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Short report

SARS-CoV-2 omicron breakthrough infections in patients with multiple sclerosis

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ABSTRACT

Background It is unclear which patients with multiple sclerosis (MS) are most susceptible for omicron breakthrough infections.

Methods We assessed omicron breakthrough infections in vaccinated patients with MS with and without disease-modifying therapies enrolled in an ongoing large prospective study. We longitudinally studied humoral responses after primary and booster vaccinations and breakthrough infections.

Results Omicron breakthrough infections were reported in 110/312 (36%) patients with MS, and in 105/110 (96%) infections were mild. Omicron breakthrough infections occurred more frequently in patients treated with anti-CD20 therapies and sphingosine-1 phosphate receptor (S1PR) modulators, patients with impaired humoral responses after primary immunisation (regardless of treatment) and patients without prior SARS-CoV-2 infections. After infection, antibody titres increased in patients on S1PR modulator treatment while anti-CD20 treated patients did not show an increase.

Conclusions SARS-COV-2 omicron breakthrough infections are more prevalent in patients with MS on anti-CD20 therapies and S1PR modulators compared with other patients with MS, which correlated with decreased humoral responses after vaccination. Humoral responses after infection were higher in S1PR modulator-treated patients in comparison to patients on anti-CD20 therapies, suggesting that immunological protection from contracting infection or repeated exposures may differ between these therapies.

INTRODUCTION

The COVID-19 pandemic is continuously changing due to ongoing mutations of SARS-CoV-2. Although omicron variants mostly induce less severe COVID-19 compared with the delta variant due to differences in pathogenesis, transmissibility of these variants is higher despite vaccination.[1]

In patients with multiple sclerosis (MS), anti-CD20 therapies (eg, ocrelizumab, rituximab) and sphingosine-1 phosphate receptor (S1PR) modulators (eg, fingolimod and ozanimod) are associated with decreased humoral immune responses after SARS-CoV-2 vaccination. Patients with MS treated with anti-CD20 therapies also have increased risks of severe COVID-19, at least for SARS-CoV-2 variants up to delta.[2 3] Despite both reduced humoral and cellular responses, treatment with S1PR modulators has not been associated with increased risks of severe COVID-19.[4]

The aim of this study was to assess the risk and severity of omicron breakthrough infections in patients with MS with and without disease-modifying treatment (DMTs) in relation to humoral responses after primary and booster vaccination. Furthermore, humoral responses after omicron breakthrough infection will be compared.

METHODS

Study design

This is a substudy of an ongoing prospective multiple-arm multicentre cohort study, the T2B! study (Trial ID NL8900; Dutch Trial Register), studying SARS-CoV-2 vaccination responses and infections in patients with immune-mediated inflammatory disorders. The study protocol, data on patient characteristics and SARS-CoV-2 (breakthrough) infections of the full cohort have been published previously.[5 6] The medical ethical committee of the Amsterdam UMC, location AMC (2020.194), approved the study and all participants provided written informed consent.

Patient selection

For this substudy, we included patients with MS with and without DMTs who had completed primary vaccination. In the Netherlands, in September 2021, an additional vaccination was offered to individuals treated with 'strongly antibody-impairing immunosuppressants' such as anti-CD20 therapies and S1PR modulators. From December 2021 onwards, additional ('booster') vaccinations were offered to all Dutch individuals (including the MS population without strongly antibody-impairing immunosuppressants). As the booster vaccination programme took a long time to complete and was age dependent (elderly people first), only a very low number of participants of this study without immunosuppressants received a booster vaccination during the observation period (see table 1). The observation period ranged between 1 January and 1 April first when omicron variants BA.1 and BA.2 were dominant in the Netherlands.

