CLINICAL SCIENCE

Efficacy and safety of SARS-CoV-2 revaccination in non-responders with immune-mediated inflammatory disease

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Handling editor Johannes WJ Bijlsma

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2021-221554).

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Received 22 September 2021
Accepted 19 October 2021

To cite: Simon D, Tascilar K, Fagni F, *et al*. *Ann Rheum Dis* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/annrheumdis-2021-221554

ABSTRACT

Objectives To test whether patients with immune-mediated inflammatory disease (IMIDs), who did not respond to two doses of the SARS-CoV-2 vaccine, develop protective immunity, if a third vaccine dose is administered.

Methods Patients with IMID who failed to seroconvert after two doses of SARS-CoV-2 vaccine were subjected to a third vaccination with either mRNA or vector-based vaccines. Anti-SARS-CoV-2 IgG, neutralising activity and T cell responses were assessed at baseline and 3 weeks after revaccination and also evaluated seprarately in rituximab (RTX) and non-RTX exposed patients.

Results 66 non-responders were recruited, 33 treated with RTX, and 33 non-exposed to RTX. Overall, 49.2% patients seroconverted and 50.0% developed neutralising antibody activity. Seroconversion (78.8% vs 18.2%) and neutralising activity (80.0% vs 21.9%) was higher in non-RTX than RTX-treated patients with IMID, respectively. Humoral vaccination responses were not different among patients showing positive (59.3%) or negative (49.7%) T cell responses at baseline. Patients remaining on mRNA-based vaccines showed similar vaccination responses compared with those switching to vector-based vaccines.

Conclusions Overall, these data strongly argue in favor of a third vaccination in patients with IMID lacking response to standard vaccination irrespective of their B cell status.

Key messages

What is already known about this subject?

► While it is known that SARS-CoV-2 vaccination achieves protective immunity in the majority of patients with immune-mediated inflammatory diseases, it is currently unknown whether patients not achieving protective immunity while profit from revaccination .

What does this study add?

► The study shows that revaccination of non-responders is effective and safe. The vast majority of non-responder patients that have not experienced previous treatment with B cell depleting agents seroconvert and mount protective immunity after SARS-CoV-2 revaccination, while responses are substantially lower in patients pre-exposed to B cell depleting agents. Vaccination responses are achieved in patients with homologous (mRNA-mRNA) as well as heterologous (mRNA-vector) revaccination.

How might this impact on clinical practice or future developments?

► These data suggest that fast SARS-CoV-2 revaccination should be considered in patients with immune mediated inflammatory diseases that did not achieve protective immunity after two SARS-CoV-2 vaccinations.

INTRODUCTION

Patients with immune-mediated inflammatory diseases (IMIDs) are a vulnerable population during the COVID-19 pandemic.[1] Patients with IMID in general[2] and particularly those treated with methotrexate,[3] mycophenolate, glucocorticoids, abatacept[4] and with an even greater magnitude, those receiving B cell depleting agents[5] show reduced humoral immune responses to anti-SARS-CoV-2 vaccination. Hence, since a considerable fraction of patients with IMID experiences insufficient vaccination responses, alternative SARS-CoV-2 vaccination strategies need to be considered, that is, the fast re-exposure of patients that did not respond to double vaccination in order to achieve sufficient protection in this vulnerable patient group. Based on these observations and since antibody responses to SARS-CoV-2 vaccines decline even in healthy individuals,[6] public health authorities such as the US Food and Drug Administration advocate for booster SARS-CoV-2 vaccination for immunocompromised individuals.

Current data on the efficacy and safety of revaccination of non-responder patients with IMID are limited to two case reports[7 8] suggesting that such a strategy may work. The success of revaccination may depend on a functional adaptive immune system, which is particularly blunted in patients that have received B cell depleting agents (rituximab, RTX). A preprint of a study investigating the response to SARS-CoV-2 revaccination in patients exposed RTX showed that

a limited number of patients (27%) manage to seroconvert with no difference whether they switched from an mRNA to a vector, based vaccine or whether they stayed on an mRNA-based vaccine.[9] Whether and how patients with IMID who are not exposed to RTX but failed to achieve response to SARS-CoV-2 vaccination will respond to revaccination is currently unclear. Furthermore, recent studies in healthy individuals indicated better response to heterologous vector/mRNA vaccination regimens compared with homologous mRNA/mRNA or vector/vector regimens[10–13] which brings about the question as to whether a switch of vaccination strategy should be considered in non-responders.

