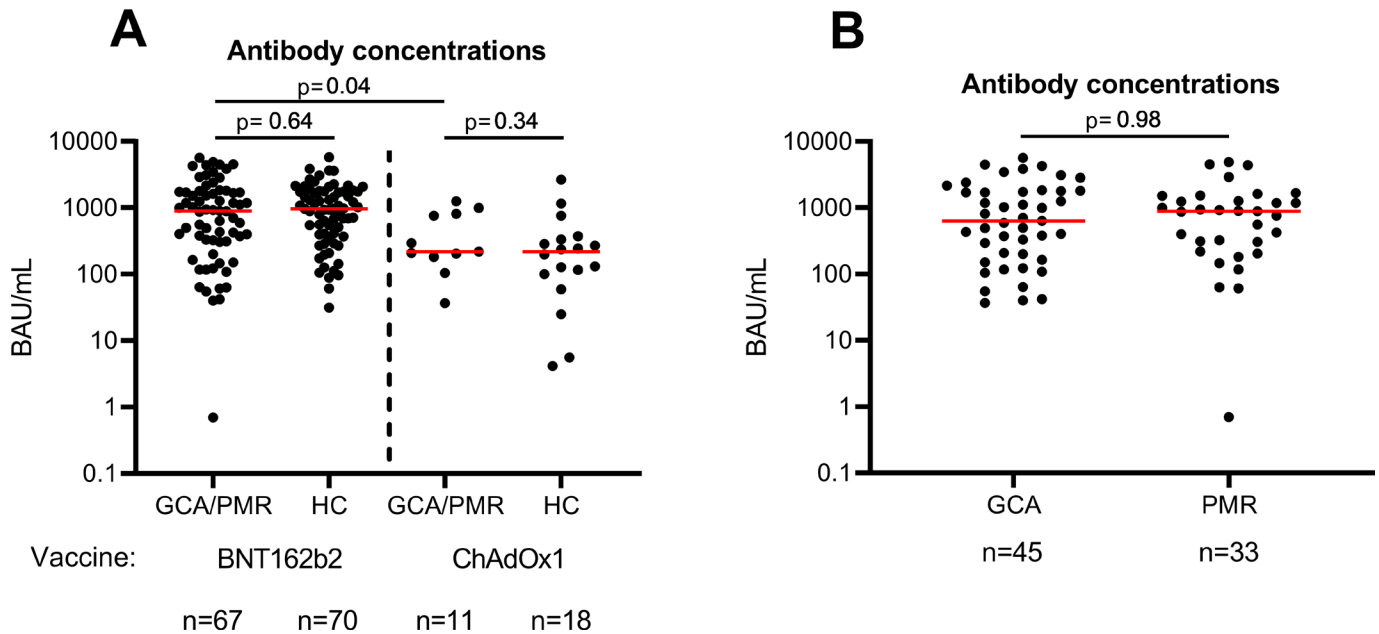
Figure 1 SARS-CoV-2-Spike protein antibody concentrations in GCA and PMR patients after vaccination. (A) Antibody concentrations of GCA/PMR patients are compared with age- and sex-matched controls, split per vaccine. BNT162b2: n=67 for GCA/PMR and n=70 for HC. ChAdOx1: n=11 for GCA/PMR and n=18 for HC. (B) Antibody concentrations are compared between GCA (n=45) and PMR (n=33) patients. Data are expressed in BAU (binding antibody units). Group differences are compared using the Mann-Whitney U test. GCA, giant cell arteritis; PMR, polymyalgia rheumatica.

Use of MTX and >10 mg/day prednisolone are associated with reduced antibody concentrations

We next investigated whether immune-modulating medication influences the humoral response to the SARS-CoV-2 vaccination using a lineal regression model (table 2). In addition to the vaccine type, we show that MTX use and a daily prednisolone dose of >10 mg are independent predictors of lower antibody concentrations in GCA/PMR patients.

