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Wieske, L.; Stalman, E.W.; Dam, P.J.K. van; Kummer, L.Y.; Steenhuis, M.; Kempen, Z.L.E. van; ... ; T2B Immunity SARS CoV 2 Study Grp

Citation

Wieske, L., Stalman, E. W., Dam, P. J. K. van, Kummer, L. Y., Steenhuis, M., Kempen, Z. L. E. van, ... Eftimov, F. (2023). Persistence of seroconversion at 6 months following primary immunisation in patients with immune-mediated inflammatory diseases. *Annals Of The Rheumatic Diseases*, 82(6), 883-885. doi:10.1136/ard-2022-223464

Version: Publisher's Version

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Downloaded from: <https://hdl.handle.net/1887/3677643>

Note: To cite this publication please use the final published version (if applicable).

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

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

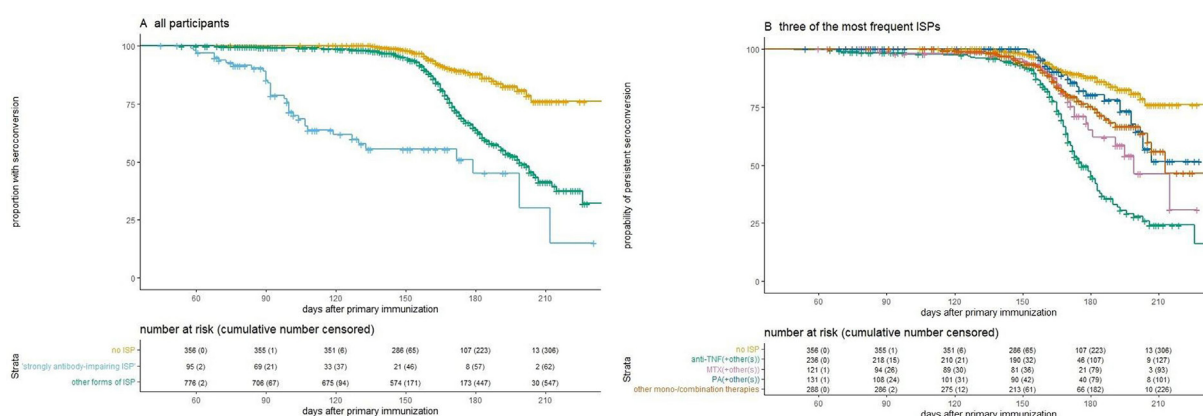


Figure 1 Changes in seroconversion after primary immunisation. Figure showing changes in seroconversion after primary immunisation, censored for measurements when taking place. (A) compares patients with immune-mediated inflammatory diseases (IMIDs) on ‘strongly antibody-impairing immunosuppressants’ (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/combotherapy group’ are detailed in online supplemental 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.

Luuk Wieske,^{1,2} Eileen W Stalman ,¹ P J Koos van Dam ,¹ Laura Y Kummer,^{1,3} Maurice Steenhuis,³ Zoe L E van Kempen,⁴ Joep Killestein,⁴ Adriaan G Volkers,⁵ Sander W Tas,⁶ Laura Boekel ,⁷ Gertjan Wolbink,^{3,7} Anneke Van der Kooi,¹ Joost Raaphorst,¹ Mark Löwenberg,⁵ Bart Takkenberg,⁵ Geert R A M D'Haens,⁵ Phyllis I Spuls,⁸ Marcel W Bekkenk,⁹ Annelie H Musters,⁹ Nicole F Post,⁹ Angela L Bosma,⁹ Marc L Hilhorst,¹⁰ Yosta Vegting,¹⁰ Frederique J Bemelman,¹⁰ Alexandre Voskuyl,¹¹ Bo Broens,¹¹ Agner Parra Sanchez,^{5,11} Cécile A C M van Els,^{12,13} Jelle De Wit,^{14,15} Abraham Rutgers ,¹⁶ Karina de Leeuw,¹⁶ Barbara Horváth,¹⁷ Jan J G M Verschuuren,¹⁸ Annabel M Ruiter,¹⁸ Lotte van Ouwkerk ,¹⁹ Diane van der Woude,¹⁹ Cornelia F Allaart,¹⁹ Y K Onno Teng ,²⁰ Pieter van Paassen,²¹ Matthias H Busch ,^{22,23} Papay B P Jallah,²³ Esther Brusse,²⁴ Pieter A van Doorn,²⁴ Adája Elisabeth Baars ,²⁴ Dirkjan Hijnen,²⁵ Corine R G Schreurs,²⁵ W Ludo Van der Pol,²⁶ H Stephan Goedee,²⁶ Sofie Keijzer,³ Jim Keijzer,³ Olvi Cristianawati,³ Anja ten Brinke,³ Niels J M Verstegen,³ Koos A H Zwinderman,²⁷ S Marieke van Ham,^{3,28} Taco W Kuijpers,^{3,29} Theo Rispens ,³ Filip Eftimov,³⁰ On behalf of the T2B! immunity against SARS-CoV-2 study group

¹Department of Neurology and Neurophysiology, Amsterdam UMC Locatie AMC, Amsterdam, The Netherlands

²Department of Clinical Neurophysiology, St Antonius Hospital, Nieuwegein, The Netherlands

³Immunopathology, Sanquin Research and Landsteiner Laboratory, Amsterdam, The Netherlands