We, therefore, prospectively recruited patients with IMID (both RTX exposed and non-exposed) that did not respond to two doses of the SARS-CoV-2 vaccine to evaluate the humoral and cellular immune response after homologous or heterologous anti-SARS-CoV-2 revaccination.

METHODS

Participants

This prospective study included patients with IMID (only rheumatic diseases) who failed to develop SARS-CoV-2 spike protein antibodies (OD450nm<1.1 in the Euroimmun anti-SARS-CoV-2 spike S1 protein ELISA) at least 4 weeks after the full vaccination with the mRNA vaccine BNT162b2 (Pfizer/Biontech) or the vector vaccine ChAdOx1 (AstraZeneca). Patients with a history of SARS-CoV-2-specific antibodies or PCR-confirmed SARS-CoV-2 infection before vaccination were excluded. All patients remained under stable treatment throughout the whole study period. The IMID non-responders were recruited from a large longitudinal COVID-19 study at the Deutsche Zentrum Immuntherapie that has been initiated in February 2020 and monitors anti-SARS-CoV-2 antibody responses over time.[14] Demographic, disease-specific and vaccination data were recorded in all participants.

Table 1 Baseline demographics and clinical characteristics of patients with IMID

	Overall	Non-RTX	RTX
N	66	33	33
Age, years, mean (SD)	63.3 (14.0)	63.9 (14.1)	62.8 (14.0)
Gender, N (%)			
Male	26 (39.4)	13 (39.4)	13 (39.4)
Female	40 (60.6)	20 (60.6)	20 (60.6)
BMI, mean (SD)	26.4 (6.6)	26.1 (4.1)	26.7 (8.0)
Diagnosis, N (%)			
Rheumatoid arthritis	30 (45.5)	17 (51.5)	13 (39.4)
Spondyloarthritis*	4 (6.1)	4 (12.1)	0
Connective tissue disease	13 (19.7)	5 (15.2)	8 (24.2)
Others	5 (7.6)	3 (9.1)	2 (6.1)
Systemic vasculitis	14 (21.2)	4 (12.1)	10 (30.3)
Comorbidities, N (%)			
Diabetes	9 (13.6)	4 (12.1)	5 (15.2)
Hypertension	25 (37.9)	16 (48.5)	9 (27.3)
Ischaemic heart disease	4 (6.1)	2 (6.1)	2 (6.1)
Cancer	6 (9.1)	3 (9.1)	3 (9.1)
Lung disease	11 (16.7)	3 (9.1)	8 (24.2)
Treatment, N (%)			
Tumour necrosis factor-alpha	5 (7.6)	5 (15.2)	0
Interleukin-17	2 (3.0)	2 (6.1)	0
Interleukin –6	1 (1.5)	1 (3.0)	0
Interleukin –1	1 (1.5)	1 (3.0)	0
CD-20	33 (50.0)	0	33 (100.0)
CD80/86	5 (7.6)	3 (9.1)	2 (6.1)
Integrin α4β7	1 (1.5)	1 (3.0)	0
JAKi	7 (21.2)	7 (21.2)	0
csDMARD	22 (33.3)	17 (51.5)	5 (15.2)
Glucocorticoids	30 (45.5)	14 (42.4)	16 (48.5)
Vaccination, N (%)			
Primary mRNA vaccine	58 (87.9)	29 (87.9)	29 (87.9)
Primary vector vaccine	8 (12.1)	4 (12.1)	4 (12.1)
Timing, median (IQR)			
Days to second vaccination	42 (22.5–42)	41.5 (23–42)	42 (22–42)
Days to third vaccination after second vaccination	83 (55–112)	93 (64–128)	69 (47–95)
Days to sampling after third vaccination	20 (15.5–28)	20.5 (15–28)	20 (17–27)

*Including psoriatic arthritis.
BMI, body mass index; csDMARD, conventional synthetic disease modifying anti-rheumatic drugs; IMID, immune-mediated inflammatory disease; JAKi, Janus kinase inhibitors; RTX, rituximab.

