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Humoral SARS–CoV-2 Vaccine Responses in Patients With Giant Cell Arteritis and Polymyalgia Rheumatica: Decay After Primary Vaccination and Effects of the Booster

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Objective. Vaccination remains essential in preventing morbidity of SARS–CoV-2 infections. We previously showed that >10 mg/day of prednisolone and methotrexate was associated with reduced antibody concentrations after primary vaccination in patients with giant cell arteritis (GCA) and polymyalgia rheumatica (PMR). This follow-up study was undertaken to measure the decay of antibody concentrations and the immunogenicity of SARS–CoV-2 booster vaccination.

Methods. Patients with GCA/PMR included in the primary vaccination (BNT162b2 [Pfizer-BioNTech] or ChAdOx1 [Oxford/AstraZeneca]) study were asked again to donate blood samples 6 months after primary vaccination (n = 24) and 1 month after booster vaccination (n = 46, BNT162b2 or mRNA1273). Data were compared to those of age-, sex-, and vaccine-matched controls (n = 58 and n = 42, respectively). Multiple linear regression was performed with post-booster antibody concentrations as dependent variable and post-primary vaccination antibodies, prednisolone >10mg/day, and methotrexate use as predicting variables.

Results. Antibody concentrations decreased faster over time in GCA/PMR patients than in controls, which was associated with prednisolone treatment during primary vaccination. Post-booster antibody concentrations were comparable between patients and controls. Antibody concentrations post primary vaccination, but not treatment during booster vaccination, were predictive for antibody concentrations post booster vaccination.

Conclusion. These results indicate that the decay of humoral immunity after primary vaccination is associated with prednisolone treatment, whereas the subsequent increase after booster vaccination, was not. Patients with low antibody concentrations following primary vaccination remained at an immunogenic disadvantage after a single booster vaccination. This longitudinal study in GCA/PMR patients stresses the importance of repeated booster vaccination for patients with poor responses to primary vaccination.

INTRODUCTION

Vaccination has been effective in preventing cases of severe SARS–CoV-2 infections since their roll-out in 2020. However, waning immunity following vaccination increases the risk of breakthrough infections, which sometimes can be severe. Moreover, immune-evading variants of the SARS–CoV-2 virus, such as the delta and omicron variants, have spread through the population. Higher anti-SARS–CoV-2 antibody concentrations are required to neutralize these variants compared to the original virus. Fortunately, booster vaccines substantially boost the antibody concentrations to a peak that is substantially higher than the levels directly post primary vaccination (1).

Vaccination is particularly important for patients using immunosuppressive medication who have a higher risk of severe infections, including patients with giant cell arteritis (GCA) and polymyalgia rheumatica (PMR). GCA and PMR are overlapping autoinflammatory diseases occurring almost exclusively in patients >50 years of age (2). Both diseases are commonly treated with prednisolone. Other drugs that are prescribed often in relapsing patients are methotrexate and tocilizumab.

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SIGNIFICANCE & INNOVATIONS

- Decay of antibody concentrations after primary SARS–CoV-2 vaccination appears faster in giant cell arteritis/polymyalgia rheumatica (GCA/PMR) patients than in controls.
- The immunogenicity of SARS–CoV-2 booster vaccination is not reduced in GCA/PMR patients compared to controls.
- Antibody concentrations in boosted patients who had taken high-dose prednisolone/methotrexate do not catch up completely.

Particularly high daily dosages of prednisolone have been associated with more severe SARS–CoV-2 infections (3).

Despite the urgent need for protection by vaccination in these vulnerable patients, the effectiveness of vaccination may be lower. EULAR guidelines have named prednisolone and methotrexate among the few immunosuppressive drugs that likely impact vaccine immunogenicity. Our previous study in GCA and PMR patients, in congruence with further studies in these patients, highlighted that methotrexate and higher dosages of prednisolone associated with hampered humoral vaccine responses (4–6), and in patients using >10 mg/day prednisolone, also cellular immunity was impaired.

To investigate whether GCA/PMR patients using methotrexate and/or high dosages prednisolone are at higher risk of severe breakthrough infections, we studied both occurrence of breakthrough infections after primary vaccination as well as the decay of antibody responses at 6 months post primary vaccination in patients and controls without breakthrough infections. Finally, we measured humoral responses to booster vaccination in patients and controls to understand whether the patients using immunosuppressive medication remain more at risk for SARS–CoV-2 breakthrough infections.

