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ABSTRACT

For patients with immune-mediated inflammatory diseases (IMIDs), concerns exist about increased disease activity after vaccination. We aimed to assess changes in disease activity after SARS-CoV-2 vaccination in patients with IMIDs, and determine risk factors for increased disease activity. In this substudy of a prospective observational cohort study (Target-to-B!), we included patients with IMIDs who received a SARS-CoV-2 vaccine. Patients reported changes in disease activity on a five-point Likert scale every 60 days for up to twelve months after first vaccination. In case of self-reported increased activity, hospital records were screened whether the treating physician reported increased activity, and for potential intensification of immunosuppressive (ISP) treatment. Mixed models were used to study determinants for self-reported increased disease activity. In total, 2111 patients were included for analysis after primary immunization (mean age 49.7 years [SD 13.7], 1329/2111 (63.0%) female), from which 1266 patients for analysis after first additional vaccination. Increased disease activity at 60 days after start of primary immunization was reported by 223/2111 (10.6%). In 96/223 (43.0%) the increase was confirmed by the treating physician and in 36/223 (16.1%) ISP treatment was intensified. Increased disease activity at seven to 60 days after additional vaccination, was reported by 139/1266 (11.0%). Vaccinations were not temporally associated with self-reported increased disease activity. Conversely, increased disease activity before first vaccination, neuromuscular disease, and multiple sclerosis were associated. Altogether, self-reported increased disease activity after vaccination against SARS-CoV-2 was recorded in a minority of patients and was generally mild. Moreover, multivariate analyses suggest that disease related factors, but not vaccinations are the major determinants for self-reported increased disease activity.

1. Introduction

Vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is crucial for protection of individuals against infection with (severe) coronavirus disease 2019 (COVID-19), especially in patients with patients with immune-mediated inflammatory diseases (IMIDs) on immunosuppressive (ISP) treatment [1–3]. However, concerns remain whether vaccination can lead to increased disease activity in these patients, as illustrated by a survey in IMID patients before the start of the Dutch SARS-CoV-2 vaccination campaign [4]. This may lead to vaccination hesitancy in some patients despite the importance of (repeated) vaccinations in this group [5].

The available studies so far report that increased disease activity after vaccination is infrequent and usually mild [6–11]. Duration of follow-up differed between studies, most studies focused on single IMID groups, and some assessed disease activity retrospectively or used either patient or physician reported data. To our knowledge, only two studies investigated if a relationship exists between vaccination against SARS-CoV-2 and disease activity in IMID patients [10,11]. Despite the lack of effect from vaccination on disease activity in these two studies, comprehensive data on disease activity after SARS-CoV-2 vaccination from the patient and physician perspective, across a wide range of IMIDs is needed to better understand the safety of vaccination and inform patients.

We aimed to assess changes in disease activity after vaccination against SARS-CoV-2 in a large prospective cohort of different IMIDs, and to explore determinants of increased disease activity in a multidisciplinary approach.

2. Material and methods

2.1. Study design

We performed a substudy within an ongoing national prospective observational multicenter cohort study in patients with prevalent IMIDs with the primary objective to study humoral immune responses after vaccination. The Target-to-B! (T2B!) study was approved by the medical ethical committee (NL74974.018.20 and EudraCT 2021-001102-30) and registered in Dutch Trial Register (Trial ID NL8900). All participants provided signed informed consent. Here we report on a predefined secondary outcome of this cohort study, i.e. disease activity of the IMID after vaccination against SARS-CoV-2. Results on humoral responses after vaccinations, incidence of breakthrough infections, and risk factors for short-term adverse events after vaccination against SARS-CoV-2 have been published before [3,12,13]. A detailed description of the T2B! study protocol, including eligibility criteria, was published earlier [3].

2.2. Setting and participants

The T2B! cohort consists of IMID patients on and not on ISP treatment, and healthy controls. Participants were vaccinated either through the national vaccination campaign or as part of the ongoing study with one or two doses of any of the four different vaccines available in the Netherlands during 2021; BNT162b2 (Pfizer/BioNTech), CX-024414 (Moderna), ChAdOx1nCoV-19 (AstraZeneca) or Ad.26.COV2.S (Janssen) as primary immunization and CX-024414 or BNT162b2 as additional vaccinations (i.e. a third and/or booster vaccinations). In this cohort, primary immunizations ranged from March 1st, 2021 to December 10th, 2021, while additional vaccinations ranged from September 27th, 2021 to July 6th, 2022.

For this substudy, we selected IMID patients who received at least one vaccination as part of primary immunization, and who at least completed the survey at baseline and at 60 days follow-up after start of primary immunization.

2.3. Clinical data collection

Clinical data were collected by the investigators using a standardized electronic case record form (eCRF) and by sending online surveys to participants. A baseline survey was sent at enrollment and registered demographics and whether the participant had experienced increased disease activity in the three months before enrollment. Vaccination data were registered using additional surveys. Follow-up surveys were sent every 60 days after start of primary immunization for up to 12 months. Therefore, the timing of the surveys in relation to a vaccination varied depending on the type of vaccination/vaccination scheme (see Supplemental Fig. 1). In each follow-up survey participants were asked to rate changes in disease activity compared to the previous survey on a five-point Likert-scale.

In case participants reported increased disease activity in the follow-up survey at 60 days after start of primary immunization or at 7–60 days after first additional vaccination, the patient file was reviewed by the investigators to determine whether the treating physician confirmed the reported increased disease activity (physician confirmed), and whether

ISP treatment of the IMID was increased in dosing, frequency, or a new ISP initiated or added, as a consequence of increased disease activity (treatment intensification).