Based on this linear regression model, we divided the study population in two subpopulations: patients using MTX and/or >10 mg/day prednisolone, and a group with no MTX and ≤10 mg or no prednisolone. Patients on MTX and/or >10 mg/day prednisolone indeed showed significantly lower antibody concentrations after BNT162b2 vaccination compared with patients without MTX/>10 mg prednisolone or patients in treatment-free remission (figure 2). The same pattern was observed in patients vaccinated with ChAdOx1, although not significant due to a low n (online supplemental figure S4A). Counts of circulating B-cells, CD4 T-cells and CD8 T-cells pre-vaccination showed a weak but significant correlation

Table 2 Variables predicting serological response to vaccination

Dependent variable	Predicting variable	Final model of multiple linear regression B (95% CI)	P value
SARS-CoV-2 antibody concentrations (BAU/mL)	Age	(-)	
	Vaccine type	766 (95 to 1675)*	0.022
	Anti-N seropositive	(-)	
	Prednisolone dose >10 mg	−437 (−547 to −8)*	0.047
	Methotrexate use	−386 (−529 to −111)*	0.011
	Leflunomide use	(-)	
	Tocilizumab use	(-)	

Data are shown for patients with GCA and/or PMR (n=78). Antibody concentrations were not normally distributed, and were therefore transformed by square root. Multiple linear regression analysis was performed with backward exclusion of predicting variables. The probability of F for removal was 0.10. Values of p<0.05 were considered statistical significant. Results of the final model are shown.
Vaccine type: 0=ChAdOx1, 1=BNT162b2. Antinucleocapsid (N) seropositive, prednisolone dose >10 mg, methotrexate use, leflunomide use, tocilizumab use: 0=no, 1=yes. (-) Variable removed due to backward exclusion. Medication use was assessed at the time of the first vaccination.
*R^2=0.161, $F(3,74)$ =4.751, p=0.004.
BAU, binding antibody units. GCA, giant cell arteritis; PMR, polymyalgia rheumatica;
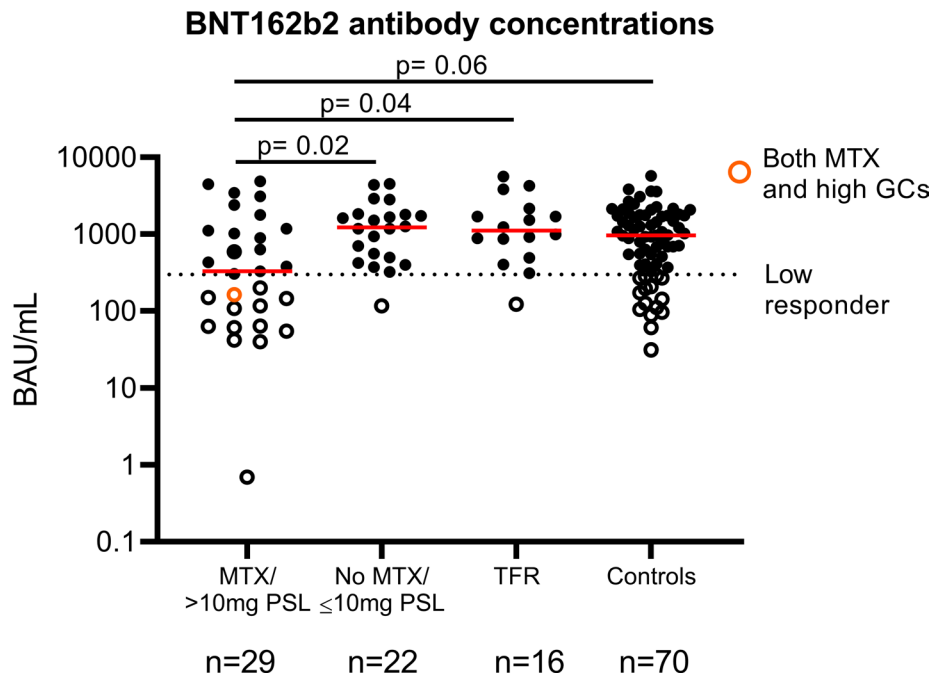
Figure 2 Antibody concentrations are lower in GCA/PMR patients at risk due to MTX or >10 mg/day PSL use. Shown are antibody concentrations in patients and controls after vaccination with BNT162b2. The GCA/PMR patient population has been divided based on the use of MTX and/or a high PSL dose (>10 mg/day) at the time of the first vaccination. A low-responder cut-off is shown to indicate a titre of 300 BAU/mL, which corresponded with the minimum antibody titre sufficient to elicit viral neutralisation in mRNA-1273 vaccinated individuals.[25] Low responders are indicated by open circles. Statistical testing with Kruskal-Wallis followed by Dunn's post hoc tests. BAU, binding antibody units; MTX, methotrexate; PSL, prednisolone; TFR, treatment-free remission.

with antibody concentrations (online supplemental figure S5A,B).