PATIENTS AND METHODS

Patients and controls. This study follows patients who were included in our primary vaccination study (6) (see Supplementary Figure 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25173, for a patient flow chart). Participants in the primary study were recruited from the longitudinal GPS (GCA, PMR, SENEX) cohort. In the GPS cohort, immunosuppressive medication use is recorded at each outpatient visit. For each participant in the primary vaccination study, we have recorded whether they tested positive for SARS–CoV-2 infection during the follow-up period prior to booster vaccination between June 1 and December 4, 2022. Patients were either asked about SARS–CoV-2 infections at visits to the outpatient clinic, via email or by phone.

During the regularly scheduled visits, GCA/PMR patients donated blood samples. To investigate long-term immune responses after primary vaccination, we collected blood from patients that had received the second shot (Vac#2) of the BNT162b2 (Pfizer/Biontech) or ChAdOx1 (Oxford/AstraZeneca) vaccine 6 months before (Vac#2+6m). Next, we collected data of patients post-booster vaccination (Vac#3). Patients visited at least 2 weeks and maximally 2 months since booster vaccination (Vac#3+1m). Primary vaccination of the patients was BNT162b2 or ChAdOx1, and the patients received either the BNT162b2 or mRNA1273 (Moderna) booster vaccines which were administered over a time span of 3 months (December 2021 to February 2022) as part of the Dutch national vaccination program. Not every patient who participated in the primary vaccination study participated in this follow-up study, mainly due to logistical reasons.

For comparison, we also added post-booster samples of an additional group of GCA/PMR patients who were vaccinated prior to diagnosis and subsequently received a booster vaccination during treatment (n = 8). Approval from the institutional review board for this study was obtained (Metc2021/251), and all participants signed for informed consent. Additionally, we added data from age-, sex- and vaccine-matched controls (n = 58) from a population-based cohort (7).

Antibody responses. Antibodies against the Spike protein S1 and nucleocapsid protein of SARS–CoV-2 were assessed using the same multiplex bead-based Immuno assay as the primary vaccination study and expressed in binding antibody units (BAU) (6,8). Patients and controls who showed a strong increase in antinucleocapsid antibodies during follow-up and those who had reported a positive SARS–CoV-2 test were considered infected. These participants were excluded from further analyses on antibody responses.

Statistics. No formal power calculation was done for this study, as every patient that was eligible was included. Antibody concentrations and fold changes in concentrations were not normally distributed. Therefore, differences between 2 groups were tested by Mann-Whitney U test, and correlations calculated by the Spearman's R correlation coefficient. Multiple linear regression was performed with backward exclusion of predicting variables on log-transformed antibody concentrations and fold changes. *P* values less than 0.05 were considered statistically significant (2-sided). Data were analyzed with IBM SPSS Statistics for Windows, version 19.0 and Graphpad Prism V.7.02.

RESULTS

GCA and PMR patients with breakthrough infections after primary BNT162b2 vaccination. Of 67 GCA/PMR patients, 7 had a SARS–CoV-2 infection between Vac#2 and Vac#3 (see Supplementary Table 1, available on the

Arthritis Care & Research website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25173). Median antibody concentrations had been lower at Vac#2+1m in the infected patients (331 BAU/ml) compared to the noninfected patients (896 BAU/ml), albeit not statistically significant (P = 0.45). Infected patients took prednisolone more often than patients that were not infected (6 of 7, 86%) versus 28 of 60 (47%) patients, Fisher's exact test P = 0.04). One patient had to be hospitalized due to SARS–CoV-2 infection. This patient had an antibody concentration of 117 BAU/ml (median of GCA/PMR patients was 896 BAU/ml) and took 10 mg/day prednisolone during the primary vaccinations.

Waning humoral vaccine responses in GCA and PMR patients. Samples of 24 noninfected GCA/PMR patients were assessed 6 months post primary vaccination, and these showed uniformly decreasing antibody concentrations over time that lead to significantly lower values at Vac#2+6m than found in controls (Figure 1A and Supplementary Table 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25173). The age- and vaccine-matched control group showed significantly less decrease (median fold change 0.16) in antibody concentrations compared to the BNT162b2-vacicnated GCA/PMR patients (fold change 0.09, $P < 0.001$) (Figure 1B). The control group however, showed a large heterogeneity in fold change of antibody concentrations over time (Figure 1B). Even though the median time since Vac#2 was slightly longer in patients than controls, we found no association of this duration with the fold decreases among the GCA/PMR patients (see Supplementary Figure 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25173).

