EPIDEMIOLOGICAL SCIENCE

Breakthrough infections with the SARS-CoV-2 omicron (B.1.1.529) variant in patients with immune-mediated inflammatory diseases

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ABSTRACT

Objectives To compare the cumulative incidence and disease severity of reported SARS-CoV-2 omicron breakthrough infections between patients with immune-mediated inflammatory diseases (IMID) on immunosuppressants and controls, and to investigate determinants for breakthrough infections.

Methods Data were used from an ongoing national prospective multicentre cohort study on SARS-CoV-2 vaccination responses in patients with IMID in the Netherlands (Target-to-B! (T2B!) study). Patients wih IMID on immunosuppressants and controls (patients with IMID not on immunosuppressants and healthy controls) who completed primary immunisation were included. The observation period was between 1 January 2022 and 1 April 2022, during which the SARS-CoV-2 omicron (BA.1 and BA.2 subvariant) was dominant. A SARS-CoV-2 breakthrough infection was defined as a reported positive PCR and/or antigen test at least 14 days after primary immunisation. A multivariate logistic regression model was used to investigate determinants.

Results 1593 patients with IMID on immunosuppressants and 579 controls were included. The cumulative incidence of breakthrough infections was 472/1593 (29.6%; 95% CI 27% to 32%) in patients with IMID on immunosuppressants and 181/579 (31.3%; 95% CI 28% to 35%) in controls (p=0.42). Three (0.5%) participants had severe disease. Seroconversion after primary immunisation (relative risk, RR 0.71; 95% CI 0.52 to 0.96), additional vaccinations (RR 0.61; 95% CI 0.49 to 0.76) and a prior SARS-CoV-2 infection (RR 0.60; 95% CI 0.48 to 0.75) were associated with decreased risk of breakthrough infection.

Conclusions The cumulative incidence of reported SARS-CoV-2 omicron breakthrough infections was high, but similar between patients with IMID on immunosuppressants and controls, and disease severity was mostly mild. Additional vaccinations and prior SARS-CoV-2 infections may reduce the incidence of breakthrough infections.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Some immunosuppressants used in patients with immune-mediated inflammatory diseases (IMIDs) impair humoral or cellular immune responses after SARS-CoV-2 vaccination.

⇒ These patients may, therefore, be at increased risk of (severe) SARS-CoV-2 breakthrough infections.

INTRODUCTION

The emergence of the SARS-CoV-2 variant omicron has led to an unprecedented number of SARS-CoV-2 cases worldwide. Multiple mutations in the receptor binding domain (RBD) of the spike (S) protein of this variant increased transmissibility and infectivity, and reduced effectiveness of

WHAT THIS STUDY ADDS

- ⇒ SARS-CoV-2 omicron breakthrough infections in patients with IMID on immunosuppressants are frequent but mostly mild and incidence and severity is similar to controls.
- ⇒ Humoral responses after primary immunisation, additional vaccinations and hybrid immunity, resulting from prior SARS-CoV-2 infections, were associated with a lower risk of SARS-CoV-2 omicron breakthrough omicron infections in both patients with IMID on immunosuppressants and controls.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ Our findings suggest that additional vaccinations and development of hybrid immunity both contribute in reducing the risk of SARS-CoV-2 omicron breakthrough infections in patients with IMID, even despite the use of immunosuppressants. Severe SARS-CoV-2 breakthrough infections are rare for the omicron variant.
- ⇒ In case of new SARS-CoV-2 infection waves, it can be speculated that offering additional and/or updated vaccinations is an effective strategy to reduce risks, also for patients with IMID.

standard SARS-CoV-2 vaccination regimens.[1–3] In the general population, disease severity after infection with the SARS-CoV-2 omicron variant were shown to be generally mild and less severe compared with the delta variant.[4–7] Booster vaccinations help to protect against symptomatic infection by increasing SARS-CoV-2 omicron neutralising antibodies and by broadening the antibody repertoire.[8–12] However, in patients with immune-mediated inflammatory diseases (IMIDs) treated with specific immunosuppressants, cellular and humoral efficacy of (booster) vaccinations may be impaired.[13–17] Therefore, these patients may be at increased risk for more severe SARS-CoV-2 breakthrough infections. We previously reported that there was no difference in incidence of SARS-CoV-2 delta variant breakthrough infections and disease severity between patients with IMID on immunosuppressants compared with controls, with the exception of anti-CD20 treatment in patients with additional risk factors (ie, older age and comorbidities).[6] The primary objective of this study is to compare cumulative incidence and disease severity of reported SARS-CoV-2 omicron breakthrough infections between patients with IMID on immunosuppressants, and controls (patients with IMID not on immunosuppressants and healthy controls). The secondary objective is to explore determinants associated with the risk of SARS-CoV-2 omicron breakthrough infections, including use of immunosuppressants, humoral responses after primary immunisation, administration of additional vaccines and prior SARS-CoV-2 infections.

