Persistence of seroconversion at 6 months following primary immunisation in patients with immune-mediated inflammatory diseases

T2B! immunity against SARS-CoV-2 study group; Wieske, Luuk; Stalman, Eileen W; van Dam, P J Koos; Kummer, Laura Y; Steenhuis, Maurice; van Kempen, Zoe L E; Killestein, Joep; Volkers, Adriaan G; Tas, Sander W

Published in:
Annals of the Rheumatic Diseases

DOI:
10.1136/ard-2022-223464

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Patients with immune-mediated inflammatory diseases (IMIDs) may have impaired initial humoral responses after SARS-CoV-2 vaccination depending on the type of immunosuppression (ISP) used.[1] It is largely unknown how antibody titres develop over time and whether it is needed to adjust timing of booster campaigns for patients with IMID.

This is a study on long-term persistence of seroconversion after vaccination in patients with IMID on ISP, patients with IMID not on ISP and healthy controls. This study is part of an ongoing national prospective multicentre cohort study in the Netherlands (Target-to-B! study; trial ID NL8900). Participants were included from 2 February 2021 and 1 October 2021. Participants with seroconversion (ie, >4 AU/mL) after primary immunisation with either BNT162b2 or CX-024414 in whom serum samples were collected 28 days after primary immunisation and before the first additional vaccination were included. Patients with IMID on 'strongly antibody-impairing immunosuppressants' (ie, anti-CD20 therapies, sphingosine 1-phosphate receptor (S1PR) modulators and mycophenolate mofetil (MMF)) were offered a first additional vaccination 3 months after primary immunisation; others after 5–6 months. Participants with a SARS-CoV-2 breakthrough infection were excluded; inclusion and exclusion criteria for the overall study are described elsewhere.[1] Clinical and serological data collection is described in the supplement. We measured anti-RBD IgG responses using ELISA.[2] Serum samples used for this analyses were collected prior to the first additional vaccination. For analysis, patients with IMID with 'strongly antibody-impairing immunosuppressants' were separated from other ISPs (analysed as group and apart for the most frequently used other ISPs, ie, anti-TNF, methotrexate and purine antagonists).

A total of 877 patients with IMID with ISP (99 with 'strongly antibody-impairing immunosuppressants' and 778 other ISP) were compared with 356 controls (243 patients with IMID without ISP and 113 healthy controls; see online supplemental figure S1). Online supplemental table S1 shows demographics and humoral responses. Based on a Kaplan-Meier analysis, the estimated proportion of persistent seroconversion at 6 months after primary immunisation was 45% (95% CI 31% to 65%) for patients with IMID with 'strongly antibody-impairing immunosuppressants', 64% (95% CI 59% to 69%) for other ISPs and 88% (95% CI 84% to 92%) for controls ($p<0.01$ for 'strongly antibody-impairing immunosuppressants' and other ISP when compared with controls; figure 1A). Of the frequently used other ISPs, anti-TNF was associated with the lowest proportion of persisting seroconversion (45%; 95% CI 38% to 55%; figure 1B and online supplemental figure S2 and S3). In the 'strongly antibody-impairing immunosuppressants', seroconversion at 6 months persisted in 21/46 (46%) patients with anti-CD20 therapies, in 9/19 (47%) S1PR and in 33/34 (97%) MMF