2.4. Outcome definitions

The primary outcome was the incidence of participants with self-reported increased disease activity at 60 days after the start of primary immunization. Self-reported increased disease activity was defined as either "worse" and "much worse" on the Likert scale, decreased disease activity as "better" and "much better", and stable disease activity as "same". Secondary outcomes included the proportion of patients with a physician confirmed increased disease activity, the proportion of patients with a treatment intensification, and the proportion of hospitalized patients as a direct consequence of the increased disease activity, all relating to the episode reported by the patient, as gradation of severity of the self-reported increased disease activity. All of the outcomes above were also analyzed after the first additional vaccination. For the incidence of participants with self-reported increased disease activity after the first additional vaccination, we analyzed surveys that were sent seven to 60 days after vaccination. As we lacked prospective data on disease activity before the first vaccination of the primary immunization, we investigated the temporal relation of self-reported increase after vaccination by comparing increased disease activity reported in follow-up surveys within 60 days after vaccination to follow-up surveys not within 60 days after vaccination. Finally, we explored determinants of increased disease activity.

A SARS-CoV-2 infection before vaccination was defined as either a self-reported positive polymerase chain reaction (PCR), antigen test, a positive SARS-CoV-2 anti-receptor binding domain antibody test at baseline, or a positive anti-nucleocapsid protein antibody test before vaccination. Definitions for ISP, active treatment, and grouping of combination therapies have been described elsewhere [3].

2.5. Statistical analysis

For the primary analysis the incidence of patients with self-reported increased disease activity after primary immunization was calculated with corresponding 95% confidence intervals (95% CI). For the secondary analysis on severity of increased disease activity, we calculated the proportion of patients with physician confirmed increased disease activity, treatment intensification, and hospitalization as a consequence of increased disease activity, from the patients with self-reported increased disease activity. These analyses were performed for disease activity after primary immunization as well as after first additional vaccination. Differences in the incidence of self-reported increased disease activity between IMID diagnoses and vaccines were assessed using the Fisher exact test or Chi-squared test, when appropriate. Differences in incidence of self-reported increased disease activity after primary and first additional vaccination were assessed using McNemar's test. To investigate the temporal relation between vaccination and increased disease activity, and identify determinants of self-reported increased disease activity, we constructed three logistic mixed-effects models to enable analysis of repeated measurements using all completed surveys up to twelve months after first vaccination. In the first univariate mixed model, we assessed the temporal relation between self-reported increased disease activity in a survey and whether or not a participant had been vaccinated in the 60 days preceding that survey. In the second univariate model, we assessed the association between self-reported increased disease activity and IMID diagnosis groups. IMID diagnoses were grouped into neuromuscular disease, multiple sclerosis (MS) and neuromyelitis optica (NMO), gastrointestinal disease, rheumatic disease, and dermatological disease. Gastrointestinal disease was chosen as a reference group, since it reported the least increased disease activity with a reasonable group size. Participants with IMID diagnosis 'other' were excluded for mixed model analyses because of the low number of participants. Lastly, we combined these two determinants in a multivariate model and added other potential determinants being age, sex, body mass index (BMI) [14,15], self-reported increased disease activity in the three months preceding the baseline survey, and use of immunosuppressants (ISP) during primary immunization. Determinants are reported as relative risks (RR) with associated 95% CI. Missing data were assumed to be at random, no data was imputed. Data analysis was performed by two authors (KPJvD and LW) using R version 4.2.1 (R foundation for Statistical Computing, Vienna, Austria).

3. Results

Participants were recruited between February 16th, 2021, and August 1st, 2021. From the 3227 included participants, 2111 patients were eligible for analysis after primary immunization, and data after the first additional vaccination was available in 1266 patients (60%) (Fig. 1). Characteristics of (excluded) participants without completed follow-up survey were similar to the participants included in this analysis (Supplemental Table 1). All participants characteristics are shown in Table 1. The mean age was 49.7 years [SD 13.7], 1329/2111 (63.0%) of patients were females. Most frequent diagnoses were MS and NMO 349/2111 (16.5%), Crohn's disease 309/2111 (14.6%), and rheumatoid arthritis 263/2111 (12.5%). From all patients, 1665/2111 (78.9%) were on ISP, of which 1249/1665 (75.0%) were on monotherapy, and 416/1665 (25.0%) on combination therapy. Most common ISP treatments were tumor necrosis factor alpha inhibitor monotherapy 250/2111 (11.8%), anti-CD20 monotherapy 150/2111 (7.1%), methotrexate monotherapy 142/2111 (6.7%), and purine antagonist monotherapy 130/2111 (6.2%). At enrollment, increased disease activity in the preceding three months was reported by 547/1733 (31.6%) patients. At 60 days after the start of primary immunization, 1848/2111 (87.5%) had received two vaccine doses, and 263/2111 (12.5%) had received one vaccine dose. Median time between first and second vaccine dose was 36 days [IQR 35–42]. After completed primary immunization, 1266/2111 (60.0%) patients received a first additional vaccination and completed a follow-up survey within seven to 60 days thereafter. A SARS-CoV-2 infection before primary immunization was reported by 328/2111 (15.5%) patients. After first additional vaccination, follow-up surveys were completed at a median of 27 days [IQR 16–44]. For the number of completed surveys at different follow-up moments, see Supplemental Fig. 2.