METHODS

Study design

This is a study on SARS-CoV-2 omicron breakthrough infections from an ongoing prospective multiple-arm multicentre cohort study, the T2B! study (Trial ID NL8900; Dutch Trial Register). The primary objective of the T2B! study was to assess humoral and cellular immune responses after SARS-CoV-2 vaccination in patients with various IMIDs treated with predefined types of immunosuppressants. Monitoring SARS-CoV-2 breakthrough infections is a predefined secondary outcome in the study. Full study protocol, data on patient characteristics, humoral and cellular responses and SARS-CoV-2 infections other than omicron has been published elsewhere.[6 15–18]

Participants

Patients with IMID on immunosuppressants during primary immunisation and a combined control group of patients with IMID without systemic immunosuppressants and healthy controls who had been included as part of the overall study between 2 February 2021 and 1 October 2021 were included. Participants were included if primary immunisation with either with two doses of BNT162b2 (Pfizer/BioNtech), CX-024414 (Moderna) or ChAdOx1 nCoV-19 (AstraZeneca), or one dose of Ad.26.COV2.S (Janssen/Johnson & Johnson) was completed. Participants with a SARS-CoV-2 infection prior to or within 90 days after first vaccination who had received only one dose of any of the above vaccines were also included. See online supplemental methods for the full inclusion and exclusion criteria.

Vaccination campaign Netherlands

See online supplemental methods for information about the vaccination campaign in the Netherlands. In short, in September 2021 an additional ('third') vaccination was offered to several vulnerable groups, including patients with IMID treated with 'strongly antibody-impairing immunosuppressants' (see below) and from December 2021 onwards additional ('booster') vaccinations were offered to all individuals in the Netherlands.

Procedures

Electronic questionnaires were sent to participants every 2 months after first vaccination. An extra questionnaire was sent on 13 April 2022 to those who had not completed follow-up questionnaires. Demographics and data on SARS-CoV-2 (breakthrough) infections were retrieved from these questionnaires. Medical files were used to register IMID and start, and stop dates of all immunosuppressants. Testing for a SARS-CoV-2 infection was participant driven and performed independently of this study. When a participant 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 disease severity. If hospital admission was reported, clinical discharge letters were retrieved to assess disease severity.

From the ongoing T2B! cohort study, serum samples collected at baseline (before vaccination) and at 28 days after first and second vaccination (when applicable). Anti-RBD and anti-NP antibodies were measured at Sanquin as described before (see online supplemental methods).

Outcomes

The primary outcome was the cumulative incidence of reported breakthrough infections with the SARS-CoV-2 omicron variant in patients with IMID on immunosuppressants and controls. Patients with IMID not on immunosuppressants and healthy controls were combined in one control group because we did not observe differences between these groups in humoral responses after SARS-CoV-2 vaccination nor in the incidence of the delta variant breakthrough infections.[6 17] A SARS-CoV-2 omicron breakthrough infection was defined as a reported PCR or antigen confirmed infection at least 14 days after primary immunisation occurring between 1 January 2022 and 1 April 2022 when the SARS-CoV-2 omicron variant (BA.1 and BA.2 subvariant) was dominant in the Netherlands.[19]

Disease severity and determinants for breakthrough infections were secondary outcomes. Disease severity was based on the WHO classification and was defined as either asymptomatic (WHO 1), mild symptomatic (WHO 2–3), hospitalised moderate disease (WHO 4–5), hospitalised severe disease (WHO 6–9) or dead (WHO 10).[20] Definitions of immunosuppressants as monotherapy or as part of combination therapy and definition of active treatment are described in online supplemental methods. A SARS-CoV-2 infection prior to SARS-CoV-2 omicron breakthrough infection was defined as having one or more positive PCR or antigen tests prior to 1 January 2022, presence of anti-RBD antibodies in any serum sample obtained prior to vaccination or the presence of anti-NP antibodies prior to 1 January 2022. Seroconversion after primary immunisation was defined as an anti-RBD IgG response of >4.0 AU/mL measured at 28 days after primary immunisation.[21]

Analysis

Sample size calculation for the primary outcomes of the T2B! study have been described previously.[17] As primary analysis, we calculated the 95% CIs for the cumulative incidence of reported SARS-CoV-2 omicron breakthrough infections in patients with IMID on immunosuppressants and controls. A post hoc sensitivity analysis was done to compare characteristics of participants included for analyses compared with participants who were lost to follow-up. Differences in disease severity of reported SARS-CoV-2 omicron breakthrough infections between patients with IMID on immunosuppressants and controls were compared using the WHO COVID-19 Clinical Progression Scale.[20]

As a secondary analysis, we investigated possible determinants of SARS-CoV-2 omicron breakthrough infections. Previously, we showed that seroconversion after primary immunisation and hybrid immunity (ie, immunity after both infection and vaccination) were the most important determinants of breakthrough infections with the delta variant.[6] To this end, we compared the cumulative incidences of SARS-CoV-2 omicron breakthrough infections between participants with and without seroconversion after primary immunisation. In addition, we defined three medication groups: (1) treatment with anti-CD20 (combination) therapy, S1P modulators or MMF (combination) therapy as 'strongly antibody-impairing immunosuppressants' as we previously showed strongly reduced seroconversion rates with these treatments, (2) other immunosuppressants or (3) no immunosuppressants.[17] We compared the cumulative incidences of SARS-CoV-2 omicron breakthrough infections between these three medication groups. To investigate the role of additional vaccinations, that is, vaccinations after primary immunisation, we compared the cumulative incidence of SARS-CoV-2 omicron breakthrough infections in participants with and without additional vaccinations, separately for patients with IMID on immunosuppressants and controls. Participants vaccinated against SARS-CoV-2 less than 14 days prior to a SARS-CoV-2 omicron breakthrough infection (N:32) were analysed as not having received an additional vaccination. Also, we compared the proportion of participants with a SARS-CoV-2 omicron breakthrough infection who had received 0, 1 or 2 additional vaccinations separately for the three medication groups. To assess the impact of hybrid immunity, the incidence of SARS-CoV-2 omicron breakthrough infections was compared between participants with and without a prior SARS-CoV-2 infection at the start of the SARS-CoV-2 omicron wave on 1 January 2022, separately for patients with IMID on immunosuppressants and controls.