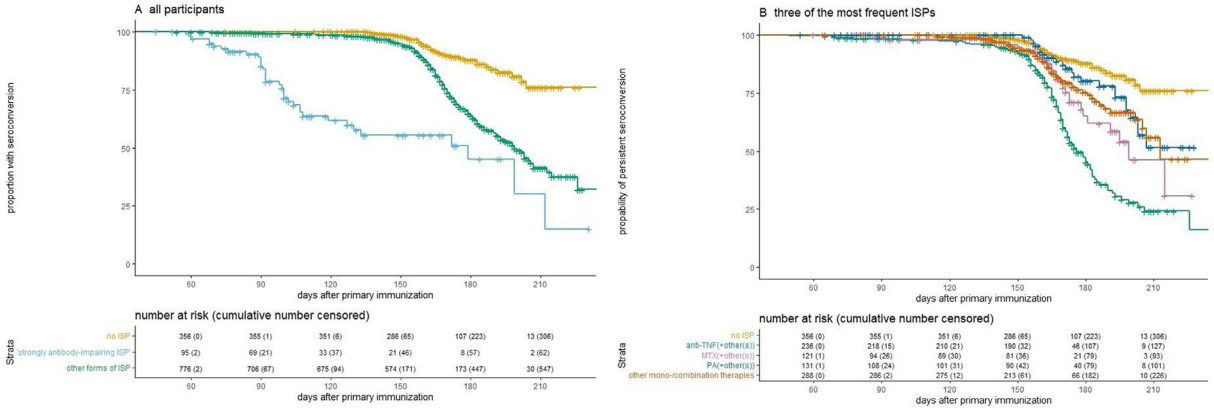

Figure 1 Changes in seroconversion after primary immunisation. Figure showing changes in seroconversion after primary immunisation, censored for measurements when taking place. (A) compares patients with immune-mediated inflammatory diseases (IMIDs) on 'strongly antibody-impairing immunosuppressants' (ie, anti-CD20 therapies, sphingosine 1-phosphate receptor modulators or mycophenolate mofetil), patients with IMID on other forms of ISP and controls (patients with IMIDs without immunosuppressants and healthy controls). (B) compares changes in seroconversion rates after primary immunisation for three of the most frequent immunosuppressants used in our cohort, that is, methotrexate (MTX), purine antagonists (PA) and anti-TNF therapy. Immunosuppressants in the 'other monotherapy/combination therapy group' are detailed in online suppplemental table S1. ISP, immunosuppression.

(online supplemental table S1). Using a multivariate Cox model, the same ISP s together with SARS-CoV-2 infections prior to vaccination and higher anti-RBD titres 28 days after primary immunisation were identified as independent determinants for the persistence of seroconversion (online supplemental figure S4).

Use of ISP is associated with a greater decline in humoral responses 6 months after primary immunisation and this association was most pronounced in anti-CD20 therapies, S1PR and anti-TNF. Although lower initial titres may explain this in part, ISP use was an independent determinant. Moreover, differences in loss of seroconversion between ISPs did not correlate with initial titres. Most notably, anti-TNF showed a great decline while initial antibody titres are only moderately reduced.[3] This suggests that some ISP, like anti-TNF, affect duration or quality of the germinal centre reactions and/or establishment of the long-lived plasma cell compartment.[4]

This report has some limitations. Patients on 'strongly antibody-impairing immunosuppressants' received their first additional vaccine earlier when compared with patients on other ISPs and controls because of differences in the design of the national vaccination campaign. This might have led to an underestimate of the loss of seroconversion at later time points in this group. Timing of the vaccination campaign was similar for patients treated with other ISPs and controls. We did not investigate a potential effect of the IMID diagnosis itself, regardless of ISP use or the level of IMID disease activity. Previously, we did not observe an association between short-term antibody responses and the type of IMID.[1]

Disease severity of current SARS-CoV-2 variants is mostly mild, despite a higher risk of SARS-CoV-2 breakthrough infections in patients with IMID with impaired humoral responses, possibly as a result of unaffected cellular immunity and/or hybrid immunity.[5 6] However, as long as the contribution of these factors to the protection against new variants is unknown, our results suggest that patients with IMID with ISP should receive additional vaccinations earlier than 6 months after their last vaccination.

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Handling editor Josef S Smolen

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Acknowledgements We thank ZonMw (The Netherlands Organisation for Health Research and Development, grant 10430072010007) for the funding of the study and the T2B partners, including the patient groups, and Health Holland for the support in this study. This collaboration project is financed by the PPP Allowance made available by Top Sector Life Sciences & Health to Samenwerkende Gezondheidsfondsen (SGF) under project number LSHM18055-SGF to stimulate public–private partnerships and co-financing by health foundations that are part of the SGF. We also thank E P Moll van Charante (Department of Public and Occupational Health and Department of General Practice, Amsterdam UMC, University of Amsterdam; and Amsterdam Public Health Research Institute, Amsterdam, Netherlands), J A Bogaards (Department of Epidemiology and Data Science), Amsterdam UMC), and R A Scholte (Clinical Research Unit, Amsterdam UMC, University of Amsterdam) for their guidance in the data safety monitoring board.

Contributors All authors met the criteria for authorship set by the International Committee of Medical Journal Editors. TR, MS, SK, JK, AEB and OC did the serological assays; all other authors contributed in data acquisition. LW, EWS, TWK and FE wrote the first draft of the manuscript. LW and EWS did the data analyses. EWS, LW, PJKvD and LYK 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.

Funding This study was supported by ZonMw (The Netherlands Organisation for Health Research and Development, grant 10430072010007).

Disclaimer The sponsor had no role in the design, analyses or reporting of the study.