Increased disease activity after primary immunization was reported by 223/2111 (10.6% [95% CI 9.3–11.9]) patients. Decreased disease

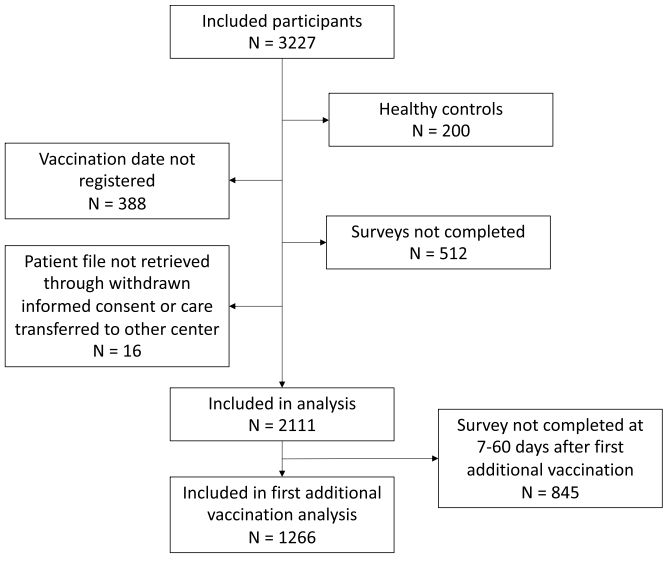

Fig. 1. Study flowchart.

Table 1
Participants characteristics Participant characteristics, by self-reported increased disease activity at 60 days after start of primary immunization.

	Increased disease activity (N = 223)	No increased disease activity (N = 1888)	Overall (N = 2111)
Age			
Years, mean (SD)	49.4 (14.3)	49.8 (13.7)	49.7 (13.7)
Sex, No (%)			
Female	162 (72.6)	1167 (61.8)	1329 (63.0)
Male	61 (27.4)	721 (38.2)	782 (37.0)
BMI, No (%)			
Mean (SD)	25.8 (5.4)	25.5 (5.0)	25.5 (5.1)
IMID diagnosis, No (%)			
Rheumatic disease rowhead			
Rheumatoid arthritis	25 (11.2)	238 (12.6)	263 (12.5)
Spondylarthritis	14 (6.3)	101 (5.4)	115 (5.5)
SLE	10 (4.5)	150 (7.9)	160 (7.6)
Vasculitis	8 (3.6)	61 (3.2)	69 (3.3)
Other rheumatological	3 (1.4)	27 (1.4)	30 (1.4)
Neurological disease			
MS and NMO	37 (16.6)	312 (16.5)	349 (16.5)
Inflammatory neuropathies and myopathies	24 (10.8)	128 (6.8)	152 (7.2)
Myasthenia gravis	25 (11.2)	104 (5.5)	129 (6.1)
Gastro-intestinal disease			
Crohn's disease	29 (13.0)	280 (14.8)	309 (14.6)
Ulcerative colitis	11 (4.9)	156 (8.3)	167 (7.9)
Other IBD	5 (2.2)	35 (1.9)	40 (1.9)
Dermatological disease			
Atopic dermatitis	10 (4.5)	110 (5.8)	120 (5.7)
Other dermatological	21 (9.4)	183 (9.7)	204 (9.7)
Other	1 (0.4)	3 (0.2)	4 (0.2)
ISP treatment, No (%)			
On ISP	170 (76.2)	1495 (79.2)	1665 (78.9)
Monotherapy	124 (72.9)	1125 (75.3)	1249 (75.0)
Combination therapy	46 (27.1)	370 (24.7)	416 (25.0)
Not on ISP	53 (23.8)	393 (20.8)	446 (21.1)
Increased disease activity in three months preceding baseline survey, No (%)[a]			
Yes	94 (51.1)	453 (29.2)	547 (31.6)
No	90 (48.9)	1096 (70.8)	1186 (68.4)
Vaccine in primary immunization, No (%)			
BNT162b2	117 (52.5)	1041 (55.1)	1158 (54.9)
CX-024414	67 (30.0)	610 (32.3)	677 (32.1)
ChAdOx1 nCoV-19	30 (13.5)	171 (9.1)	201 (9.5)
Ad.26.COV2.S	4 (1.8)	44 (2.3)	48 (2.3)
Moderna/Pfizer	5 (2.2)	22 (1.2)	27 (1.3)
Received vaccine doses at 60 days after start primary immunization, No (%)			
One vaccine	32 (14.3)	231 (12.2)	263 (12.5)
Two vaccines	191 (85.7)	1657 (87.8)	1848 (87.5)
Time between vaccines in primary immunization			
Days, median [Q1,Q3]	36.0 [35.0,42.0]	36.0 [35.0,42.0]	36.0 [35.0,42.0]
Time between last vaccination of primary immunization and first additional vaccination			
Days, median [Q1,Q3]	191 [165,205]	187 [159,202]	188 [159,203]
Additional vaccination, No (%)			
One	155 (69.5)	1342 (71.1)	1497 (70.9)
Two	25 (11.2)	268 (14.2)	293 (13.9)
None	43 (19.3)	278 (14.7)	321 (15.2)
SARS-CoV-2 infection before start of primary immunization, No (%)			
Yes	39 (17.5)	289 (15.3)	328 (15.5)
No	184 (82.5)	1599 (84.7)	1783 (84.5)

ISP: immunosuppressant; MS: multiple sclerosis; NMO: neuromyelitis optica; SD: standard deviation; SLE: systemic lupus erythematosus.