A time-to-event curve was constructed from the start of the omicron wave (ie, 1 January 2022) up to the time of SARS-CoV-2 omicron breakthrough infection or 1 April 2022 stratified for the different determinants except for seroconversion (due to low number of observations in subgroups) and medication group (due to no observed difference; see online supplemental figure 1 for curves). As the proportional hazard assumption was not met for all determinants, we used a multivariate logistic regression model (reported with relative risk and 95% CIs) to investigate risk associations for the potential determinants. The following determinants were studied: medication group (strongly antibody-impairing immunosuppressants/other immunosuppressants/no immunosuppressants), prior SARS-CoV-2 infection at the start of the omicron wave (yes/no), additional vaccination (yes/no) and seroconversion after primary immunisation (yes/no). Age and sex were added as confounders to the multivariate model. Interaction terms between determinants were explored, but were not significant. Differences between cumulative incidences were analysed using a χ^2 test. Analysis was done using R V.4.2.0.

RESULTS

A total of 1593 patients with IMID on immunosuppressants and 579 controls, consisting of 398 patients with IMID not on immunosuppressants and 181 healthy controls were included. Figure 1 shows the flow chart of this study. Table 1 shows baseline characteristics of all participants. The mean age of patients with IMID on immunosuppressants was 51 years (SD 14) and controls 52 years (SD 12), and most participants were female (62% and 67%, respectively). A total of 336/1593 (21.1%) patients with IMID were treated with strongly antibody-impairing immunosuppressants (anti-CD20 (combination) therapy, S1P modulators or MMF (combination) therapy). Online supplemental table 1 shows characteristics of participants included for analyses compared with those who were lost to follow-up. Participants included for analyses were older (51 years (SD 13) vs 41 years (SD 14), p<0.01) and more frequently female (36% vs 46%, p<0.01) compared with those lost to follow-up. Online supplemental table 2 shows characteristics separate for patients with IMID on immunosuppressants, patients with IMID not on immunosuppressants and healthy controls. Online supplemental table 3 shows characteristics separately for the different strongly antibody-impairing immunosuppressants.

Cumulative incidence of reported SARS-CoV-2 omicron breakthrough infections

SARS-CoV-2 omicron breakthrough infections were reported by 472/1593 (29.6%; 95% CI 27% to 32%) patients with IMID on immunosuppressants and by 181/579 (31.3%; 95% CI 28% to 35%) controls (p=0.42; controls: 126/398 (32%) patients with IMID not on immunosuppressants and 55/181 (30.4%) healthy controls). Figure 2 shows the incidence rate of SARS-CoV-2 omicron breakthrough infections per week during the observation period. No difference in trends of incidence rates was observed between patients with IMID on immunosuppressants and controls.

Determinants of SARS-CoV-2 omicron breakthrough infection

A total of 1746/1961 (89.0%) of all participants reached seroconversion after primary immunisation. Patients with IMID on strongly antibody-impairing immunosuppressants reached seroconversion in 150/314 (47.8%), while 1100/1143 (96.2%) in patients with IMID on other immunosuppressants and 496/504 (98.4%) in controls reached seroconversion. SARS-CoV-2 omicron breakthrough infections were detected in 81/215 (37.7%) of participants without seroconversion after primary immunisation compared with 508/1746 (29.1%) of participants