Competing interests FE and TWK report (governmental) grants from ZonMw to studyimmune response after SARS-Cov-2 vaccination in autoimmune diseases. FE 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 CSlBehring; and honoraria from Grifols. AJvdK reports grants from CSLBehring and participation on an advisory board for Argen-X. ML reports agrant from Galapagos not related to this study, and honoraria from BristolMyers Squibb, Pfizer, Takeda and Tillotts. PIS is involved in clinical trials with many pharmaceutical industries that manufacture drugs used for the treatment of, for example, psoriasis and atopic dermatitis, for which financial compensation is paid to the department or hospital, and is achief investigator of the TREAT NL registry taskforce and SECURE-AD registry. MWB is a secretary for the Dutch Experimental Dermatology Board; head of the pigmentary disorders group within the Dutch Dermatology Board; and reports honoraria from Pfizer, Sanofi, Novartis, and Fondation René Touraine. JK has speaking relationships with MerckSerono, Biogen Idec, TEVA, Sanofi, Genzyme, Roche and Novartis; received financial support to his institution for researchactivities from Merck Serono, Bayer Shcering Pharma, Biogen Idec, GlaxoSmithKline (GSK), Roche, Teva, Sanofi, Genzyme and Novartis. BH reports unpaid positions as a medical adviser for several patient groups, aboard position for ERN-SKIN, and associate editor for The British Journalof Dermatology; reports grants from AbbVIe, Akari Therapeutics, Celgene and Novartis; consulting fees from UCB Pharma, Novartis, and Janssen; and honoraria from AbbVie. JJGMV reports consulting fees from Argenx, Alexion and NMD Pharma, and is a coinventor on patent applicationsbased on MuSK-related research. DJH reportsgrants from AbbVie, AstraZeneca, Janssen, LEO Pharma and UCB; honoraria from AbbVie, Galderma, Janssen, Lilly, Pfizer, Sanofi, and UCB; and a paid position on an advisory board for BIOMAP IMI. PAvD participated on an advisory board for Octapharma. PvP reports grantsfrom Alexion Pharma and GSK, and participation on advisory boards for GSK and Vifor Pharma. GRAMD'H reports consulting fees from AbbVie, Agomab, AstraZeneca, AM Pharma, AMT, Arena Pharmaceuticals, BristolMyers Squibb, Boehringer Ingelheim, Celltrion, Eli Lilly, ExeliomBiosciences, Exo Biologics, Galapagos, Index Pharmaceuticals, Kaleido, Roche, Gilead, GSK, Gossamerbio, Pfizer, Immunic, Johnson and Johnson, Origo, Polpharma, Procise Diagnostics, Prometheus Laboratories, Prometheus Biosciences, Progenity and Protagonist; honoraria from AbbVie, Arena, Galapagos, Gilead, Pfizer, Bristol MyersSquibb and Takeda; and participation on advisory boards for AbbVie, Seres Health, Galapagos, and AstraZeneca. RBT reports honoraria fromSobi and Norgine, and participation on an advisory board for Norgine. SHG is a board member of the Dutch Society of Clinical Neurophysiology (unpaid), reports grants from Prinses Beatrix Spierfonds, and receivedspeaker fees from Shire/Takeda. KAHZ reports paid data safetymonitoring board positions for Torrent and Foresee.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Consent obtained directly from patient(s).

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

Provenance and peer review Not commissioned; externally peer reviewed.

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/ard-2022-223464).

LW and EWS contributed equally.

To cite Wieske L, Stalman EW, van Dam PJK, *et al*. *Ann Rheum Dis* 2023;**82**:883–885.

Received 12 October 2022
Accepted 16 January 2023
Published Online First 31 January 2023

Ann Rheum Dis 2023;**82**:883–885. doi:10.1136/ard-2022-223464

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Supplementary appendix:

"Persistence of seroconversion at six months following primary immunization in patients with immune-mediated inflammatory diseases"

Wieske L, Stalman EW et al.

The T2B! immunity against SARS-CoV-2 study group

Contents

Supplementary methods

Participants completed two monthly electronic questionnaires which included questions on potential SARS-CoV-2 infections and vaccination dates. Clinical data on ISP use, diagnosis and demographics were extracted from the medical records by the investigators. Definitions for active ISP use have been described before.[ref] In short, immunosuppressants were defined as active when used in the 3 months before first vaccination or during primary immunization, or in the 12 months before vaccination in case of long-acting therapies (i.e anti-CD20 therapies, cyclophosphamide, cladribine, alemtuzumab). Combination therapies were grouped in the following order: any combination therapy involving anti-CD20 therapy, MMF, methotrexate, TNF-inhibitors and any other ISP.