Table 2 Humoral and cellular immune responses before and after revaccination

	All			Non-RTX		RTX		
	N=66			N=33		N=33		
	Before	After	P value*	Before	After	Before	After	P value†
Seroconversion (anti-Spike S1 IgG)								
Negative, N (%)	66 (100)	33 (50.8)	<0.0001	33 (100)	6 (18.7)	33 (100)	27 (81.8)	<0.0001
Positive, N (%)	0 (0)	32 (49.2)		0 (0)	26 (78.8)	0 (0)	6 (18.2)	
Missing, N	0	1		0	1	0	0	
Neutralising capacity								
Negative, N (%)	50 (89.3)	31 (50.0)	<0.0001	24 (80.0)	6 (20.0)	26 (100)	25 (78.1)	<0.0001
Positive, N (%)	6 (10.7)	31 (50.0)		6 (20.0)	24 (80.0)	0 (0)	7 (21.9)	
Missing, N	10	4		3	3	7	1	
Anti-spike S1 IFN-gamma								
Negative, N (%)	22 (40.7)	16 (26.7)	0.08	12 (54.5)	12 (40.0)	10 (31.2)	4 (13.3)	0.039
Positive, N (%)	32 (59.3)	44 (73.3)		10 (45.5)	18 (60.0)	22 (68.8)	26 (86.7)	
Missing, N	12	6		11	3	1	3	

The number of patients with non-missing data constitute the denominator in all cross-tabulations.
*McNemar test for paired categorical data before and after third vaccination.
†Fisher exact test comparing proportions after third vaccination.
IFN, interferon ; RTX, rituximab.

Procedure

Patients received either BNT162b2 or ChAdOx1 nCoV-19 vaccine. The vaccination centre of the city of Erlangen provided the vaccines for this study free of charge through the Central Pharmacy of the University Hospital of Erlangen. IgG antibodies were tested by a commercial ELISA (Euroimmun, Lübeck, Germany) with a cut-off OD450nm of 1.1. For neutralisation activity, a CE-In Vitro Diagnostics-certified SARS-CoV-2 surrogate virus neutralisation assay (cPASS, Medac, Wedel, Germany) was used with a cut-off of 30% inhibition. The detection of SARS-CoV-2 specific T-cells was conducted via an IFN-γ ELISpot Assay (T-SPOT.COVID, Oxford Immunotec), a response was considered positive when the number of spots was ≥8 spot forming units (SFUs) above the negative control. A detailed description of laboratory assessments is provided in online supplemental file. IgG antibodies, neutralising capacity and T-cells responses were measured before and 3 weeks after the revaccination.

Statistical analysis

We summarised participant characteristics using means, SDs, quantiles or proportions as appropriate. We used McNemar's test to compare paired categorical observations and Fisher's exact test to compare proportions. To compare the proportion of patients with a humoral response after the third vaccination by categories of T-cell response before the third dose we used the Cochran-Mantel-Haenszel test in order to account for a possible differential effect caused by RTX treatment. Two-sided p values less than 0.05 were considered significant without adjustment for multiple testing. Missing data were assumed to be missing completely at random and not imputed.

Patient and public involvement

The study was primarily motivated by frequent inquiries from patients with IMID on the subject matter but undertaken without any direct public involvement.

RESULTS

Patient characteristics

Sixty-six patients with IMID were included, 33 of whom were exposed to RTX. Most patients had rheumatoid arthritis (45.5%), followed by systemic vasculitis (21.2%) and connective tissue disease (19.7%). Fifty-eight patients had been fully immunised with two doses of mRNA vaccine BNT162b2, the remaining eight patients had been fully immunised with the vector vaccine. Patients receiving RTX had received a median (IQR) of 7 (4–7.5) cycles and the last treatment cycle had been given a median (IQR) of 4.5 (3–8) months before the third vaccination. The median (IQR) CD19 cell count in the RTX-treated patients was 0/mm^3 (range 0–68). Details of demographics and clinical characteristics of patients are depicted in table 1.

Humoral immune response to revaccination

After revaccination, 32/65 patients (49.2%) seroconverted and developed positive anti-SARS-CoV-2 IgG antibodies (p<0.0001 compared with baseline). This increase was largely driven by the non-RTX pretreated group, in which 26/33 (78.8%) patients achieved seroconversion, while in the RTX pretreated group, only 6/33 (18.2%) patients responded (p<0.0001, table 2). Neutralising antibodies were present in 31/62 patients (50%) after the third vaccination (p<0.0001 compared with baseline). 24/30 (80.0%) of patients in the non-RTX pretreated group had neutralising antibodies compared with only 7/32 (21.9%) among patients pretreated with RTX (p<0.0001). The time course of antibody and neutralising activity levels are depicted in figure 1. The correlation between the time from last RTX administration and antibody response was low (Spearman's r=0.31, p=0.093).