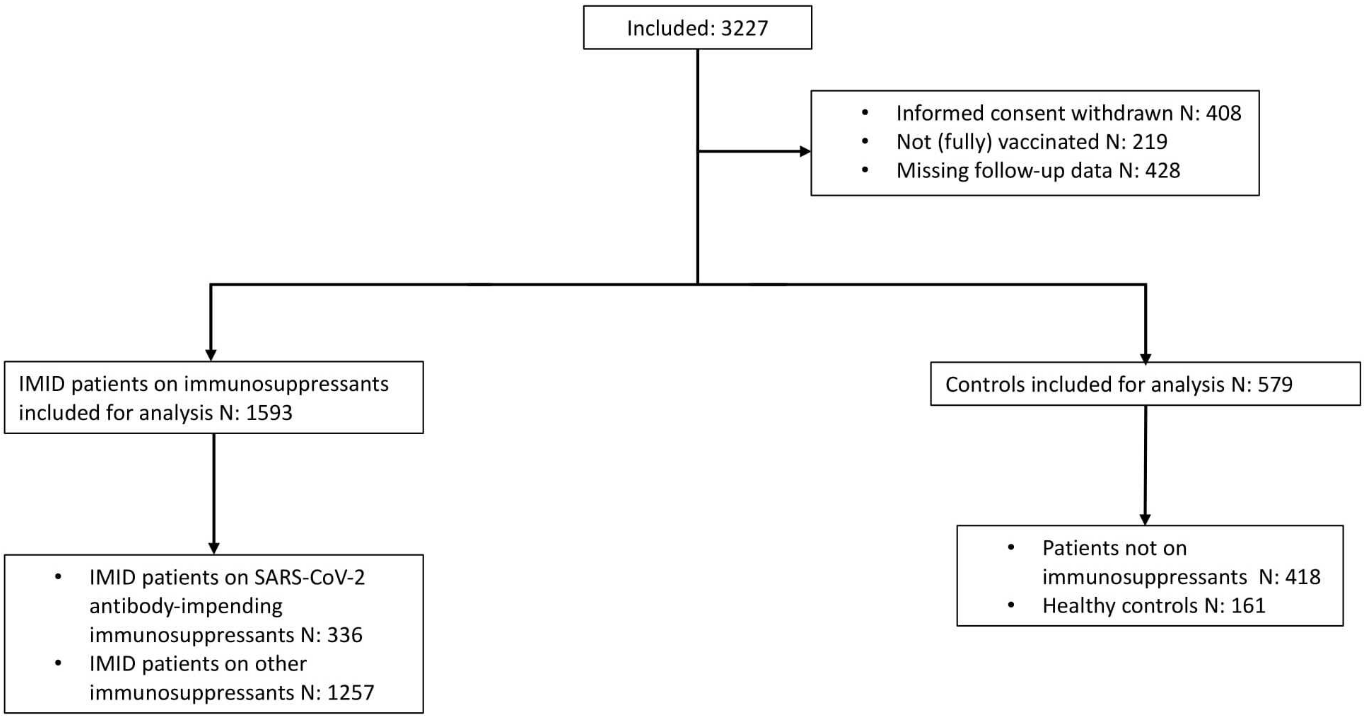

Figure 1 Shows baseline characteristics of flow chart. Figure showing the flow chart of the study. IMID, immune-mediated inflammatory disease.

with seroconversion (p=0.01). SARS-CoV-2 omicron breakthrough infections were detected in 122/336 (36.3%) of patients with IMID on strongly antibody-impairing immunosuppressants as opposed to 350/1257 (27.8%) of patients with IMID on other immunosuppressants (p<0.01). SARS-CoV-2 omicron breakthrough infections were observed more frequently in patients with IMID on S1P modulators compared with other immunosuppressants (table 1).

In 1403/1593 (88.1%) of patients with IMID on immunosuppressants and 490/579 (84.6%) of controls, additional vaccinations were administered. In patients with IMID on immunosuppressants, 387/472 (82.0%) with a SARS-CoV-2 omicron breakthrough infection had received any additional vaccination compared with 1016/1121 (90.6%) without a SARS-CoV-2 omicron breakthrough infection (p<0.01). In controls, 134/181 (74.0%) with a SARS-CoV-2 omicron breakthrough infection had received any additional vaccination compared with 356/398 (89.4%) without a SARS-CoV-2 omicron breakthrough infection (p<0.01). Figure 3 displays the proportion of SARS-CoV-2 omicron breakthrough according to the number of additional vaccines received for the different medication groups. Only in patients with IMID treated with strongly antibody-impairing immunosuppressants, we observed a lower proportion of breakthrough infections in those who had received two additional vaccinations as compared with one additional vaccination.

A total of 344/1593 (21.6%) patients with IMID on immunosuppressants and 158/579 (27.3%) controls had one or more prior SARS-CoV-2 infections. In patients with IMID on immunosuppressants, 78/472 (16.5%) with a SARS-CoV-2 omicron breakthrough infection had a prior SARS-CoV-2 infection compared with 266/1121 (23.7%) without a SARS-CoV-2 omicron breakthrough infection (p<0.01; table 1). In controls, 38/181 (21.1%) with a SARS-CoV-2 omicron breakthrough infection had a prior SARS-CoV-2 infection compared with 120/398 (30.2%) without a SARS-CoV-2 omicron breakthrough infection (p=0.03; table 1).

Figure 4 shows the combined effects of additional vaccination and prior SARS-CoV-2 infections on the cumulative incidence of SARS-CoV-2 omicron breakthrough infections. The cumulative incidence of SARS-CoV-2 omicron breakthrough infections ranged from 72/381 (18.8%) for participants with additional vaccination(s) and prior SARS-CoV-2 infection to 88/158 (55.7%) for participants without additional vaccination and prior SARS-CoV-2 infection. Figure 5 shows the results when combining the potential determinants into a logistic regression model. Reaching seroconversion after primary immunisation, any additional vaccination and a prior SARS-CoV-2 infection were associated with decreased risks for SARS-CoV-2 omicron breakthrough infections while the type of immunosuppressants was not a risk factor.