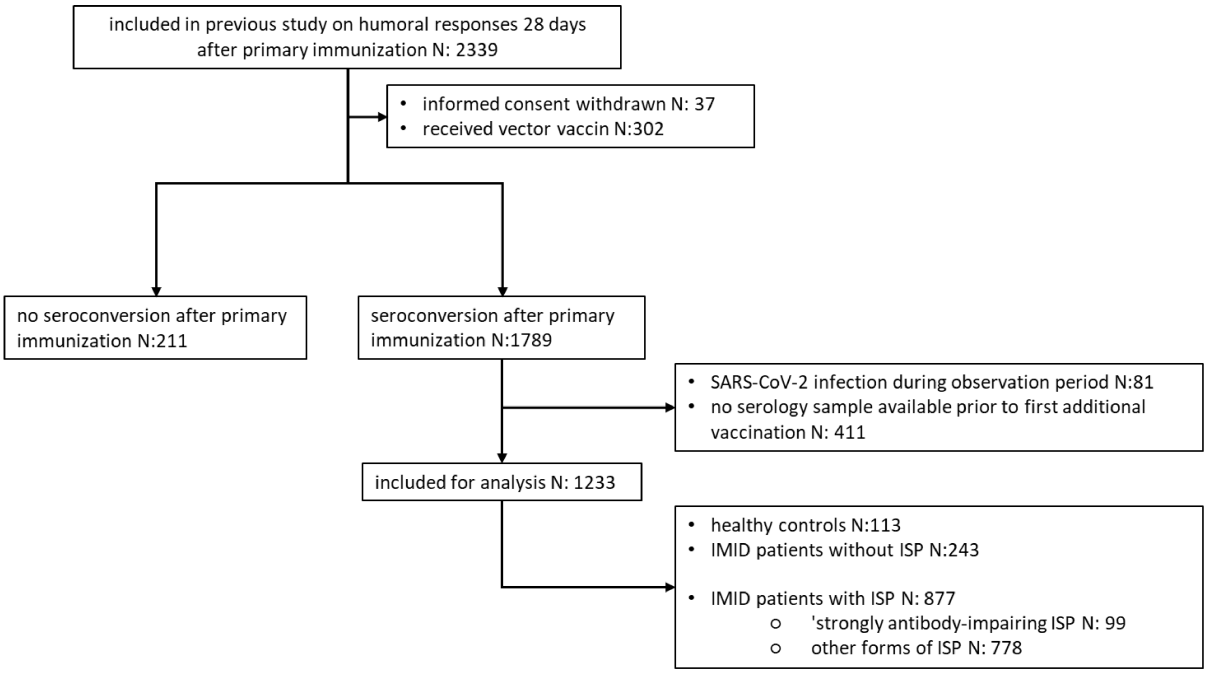
Humoral responses were measured in serum obtained using fingerprick (custom set, DaklaPack Europe, Lelystad, Netherlands) at home or in serum samples collected at the study site. For this sub study we used the sample taken 28 days after primary immunization and the latest follow-up sample taken before the first additional vaccination of that patient. In the Netherlands, primary immunization for this cohort took place between March and September 2021. In September 2021, additional ('third') vaccinations were offered to specific vulnerable groups including IMID patients treated with so-called 'strong antibody-impairing ISP' (i.e. anti-CD20 therapies, S1PR modulators, mycophenolate mofetil). Starting in December 2021, additional ('booster') vaccinations were offered to the general Dutch population.

Previous publications

Data from the ongoing national prospective multicenter cohort study on SARS-CoV-2 vaccination responses in IMID patients in the Netherlands (Target-to-B! (T2B!) study), including data from participants described in this substudy, has been used in the following publications.[1–5]

Figure S1: study flowchart

Figure describing the flow of participants from the original publication on serological responses at 28 days after primary immunization.



IMID: immune-mediated inflammatory diseases; ISP: immunosuppressants

Supplementary table S1: characteristics and humoral responses per immunosuppression group

Table showing characteristics and humoral response after primary immunization and at follow-up measurement in the different groups of immunosuppressants. The control group is composed of patients with immune-mediated inflammatory diseases (IMID) and healthy controls.