[a] Missing for 39/223 (17.5%) of patients with an increase and 339/1888 (18.0%) patients without increase.

activity was reported by 165/2111 (7.8% [95% CI 6.7–9.0]) patients, while stable disease activity was reported by 1723/2111 (81.6% [95% CI 79.9–83.2]) patients. In 96/223 (43.0%) patients the reported increased disease activity was confirmed by the treating physician and in 36/223 (16.1%) patients with self-reported increased disease activity, treatment was adjusted as a consequence. Overall, in 36/2111 (1.7%) of all patients treatment was adjusted. From the patients with self-reported increased disease activity, 3/223 (1.3%) were hospitalized as a consequence of the increase. This concerned three patients with myasthenia gravis, inflammatory neuropathy, and ulcerative colitis. During hospitalization, the patients with myasthenia gravis and inflammatory neuropathy received intravenous immunoglobulins, and the patient with ulcerative colitis received intravenous treatment with prednisolone and cyclosporine. All patients recovered after treatment.

Increased disease activity after first additional vaccination was reported in 139/1266 (11.0% [95% CI 9.4–12.8]) patients. In 42/139 (30.2%) patients the self-reported increased disease activity was confirmed by the treating physician, and in 7/139 (5.0%) patients ISP treatment was adjusted as a consequence. Overall, in 7/1266 (0.6%) of all patients treatment was adjusted, and none were hospitalized as a consequence of the increase.

When categorized per IMID, increased disease activity in 60 days after start of primary immunization was reported in 25/129 (19.4% [95% CI 13.2–27.5]) patients with myasthenia gravis and in 24/151 (15.8% [95% CI 10.6–22.8]) patients with inflammatory neuropathies or myopathies, which was more frequently compared to 174/1830 (9.5% [95% CI 8.2–10.9]) in the other IMID categories combined, $p < 0.001$ and $p = 0.01$, respectively. Participants with myasthenia gravis and inflammatory neuropathies or myopathies, did not report increased disease activity in the three months before enrollment more frequently than other diagnoses (data not shown). In systemic lupus erythematosus, ulcerative colitis and atopic dermatitis self-reported increased disease activity after vaccination was least frequent (Fig. 2). Supplemental Fig. 3 shows the distribution for the different categories of the Likert scale per IMID group. The proportions of self-reported increased disease activity did not differ significantly between vaccines ($p = 0.15$; Supplemental Fig. 4).

In patients with data after both primary immunization and first additional vaccination, 111/1266 (8.8%) reported increased disease activity after primary immunization, which was lower compared to 139/1266 (11.0%) after first additional vaccination ($p = 0.05$). Of the patients with increased disease activity after primary immunization, 31/111 (27.9%) also reported increased disease activity after the first additional vaccination. Treatment was intensified in 1/31 (3.2%) after primary immunization, in 3/31 (9.7%) after first additional vaccination, and in 2/31 (6.5%) both after primary and first additional vaccination as a consequence of the increased disease activity. The percentage of self-reported increased disease activity per follow-up moment is shown in Fig. 3.

In the univariate logistic mixed effect model on self-reported increased disease activity in surveys within 60 days after vaccination compared to surveys at other follow-up moments (not within 60 days after vaccination), a survey within 60 days after vaccination was not associated with self-reported increased disease activity (RR 0.93 [95% CI 0.82–1.06]). In the univariate logistic mixed effect model on self-reported increase in disease activity in any follow-up survey and IMID group, only neuromuscular disease (RR 1.39 [95% CI 1.08–1.81]), and MS and NMO (RR 1.36 [95% CI 1.07–1.74]) were associated with more frequent self-reported increase in disease activity.

In the multivariate logistic mixed effect model on self-reported increased disease activity, self-reported increased disease activity in the three months preceding enrollment (RR 2.22 [95% CI 1.86–2.65]), neuromuscular disease (RR 1.46 [95% CI 1.07–1.99]), and MS and NMO (RR 1.39 [95% CI 1.04–1.87]) were associated with an increased risk on self-reported increased disease activity (Fig. 4). Any SARS-CoV-2 vaccination within 60 days of a survey, age, sex, BMI, other IMID