Disease severity of reported SARS-CoV-2 omicron breakthrough infections

SARS-CoV-2 omicron breakthrough infections were asymptomatic in 6/472 (1.3%) of patients with IMID on immunosuppressants compared with 5/181 (2.8%) in controls, mild symptomatic in 464/472 (98.3%) compared with 175/181 (96.7%) in controls, while hospitalisation was required in 2/472 (0.4%) compared with 1/181 (0.6%) in controls. Four out of 472 (0.8%) patients with IMID on immunosuppressants had been treated with recombinant anti-SARS-CoV-2 monoclonal antibodies during January–March 2022 and were not admitted to the hospital. Of the three hospitalised participants, none required oxygen therapy. The first hospitalised patient with IMID on immunosuppressants was treated with anti-CD20 therapy, did not reach seroconversion after primary immunisation and had received an additional vaccination. The second patient with IMID was treated with corticosteroids, reached seroconversion after primary immunisation and had not received an additional vaccination. The third participant did not use any immunosuppressants, reached seroconversion and had received

Table 1 Baseline characteristics

	Patients with immune-mediated inflammatory disorders on immunsuppressants (n=1593)				Controls (n=579)			
	With SARS-CoV-2 omicron breakthrough infection (n=472)		Without SARS-CoV-2 omicron breakthrough infection (n=1121)		With SARS-CoV-2 omicron breakthrough infection (n=181)		Without SARS-CoV-2 omicron breakthrough infection (n=398)	
Group—no (%)								
Patients with IMID	472	(100)	1121	(100)	126	(70)	292	(73)
Healthy controls	–		–		55	(30)	106	(27)
Patient characteristics								
Age, years—mean (SD)	46	(13)	53	(13)	48	(13)	53	(11)
Female sex—no (%)	317	(67)	675	(60)	128	(71)	261	(66)
Comorbidities—no (%)								
Cardiovascular disease	37	(8)	113	(10)	6	(4)	30	(9)
Chronic pulmonary disease	19	(4)	93	(8)	3	(2)	17	(5)
Diabetes	13	(3)	56	(5)	3	(2)	13	(4)
Obesity	195	(42)	553	(50)	75	(42)	182	(46)
Missing	0	0	0	0	26	(14)	51	(13)
IMID type—no (%)								
Rheumatological diseases	157	(33)	425	(38)	22	(12)	44	(11)
Rheumatoid arthritis	53	(11)	181	(16)	8	(4)	13	(3)
Spondylarthritis	29	(6)	71	(6)	7	(4)	12	(3)
Systemic lupus erythematosus	53	(11)	100	(9)	3	(2)	11	(3)
Other rheumatological*	22	(5)	73	(7)	4	(2)	8	(2)
Neurological†	140	(30)	307	(27)	42	(23)	120	(23)
Gastroenterological‡	127	(27)	246	(22)	22	(12)	68	(17)
Dermatological§	48	(10)	143	(13)	39	(22)	58	(15)
Immunosuppressants—no (%)¶								
Other immunosuppressants	192	(41)	502	(45)	–		–	
MTX	58	(12)	225	(20)	–		–	
TNF-inhibitors	100	(21)	180	(16)	–		–	
Anti-CD20	64	(14)	129	(12)	–		–	
MMF	27	(6)	56	(50)	–		–	
S1P modulator	31	(7)	29	(26)	–		–	
Prior SARS-CoV-2 infection—no (%)								
Any infection prior omicron wave	78	(17)	266	(24)	38	(21)	120	(30)
Two infections prior to omicron wave	1	(0.2)	4	(0.4)	1	(0.6)	3	(0.8)
Additional vaccination prior to SARS-CoV-2 omicron—no (%)								
Any additional vaccination	387	(82)	1016	(91)	134	(74)	356	(89)
Two additional vaccinations	62	(13)	170	(15)	0	0	4	(1)
Available humoral response data after primary vaccination—no (%)	n=431		n=1026		n=158		n=346	
Seroconversion	354	(82)	896	(87)	154	(97)	342	(99)

Table showing baseline characteristics of participants divided into patients with immune-mediated inflammatory disorders on immunosuppressants and controls (patients with immune-mediated inflammatory diseases not on immunosuppressants and healthy controls), with and without a SARS-CoV-2 omicron breakthrough infection.

*Including vasculitis (small-vessel, medium-vessel and large-vessel vasculitis and other forms of vasculitis except giant cell arteritis), other rheumatological (giant-cell arteritis, polymyalgia rheumatica and others).

†Multiple sclerosis and neuromyelitis optica spectrum disorder, Inflammatory neuropathies and myopathies (chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and inflammatory myositis), myasthenia gravis.

‡Crohn's disease, ulcerative colitis, autoimmune hepatitis, other inflammatory bowel disorders (autoimmune hepatitis, autoimmune sclerosing cholangitis).

§Atopic dermatitis, psoriasis, pemphigus, other dermatological (vitiligo, pemphigus, psoriasis and others); e: anti-CD20 therapy, sphingosine-1-phosphate receptor (S1P) modulators and MMF.

¶Therapies are either monotherapy or combination therapy, calculated percentage of total patients with IMID treated with a type of immunosuppressant.

IMID, immune-mediated inflammatory disease; MMF, mycophenolate mofetil; MTX, methotrexate; S1P, sphingosine-1-phosphate receptor; TNF-inhibitor, tumour necrosis factor inhibitor.