	controls		strongly antibody-impairing ISP			other forms of ISP			
	Healthy controls	IMID not on ISP	a-CD20 +other(s)[a]	S1PR-modulators	MMF +other(s)[b]	anti-TNF +other(s)[c]	MTX +other(s)[d]	PA +other(s)[e]	other mono-/combination therapies[f]
	N=113	N=243	N=46	N=19	N=34	N=237	N=121	N=132	N=288
Age									
Mean (SD)	49.5 (10.1)	51.2 (11.5)	49.4 (11.6)	45.3 (8.35)	45.7 (13.6)	48.6 (14.6)	56.8 (12.0)	47.2 (14.2)	50.5 (13.1)
Sex									
Male	40 (35.4%)	78 (32.1%)	14 (30.4%)	9 (47.4%)	8 (23.5%)	91 (38.4%)	33 (27.3%)	51 (38.6%)	120 (41.7%)
Female	73 (64.6%)	165 (67.9%)	32 (69.6%)	10 (52.6%)	26 (76.5%)	146 (61.6%)	88 (72.7%)	81 (61.4%)	168 (58.3%)
IMID diagnosis									
IBD	0 (0%)	59 (24.3%)	0 (0%)	0 (0%)	4 (11.8%)	119 (50.2%)	2 (1.65%)	69 (52.3%)	51 (17.7%)
dermatological	0 (0%)	52 (21.4%)	0 (0%)	0 (0%)	6 (17.6%)	6 (2.53%)	28 (23.1%)	0 (0%)	87 (30.2%)
neurological	0 (0%)	91 (37.4%)	28 (60.9%)	19 (100%)	6 (17.6%)	0 (0%)	12 (9.92%)	35 (26.5%)	96 (33.3%)
other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2.94%)	0 (0%)	0 (0%)	0 (0%)	1 (0.35%)
rheumatological	0 (0%)	41 (16.9%)	18 (39.1%)	0 (0%)	17 (50.0%)	112 (47.3%)	79 (65.3%)	28 (21.2%)	53 (18.4%)
SARS-CoV-2 infection prior to vaccination									
N (%)	46 (40.7%)	31 (12.8%)	5 (10.9%)	4 (21.1%)	6 (17.6%)	40 (16.9%)	14 (11.6%)	12 (9.09%)	53 (18.4%)
Anti-RBD IgG titer after primary immunization									
Median [Q1,Q3]	252 [174,401]	186 [104,314]	19.6 [7.19,61.9]	10.7 [5.30,19.6]	154 [55.1,233]	116 [53.3,213]	123 [41.4,296]	140 [75.5,260]	155 [85.5,270]

	controls		strongly antibody-impairing ISP			other forms of ISP			
	Healthy controls	**IMID not on ISP**	**a-CD20 +other(s)[a]**	**S1PR-modulators**	**MMF +other(s)[b]**	**anti-TNF +other(s)[c]**	**MTX +other(s)[d]**	**PA +other(s)[e]**	**other mono-/combination therapies[f]**
	N=113	**N=243**	**N=46**	**N=19**	**N=34**	**N=237**	**N=121**	**N=132**	**N=288**
Time between primary immunization and follow-up sampling									
Median [Q1,Q3]	169 [159,192]	170 [153,183]	99.0 [90.0,116]	77.0 [69.0,117]	128 [84.3,166]	165 [155,175]	162 [98.0,174]	163 [135,192]	163 [148,176]
Persistent seroconversion at the moment of follow-up sampling									
N (%)	106 (93.8%)	211 (86,8%)	21 (45.7%)	9 (47.4%)	33 (97.1%)	132 (55.7%)	95 (78.5%)	109 (82.6%)	235 (81.6%)
Anti-RBD IgG titer in participants with persisting seroconversion									
Median [Q1,Q3]	42.2 [18.1,83.7]	26.5 [12.4,50.5]	13.7 [8.31,30.4]	7.39 [6.19,47.3]	34.9 [13.8,69.1]	14.7 [7.67,28.9]	29.0 [11.7,56.6]	24.4 [9.25,42.7]	20.8 [9.29,47.2]

[a]anti-CD20 monotherapy: 32 (69.6%), anti-CD20 + corticosteroids:6 (13.0%), anti-CD20 + corticosteroids + MTX + MMF: 1 (2.2%), anti-CD20 + corticosteroids + MMF: 1 (2.2%), anti-CD20 + corticosteroids + purine antagonist: 1 (2.2%), anti-CD20+ immunoglobulin + MMF: 1 (2.2%), anti-CD20 + MTX: 2 (4.4%), anti-CD20 + MTX + tocilizumab: 1 (2.2%), anti-CD20 + natalizumab: 1 (2.2%)

[b] MMF monotherapy: 13 (38.2%), MMF + corticosteroids:13 (38.2%), MMF + belimumab: 3 (8.8%), MMF + PA: 1 (2.9%) , MMF+ corticosteroids + PA: 1 (2.9%), MMF +corticosteroids+ methotrexate: 1 (2.9%), MMF + corticosteroids + immunoglobulin: 1 (2.9%), MMF+ calcineurin inhibitors: 1 (2.9%)

[c]anti-TNF monotherapy: 147 (62.0%), anti-TNF + MTX: 51 (21.5%), anti-TNF + PA: 16 (6.8%), anti-TNF + corticosteroids: 14 (5.9%), anti-TNF + corticosteroids + MTX: 3 (1.3%), anti-TNF + calcineurin inhibitors : 1 (0.4%), anti-TNF + corticosteroids + MTX + vedolizumab : 1 (0.4%), anti-TNF + : 1 (0.4%), anti-TNF + corticosteroids + ustekinumab: 1 (0.4%), anti-TNF + DHODH inhibitor + MTX: 1 (0.4%), anti-TNF + MTX + PA: 1 (0.4%), anti-TNF + ustekinumab + PA: 1 (0.4%)