Study procedures

Data regarding (additional) vaccinations, SARS-CoV-2 (breakthrough) infections and demographics

Table 1 Patient characteristics and humoral responses after vaccination and infection

	Anti-CD20 therapy (n:105)		S1PR modulator (n:60)		Natalizumab (n:37)		No DMT (n:110)	
Omicron breakthrough infection, n (%)	No 65 (61.9)	Yes 40 (38.1)	No 29 (48.3)	Yes 31 (51.7)	No 27 (73.0)	Yes 10 (27.0)	No 81 (73.6)	Yes 29 (26.4)
Age, mean (SD)	48.0 (10.4)	44.6 (10.3)	47.3 (8.1)	43.8 (10.2)	48.3 (10.2)	44.8 (6.01)	56.7 (9.5)	52.5 (10.7)
Female sex, n (%)	43 (66.2)	28 (70.0)	17 (58.6)	22 (71.0)	21 (77.8)	8 (80.0)	60 (74.1)	24 (82.8)
SARS-CoV-2 infection prior to omicron wave, n (%)	15 (23.1)	4 (10)	9 (31)	4 (12.9)	8 (29.6)	3 (30)	19 (23.5)	5 (17.2)
Vaccination type primary immunisation, n (%)								
AstraZeneca	14 (21.5)	4 (10.0)	2 (6.9)	2 (6.5)	4 (14.8)	0	20 (24.7)	6 (20.7)
Janssen	3 (4.6)	1 (2.5)	0	0	0	0	2 (2.5)	1 (3.5)
Moderna	36 (55.4)	24 (60.0)	15 (51.7)	13 (41.9)	5 (18.5)	3 (30.0)	25 (30.9)	13 (44.8)
Pfizer/BioNtech	12 (18.5)	11 (27.5)	12 (41.4)	16 (51.6)	18 (66.7)	7 (70.0)	34 (42.0)	9 (31.0)
Seroconversion after primary immunisation, n (%)								
Seroconversion	21 (35.0)	12 (33.3)	13 (52.0)	9 (33.3)	23 (100)	9 (100)	67 (95.7)	26 (92.9)
Serology missing	5 (7.7)	4 (10.0)	4 (13.8)	4 (12.9)	4 (14.8)	1 (10.0)	11 (13.6)	1 (3.4)
Additional vaccinations, n (%)								
0	2 (3.1)	3 (7.5)	1 (3.5)	1 (3.23)	3 (11.1)	0	7 (8.7)	3 (10.3)
1	28 (43.1)	19 (47.5)	11 (37.9)	15 (48.4)	24 (88.9)	10 (100)	70 (86.4)	26 (89.7)
2	35 (53.8)	16 (45.0)	17 (58.6)	15 (48.4)	0	0	4 (4.9)	0
Seroconversion after first booster vaccination, n (%)								
Seroconversion	23 (41.8)	10 (32.3)	12 (44.4)	14 (48.3)	–	–	–	–
Serology missing	8	6	1	1	–	–	–	–
Seroconversion after breakthrough omicron infection*, n (%)								
Seroconversion	–	6/12 (50.0)	–	12/14 (85.7)	–	5/5 (100)	–	8/8 (100)
Time between last vaccination and omicron infection								
Days, median (IQR)	–	87 (43–126)	–	65 (36–108)	–	39 (28–52)	–	74 (43–89)

Displaying patient characteristics and humoral responses after vaccination and infection separately for patients with MS treated with anti-CD20 therapy (ocrelizumab in 101/105 and rituximab in 4/105), sphingosine-1 phosphate receptor (S1PR) modulators (fingolimod in 59/60 and 1/60 ozanimod), natalizumab or patients with MS without disease modifying therapy (DMT) with or without SARS-CoV-2 omicron breakthrough infections.
*Assessed in a subgroup of infections (n=39, see methods). In 24 patients, a sample was available at day 7 after breakthrough infection and in 31 patients, a sample was available at day 28 after breakthrough infection.
MS, multiple sclerosis.

were collected via electronic questionnaires, which were sent to patients every 2 months after first vaccination. Baseline characteristics, diagnosis and use of medication were retrieved from the medical files. Only additional vaccinations administered at least 14 days prior to breakthrough omicron infection or prior to March first 2022 were used for analysis. When a patient indicated a positive PCR or antigen test, they were contacted by a researcher at least 2 weeks after the positive test to verify and determine COVID-19 severity. COVID-19 severity was based on the WHO classification.[7]