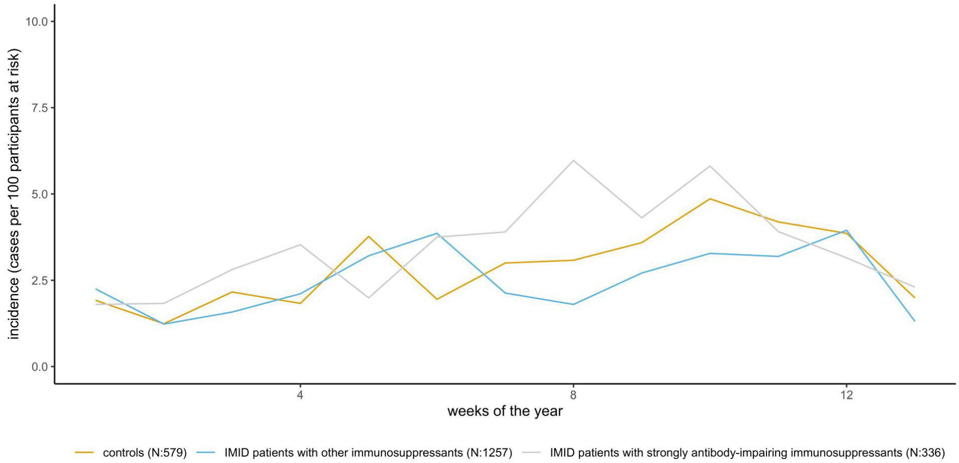

Figure 2 Incidence rates for SARS-CoV-2 omicron breakthrough infections. Figure showing the incidence rates for SARS-CoV-2 omicron breakthrough infections per week of the year for patients with immune-mediated inflammatory disorder (IMID) treated with strongly antibody-impairing immunosuppressants (ie, anti-CD20 (combination) therapy, S1P modulators or MMF (combination) therapy), patients with IMID treated with other immunosuppressants and controls (patients with IMID without immunosuppressants and healthy controls). MMF, mycophenolate mofetil.

an additional vaccination. None of the hospitalised participants had a prior SARS-CoV-2 infection.

DISCUSSION

A cumulative incidence of reported SARS-CoV-2 omicron breakthrough infections of 30% was found that did not differ between patients with IMID on immunosuppressants and controls. Overall disease severity of SARS-CoV-2 infections was mild as hospitalisation was seen in only a few cases and disease severity did not differ between patients with IMID on immunosuppressants and controls. As part of exploratory analyses, we established that the risk of SARS-CoV-2 omicron breakthrough infections was lower in participants with seroconversion after primary immunisation, with additional vaccinations, and with prior SARS-CoV-2 infections.

We found that the incidence of SARS-CoV-2 breakthrough infections with the omicron variant was considerably higher than with the delta variant of SARS-CoV-2, as observed by others and by us.[6 22 23] Disease severity of reported SARS-CoV-2 omicron breakthrough infections was generally mild in line with other studies in healthy controls[22 23] and similar to what we observed earlier for delta breakthrough infections, irrespective of the use of immunosuppressants for patients with IMID.[6 22 24] Others have reported increased disease severity of delta variant breakthrough infections when compared with omicron infections in healthy controls.[4 7] Comparing disease severity between variant strains is challenging, because of the many determinants involved, including differences in risk behaviour and evolving immunological protection induced by repeated vaccinations and/or infections with SARS-CoV-2 leading to an increased proportion of individuals having hybrid immunity which has been shown to be superior to other forms of immunity.[25–28]

Our study focused on possible determinants mitigating the risks of SARS-CoV-2 omicron breakthrough infections in patients with IMID on immunosuppressants. First, we confirm that a poor humoral response after primary immunisation is a risk factor. This is in line with previously found data for delta variant breakthrough infections and observations in

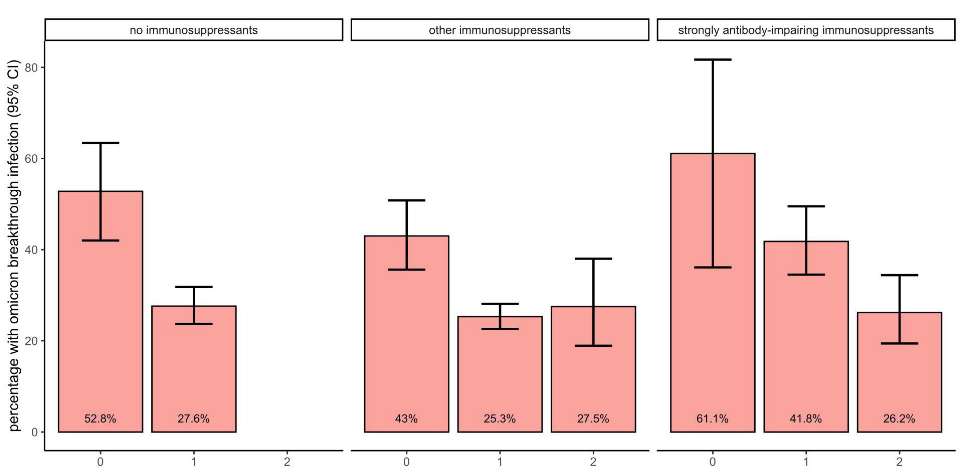

Figure 3 Proportion of SARS-CoV-2 omicron breakthrough infections and number of additional vaccinations received. Figure showing the proportion with 95% CI of SARS-CoV-2 omicron breakthrough infections for patients with immune-mediated inflammatory disorder (IMID) treated with strongly antibody-impairing immunosuppressants (ie, anti-CD20 (combination) therapy, S1P modulators or MMF (combination) therapy), patients with IMID treated with other immunosuppressants and controls (patients with IMID without immunosuppressants and healthy controls) stratified for the number of additional vaccines received. MMF, mycophenolate mofetil.