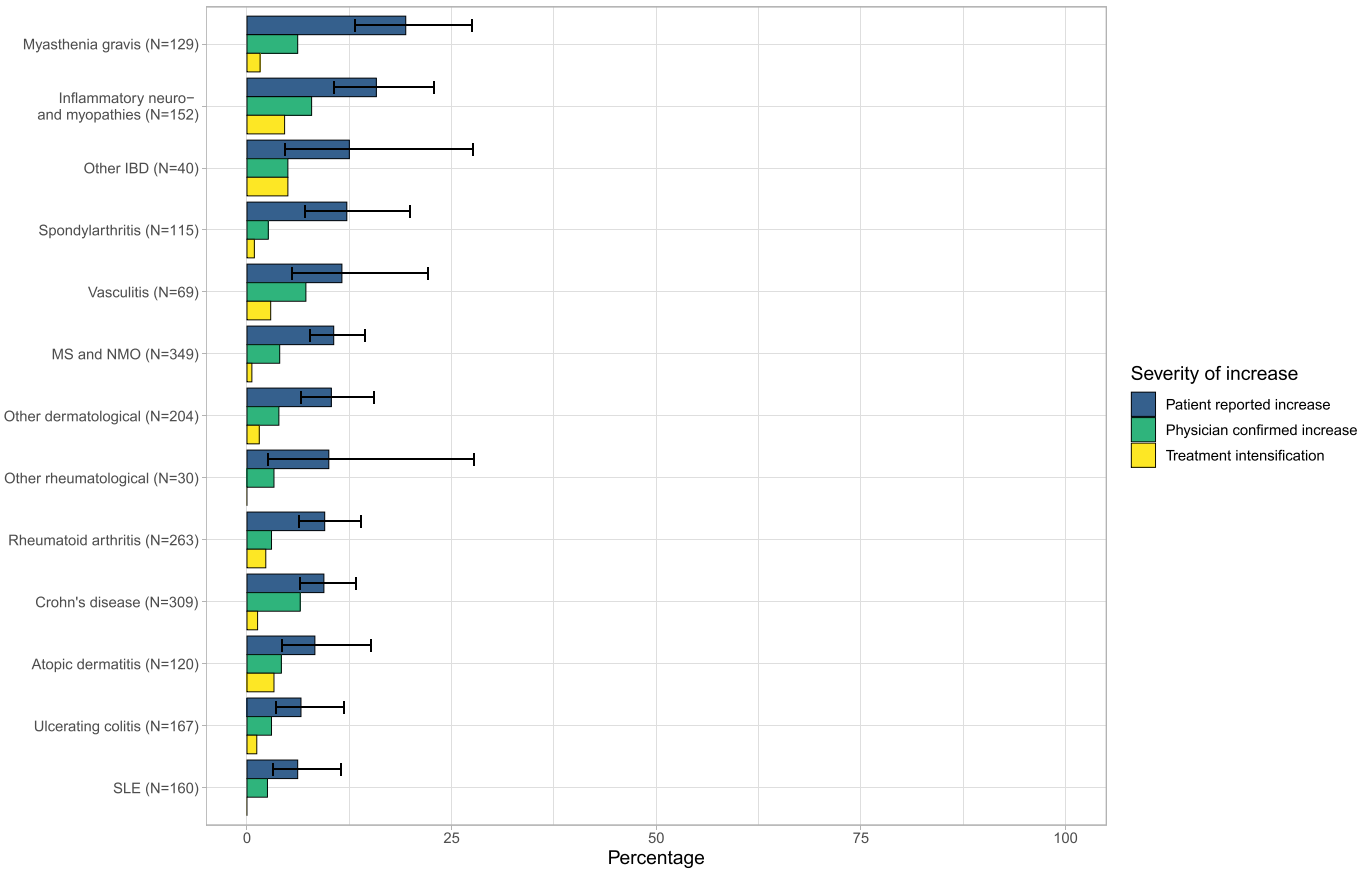

Fig. 2. Increased disease activity per IMID after primary immunization.

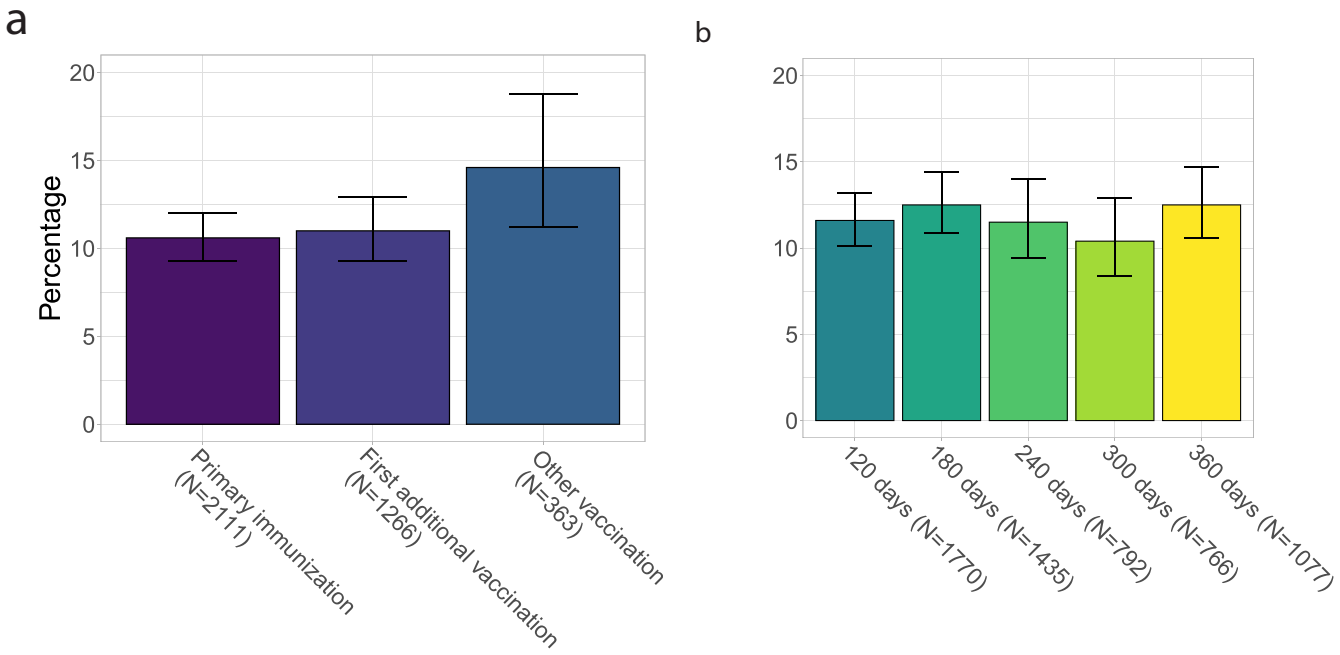

Fig. 3. Self-reported increased disease activity per follow-up moment.

groups, and ISP use were not associated with self-reported increased disease activity.