Surprisingly, the data implies that GCA/PMR patients that are not using MTX or >10 mg prednisolone might have a stronger humoral vaccine response compared with matched controls. The frequency of low responders (<300 BAU/mL[25]) after BNT162b2 among patients not using MTX/> 10 mg/day prednisolone (5%) was less compared with the control group (21%, Fisher's exact test p=0.029). The frequency of low responders in the patients using MTX/>10 mg prednisolone was much higher at 51%. In contrast to the negative effects of a high daily prednisolone dose, the cumulative glucocorticoid dose was not associated with lower antibody concentrations (online supplemental figure S4B). The lowered antibody concentrations in patients using MTX may also be dose dependent, as the four patients on 20–25 mg/week appeared to have even lower concentrations than the 19 patients on 10–15 mg/week (online supplemental figure S4C). Online supplemental figure S4D shows antibody concentrations for each drug.

Evidence of cellular vaccine response in majority of patients, but a likely weaker response in patients on >10 mg/day prednisolone

We next assessed T-cell responses against SARS-CoV-2 Spike in GCA/PMR patients after vaccination using the IFN-γ ELIspot assay. The post-vaccination SFC counts were substantially increased compared with pre-vaccination (figure 3A,B). By using a responder definition of a post-vaccination fold-change higher than two compared with the pre-vaccination sample, but only in case the SFC count was higher than 50/10^6 cells,[25] we show that 67% of GCA/PMR patients can be considered a responder. Importantly, a significant positive correlation for BNT162b2-vaccinated patients was found between antibody concentrations and specific SFC counts in the ELIspot assay (figure 3C).

A binary regression analysis showed that the use of >10 mg prednisolone tended to be an independent predictor of non-response in the ELIspot assay (online supplemental table S2). A trend to lower SFC counts in this assay compared with patients not using >10 mg prednisolone was also observed (online supplemental table S3). An additional analysis showed that patients using 10 mg prednisolone or more, had significantly reduced cellular immunity in a binary regression analysis for responders (p=0.026) and lower SFC counts (Mann-Whitney U p=0.04), probably due to a higher n. In contrast, MTX use was not associated with a lack of cellular response. These findings suggest that only patients using higher doses of prednisolone have both a hampered humoral and cellular vaccine response. SFC counts did not correlate with counts of B-cells or T-cells (online supplemental figure S5C,D).
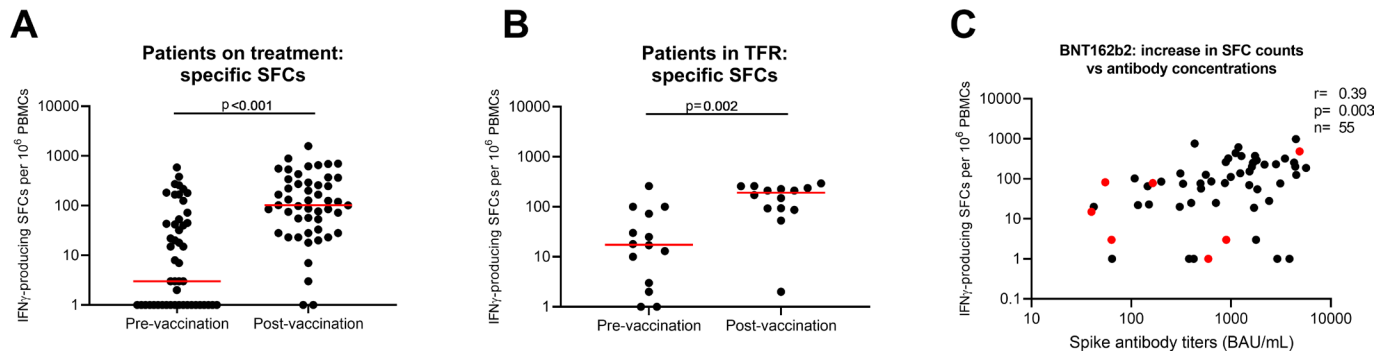
Figure 3 Spot-forming cell (SFC) counts in the ELIspot assay. Background-corrected SFC counts, indicating IFN-γ producing cells, increased significantly (Mann-Whitney U) at post-vaccination compared with pre-vaccination in treated patients and patients in treatment-free remission (TFR). Red line indicates the median (A, B). SFC counts correlated with Spike antibody concentrations in GCA/PMR patients vaccinated with BNT162b2 (C). GCA/PMR patients using >10 mg/day prednisolone are indicated in red. For the correlation, the specific SPC counts are used in the post-vaccination sample after subtracting the SPC count in the pre-vaccination sample. Statistical analysis by the Spearman correlation coefficient. BAU, binding antibody units; GCA, giant cell arteritis; PMR, polymyalgia rheumatica.