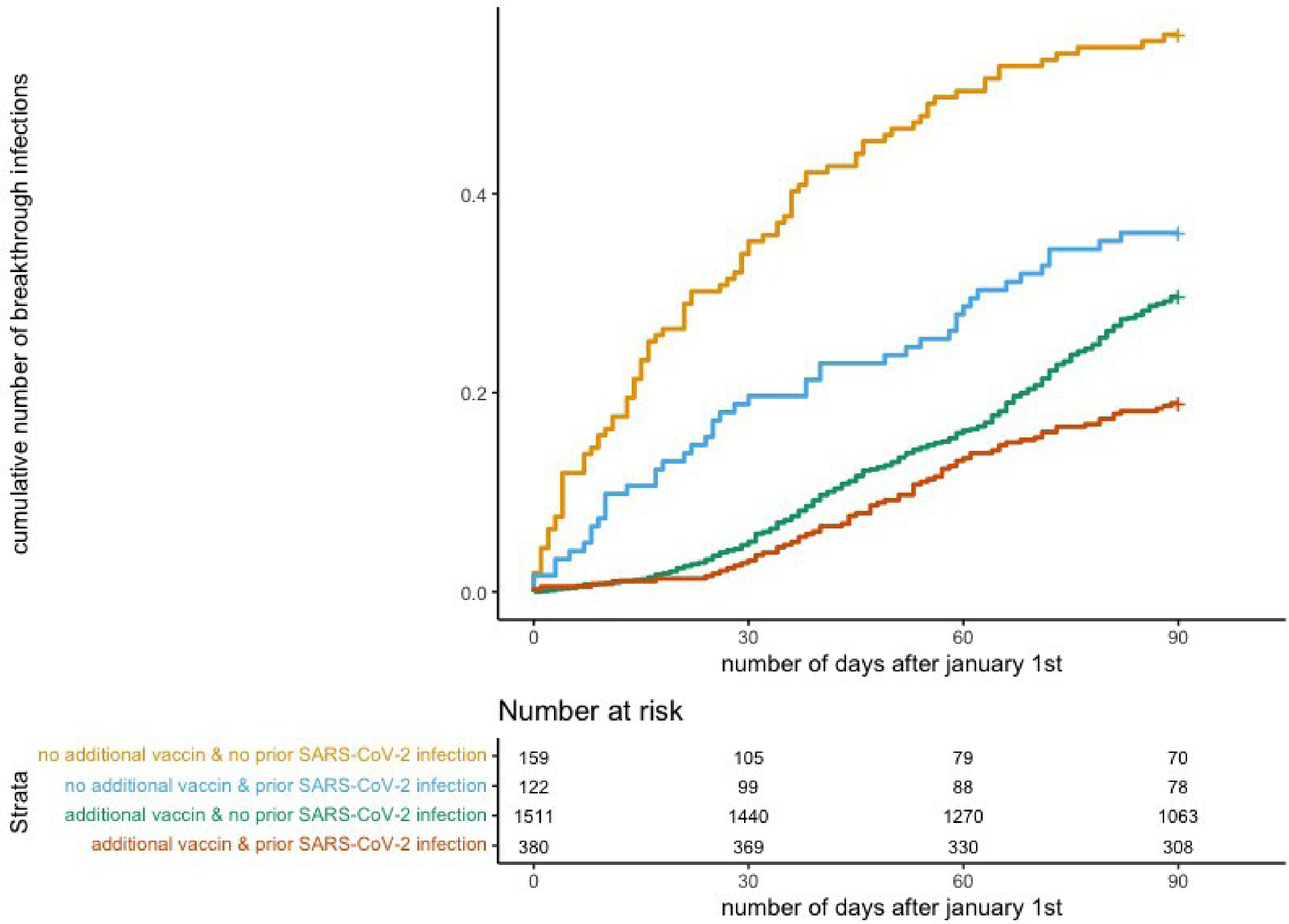

Figure 4 Cumulative event curves for SARS-CoV-2 omicron breakthrough infections. Figure showing the cumulative incidence for SARS-CoV-2 Omicron breakthrough infections stratified for having received an additional vaccination and prior SARS-CoV-2 infection.

other SARS-CoV-2 vaccination trials.[6] Of note, the humoral response after primary immunisation in this analysis should not be interpreted as a direct reflection of humoral immunity at the moment of the omicron breakthrough infections (eg, antibody titres or antibody affinity), but more as an indirect risk factor reflecting an overall decreased (humoral) response after

