Limited antibody response after BA.4/5 adapted booster vaccination in rheumatic patients receiving anti-TNF therapy: results of a case series

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July 13, 2023

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Ethics

The study was approved by the ethics committee of the Christian-Albrecht University Kiel (D409/21). All patients signed informed consent. The study is registered at DRKS (DRKS00024214).

To the editor,

Recently, it has been demonstrated that the humoral immune response against SARS-CoV-2 is impaired in patients receiving drugs that inhibit tumor necrosis factor alpha (TNF) (1, 2). These agents, such as adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab, prevent activation of leukocytes, synoviocytes, endothelial cells, and osteoclasts (3) by binding either only TNF or both, TNF and Lymphotoxin-α (4).

Vaccinated anti-TNF patients showed a significantly reduced antibody response against Omicron variants BA.1 and BA.2 circulating in the first half of 2022 (5). Because of the continuous occurrence of SARS-CoV-2 variants that are only partially covered by vaccine-induced antibodies (6), the question arises whether patients on anti-TNF therapy in particular can mount an adequate humoral immune response. Recently, the first data on the effect of mRNA booster vaccination in patients receiving such immunomodulators were presented. These results are based on neutralization experiments with pseudotyped lentiviruses carrying the spike protein of SARS-CoV-2 wild type and Omicron BA.1 as well as BA.5; newer virus variants were not considered. In addition, the authors have not yet been able to investigate the effect of mRNA vaccines adapted to Omicron BA.4/5 (7). The case series presented here with data on serum neutralization of SARS-CoV-2 variants B.1.513, Alpha (B.1.1.7), Delta (B.1.617.2), and Omicron (BA.1.17.2, BA.2, BA.5 .2.1, BQ.1 .1.1, and XBB.1.5) in anti-TNF-treated patients who received an Omicron-matched booster vaccination will help fill these knowledge gaps. This report includes three patients with rheumatoid arthritis and one patient with polyarthritis, all receiving anti-TNF therapy and three healthy individuals. All subjects are females and received booster vaccination with a vaccine adapted to Omicron BA.4 and BA.5. Sera were collected and examined on the day of the fourth or fifth vaccination and 7 days later (Table 1). The assays and methods used are described in the Supplement.

Patients had lower SARS-CoV-2 IgG levels (Figure 1a) and generally lower virus neutralization titers (Figure 1b), whereas consistently high IgG avidity was measured (Table 1).

Against the pre-omicron variants B.1.513, Alpha and Delta, patients showed borderline neutralizing titers on the day of the booster dose, which increased 6- to 9-fold thereafter. In contrast to controls, some patient sera failed to neutralize Omicron variants BA.1.17.2, BA.2, BA.5.2.1, and BQ.1.1.1 with sufficient titer levels after booster vaccination (see also Supplementary Figure 1, which illustrates the marked immune escape of the different Omicron variants compared to the pre-Omicron strains). Strikingly, after booster vaccination,

the recombinant XBB.1.5 variant could only be neutralized by serum from a healthy individual who had serologic evidence of prior SARS-CoV-2 infection.

According to this small case series, anti-TNF therapy may prevent patients from achieving neutralizing antibody titers against different Omicron variants, even after a booster dose. The results are consistent with the observation of Cheung et al. that at each time point, a significant proportion of anti-TNF patients had neutralizing titers against BA.1 and BA.5 that were at the lower limit of detection (7). The reduced B-cell response shown in previous SARS-CoV-2 and influenza immunization studies (1, 5, 8) is particularly evident in the present study. It is worth noting that all subjects received mRNA vaccines matched to Omicron variants BA.4/5. Although the mechanism by which anti-TNF drugs affect antibody formation remains unclear, experimental data suggest that B cell function is affected by the impairment of follicular dendritic cells and lymphoid germinal centers (9, 10).

Patients showed an up to an 11-fold increase in variant-specific neutralizing titer after booster vaccination, but this cannot be considered sufficient in every case.

From the results of the IgG antibody and IgG avidity assays, only limited conclusions can be drawn regarding current humoral anti-SARS CoV-2 immunity because the antigens used in these assays are related to the original Wuhan virus. In addition, this study does not address cellular immunity to SARS-CoV-2, which initial data suggest is also robust to Omicron in patients with immune-mediated inflammatory diseases (7).