For BNT162b2-vaccinated patients, we investigated whether the decrease in antibody concentrations was associated with treatment that impact humoral vaccine responses. We found that patients who took prednisolone at Vac#1 had a stronger decay of antibody concentrations at Vac#2+6m than patients not taking prednisolone at Vac#1 (P = 0.05) (Figure 2A). We observed no differences between patients taking >10 mg/day or <10 mg/day prednisolone (data not shown). Also, no effect on fold changes was found for the cumulative prednisolone use between Vac#1 and Vac#2+6m (Figure 2B). The enhanced decay was not found for patients who took methotrexate (Figure 2C).

Post-booster antibody concentrations. We assessed antibody concentrations in 41 patients with primary BNT162b2 vaccination, who received either a BNT162b2 (n = 14) or an mRNA1273 booster at a median of 213 days after Vac#2 (n = 27; see Supplementary Table 3, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25173). Booster responses in patients with BNT162b2 primary vaccination were compared to age- sex, and booster vaccine–matched controls (n = 8 BTN162b2 and n = 35 mRNA1273 at a median of 209 days after Vac#2) primary vaccinated with BNT162b2. Almost all patients and controls had higher antibody concentrations after booster vaccination. Antibody concentrations and fold changes post-booster vaccination were not significantly different in GCA/PMR patients compared to controls (Figures 3A and B).

Five patients, who initially received a ChAdOx1 primary vaccination, showed similar antibody responses after a BNT162b2 (n = 2) or mRNA1273 booster (n = 3) when compared to patients receiving a primary BNT162b2, although the fold increase tended be somewhat higher for primary ChAdOx1 (P = 0.05; see Supplementary Figure 3, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25173).

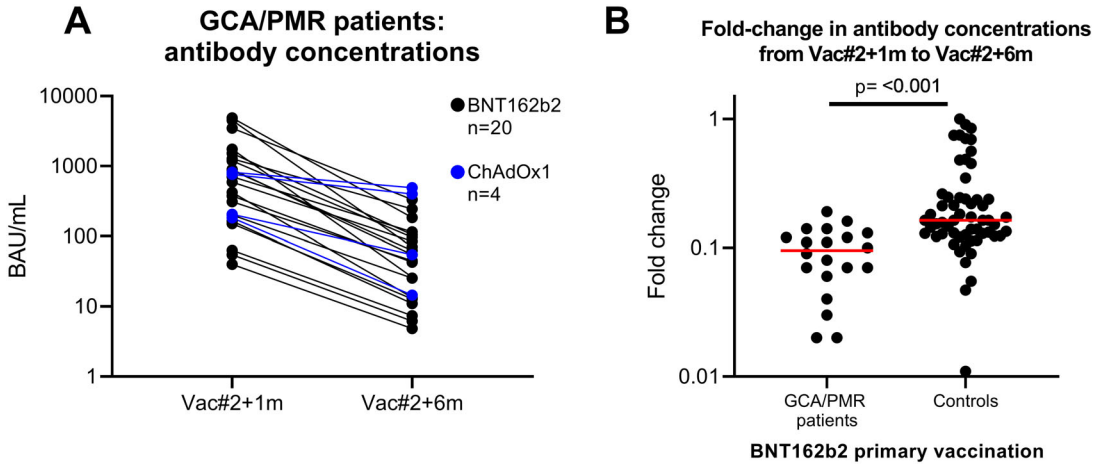

Figure 1. Decreasing SARS–CoV-2 antibody concentrations in giant cell arteritis/polymyalgia rheumatica (GCA/PMR) patients and controls. **A**, Antibody concentrations at 1 month (Vac#2+1m) and 6 months (Vac#2+6m) post primary vaccination in patients with GCA/PMR. **B**, Fold-changes in antibodies between Vac#2+1m and Vac#2+6m were lower in patients than controls (n = 58). BAU = binding antibody units; BNT162b2 = Pfizer-BioNTech COVID-19 vaccine; ChAdOx1 = Oxford/AstraZeneca COVID-19 vaccine.