SARS-CoV-2 vaccination appears to be safe for GCA and PMR patients

BNT162b2 and ChAdOx1 side effect frequencies of GCA/PMR patients were compared with age- and sex-matched controls (table 3). Side effects were typically mild and comparable to controls, except five side effects that were over-represented or under-represented in GCA/PMR patients. The reporting of any vaccination side effect was not associated with a higher antibody titre (p=0.37, online supplemental figure S6).

No evidence was found for an increase in disease activity in GCA/PMR patients after vaccination. We show that the proportion of patients with active disease did not increase at the post-vaccination visit when compared with the pre-vaccination visit (online supplemental table S4). Five patients that were in remission at the pre-vaccination visit, had active disease at post-vaccination. Conversely, eight patients that had active disease at the pre-vaccination visit, were in remission at the post-vaccination visit. In addition, levels of acute-phase markers CRP and ESR were not significantly altered.

DISCUSSION

Here, we show that GCA and PMR patients have a similar immune response after vaccination with BNT162b2 or ChAdOx1 in comparison with age-matched controls. This was not only based on anti-Spike antibody

Table 3 Side effects in GCA/PMR after SARS-CoV-2 vaccination

	BNT162b2				ChAdOx1			
	1st dose		2nd dose		1st dose		2nd dose	
	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls
	n=56	n=244	n=56	n=244	n=10	n=40	n=10	n=40
Headache	7%	7%	9%	8%	**10%**	50%	0%	10%
Joint pain	**14%**	2%	5%	6%	10%	0%	0%	0%
Fatigue	**0%**	13%	16%	12%	10%	43%	0%	20%
Fever	2%	2%	0%	2%	0%	23%	10%	0%
Cold chills	**13%**	2%	7%	4%	20%	30%	0%	0%
Muscle aches	4%	10%	13%	12%	20%	25%	0%	20%
Nausea	4%	2%	4%	2%	10%	18%	0%	0%
Arm redness	0%	1%	2%	2%	0%	8%	0%	0%
Arm oedema	0%	3%	2%	2%	0%	3%	0%	0%
Arm pain	25%	21%	**36%**	13%	30%	30%	10%	10%
Any complaints	38%	34%	**45%**	26%	40%	70%	20%	18%

Patients completed a questionnaire on vaccination-related side effects. Frequency of side effects was compared to data of age- and sex-matched controls extracted from the database of the Pharmacovigilance Centre Lareb. Statistically significant differences (p<0.05) between GCA/PMR patients and controls, by Fisher's exact test, are indicated in bold.
GCA, giant cell arteritis; PMR, polymyalgia rheumatica.

concentrations which we could directly compare to an age-matched control group, but also on T cell-mediated cellular immune responses, which were present in 67% of patients. The latter is in line with findings in healthy controls in studies with similar setups.[25] However, a subpopulation of patients using MTX and/or >10 mg prednisolone is at greater risk of having lower humoral and/or cellular vaccine responses. Finally, this study shows that vaccination against SARS-CoV-2 is safe, both in terms of side effects and disease activity, which is in line with EULAR guidelines on vaccination safety in the immunocompromised.[17 18 26] This is so far the largest study on SARS-CoV-2 vaccination in GCA/PMR patients, a patient population characterised by their high mean age, and the first study investigating their cellular vaccine responses and the vaccination safety profile.