In summary, present data indicate that only low virus-neutralizing titers against current SARS-CoV-2 variants can be induced, particularly in anti-TNF-treated patients, even after adapted booster vaccination. This small case series thus provides a rationale for seeking improved vaccines and vaccination regimens for this patient population. Furthermore, the results suggest that breakthrough infections may contribute to the development of broader immunity.

AUTHOR CONTRIBUTIONS

Ulf Martin Geisen, Jan Henrik Schirmer, Bimba Franziska Hoyer, Melike Sümbül, Florian Tran, Dennis Berner, Ann Carolin Longardt, Paula Hoff, and Sascha Gerdes: Patient recruitment and sampling; Ulf Martin Geisen, Mathias Voß, Ruben Rose, Franziska Neumann, Carina Bäumler, Sina Müller, Elena Hildebrand, Andi Krumbholz, and Bimba Hoyer: Antibody testing; Lea Paltzow, Christina Martínez Christophersen, Merle Münier, Ruben Rose, Mathias Voß, Andi Krumbholz: Recovery and characterization of SARS-CoV-2 isolates; Ulf Martin Geisen, Helmut Fickenscher, Andi Krumbholz, and Bimba Hoyer: Conceptualization of the study and writing of the draft manuscript; Ulf Martin Geisen, Mathias Voß, Ruben Rose, and Franziska Neumann: Analysis and presentation of the results; Thomas Lorentz, Helmut Fickenscher, Stefan Schreiber, and Bimba Hoyer: Provision of technical resources; All authors: review of the final manuscript.

Conflict of Interest Statement

The authors declare no conflicts of interest.

Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Medical Faculty of the Christian-Albrecht University of Kiel under file number D409/21. All subjects gave written informed consent. Vaccinations were not part of this observational study and were performed by local physicians or vaccination centers according to German regulations.

Funding

Cross-funded by in-house funding and by the Deutsche Forschungs-Gemeinschaft Cluster of Excellence Precision Medicine in Chronic Inflammation.

Conflict of Interests

BFH, PH and SS received funding from Pfizer.

The authors state no conflicts of interest in the context of this study.

Data availability

The data that support the findings of this study are available from the corresponding author, (BFH), upon reasonable request.

Acknowledgement

The authors thank Ina Martens, Vanessa März and Meike Zahnen for their excellent technical and organizational support.

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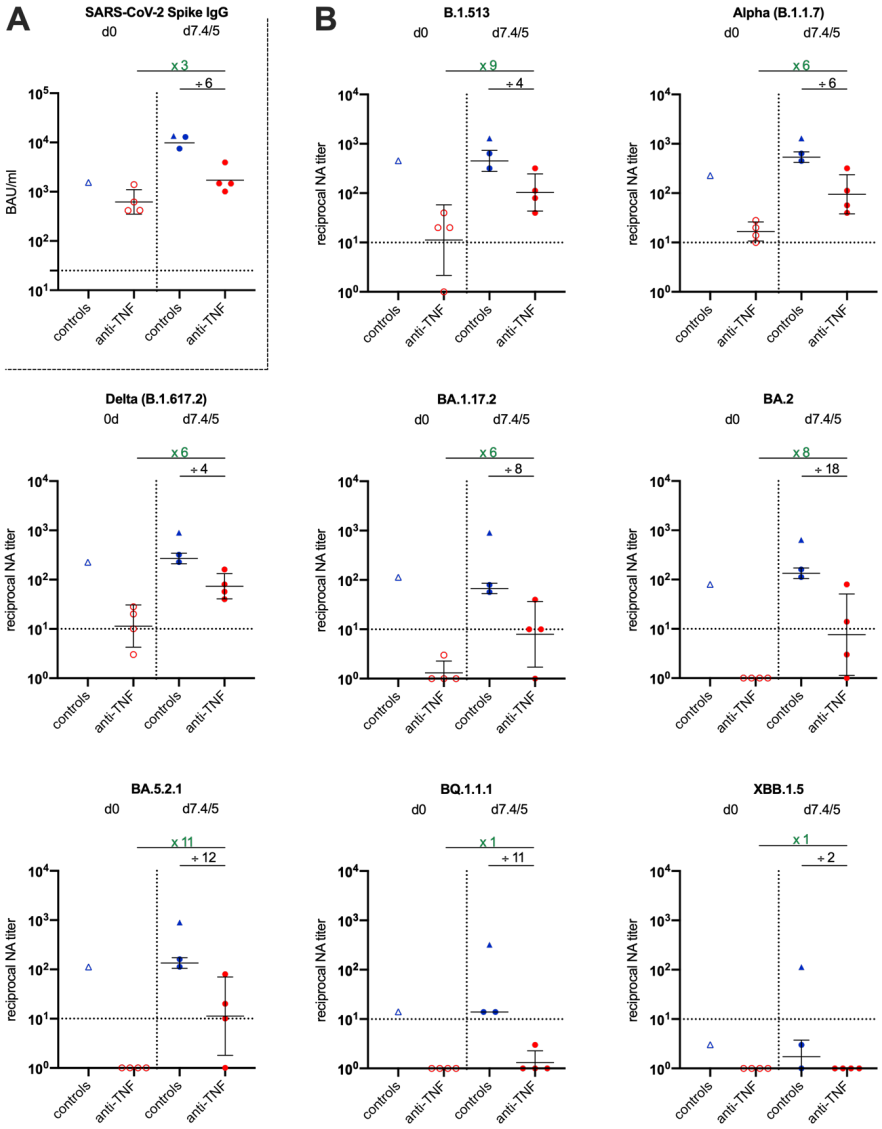
Legends