Humoral responses after SARS-CoV-2 vaccination and/or infection were assessed through serum samples (collected via a fingerprick blood collection at home) collected at baseline (before vaccination), at 28 days after primary vaccination in all patients and at 28 days after booster vaccinations for patients treated with S1PR and anti-CD20 therapy. In a subset of patients who volunteered for additional sampling, humoral responses after omicron breakthrough were measured at 7 and/or 28 days after start of symptoms. The concentration of SARS-CoV-2 antibodies in serum samples was measured using an in-house anti-receptor binding domain (RBD) IgG ELISA. The highest anti-RBD IgG titre after infection (either at day seven or 28) was used for analysis. Wuhan variant-specific anti-RBD IgG antibodies were measured at Sanquin Laboratory, Amsterdam, the Netherlands as described earlier.[8] Seroconversion was defined as anti-RBD IgG titre >4.0 AU/mL.[8]

Statistics

Differences in proportions were analysed using a Fisher's exact test, differences between continuous variables were analysed using a Wilcoxon-rank sum test or Wilcoxon signed rank test in case of paired samples. When applicable, proportions are shown with associated 95% CI. Analyses were performed in R (V.4.1.0).

Data availability statement

Anonymised research data will be shared on reasonable request with any qualified investigator.

RESULTS

In this substudy, 312 patients with MS were included. Table 1 describes patient characteristics, omicron breakthrough infections and humoral responses. Overall, 110/312 patients with MS (35.5%) reported an omicron breakthrough infection.

Breakthrough infections

MS patients treated with S1PR modulators (31/60; 51.7%) or anti-CD20 therapies (40/105; 38.1%) experienced omicron breakthrough infections more frequently than patients on natalizumab (10/37; 27.0%) and without DMTs (29/110; 26.4%; p<0.01).

Patients with MS with an omicron breakthrough infection less frequently showed seroconversion after primary immunisation compared with patients with MS without omicron breakthrough infection (56/100; 56% vs 124/178; 69.7%, respectively; p: 0.03). Furthermore, patients with MS with an omicron breakthrough infection had lower anti-RBD IgG titres at 28 days after primary immunisation compared with patients with MS without omicron breakthrough infection (median 5.8 AU/mL (IQR: 0.1–99.2) vs 26.3 (IQR: 1.8–146), respectively; p: 0.04).

Additional vaccines were received by 189/202 (93.6%) patients without breakthrough infections compared with 102/110 (92.7%) with breakthrough infections (p: 0.82; table 1).

The proportion of omicron breakthrough infections was higher in patients with MS treated with S1PR modulators (31/60; 51.7%) compared with patients treated with anti-CD20 therapies (40/105; 38.1%) but this did not reach significance (p: 0.10; table 1). Seroconversion rates after the first additional vaccination were similar for patients on anti-CD20 therapies and patients on S1PR modulators (33/91; 36.2% vs 26/58; 44.2%, respectively, p: 0.39). Anti-RBD IgG titres after additional vaccination were also comparable between patients on anti-CD20 therapies and S1PR modulators (median 2.0 AU/mL (IQR: 0.1–10.1) vs 2.4 (IQR: 0.1–12.1), respectively; p: 0.38).

Patients with MS with an omicron breakthrough infection had less frequently experienced prior infections with another SARS-CoV-2 variant compared with patients with MS without omicron breakthrough infections (16/110; 14.5% vs 51/202; 25.2%, respectively; p: 0.03, table 1).

COVID-19 severity of breakthrough infections

The majority (105/110, 95.5%) of breakthrough omicron infections was mild. Four patients were asymptomatic and one patient had a moderate disease severity. This patient was treated with anti-CD20 therapy and developed a SARS-CoV-2 breakthrough infection 2 months after the second additional vaccination. The patient did not seroconvert after primary and first additional vaccination.