An important conclusion is that the majority of GCA and PMR patients display a strong humoral and cellular vaccine response after SARS-CoV-2 vaccination. This could be taken as evidence that the majority of GCA/PMR patients do not have increased risk of breakthrough infections, even though no real-life data on this are available. Even though no clear cut-off can be calculated for antibody concentrations that are sufficient to prevent SARS-CoV-2 infection after vaccination, binding concentrations above 300 BAU/ml do correlate strongly with protective immunity against the original SARS-CoV-2 virus in neutralising antibody assays.[25 27] However, this cut-off was determined in individuals after vaccination with mRNA-1273 and should therefore be treated with caution in the BNT162b2 vaccinated population. Another important defence mechanism against severe SARS-CoV-2 infection are responsive IFN-γ producing T-cells, both CD4+ and CD8+.[28] There is evidence that despite the drop in antibody concentrations over time, these T-cells continue to protect against severe SARS-CoV-2 infection.[29]

Surprisingly, some evidence points out that GCA/PMR patients not using MTX/>10 mg prednisolone might even have an enhanced vaccine response, as they were less often low-responders than the controls. This is particularly surprising as GCA/PMR patients often become lymphopenic after long-term treatment.[30] More research is needed to investigate long-term vaccine responses in these patients.

MTX had a negative effect on humoral rather than cellular immune responses in our study. The reduced immunogenicity of the SARS-CoV-2 vaccines for patients using MTX has recently been described in other studies. Patients with rheumatic/autoimmune diseases using MTX have reduced humoral responses after mRNA SARS-CoV-2 vaccination, when compared with patients not using MTX or healthy controls.[27 31–35] A few studies however find no effect of MTX on humoral immunity after two doses, even though responses after one dose are decreased.[32 36] Mahil et al showed that psoriasis patients using MTX did not only have reduced antibody concentrations after one dose, but consequently also lower

viral neutralising capacity.[27] This study found no effect of MTX on the frequency of specific T-cells producing IFN-γ, IL-22 and IL-2, which matches the ELIspot assay data in the current study. However, Haberman et al showed that patients using MTX lacked CD8+ T cell activation after complete vaccination.[34] Importantly, the ELIspot assay showing IFN-γ producing cells does not distinguish between CD4+ and CD8+ T cell responses. Also, age differences may explain the different findings in the study by Haberman et al. MTX is the most used anti-rheumatic drug that regulates nearly every type of immune cell subset, including the prevention of T cell activation.[37] Thus, more studies, also after booster vaccinations, are needed to investigate whether patients using MTX have protective cellular immunity after vaccination.

The current study suggests that higher doses of prednisolone may negatively impact both the humoral and cellular vaccine response. Importantly, our data indicates that current daily prednisolone dose, rather than cumulative dose, is more relevant for the humoral vaccine response. Prior findings on the effects of prednisolone on SARS-CoV-2 vaccine responses are mixed, with some studies showing reduced antibody concentrations, whereas others show no effect after two doses.[31 32 35 36 38–40] Delvino et al did show reduced humoral responses in GCA patients on 7.5 mg/day prednisolone after one dose, but not (significantly) after two doses.[31] Our data, showing lower cellular response in GCA/PMR patients using ≥10 mg prednisolone, suggest that a booster vaccination is important for these patients, as they may have a substantially higher risk for severe infection. Fortunately, the vast majority of GCA/PMR patients uses a dose of ≥10 mg prednisolone only for a relatively short time-frame, implying that a booster vaccination in a situation when patients were able to taper to a lower dose prednisolone will likely lead to a substantial increase in immunity.

The safety profile of the BNT162b2 and ChAdOx1 vaccines for GCA/PMR patients is reassuring. As vaccination activates the immune system, it is important that this does not lead to reactivation of GCA or PMR. We observed no evidence of a vaccination effect on disease activity nor on acute-phase markers. GCA/PMR disease activity is known to fluctuate over time, and the majority of patients experiences at least one relapse, often accompanied by an increase in CRP/ESR.[4 30] No effect of vaccination on disease activity was found in many other autoinflammatory/autoimmune diseases such as rheumatoid arthritis and lupus erythematosus.[18 39] The frequency of a small number of common side effects, although mild, differed significantly from age- and sex-matched controls. Whether this is due to differences in reporting methods, the fact that disease symptoms can present similarly like vaccination side effects or possibly the effect of immunosuppressive drugs, is unknown.