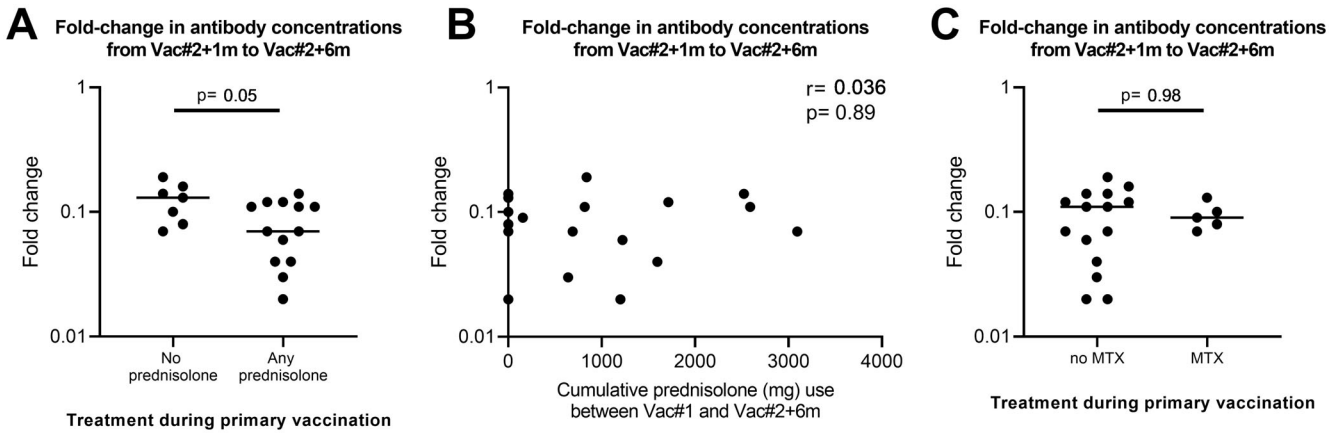

Figure 2. In patients vaccinated with the BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine (n = 20), the decrease in antibody concentrations over time is associated with prednisolone use during primary vaccination. **A**, The decay of antibody concentrations was stronger in patients using prednisolone during primary vaccination than in patients who did not. **B**, The cumulative prednisolone dose in the time between primary vaccination and the visit at 6 months after the second vaccination (Vac#2+6m) was not associated with the fold-change decrease. **C**, The use of methotrexate (MTX) during the primary vaccination was not associated with a stronger decay. Vac#2+1m = the visit at 1 month after the second vaccination.

Among GCA/PMR patients with a BNT162b2 primary vaccination, antibody concentrations after mRNA1273 booster were significantly higher when compared to patients with a BNT162b2 booster (see Supplementary Figure 4, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25173). However, patients who received the BNT162b2 booster had already significantly lower antibody concentrations at Vac#2+1m compared to patients with the mRNA1273 booster. Consequently, the fold increase in antibody concentrations was similar for both booster types.

Our multiple linear regression analysis (see Supplementary Table 4, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25173) showed that antibody concentrations at Vac#3+1m correlated strongly with antibodies at Vac#2+1m (R^2 = 0.25, B = 0.83 [95% confidence interval (95% CI) 0.33, 1.34], P = 0.002) (Figure 4A). However, the fold change of post-booster vaccination showed a slight negative correlation with the Vac#2+1m antibodies (R^2 = 0.21, B = –0.002 [95% CI –0.004, –0.001], P = 0.006) (see also Figure 4B). In the current study, treatment in the form of prednisolone >10 mg or methotrexate during booster vaccination was not associated with post-booster vaccine antibody responses in the regression analyses. In these analyses, we did not correct for booster vaccine type, as fold increases were similar for both boosters.

Additionally, booster responses were measured in patients who were diagnosed with GCA or PMR after receiving the primary vaccinations, but before the booster vaccination. These 8 patients, of which 6 took prednisolone during the booster vaccination, had comparable antibody concentrations at Vac#3+1m