Cellular immune response to revaccination

A T-cell response was present in 59.3% of all patients at baseline. After revaccination, this overall increased to 73.3% (p=0.08) (table 2). The prevalence of T-cell responses was higher in RTX-pretreated patients before the third vaccination (68.8%) and significantly (p=0.0039) thereafter (86.7%). The increasing proportion of T-cell response after the third dose was largely attributable to RTX-treated patients. T cell responses to SARS-CoV-2 at baseline were not associated with subsequent antibody

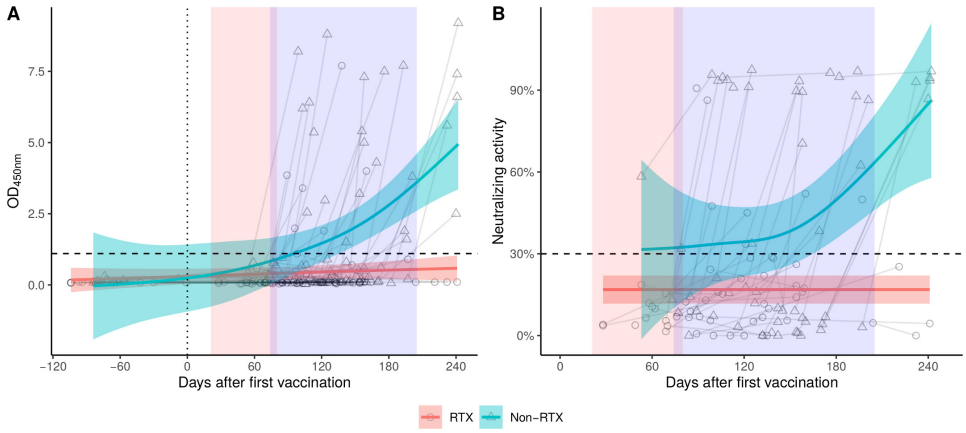

Figure 1 The time course of humoral response to revaccination showing optical densities corresponding to SARS-Cov2 S1 IgG antibody levels (A) and per cent neutralising activity (B). Red and blue shaded areas indicate the respective periods during which second and third vaccinations were administered. Horizontal dotted lines indicate the corresponding cut-off values for the antibody and neutralisation assays. Curves with 95% confidence bands indicate the mean values over time for rituximab (RTX, red) and non-RTX (non-RTX, turquoise) groups.

development (p=0.08 by Cochran-Mantel-Haenszel test stratified by RTX use, online supplemental table 1).

Comparison of homologous and heterologous vaccination strategies

When separately analysing the seroconversion rates in patients receiving homologous (mRNA-mRNA) versus heterologous vaccinations, we did not find significant differences between the two strategies (homologous: 40% seroconversion, heterologous: 55% seroconversion) (online supplemental table 2). Also, concerning neutralising capacities (40% vs 56.8%) and T cell responses (65.2% vs 78.4%) no differences between the two vaccination strategies were found.

Safety of revaccination in non-responders

Analysis of the tolerability of SARS-CoV-2 revaccination showed good safety. Overall 38/66 (58%) participants reported no side effects. The most frequently reported complaints were fatigue (25.8%), pain at the injection site (22.7%), headache (10.6%) and myalgia (9.1%) (online supplemental table 3).

DISCUSSION

Our data show that revaccination is highly effective to mount humoral immune responses in patients with IMID that have previously not responded to double vaccination. These data are important and reassuring for patients with IMID, as previous data have shown that vaccination responses are blunted and one out of 10 patients with IMID does not develop neutralising antibodies after the first and second SARS-CoV-2 vaccination.[2] About half of the patients profited from a revaccination, with seroconversion, the presence of neutralising activity and enhanced T cell responses. Importantly these data do not reflect a 'booster' effect, meaning revaccination of individuals that have responded to first and second vaccination, but gradually lost their immune response later on. These data exclusively refer to patients that failed to develop humoral immunity to first and second vaccination.