Strengths of this study include its prospective design and inclusion of well-characterised patients with GCA/PMR. In addition, we investigated the cellular vaccine response according to validated techniques, in addition

to the humoral response. Moreover, data regarding humoral responses were compared with a large group of age- and sex-matched controls from the general population, whereas safety data were compared with a nationwide database. Not all GCA patients fulfilled the 1990 ACR criteria, however, this likely reflects the inclusion of patients throughout the whole spectrum of GCA, which also includes large-vessel GCA that does not always lead to cranial symptoms. Following the more recent 2018 EULAR recommendations, diagnosis of GCA was based on either a positive biopsy or imaging.[41] A limitation might be that no data was collected on the neutralisation capacity of the antibodies, but a strong correlation of binding antibody concentrations with neutralising capacity has been shown.[27] Finally, data on the ChAdOx1-vaccinated patients is scarce, thus comparisons of antibody concentrations should be interpreted carefully.

The SARS-CoV-2 pandemic has had a tremendous impact on GCA and PMR patients. Outcomes of questionnaires distributed by the Dutch Vasculitis Patient Foundation revealed that the majority of patients suffered from increased anxiety, and many reported worries about taking prednisolone.[41] It is therefore reassuring that vaccination leads to strong humoral and cellular responses in this population, giving these patients means to protect themselves against severe infection. However, immunity tends to wane over time, particularly against new SARS-CoV-2 variants. So far, no studies have been performed on the immunogenicity of booster vaccinations in GCA/PMR patients. However, repeated booster vaccinations should likely be recommended to all GCA and PMR patients, but particularly to those that use MTX and/or >10 mg prednisolone at the time of the first vaccination.

Author affiliations
[1]Department of Rheumatology and Clinical Immunology, University Medical Center Groningen, Groningen, The Netherlands
[2]Department of Medical Microbiology and Infection Prevention, University Medical Center Groningen, Groningen, The Netherlands
[3]Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, The Netherlands
[4]Centre for Infectious Disease Control, National Institute for Public Health and the Environment, Bilthoven, The Netherlands

Twitter Yannick van Sleen @sleenyannick

Contributors Study design: YvS and EB. Collecting data: YvS, RDR, IE, JHT, ER-E, MvdH, TL and AMB. Analysing data: YvS, KSMvdG and RDR. Interpretation of data: YvS, KSMvdG, DvB, MS and EB. Drafting manuscript: YvS. Correcting manuscript: all authors. YvS is responsible for the overall content as the guarantor.

Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s)

Ethics approval Approval from the institutional review board for this study was obtained (Metc2021/251) and all participants signed for informed consent. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Study protocol and individual data collected in this study can be made available to others after publication on reasonable request (y.van.sleen@umcg.nl).

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ORCID iDs
Yannick van Sleen http://orcid.org/0000-0002-7382-8322
Kornelis S M van der Geest http://orcid.org/0000-0003-2798-6765
Elisabeth Brouwer http://orcid.org/0000-0002-4809-0653