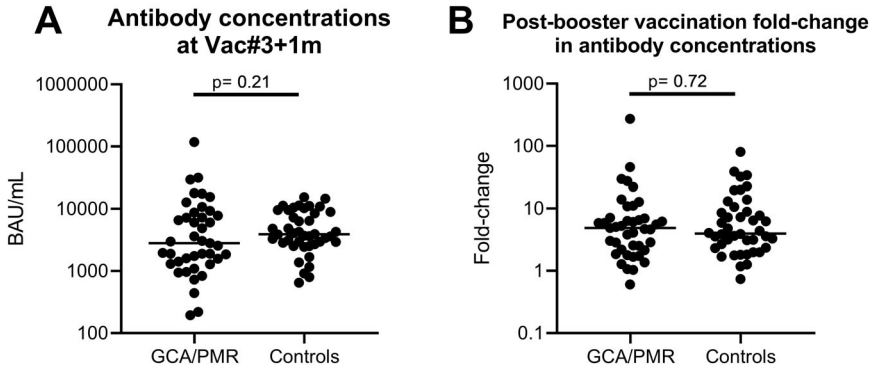

Figure 3. Antibody concentrations in giant cell arteritis/polymyalgia rheumatica (GCA/PMR) patients and controls post booster vaccination. Concentrations (**A**) and fold changes (**B**) of SARS–CoV-2 antibodies are compared in GCA/PMR patients (n = 41) and age- and sex-matched controls (n = 42) who were boosted with the BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) COVID-19 vaccines after primary BNT162b2 vaccination. BAU = binding antibody units; Vac#3+1m = the visit at 1 month after the third vaccination.

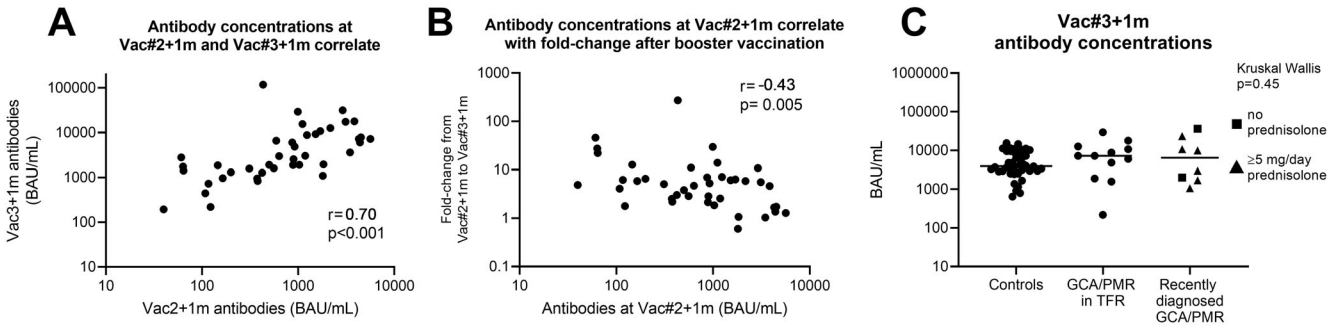

Figure 4. Determinants of antibody concentrations and fold changes after booster vaccination in giant cell arteritis/polymyalgia rheumatica (GCA/PMR) patients. **A**, Antibody concentrations at the visit at 1 month after the third vaccination (Vac#3+1m) correlate strongly with antibody concentrations at the visit at 1 month after the second vaccination (Vac#2+1m). **B**, Moderate negative correlation between the fold-change increase from Vac#2+1m to Vac#3+1m and the absolute levels of antibodies at Vac#2+1m. In **A** and **B**, Spearman's correlation coefficients (r) and *P* values are shown. In **C**, controls and patients in treatment-free remission (TFR) during all vaccinations are compared with patients who were recently, post primary BNT162b2 (Pfizer-BioNTech) COVID-19 vaccination, diagnosed with GCA/PMR. Shown are individual values with medians and statistical testing by Mann-Whitney U test. BAU = binding antibody units.

compared to controls and patients in treatment-free remission (Figure 4C).

DISCUSSION

This is the first study investigating long-term and booster SARS–CoV-2 vaccine responses in GCA and PMR patients. Antibody responses after primary vaccination appear to wane faster in patients than in age-, sex- and vaccine-matched controls, which was associated with prednisolone treatment. The immunogenicity of the booster vaccines in GCA and PMR patients is likely not associated with their disease or treatment. However, patients with a low primary vaccine response, due to immunosuppressive medication or other causes, do not catch up completely after a single booster vaccination.