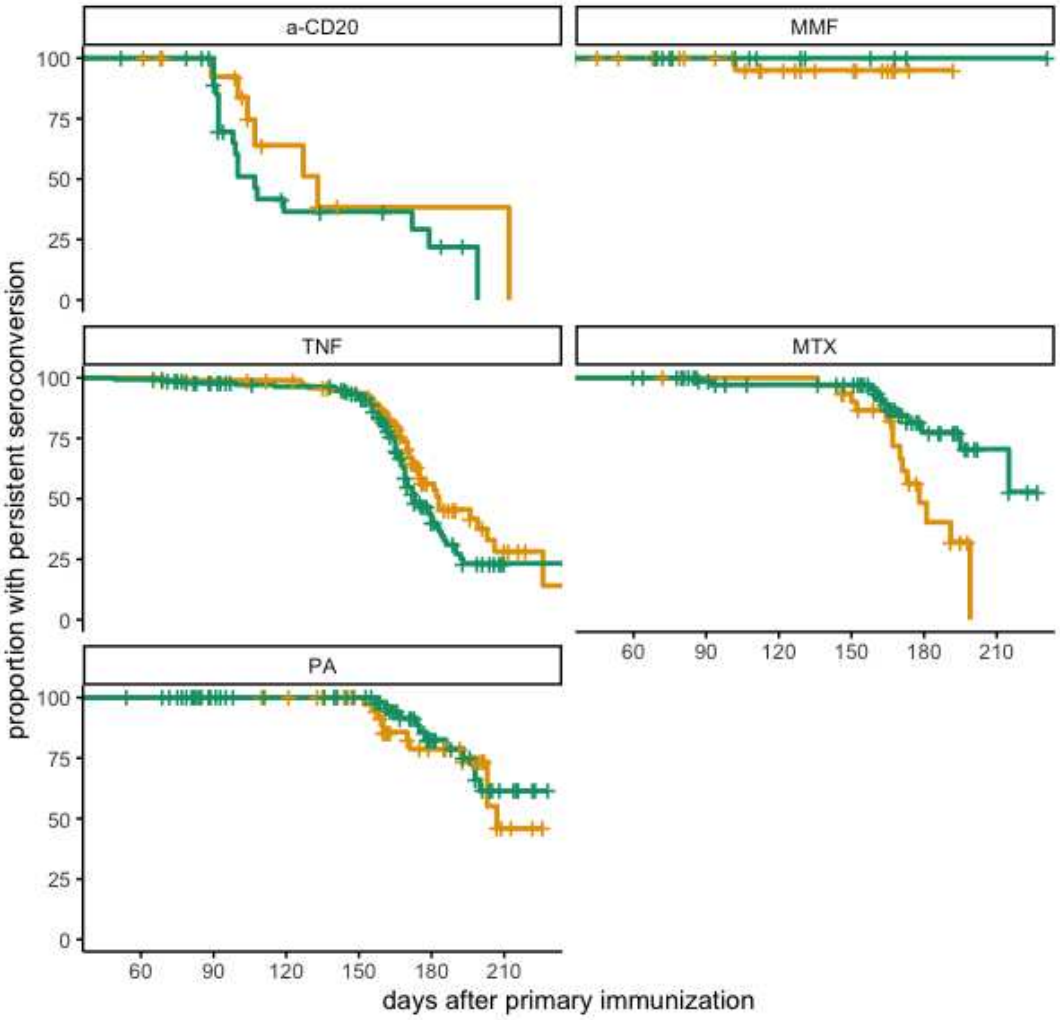
[d]MTX monotherapy: 89 (73.6%), MTX + corticosteroids + abatacept: 1 (0.8%) , MTX + abatacept: 7 (5.8%), MTX + belimumab: 1 (0.8%), MTX + calcineurin inhibitors: 2 (1.7%), MTX + corticosteroids: 13 (10.7%), MTX + dupilumab: 4 (3.3%), MTX + JAK inhibitor: 1 (0.8%), MTX + ustekinumab : 2 (1.7%), MTX + vedolizumab: 1 (0.8%)

[e]PA: 91 (68.9%), PA + corticosteroids: 33 (25.0%), PA + belimumab + corticosteroids: 1 (0.8%), PA + calcineurin inhibitors + corticosteroids: 1 (0.8%), PA + calcineurin inhibitors: 2 (1.5%), PA + corticosteroids + immunoglobulin: 3 (2.3%), PA + immunoglobulin: 1 (0.8%)