REFERENCES

1 Dejaco C, Duftner C, Buttgereit F, et al. The spectrum of giant cell arteritis and polymyalgia rheumatica: revisiting the concept of the disease. *Rheumatology* 2016;34:kew273–15.
2 Hunder GG. The early history of giant cell arteritis and polymyalgia rheumatica: first descriptions to 1970. *Mayo Clin Proc* 2006;81:1071–83.
3 Broder MS, Sarsour K, Chang E, et al. Corticosteroid-related adverse events in patients with giant cell arteritis: a claims-based analysis. *Semin Arthritis Rheum* 2016;46:246–52.
4 Restuccia G, Boiardi L, Cavazza A, et al. Flares in biopsy-proven giant cell arteritis in northern Italy: characteristics and predictors in a long-term follow-up study. *Medicine* 2016;95:e3524.
5 Zen M, Canova M, Campana C, et al. The kaleidoscope of glucocorticoid effects on immune system. *Autoimmun Rev* 2011;10:305–10.
6 Lally L, Forbess L, Hatzis C, et al. Brief report: a prospective open-label phase IIA trial of tocilizumab in the treatment of polymyalgia rheumatica. *Arthritis Rheumatol* 2016;68:2550–4.
7 Stone JH, Tuckwell K, Dimonaco S, et al. Trial of tocilizumab in giant-cell arteritis. *N Engl J Med* 2017;377:317–28.
8 Koster MJ, Yeruva K, Crowson CS, et al. Efficacy of methotrexate in real-world management of giant cell arteritis: a case-control study. *J Rheumatol* 2019;46:501–8.
9 George MD, Baker JF, Winthrop K, et al. Risk for serious Infection with low-dose Glucocorticoids in patients with rheumatoid arthritis : a cohort study. *Ann Intern Med* 2020;173:870–8.
10 Schmidt J, Smail A, Roche B, et al. Incidence of severe infections and infection-related mortality during the course of giant cell arteritis: a multicenter, prospective, double-cohort study. *Arthritis Rheumatol* 2016;68:1477–82.
11 Petri H, Nevitt A, Sarsour K, et al. Incidence of giant cell arteritis and characteristics of patients: data-driven analysis of comorbidities. *Arthritis Care Res* 2015;67:390–5.
12 Proven A, Gabriel SE, Orces C, et al. Glucocorticoid therapy in giant cell arteritis: duration and adverse outcomes. *Arthritis Rheum* 2003;49:703–8.
13 Sattui SE, Conway R, Putman MS, et al. Outcomes of COVID-19 in patients with primary systemic vasculitis or polymyalgia rheumatica from the COVID-19 global rheumatology alliance physician registry: a retrospective cohort study. *Lancet Rheumatol* 2021;3:e855–64.
14 Conway R, Grimshaw AA, Konig MF, et al. SARS-CoV-2 infection and COVID-19 outcomes in rheumatic diseases: a systematic literature review and meta-analysis. *Arthritis Rheumatol* 2022;74:766–75.
15 Kroon FPB, Najm A, Alunno A, et al. Risk and prognosis of SARS-CoV-2 infection and vaccination against SARS-CoV-2 in rheumatic and musculoskeletal diseases: a systematic literature review to inform EULAR recommendations. *Ann Rheum Dis* 2022;81:422–32.
16 Landewé RBM, Kroon FPB, Alunno A, et al. EULAR recommendations for the management and vaccination of people with rheumatic and musculoskeletal diseases in the context of SARS-CoV-2: the November 2021 update. *Ann Rheum Dis* 2022. doi:10.1136/annrheumdis-2021-222006. [Epub ahead of print: 23 Feb 2022].
17 Furer V, Rondaan C, Heijstek MW, et al. 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis* 2020;79:39–52.

18 Rondaan C, Furer V, Heijstek MW, *et al*. Efficacy, immunogenicity and safety of vaccination in adult patients with autoimmune inflammatory rheumatic diseases: a systematic literature review for the 2019 update of EULAR recommendations. *RMD Open* 2019;5:e001035.

19 Hellmich B, Agueda A, Monti S, *et al*. 2018 update of the EULAR recommendations for the management of large vessel vasculitis. *Ann Rheum Dis* 2020;79:19–30.

20 Dasgupta B, Borg FA, Hassan N, *et al*. BSR and BHPR guidelines for the management of giant cell arteritis. *Rheumatology* 2010;49:1594–7.

21 Dasgupta B, Borg FA, Hassan N, *et al*. BSR and BHPR guidelines for the management of polymyalgia rheumatica. *Rheumatology* 2010;49:186–90.

22 Verschuren WMM, Blokstra A, Picavet HSJ, *et al*. Cohort profile: the Doetinchem cohort study. *Int J Epidemiol* 2008;37:1236–41.

23 Picavet HSJ, Blokstra A, Spijkerman AMW, *et al*. Cohort profile update: the Doetinchem cohort study 1987-2017: lifestyle, health and chronic diseases in a life course and ageing perspective. *Int J Epidemiol* 2017;46:1751–1751g.