Figure 1: Level of anti-Spike IgG antibodies (**A**) and (**B**) presence of SARS-CoV-2 neutralizing antibodies (NA) in sera from healthy individuals (blue, controls) and in patients receiving drugs that inhibit tumor necrosis factor (red, anti-TNF). The horizontal lines indicate the cut-off values of the IgG enzyme immunoassay (25 BAU/ml) and virus neutralization assay (reciprocal titer >10), respectively. Where appropriate, the geometric mean and standard deviation of virus-neutralizing antibody titers were calculated. Individual samples were collected on the day of the fourth or fifth SARS-CoV-2 vaccination (0 days, empty triangle and circles) and one week later (7 days, filled triangle and circles). Details of the vaccination schedule used

are provided in Table 1. Titers were determined with a Vero cell-based virus neutralization assay using a member of the 2020 lineage B.1.513, and previous or current SARS-CoV-2 variants Alpha (B.1.1.7), Delta (B.1.617.2), and Omicron (BA.1.17.2, BA.2, BA.5.2.1, BQ.1.1.1, XBB.1.5) as antigens. These strains were isolated by us under BSL-3 conditions from patient material and characterized by whole genome sequencing. The x-fold increase in geometric mean titer between day 0 and day 7 is shown in green for anti-TNF patients. In addition, the x-fold decrease (÷) in geometric mean titers between controls and anti-TNF patients is reported for day 7 after booster vaccination. Anti-nucleoprotein IgG was detected in one subject in the control group, indicating that she had undergone SARS-CoV-2 infection. Her results are therefore presented separately (blue triangle) and not included in the calculation of the geometric mean titer of the control group.

Table 1: Characteristics of four patients treated with anti-tumor necrosis factor (TNF) agents and three healthy control subjects. All individuals are female. Previous SARS-CoV-2 vaccinations are indicated in order of application. Sera were collected on the day of a booster vaccination with mRNA vaccine adapted to Omicron BA.4 and BA.5 and 7 days later. IgG avidity was measured by immunoblot. Based on the comparison of band intensities of the avidity reagent-treated sample with the untreated sample, IgG avidity is classified as low, medium, and high. The intensity ratios measured are also listed. The presence of anti-nucleoprotein IgG (data not shown) in the immunoblot of subject #5 indicates that she had COVID-19. Abbreviations: messenger RNA-based SARS-CoV-2 vaccines, BNT162b2 and mRNA-1273; replication-deficient chimpanzee adenoviral vector containing the SARS-CoV-2 spike protein, ChAdOx1; healthy control, HC; Rheumatoid arthritis, RA; receptor-binding domain of the spike protein, RBD; subunit 1 of the spike protein, S1; wild type, wt.



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