abatacept: 2 (0.7%), abatacept+ corticosteroids: 1 (0.3%), belimumab: 2 (0.7%), belimumab + corticosteroids: 1 (0.3%), calcineurin inhibitors: 13 (4.5%), calcineurin inhibitors + corticosteroids: 1 (0.3%), calcineurin inhibitors+ dupilumab: 4 (1.4%), calcineurin inhibitors + dupilumab + JAK inhibitor: 1 (0.3%), cladribine, corticosteroids: 1 (0.3%), corticosteroids: 30 (10.4%), corticosteroids + DHODH inhibitor: 1 (0.3%), corticosteroids+ DHODH inhibitor+ JAK inhibitor+ tocilizumab: 1 (0.3%), corticosteroids+ dupilumab: 1 (0.3%), corticosteroids+ immunoglobulin: 1 (0.3%), corticosteroids + tocilizumab: 1 (0.3%), corticosteroids+ vedolizumab: 1 (0.3%), DHODH inhibitor: 2 (0.7%), dimethylfumarate: 3 (1.0%), dupilumab: 48 (16.7%), glatiramer:: (0.3%), hydroxychloroquine: 25 (8.7%), IL-17A antagonist: 1 (0.3%), immunoglobulin: 53 (18.4%), interferon-beta: 1 (0.3%), JAK inhibitor: 15 (5.2%), JAK inhibitor + vedolizumab: 2 (0.7%), natalizumab: (7.6%), omalizumab: 1 (0.3%), tocilizumab: 2 (0.7%), ustekinumab: (11.8%), ustekinumab + vedolizumab: 1 (0.3%), vedolizumab: 15 (5.2%)

Supplementary figure S2: changes in seroconversion after primary immunization for mono- and combination therapies

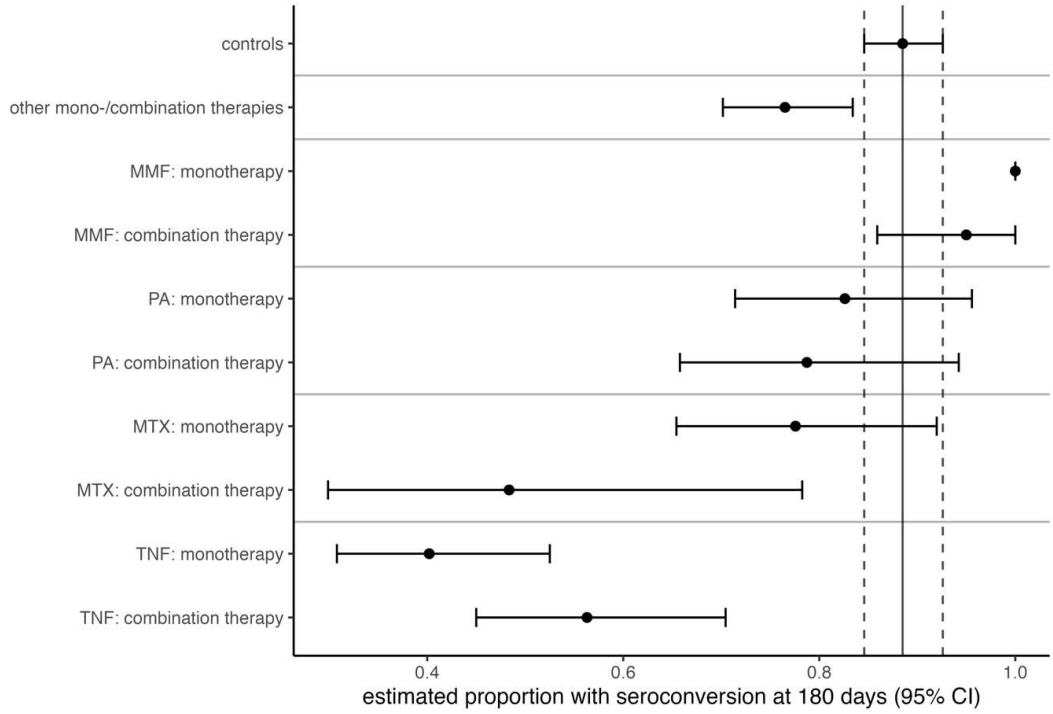
Figure showing changes in seroconversion after primary immunization, censored for measurements when taking place, for patients receiving immunosuppression as monotherapy or as part of a combination therapy for the most frequently used forms in immunosuppression in this study. Green lines indicate the monotherapy groups; yellow lines indicate the combination therapy groups. Immunosuppressants in the 'combination therapy groups' are detailed in table S1. Sphingosine 1-phosphate receptor modulators are excluded from this figure as this is always used as monotherapy.



a-CD20: anti-CD20 therapy; MMF: mycophenolate mofetil; PA: purine antagonists; MTX: methotrexate; TNF: anti-tumor necrosis factor therapy

Supplementary figure S3: estimated proportions of persistent seroconversion at 6 months after primary immunization for the different forms of immunosuppression.