Humoral response after breakthrough infection

All patients with MS on natalizumab (5/5; 100%) and without DMTs (8/8; 100%) showed seropositivity after infection (figure 1). Patients with MS on S1PR modulators tended to show seropositivity more frequently after infection (12/14; 85.7%) compared with anti-CD20-treated patients (6/12; 50%; p: 0.09). Furthermore, patients on S1PR modulators showed an increase in anti-RBD IgG titres after infection (p<0.01; figure 1) when compared with anti-RBD IgG titres after first additional vaccination, whereas patients on anti-CD20 therapies did not (p:0.58; figure 1).

DISCUSSION

In this study, omicron breakthrough infections were more prevalent in patients with MS on anti-CD20 therapies and S1PR modulators compared with patients on natalizumab or without DMTs. Similar to what has been reported by Sormani *et al*, lower antibody titres after vaccination was a risk factors for an omicron

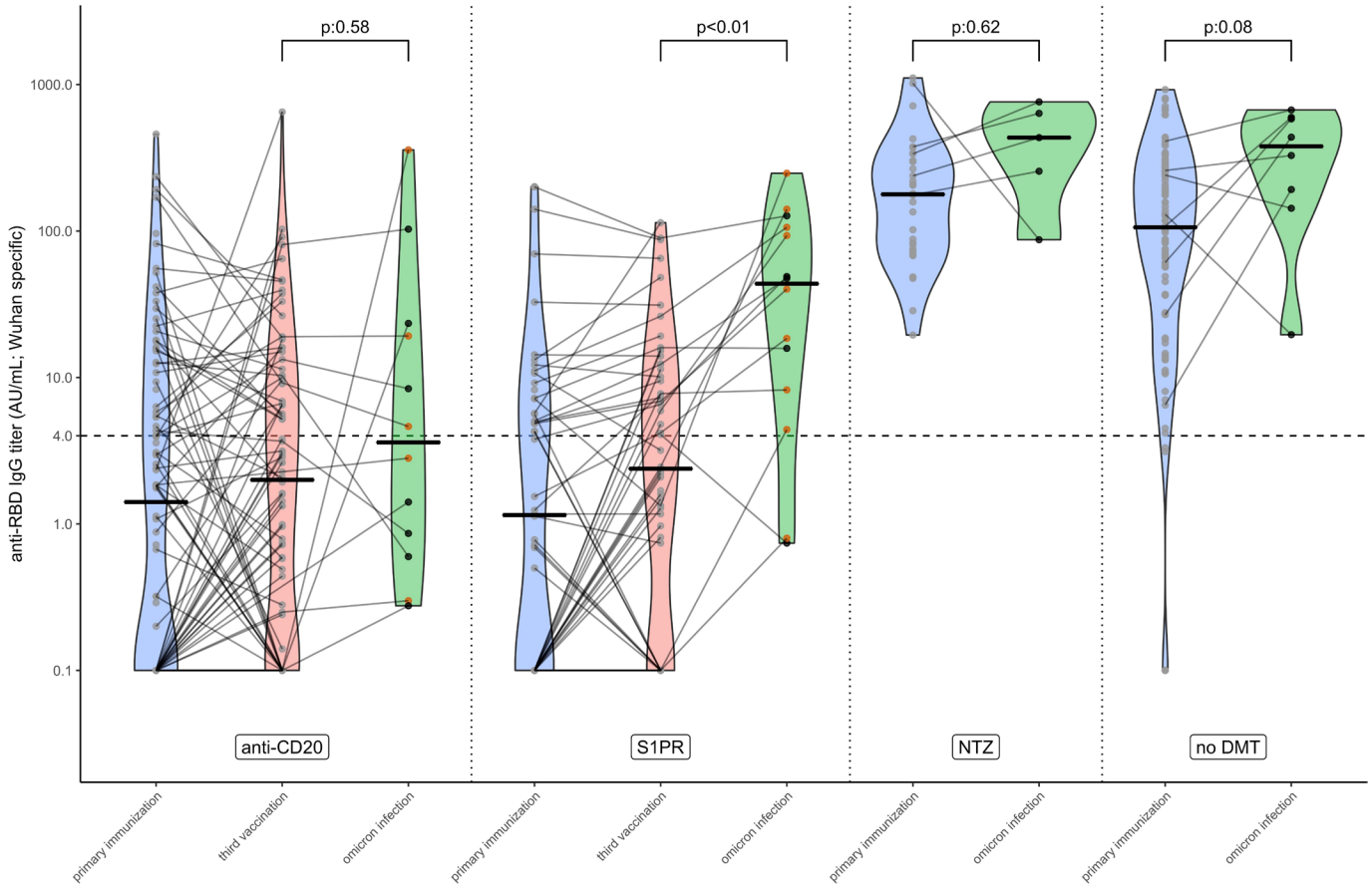

Figure 1 Humoral responses after SARS-CoV-2 vaccination and omicron breakthrough infections. Showing SARS-CoV-2 titres against RBD 28 days after primary immunisation (blue violin), 28 days after first additional ('booster') vaccination (red violin) and the highest titre of two timepoints after omicron breakthrough infection (ie, day 7 or 28; green violin). Cut-off for seroconversion is 4 AU/mL. Black dots after an omicron breakthrough infection indicate that one additional vaccine was administered prior to infection; orange dots indicate that two additional vaccines were administered prior to infection. Median time from last vaccination to omicron infection was 87 (IQR 43–126) days in patients on anti-CD20 therapies, 65 (IQR 36–108) days in patients on S1PR (sphingosine-1 phosphate receptor) modulators, 39 (IQR 28–52) days in patients on NTZ and 74 IQR (43-89) in patients without disease DMTs. DMTs, disease modifying therapies; NTZ, natalizumab.

breakthrough infection.[9] Most omicron breakthrough infections described in this cohort were mild confirming that omicron breakthrough infections are less severe compared with other variants, which is in agreement with other studies.[1]