4. Discussion

We found that increased disease activity after primary immunization and first additional vaccination against SARS-CoV-2 is reported only by

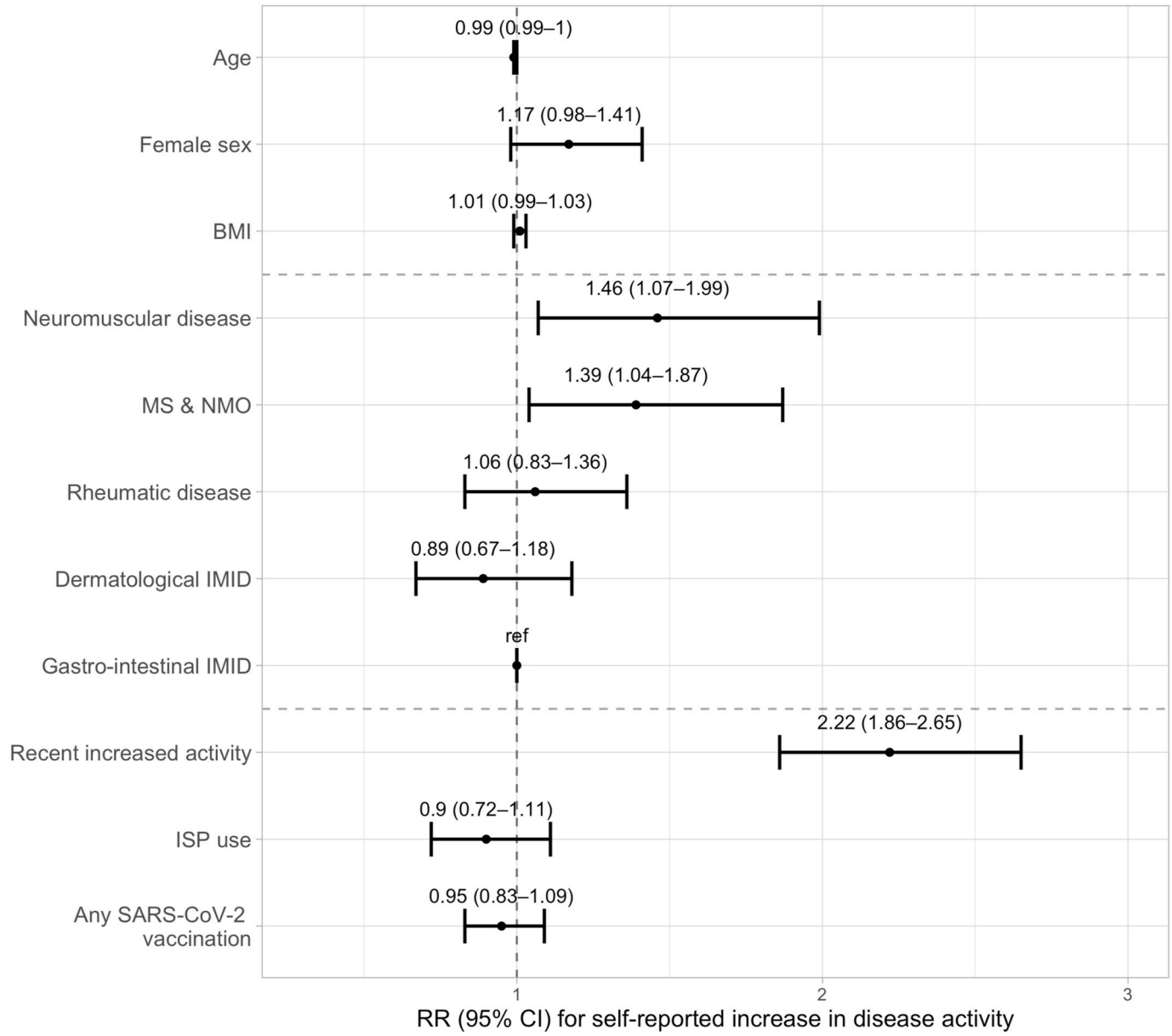

Fig. 4. Determinants of self-reported increased disease activity.

a minority of IMID patients. This self-reported increase was confirmed by the treating physician in almost half of cases, resulting occasionally in treatment intensification, and seldom to hospitalization. Self-reported increased disease activity occurred more frequently in patients with myasthenia gravis, inflammatory neuropathies or myopathies, and MS and NMO. Importantly, we did not observe a temporal relation between any SARS-CoV-2 vaccination and self-reported increased disease activity. Instead, self-perceived disease activity before enrollment in the study was the most important risk factor for reporting increased disease activity after vaccination. These results may be reassuring for IMID patients and their caregivers, and may assist in decision making about (repeated) vaccination against SARS-CoV-2.

Since different IMIDs use different disease activity scores and definitions for disease flares, we used a generic Likert scale to identify self-reported increased disease activity. To assess the severity of the reported increased disease activity, we used a set of proxy variables based on assumptions applicable to all IMIDs. First, we considered that patients would likely report substantially increased disease activity to their physicians. Second, that a clinically significant increase in disease activity would often lead to an intensification of ISP treatment. Third, that severe disease activity would lead to hospitalization for supportive care and/or intensive immunosuppressive treatment. Collectively, with 10.6% of the patients in our cohort reporting increased disease activity after SARS-CoV-2 vaccination, and 1.8% of the total cohort requiring treatment intensification, self-reported increased disease activity was judged to be generally mild.