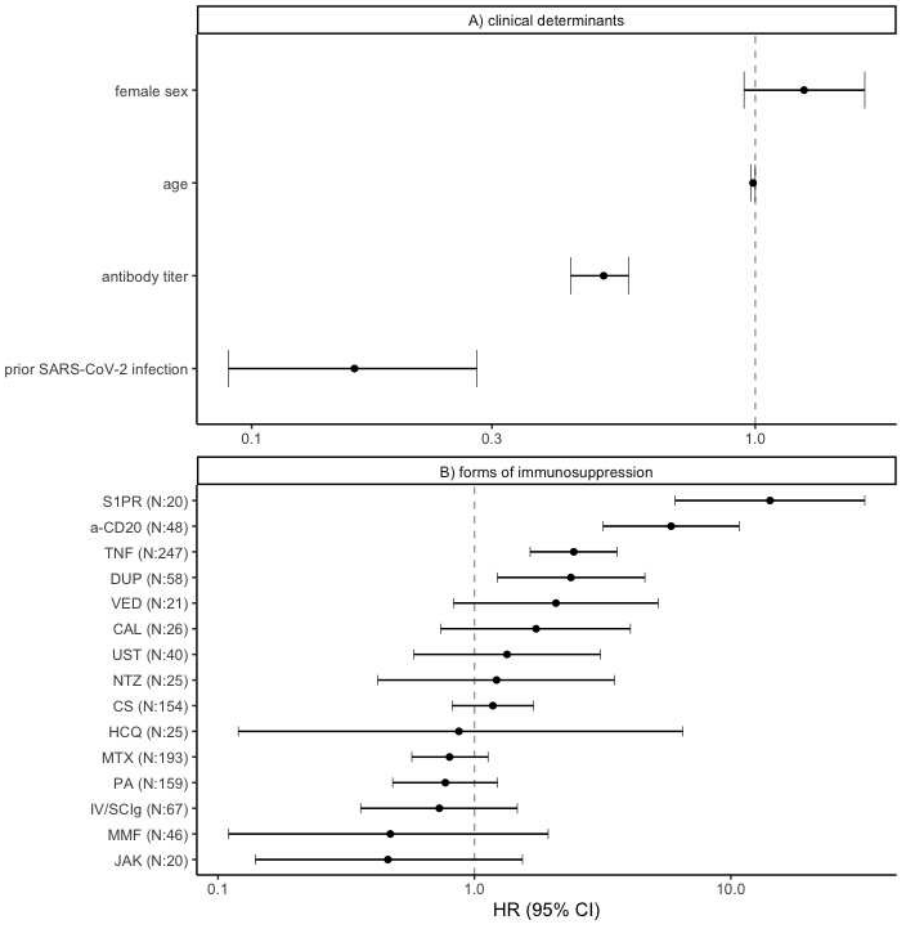
Figure showing proportion with associated 95% confidence interval of participants with persistent seroconversion at 6 months after primary immunization for the different forms of immunosuppression, either as monotherapy or combination therapy, as the estimated using a Kaplan-Meier analysis, excluding patients treated anti-CD20 therapies or sphingosine 1-phosphate receptor modulators because too few observations were available for this timepoint. Immunosuppressants in the 'other mono-/combination therapy group' and used as part of combination therapies are detailed in table S1. The solid grey line indicates the estimated proportion in controls. The dashed lines indicate the lower and upper limit of the 95% confidence interval for controls.



MMF: mycophenolate mofetil; PA: purine antagonists; MTX: methotrexate; TNF: anti-tumor necrosis factor therapy

Supplementary figure S4: sensitivity analysis: cox regression model

As sensitivity analysis to investigate potential influences of our choices in selecting and grouping immunosuppressants and to estimate effects of other clinical determinants, we used an alternative strategy where we included all immunosuppressants in a cox proportional hazards model together with clinical determinants. Immunosuppressants were coded as indicator variables and only immunosuppressants used in more than 20 patients were excluded (the N denotes how many observations were available for each immunosuppressant). Below shows a forest plot with the predicted hazard ratio's (HR) with associated 95% confidence interval (CI) for loss of seroconversion for clinical determinants (panel A) and each immunosuppressant (panel B) during follow-up. The observed HR for age was 0.99 (95% CI: 0.98-1.00; p:0.02; for every year increase). Antibody titer indicates the antibody titer at day 28 after primary immunization (on a log scale).



S1PR: sphingosine-1-phosphate receptor modulators; a-CD20: anti-CD20 therapy; TNF: TNF-inhibitors; DUP: dupilumab; VED: vedolizumab; CAL: calcineurin inhibitors; UST: ustekinumab; NTZ: natalizumab; CS: corticosteroids; HCQ: hydroxychloroquine; MTX: methotrexate; PA: purine antagonists; IV/SCIg: intravenous or subcutaneous immunoglobulin; MMF: mycophenolate mofetil; JAK: JAK-inhibitor

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