Humoral responses after SARS-CoV-2 vaccination are decreased to a similar degree in patients with MS on anti-CD20 therapies and S1PR modulators.[10] As we and others have shown recently, T cell immune responses, for example, the IFN-gamma release on stimulation by SARS-CoV-2-derived peptide pools, after vaccination, are preserved in patients on anti-CD20 therapies but are decreased or absent in patients on S1PR modulators.[3 11] However, anti-CD20 therapies have been previously associated with increased COVID-19 severity while S1PR modulators have not.[4] Interestingly, while most S1PR-treated patients had limited effect of the first booster vaccination on humoral responses, a clear increase in antibody titres was observed after infection. In anti-CD20-treated patients, humoral responses both after booster vaccination and infection were low. We speculate that this discrepancy may indicate that patients on S1PR modulators may benefit from repeated (vaccination or infection) exposures to develop a humoral response. This has also been observed in mycophenolate mofetil-treated patients who started to show higher humoral response only after three vaccinations.[12] Alternatively, this discrepancy may indicate that the immunological pathways activated during infection are affected less by S1PR modulators compared with pathways activated after vaccination, which could also explain why patients on S1PR modulators do not have an increased risk for severe course of COVID-19. Further studies are needed to better understand this discrepancy of humoral responses between various DMTs in patients with MS.

Our study has limitations. First, the number of patients per treatment group was relatively small. Second, humoral responses after additional vaccinations and breakthrough omicron infections were not assessed in all samples and we did not investigate cellular immune responses.

In conclusion, SARS-COV-2 omicron breakthrough infections are more prevalent in vaccinated patients with MS on anti-CD20 therapies and S1PR modulators compared with other patients with MS, which is likely due to decreased humoral responses after vaccination. Antibody titres after infection increased in S1PR modulator-treated patients but not in patients on anti-CD20 therapies suggesting either a benefit of repeated antigen exposure or that infection-induced responses are affected less in S1PR modulator-treated patients.

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Ethics approval This study involves human participants and was approved by Medical Ethical Committee of the Amsterdam UMC, location AMC (2020.194). Participants gave informed consent to participate in the study before taking part.

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