The efficacy of revaccination in non-responders was primarily dependent on whether patients received previous RTX. Hence, seroconversion rates were limited in RTX-treated non-responders (20%) while they were high (80%) in patients not exposed to RTX indicating that revaccination in B cell competent non-responders is highly effective. Similar results were observed for neutralising antibody activity. Notably, T cell responses were not influenced by RTX, as the vast majority (86%) of RTX-treated patients developed T cell immunity against SARS-CoV-2 after revaccination. The enhanced T cell responses in RTX exposed participants could be based on the known suppressive function of regulatory B cells on T cells, which is resolved on B cell depletion.[15] To date, a protective effect of SARS-CoV-2 specific T cells has not been conclusively shown, however, there is no reason to believe that such T cells response would not contribute to viral defence .Of note, SARS-CoV-2-specific T cell responses have shown to cross-react across SARS-CoV-2 strains further supporting their protective role.[16]

We also had the opportunity to study the vaccination regimen. Thus, re-exposure to mRNA vaccine in patients not responding to full vaccination with an mRNA vaccine was as effective as the switch to vector-based vaccines. These data suggest that there is no need to switch the vaccine regimen in non-responders, as the third dose of the same vaccine still allows significant seroconversion and neutralising activity.

Taken together, these data show that patients with IMID not responding to SARS-CoV-2 vaccination profit from revaccination and mount significant protective immunity. These findings also underline the importance of testing of SARS-CoV-2 antibody status in vaccinated patients with IMID in order to identify those with insufficient responses requiring revaccination. Since about 10% of patients with IMID do not adequately respond to full vaccination,[2] antibody testing in patients with IMID seems reasonable if done done at least 14 days after the second vaccine dose. Monitoring of vaccination responses to identify non-responders and their subsequent rapid re-exposure to a third vaccine dose might therefore help to achieve better protection of patients with IMID from SARS-CoV-2 infection.

Contributors Study design: DS, KT, BM, GK and GS. Sample collection: DS, AK, AR, VS, DB, JK and KM. Experiments and data analysis: DS, KT, KS, FF, KT and TH. Data interpretation: DS, KT, FF and GS. Writing of the manuscript: DS, KT, FF and GS. Critical proof reading of the manuscript: all authors. GS accepts full responsibility for the work and/or the conduct of the study, had access to the data and controlled the decision to publish.

Funding The study was supported by the Deutsche Forschungsgemeinschaft (DFG-FOR2886 PANDORA and the CRC1181 Checkpoints for Resolution of Inflammation). Additional funding was received by the Bundesministerium für Bildung und Forschung (BMBF; project MASCARA), the ERC Synergy grant 4D Nanoscope, the IMI funded project RTCure, the Emerging Fields Initiative MIRACLE of the Friedrich-Alexander-Universität Erlangen-Nürnberg, and the Else Kröner-Memorial Scholarship (DS, no. 2019_EKMS.27). KS was supported by the Hector foundation (project M2102).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Ethical approval (#157_20 B) to conduct this study was granted by the Institutional Review Board of the University Hospital Erlangen. Written informed consent was obtained from the study participants.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

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Supplementary Material

Methods

Measurements of IgG antibodies

IgG antibodies against the S1 domain of the spike protein of SARS-CoV-2 were tested by the CE version (April 2020) of the commercial ELISA from Euroimmun (Lübeck, Germany) using the EUROIMMUN Analyzer I platform and according to the manufacturers protocol. All analyses were done in duplicates. Optical density (OD) was determined at 450 nm with reference wavelength at 630 nm. A cut-off of ≥1.1 (OD 450 nm) was considered as positive.

Neutralization activity test

To assess neutralization activity of the antibodies, a CE-In Vitro Diagnostics (CE-IVD)-certified SARS-CoV-2 surrogate virus neutralization assay (cPASS, Medac,Wedel, Germany) was used. This assay measures the potential of antibodies to inhibit the binding of a labeled SARS-CoV-2 receptor-binding domain (RBD) to coated angiotensin-converting enzyme-2 (ACE2). A cut-off of 30% inhibition was considered as positive, according to the manufacture's protocol.