In this study, we show that antibody concentrations post-primary vaccination strongly associate with post-booster concentrations. As impaired primary vaccine responses were linked to high-dose prednisolone or methotrexate treatment (5,6), this implies that humoral immunity post booster is affected by medication use during the primary vaccination. However, prednisolone or methotrexate use did not impact the immunogenicity of the booster vaccines, as fold changes in antibodies were not associated with treatment in the linear regression analysis. Moreover, patients who did not take any immunosuppressive medication during primary vaccination, but were taking high-dose prednisolone during booster vaccination for recent onset GCA/PMR, still showed excellent booster vaccine responses. A possible explanation for this discrepancy could be that therapy with prednisolone and/or methotrexate mainly affects the primary immune response in individuals without prior immunity, rather than memory immune responses after booster vaccination. The primary immune response that is initiated in individuals with no prior immunity is much more complicated than that in individuals who already have been primed. Primary vaccine responses rely on an effective interaction of antigen-presenting cells, T cells and B cells in secondary lymphoid organs; processes that can all be targeted by therapy. Potentially related to this, it could be that the development of memory B cells and long-lasting plasma cells is affected by medication use during the primary vaccination, whereas short-lasting plasma cells are less affected (9). Two longitudinal studies found that patients using methotrexate, JAK inhibitors or anticytokine drugs had strong humoral booster responses, whereas patients taking prednisolone, abatacept, or B cell depletion therapy had much lower responses (10,11). The reason for the contrasting findings on prednisolone may be different patient populations, prednisolone dosing or timing between vaccinations and visits. We found no evidence that the immunogenicity of vaccination depends on the booster type. Both pre- and post-booster antibody concentrations were lower in patients who received a BNT162b2 booster compared to patients who received a mRNA1273 booster. Some studies have shown a slightly better humoral response for heterologous booster vaccination (1), but here fold increases were actually similar for both vaccine types. Rather, patients that received the BNT162b2 booster already had impaired humoral immunity prior to the booster, associated with the medication use during primary vaccination, and were prioritized to receive BNT162b2 initially available as booster.

The waning of humoral immune responses after vaccination may be faster in GCA/PMR patients using prednisolone than in controls. We show that BNT162b2-vaccinated patients had greater decreases in antibody concentrations at 6 months after primary vaccination reaching significantly lower values at Vac#2+6m. The use of prednisolone, irrespective of the dose, appeared to be responsible for this accelerated waning. The lack of an effect of the prednisolone dose was interesting, as antibody concentrations at Vac#2+1m were comparable to controls in GCA/PMR patients taking <10 mg/day of prednisolone. Furer

et al showed that patients using prednisolone, rather than methotrexate, had impaired humoral immunity at Vac#2+6m and Vac#3+1m, which is comparable to the results of the current study (11). This study did not report differences in fold decreases. A possible explanation for the accelerated waning may be that prednisolone impairs the antigen presentation and germinal center reactions that are required for long-lasting immune responses, whereas methotrexate has more effect on B cells only. This is supported by the findings in our primary study, which showed impaired cellular immunity in GCA/PMR patients taking ≥10 mg/day of prednisolone, but not in those taking methotrexate (6).

We also show here that SARS–CoV-2 breakthrough infections occurred most often in patients taking prednisolone, which could be associated with lower primary antibody concentrations. Protection against severe SARS–CoV-2 has increasingly become more dependent on cellular immunity, which the new variants have not been shown to evade, than humoral immunity (12,13). However, vaccine-evoked humoral immunity did likely aid in the prevention of infections with the delta variant, the dominant strain during the follow-up period.

A main strength of this study is the longitudinal follow-up of patients during primary and booster vaccination, allowing us to study fold changes in antibody concentrations. The inclusion of matched controls is another strength. A limitation of this study is the low power in the stratified groups, which is inherent to the longitudinal design and to the exclusion of patients infected between primary and booster vaccination. Due to the longitudinal design of the study and the different types of primary and booster vaccines, the number of patients in particular treatment subgroups was relatively small. This should be taken into account when interpreting the data, such as the lack of treatment effects on waning immunity after primary vaccination or on booster vaccine immunogenicity. Additionally, this study also did not assess the viral antibody neutralization in our patients.

Despite a good booster vaccine response, patients that responded poorly to primary vaccination, likely because they were using high-dose prednisolone and methotrexate, remained to have reduced humoral protection after the booster. An option for patients taking methotrexate may be to interrupt this treatment for 2 weeks prior to primary vaccination, which was found to have promising effects (14,15). This is however not an option for patients taking prednisolone. The importance of additional booster vaccinations, preferably with the current bivalent vaccines should therefore be stressed for patients that used these medications during primary vaccination.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. van Sleen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Van Sleen, Brouwer.
Acquisition of data. Van Sleen, Buisman.
Analysis and interpretation of data. Van Sleen, van der Geest, Buisman, Sandovici, van Baarle, Brouwer.

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