24 den Hartog G, Schepp RM, Kuijer M, *et al*. SARS-CoV-2-Specific antibody detection for seroepidemiology: a multiplex analysis approach accounting for accurate seroprevalence. *J Infect Dis* 2020;222:1452–61.

25 Oosting SF, van der Veldt AAM, GeurtsvanKessel CH, *et al*. mRNA-1273 COVID-19 vaccination in patients receiving chemotherapy, immunotherapy, or chemoimmunotherapy for solid tumours: a prospective, multicentre, non-inferiority trial. *Lancet Oncol* 2021;22:1681–91.

26 Furer V, Rondaan C, Agmon-Levin N, *et al*. Point of view on the vaccination against COVID-19 in patients with autoimmune inflammatory rheumatic diseases. *RMD Open* 2021;7:e001594.

27 Mahil SK, Bechman K, Raharja A, *et al*. The effect of methotrexate and targeted immunosuppression on humoral and cellular immune responses to the COVID-19 vaccine BNT162b2: a cohort study. *Lancet Rheumatol* 2021;3:e627–37.

28 Niessl J, Sekine T, Buggert M. T cell immunity to SARS-CoV-2. *Semin Immunol* 2021;55:101505.

29 Tarke A, Sidney J, Methot N, *et al*. Impact of SARS-CoV-2 variants on the total CD4$^+$ and CD8$^+$ T cell reactivity in infected or vaccinated individuals. *Cell Rep Med* 2021;2:100355.

30 van Sleen Y, Graver JC, Abdulahad WH, *et al*. Leukocyte dynamics reveal a persistent myeloid dominance in giant cell arteritis and polymyalgia rheumatica. *Front Immunol* 2019;10:10.

31 Delvino P, Bartoletti A, Cassaniti I. Impact of immunosuppressive treatment on the immunogenicity of mRNA Covid-19 vaccine in vulnerable patients with giant cell arteritis. *Rheumatology* 2021.

32 Boekel L, Steenhuis M, Hooijberg F, *et al*. Antibody development after COVID-19 vaccination in patients with autoimmune diseases in the Netherlands: a substudy of data from two prospective cohort studies. *Lancet Rheumatol* 2021;3:e778–88.

33 Moyon Q, Sterlin D, Miyara M, *et al*. BNT162b2 vaccine-induced humoral and cellular responses against SARS-CoV-2 variants in systemic lupus erythematosus. *Ann Rheum Dis* 2022;81:575–83.

34 Haberman RH, Herati R, Simon D, *et al*. Methotrexate hampers immunogenicity to BNT162b2 mRNA COVID-19 vaccine in immune-mediated inflammatory disease. *Ann Rheum Dis* 2021;80:1339–44.

35 Furer V, Eviatar T, Zisman D, *et al*. Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and in the general population: a multicentre study. *Ann Rheum Dis* 2021;80:1330–8.

36 Ferri C, Ursini F, Gragnani L, *et al*. Impaired immunogenicity to COVID-19 vaccines in autoimmune systemic diseases. high prevalence of non-response in different patients' subgroups. *J Autoimmun* 2021;125:102744.

37 Cronstein BN, Aune TM. Methotrexate and its mechanisms of action in inflammatory arthritis. *Nat Rev Rheumatol* 2020;16:145–54.

38 Tzioufas AG, Bakasis A-D, Goules AV, *et al*. A prospective multicenter study assessing humoral immunogenicity and safety of the mRNA SARS-CoV-2 vaccines in Greek patients with systemic autoimmune and autoinflammatory rheumatic diseases. *J Autoimmun* 2021;125:102743.

39 Izmirly PM, Kim MY, Samanovic M, *et al*. Evaluation of immune response and disease status in systemic lupus erythematosus patients following SARS-CoV-2 vaccination. *Arthritis Rheumatol* 2022;74:284–94.

40 Deepak P, Kim W, Paley MA, *et al*. Effect of Immunosuppression on the Immunogenicity of mRNA Vaccines to SARS-CoV-2 : a prospective cohort study. *Ann Intern Med* 2021;174:1572–85.

41 Mackie SL, Brouwer E, Conway R, *et al*. Clinical pathways for patients with giant cell arteritis during the COVID-19 pandemic: an international perspective. *Lancet Rheumatol* 2021;3:e71–82.