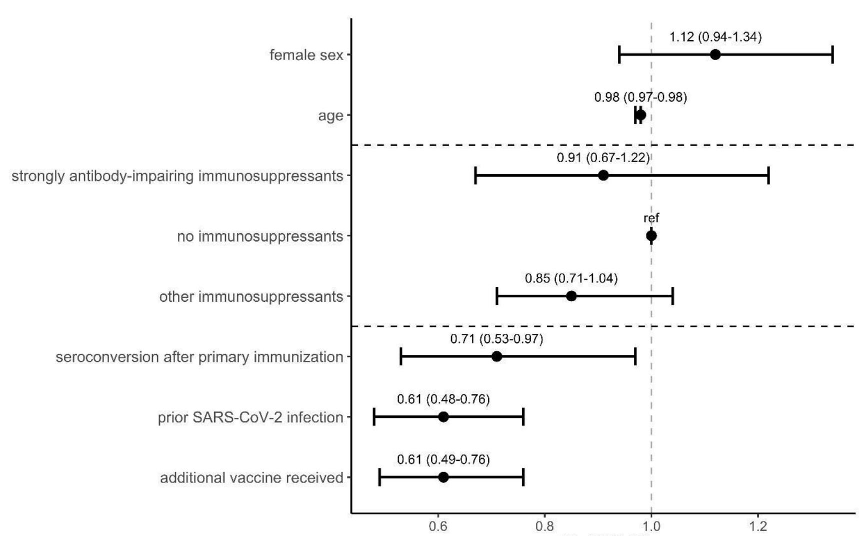

Figure 5 Risk estimates of determinants for SARS-CoV-2 omicron breakthrough infections. Figure showing the estimated relative risks (RR; shown with 95% CI) for SARS-CoV-2 Omicron breakthrough infections for the different determinants. *N: 209 participants excluded because of missing serological data after primary vaccination.

(repeated) vaccination. In many individuals with demonstrated poor humoral responses after primary immunisation, a 'third' or additional vaccination did not increase humoral response rates up to levels seen in the general population.[17] Ongoing decreased immunological responses, despite repeated vaccinations, are a likely cause for the observed increased incidence of breakthrough infections in patients with IMID on strongly antibody-impairing immunosuppressants, like anti-CD20 (combination) therapy, S1P modulators or MMF (combination) therapy, that have previously been shown to greatly impair humoral and (variably) cellular vaccination responses.[16 17 29–31] Second, for the first time we demonstrate in patients with IMID on immunosuppressants that additional vaccinations are associated with decreased risk of SARS-CoV-2 omicron breakthrough infections. This is in line with recent studies in healthy individuals showing that additional vaccinations were either highly effective against infection or disease severity with various SARS-CoV-2 variants.[8–12] Moreover, in patients with IMID treated with strongly antibody-impairing immunosuppressants, two additional vaccinations seem to be better compared with a single additional vaccination whereas this added benefit could not be observed in other groups. Third, similar to our previous results on the delta variant, we found that prior SARS-CoV-2 infections are associated with a decreased risk of new, in this case, omicron SARS-CoV-2 breakthrough infections.[6] Also in other studies, hybrid immunity, as opposed to vaccine responses only, was associated with increased protection against a SARS-CoV-2 breakthrough infections due to an increased breadth of humoral and cellular immune responses.[25 26 28]

Together, these observations suggest that for the majority of patients with IMID on immunosuppressants, immunological protection against severe disease can be achieved through vaccination and previous SARS-CoV-2 infection (or both) and that short-term as well as long-term protective immunological mechanisms are in play despite immunosuppressive treatment. No seroconversion after primary immunisation remains a risk factor, but this is only relevant for a relatively small subgroup of patients with IMID on immunosuppressants. To better understand risk profiles for individual patients with IMID, vaccinations and prior infections should be taken into account besides other known risk factors, like older age and comorbidities as suggested by our previous study in delta breakthrough infections.[6]

A limitation of our study is that we relied on a participant driven test approach to identify SARS-CoV-2 infections and did not employ a test-negative design as has been used in (phase 4) studies on vaccine efficacy. Given the mild disease course in the majority of SARS-CoV-2 omicron breakthrough infections, it is likely that the true rate of infections was higher due to undetected asymptomatic infections. We, therefore, limit our conclusions to reported infections and not all infections as antigen testing was used frequently and studies show a broad variety of sensitivity in symptomatic SARS-CoV-2 cases.[32] However, as this underestimation of the incidence of SARS-CoV-2 infections would occur throughout the cohort and would not have led to a difference between the groups. Also, we were unable to correct for risk behaviour in our analyses. Participants were aware of their SARS-CoV-2 antibody titre after vaccination and could have adapted their behaviour accordingly. In particular patients with IMID with immunosuppressants might be stricter in adhering to the infection preventive measures which could have led to an underestimation of the incidence of SARS-CoV-2 breakthrough infection in this group. Also, we did not analyse the actual humoral immune response after additional vaccination(s) or prior to breakthrough infection. Finally, although our cohort is a broad disease-overarching reflection of IMID, this inherently leads to an under-representation of various other known risk factors for increased incidence or severity of breakthrough infections. Most importantly, our cohort is composed of relatively young participants and consequently the burden of comorbidities, such as diabetes, is low. Age and comorbidities have been identified as important risk factors in many other studies and our results should therefore be interpreted with caution when dealing with older patients with IMID and/or patients with IMID with comorbidities or other known risk factors relevant for (breakthrough) infections.[33] An important strength of this study is the use of a well-characterised ongoing large cohort of participants that has been prospectively studied clinically and serologically from before the start of primary immunisation.

In conclusion, we found that the cumulative incidence of reported SARS-CoV-2 omicron breakthrough infections is relatively high compared with the delta variant, but similar between patients with IMID on immunosuppressants and controls, and that disease severity of SARS-CoV-2 infections was almost exclusively mild. Seroconversion after primary immunisation, additional vaccinations, and prior SARS-CoV-2 infections were associated with decreased risks of SARS-CoV-2 omicron breakthrough infections. Our findings suggest that offering additional vaccinations can be an effective strategy to reduce risks of (future) breakthrough infections also in patients with IMID.

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Patient consent for publication Not applicable.

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