SARS-CoV-2 specific T-cell assessment

The detection of SARS-CoV-2 specific T-cells was conducted via a IFN- γ ELISpot Assay (T-SPOT.COVID, Oxford Immunotec). Isolation of peripheral blood mononuclear cells (PBMCs) was carried out via density gradient centrifugation. Leucosep™tubes (Greiner Bio One GmbH, Frickenhausen, Germany) were filled with 15ml Lymphoflot (Bio-Rad Laboratories GmbH, Feldkirchen, Germany) and centrifuged briefly to collect the fluid under the membrane. A maximum of 30ml citrate blood was transferred to the tube and filled up to 50ml with RPMI 1640 medium (Gibco, Carlsbad, California, United States) pre-warmed to 37°C. Cells were centrifuged at 760xg for 20min and the upper layer containing PBMCs was transferred to 50ml tubes and centrifuged at 610xg for 10min. The cell pellet was then washed with 30ml 37°C-warm RPMI 1640 medium at 610xg for 10min prior to re-suspension at a concentration of 2.5x106/ml in AIM-V medium (Gibco, Carlsbad, California, United States) pre-warmed to 37°C. 50µl of either AIM-V medium, Panel A, Panel B or Positive Control were added to the wells of the pre-coated multititer ELISpot plate (Oxford Immunotec). 100µl of the cell suspension was added to each well and carefully mixed by pipetting. After an incubation period at 37°C and 7% CO2 for 16-20h, the wells were washed four times with 200µl PBS (Gibco, Carlsbad, California, United States). The conjugate reagent was diluted 1:200 in PBS and 50µl of this dilution was added to each well. Following a 60min incubation period at 4°C, the wells were washed four times with 200µl PBS. 50µl substrate solution was added to each well and incubated for 7min. The plate was washed three times with H2O and then air-dried. The spots were

counted and analyzed using an ELISpot reader (AID, Strassberg, Germany). Results are reported as SFUs (Spot forming units) per 2.5x105 cells. According to the manufacturer's guidelines, a response was considered positive when the number of spots in the respective panel was ≥ 8 SFUs above the negative control. Samples with negative controls > 10 SFUs were considered invalid.

Supplementary Table 1.

Association between baseline T cell response and seroconversion in non-responding IMID patients

	SARS-CoV-2 T cell response before re-vaccination	**IgG seroconversion after re-vaccination**	
Non-RTX		Negative	Positive
	Negative (N)	2	10
	Positive (N)	2	8
RTX		Negative	Positive
	Negative (N)	6	4
	Positive (N)	20	2

Supplementary Table 2

Humoral and cellular response after homologous and heterologous re-vaccination

	Overall		**Homologous Re-vaccination**		**Heterologous Re-vaccination**	
	N=66		N=26		N=40	
	Before	After	Before	After	Before	After
Seroconversion (anti-Spike S1 IgG)						
Negative, N (%)	66 (100%)	33 (50.8%)	26 (100%)	15 (60.0%)	40 (100%)	18 (45.0%)
Positive, N (%)	0 (0%)	32 (49.2)	0 (0%)	10 (40.0%)	0 (0%)	22 (55.0%)
Neutralizing capacity						
Negative, N (%)	50 (89.3%)	31 (50.0%)	19 (95.0%)	15 (60.0%)	31 (86.1%)	16 (43.2%)
Positive, N (%)	6 (10.7%)	31 (50.0%)	1 (5.0%)	10 (40.0%)	5 (13.9%)	21 (56.8%)
Anti-Spike S1 IFN-Gamma						
Negative, N (%)	22 (40.7%)	16 (26.7%)	9 (47.4%)	8 (34.8%)	13 (37.1%)	8 (21.6%)
Positive, N (%)	32 (59.3%)	44 (73.3%)	10 (52.6%)	15 (65.2%)	22 (62.8%)	29 (78.4%)

Supplementary Table 3.

Safety of re-vaccination in non-responding IMID patients

	All	**Non-RTX**	**RTX**
N	66	33	33
Injection site pain, N (%)	15 (22.7)	8 (24.2)	7 (21.2)
Local reddening, N (%)	2 (3.0)	1 (3.0)	1 (3.0)
Local swelling, N (%)	1 (1.5)	0 (0.0)	1 (3.0)
Fatigue, N (%)	17 (25.8)	10 (30.3)	7 (21.2)
Headache, N (%)	7 (10.6)	4 (12.1)	3 (9.1)
Arthralgia, N (%)	3 (4.5)	3 (9.1)	0 (0.0)
Myalgia, N (%)	6 (9.1)	2 (6.1)	4 (12.1)
Chills, N (%)	3 (4.5)	2 (6.1)	1 (3.0)
Fever >38°C, N (%)	1 (1.5)	1 (3.0)	0 (0.0)
Nausea/vomiting, N (%)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea, N (%)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphadenopathy, N (%)	0 (0.0)	0 (0.0)	0 (0.0)
Neurologic, N (%)	0 (0.0)	0 (0.0)	0 (0.0)
Other side effects, N (%)	0 (0.0)	0 (0.0)	0 (0.0)