Yet, increased disease activity after vaccination in general has only been described in case reports and a causal relationship remains to be proven [16]. Therefore, it is important to understand whether the incidence of increased disease activity that we found is related to the vaccinations. Thus, we used our longitudinal data to assess whether there was a temporal relation between SARS-CoV-2 vaccinations and increased disease activity, since a temporal relation is the essential criterium of a causal relationship [17]. In mixed models, we compared the incidence of increased disease activity up to 60 days after any SARS-CoV-2 vaccination and more than 60 days after a vaccination. This window was used assuming that increased disease activity presents in the first two months after vaccination, based on findings in influenza

and measles-rubella-mumps vaccination where a causal relationship was found with Guillain-Barre syndrome and idiopathic thrombocytopenic purpura, respectively [18,19]. Our models did not find a higher risk of self-reported increased disease activity in surveys within 60 days after any SARS-CoV-2 vaccination compared to surveys longer than 60 days after vaccination. Although in theory an effect of vaccination on disease activity could take longer to present, the incidence of self-reported increased disease activity was relatively stable over twelve months, suggesting such a delayed effect did not occur. Nevertheless, the response rate dropped during the study and therefore less data was available for the first additional vaccination group, which could potentially introduce bias into the analyses. One other remaining limitation is that we could not compare increased disease activity in vaccinated patients with unvaccinated patients, and therefore it might be possible that increased disease activity occurred and remained. Nonetheless, the largest risk factor for self-reported increased disease activity at any timepoint was increased disease activity before enrollment, emphasizing the influence of unstable disease before vaccination. Furthermore, neuromuscular disease and MS were other risk factors, which all point towards patient and/or disease characteristics rather than vaccination as determinants for increased disease activity. Still, although we did not find a temporal relation on the group level, we cannot rule out that in some individual patients a relation between vaccination and increased disease activity may exist, as reported elsewhere in case series [20].

In our disease overarching cohort, we could compare disease activity between different IMIDs. Remarkably, in our cohort patients with neuromuscular disease (myasthenia gravis and inflammatory neuro- and myopathies) as well as with MS and NMO reported increased disease activity more frequently than patients with other IMIDs. This finding could be intrinsic to the disease, but to our knowledge, no studies have compared the basal disease activity fluctuation profiles of different IMIDs. Alternatively, in myasthenia gravis patients concerns exist that vaccination might lead to an exacerbation of disease, which has been reported as a reason for vaccine refusal [21]. Likewise, in MS patients the proportion of patients reporting concerns that SARS-CoV-2 vaccination might increase disease activity was higher than in patients with rheumatic diseases [4]. Consequently, these concerns might have attributed to more anxiety in these patients and higher self-reported disease activity. Reassuringly, other studies on patients with neuromuscular disease or MS also found a low incidence of increased disease activity after SARS-CoV-2 vaccination [11,22,23].

In the literature, we only found two studies on the relationship between vaccination against SARS-CoV-2 and disease activity, of which one with a disease overarching, multidisciplinary design. That study involved 623 participants with various IMIDs and contained both vaccinated and unvaccinated participants [10]. More patients with myasthenia gravis were present in the group with increased disease activity compared to the group without increased disease activity. No other diagnoses were associated with a higher incidence of increased disease activity, though this might have been related to the low number of only 42 cases with increased disease activity. Importantly, they found no difference in the incidence of increased disease activity between vaccinated and unvaccinated patients. Likewise, in the other study on the relation between vaccination against SARS-CoV-2 and disease activity involving patients with neuroinflammatory disorders including MS, no difference in new or recurrent neurologic symptoms and radiological disease activity was found between patients with at least one vaccination and unvaccinated patients [11]. Regarding severity of increased disease activity, a large physician-reported registry in Europe on patients with rheumatic diseases found flares after vaccination as reported by the treating physician in 4.4% of patients, whereas treatment intensification was required in only 1.5% of patients, with an average time from first vaccination to case reporting of two months [6]. These findings are largely comparable to the incidences observed in our cohort.

The strengths of our study include the prospective disease-overarching, multidisciplinary design of a large cohort of different IMIDs. This is an important addition to the current literature, as to our knowledge all larger studies on disease activity after vaccination against SARS-CoV-2 focus on a specific group of IMIDs. In addition, by analyzing surveys up to twelve months after start of primary immunization, we were able to assess the temporal relation between vaccination and increased disease activity and evaluate any long-term trends in disease activity.

5. Conclusions

Increased IMID activity after vaccination against SARS-CoV-2 is reported in a minority of patients and is generally mild. ISP treatment was intensified in only 16% of these patients (1.8% of the total cohort). We did not find a temporal relation between any SARS-CoV-2 vaccination and increased disease activity, as increased disease activity was reported at similar rates during the follow-up of the study. Instead, self-reported increased disease activity was associated with perceived unstable (active) disease before vaccination and with neuromuscular diseases. Together, these results can proof reassuring to IMID patients and their treating physicians who are hesitant of SARS-CoV-2 vaccination due to fear of deterioration of the underlying IMID.

Contributors

All authors met the criteria for authorship set by the International Committee of Medical Journal Editors. TR, MS, SK, JKe, AB, and OC performed serological assays; all other authors contributed to data acquisition. PD, LW, SWT, and FE wrote the first draft of the manuscript. PD and LW performed the analyses. LW, PD, MS, ES and LK had full access to and verified the underlying data. All authors helped to revise the manuscript for important intellectual content and had final responsibility for the decision to submit for publication.

Data sharing

After publication, anonymized individual participant data and a data dictionary will be made available upon request to the corresponding author to researchers who provide a methodologically sound proposal. Data will be shared through a secure online platform.

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Declaration of competing interest

F Eftimov and T Kuijpers report (governmental) grants from ZonMw to study immune response after SARS-Cov-2 vaccination in autoimmune diseases. F Eftimov also reports grants from Prinses Beatrix Spierfonds, CSL Behring, Kedrion, Terumo BCT, Grifols, Takeda Pharmaceutical Company, and GBS-CIDP Foundation; consulting fees from UCB Pharma and CSL Behring; honoraria from Grifols. AJ van der Kooi reports grants from CSL Behring and participation on an advisory board for Argen-X. M Löwenberg reports a grant from Galapagos not related to this study, and honoraria from Bristol Myers Squibb, Pfizer, Takeda, and Tillotts. Ph I Spuls is involved in performing clinical trials with many pharmaceutical industries that manufacture drugs used for the treatment of e.g. psoriasis and atopic dermatitis, for which financial compensation is paid to the department/hospital and is a chief investigator of the TREAT NL registry taskforce and SECURE-AD registry. M.W. Bekkenk is a secretary for Dutch Experimental Dermatology Board and

head of the pigmentary disorders group within the Dutch Dermatology Board, and reports honoraria from Pfizer, Sanofi, Novartis and Fondation René Touraine. J Killestein has speaking relationships with Merck Serono, Biogen Idec, TEVA, Sanofi, Genzyme, Roche and Novartis; Amsterdam UMC, location VUmc, MS Center Amsterdam has received financial support for research activities from Merck Serono, Bayer Shcering Pharma, Biogen Idec, GlaxoSmithKline, Roche, Teva, Sanofi, Genzyme, GlaxoSmithKline, and Novartis. B Horváth reports unpaid positions as medical advisor for several patient groups, a board position for ERN-SKIN, and associate editor for The British Journal of Dermatology; reports grants from Abbvie, Akari Therapeutics, Celgene, and Novartis; consulting fees from UCB Pharma, Novartis and Janssen-Cilag; honoraria from Abbvie. J.J.G.M. Verschuuren reports consulting fees from Argenx, Alexion and NMD Pharma; is coinventor on patent applications based on MuSK-related research. DJ Hijnen reports grants from Abbvie, AstraZeneca, Janssen, LEO Pharma and UCB Pharma, and honoraria from Abbvie, Galderma, Janssen, Lilly, Pfizer, Sanofi and UCB Pharma, and a paid position in an advisory board for BIOMAP IMI. P.A. van Doorn participated on an advisory board for Octapharma. P. van Paassen reports grants from Alexion Pharma and GSK; and participation on GSK and Vifor Pharma advisory boards. G.R.A.M. D'Haens reports consulting fees from Abbvie, Agomab, AstraZeneca, AM Pharma, AMT, Arena Pharmaceuticals, Bristol Meiers Squibb, Boehringer Ingelheim, Celltrion, Eli Lilly, Exeliom Biosciences, Exo Biologics, Galapagos, Index Pharmaceuticals, Kaleido, Roche, Gilead, Glaxo Smith Kline, Gossamerbio, Pfizer, Immunic, Johnson and Johnson, Origo, Polpharma, Procise Diagnostics, Prometheus laboratories, Prometheus Biosciences, Progenity, and Protagonist; honoraria from Abbvie, Arena, Galapagos, Gilead, Pfizer, BMS, Takeda; participation on advisory boards for Abbvie, Seres Health, Galapagos, and AstraZeneca. R.B. Takkenberg reports honoraria from Sobi and Norgine and participation in an advisory board for Norgine. SH Goedee is a board member of the Dutch Society of Clinical Neurophysiology (unpaid), reports grants from Prinses Beatrix Spierfonds, and received speaker fees from Shire/Takeda. AH Zwinderman reports paid data safety monitoring board positions for Torrent Ltd and Foresee Pharmaceuticals Co. No other disclosures were reported.

Bar plot showing proportions of self-reported increased disease activity (with corresponding 95% CI's), physician confirmed increased disease activity, and treatment intensification, within each IMID group at 60 days after start of primary immunization.

IBD: inflammatory bowel disease; IMID: immune-mediated inflammatory disease; ISP: immunosuppressant; MS: multiple sclerosis; NMO: neuromyelitis optica; SLE: systemic lupus erythematosus.

Bar plot showing incidence of self-reported increased disease activity at different timepoints. A) self-reported increased disease activity within 60 days after vaccination: at 60 days after start of primary immunization (prim. imm.), seven to 60 days after first additional vaccination (add. vacc.), and at other follow-up moments within seven to 60 days after a vaccination other than the moments mentioned before (e.g. second vaccination of primary immunization or second additional vaccination). B) self-reported increased disease activity not within 60 days after vaccination, in the two-monthly follow-up surveys starting at first vaccination.

Figure showing the results of the multivariate mixed model on determinants of self-reported increased disease activity. RR's with corresponding 95% CI for age, female sex, BMI, IMID group (with gastrointestinal disease as reference group), recent increased disease activity (self-reported increased disease activity in the three months preceding enrollment), ISP use, and any SARS-CoV-2 vaccination in 60 days before the survey.

BMI: body mass index; CI: confidence interval; IMID: immune-mediated inflammatory disease; ISP: immunosuppressant; MS: multiple sclerosis; NMO: neuromyelitis optica; RR: relative risk; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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