⁴Department of Neurology, Amsterdam UMC Locatie VUmc, Amsterdam, The Netherlands

⁵Department of Gastroenterology and Hepatology, Amsterdam UMC Locatie AMC, Amsterdam, The Netherlands

⁶Department of Rheumatology and Clinical Immunology, Amsterdam University Medical Centres, Amsterdam, The Netherlands

⁷Department of Rheumatology, Rheumatology and immunology Center, location Reade, Amsterdam, The Netherlands

⁸Department of Dermatology, Public Health and Epidemiology; Immunity and Infections, location Academic Medical Center, Amsterdam University Medical Centres, Amsterdam, The Netherlands

⁹Department of Dermatology, Amsterdam UMC Locatie AMC, Amsterdam, The Netherlands

¹⁰Department of Internal Medicine, Section of Nephrology, Amsterdam UMC Locatie AMC, Amsterdam, The Netherlands

¹¹Department of Rheumatology and Clinical Immunology, Amsterdam UMC Locatie VUmc, Amsterdam, The Netherlands

¹²Centre for Infectious Disease Control, National Institute for Public Health and the Environment, RIVM, Bilthoven, The Netherlands

¹³Faculty of Veterinary Medicine, Utrecht University, Utrecht, The Netherlands

¹⁴Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Botnar Research Centre, University of Oxford, Oxford, UK

¹⁵Center for Infectious Diseases, National Institute for Public Health and the Environment, Bilthoven, The Netherlands

¹⁶Rheumatology and Clinical Immunology, University Medical Center, Groningen, The Netherlands

¹⁷Dermatology, University Medical Center Groningen, Groningen, The Netherlands

¹⁸Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands

¹⁹Rheumatology, Leids Universitair Medisch Centrum, Leiden, The Netherlands

²⁰Nephrology, Leiden University Medical Centre, Leiden, The Netherlands

²¹Department of Internal Medicine/Division of Clinical & Experimental Immunology, Maastricht University Medical Centre, Maastricht, The Netherlands

²²Department of Rheumatology, Maastricht UMC+, Maastricht, The Netherlands

²³Department of Nephrology and Clinical Immunology, Maastricht Universitair Medisch Centrum+, Maastricht, The Netherlands

²⁴Department of Neurology, Erasmus Universiteit Rotterdam, Rotterdam, The Netherlands

²⁵Department of Dermatology, Erasmus Universiteit Rotterdam, Rotterdam, The Netherlands

²⁶Department of Neurology and Neurosurgery, Universitair Medisch Centrum, Utrecht, The Netherlands

²⁷Clinical Research Unit, Amsterdam UMC Locatie AMC, Amsterdam, The Netherlands

²⁸Swammerdam Institute for Life Sciences, University of Amsterdam, Amsterdam, The Netherlands

²⁹Department of Pediatric Immunology, Amsterdam UMC Locatie AMC, Amsterdam, The Netherlands

³⁰Department of Neurology, University of Amsterdam, Amsterdam, The Netherlands

Correspondence to Eileen W Stalman, Department of Neurology and Neurophysiology, Amsterdam UMC Locatie AMC, Amsterdam, North Holland, Netherlands; e.w.stalman@amsterdamumc.nl

Handling editor Josef S Smolen

Twitter P J Koos van Dam @koosvandam

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 study immune 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 CSL Behring; and honoraria from Grifols. A.J.v.d.K. reports grants from CSL Behring and participation on an advisory board for Argen-X. ML reports a grant from Galapagos not related to this study, and honoraria from Bristol Myers 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 chief investigator of the TREAT NL registry taskforce and SECURE-AD registry. M.W.B. is a secretary for the Dutch Experimental Dermatology Board; head of the pigmented disorders group within the Dutch Dermatology Board; and reports honoraria from Pfizer, Sanofi, Novartis, and Fondation René Touraine. JK has speaking relationships with Merck Serono, Biogen Idec, TEVA, Sanofi, Genzyme, Roche and Novartis; received financial support to his institution for research activities from Merck Serono, Bayer Shering 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 Journal of 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 applications based on MuSK-related research. DJH reports grants 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. P.v.d. participated on an advisory board for Octapharma. P.v.P. reports grants from 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, Bristol Myers Squibb, Boehringer Ingelheim, Celltrion, Eli Lilly, Exeliom Biosciences, Exo Biologics, Galapagos, Index Pharmaceuticals, Kaleido, Roche, Gilead, GSK, GossamerBio, Pfizer, Immunic, Johnson and Johnson, Origo, Polpharma, Proclis Diagnostics, Prometheus Laboratories, Prometheus Biosciences, Progenity and Protagonist; honoraria from AbbVie, Arena, Galapagos, Gilead, Pfizer, Bristol Myers Squibb and Takeda; and participation on advisory boards for AbbVie, Seres Health, Galapagos, and AstraZeneca. RBT reports honoraria from Sobi 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 received speaker fees from Shire/Takeda. KAHZ reports paid data safety monitoring 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

ORCID iDs

Eileen W Stalman <http://orcid.org/0000-0002-9715-0915>

P J Koos van Dam <http://orcid.org/0000-0002-2602-4364>

Laura Boekel <http://orcid.org/0000-0001-5473-7786>

Abraham Rutgers <http://orcid.org/0000-0002-1641-6890>

Lotte van Ouwkerk <http://orcid.org/0000-0001-8036-950X>

Y K Onno Teng <http://orcid.org/0000-0001-9920-2195>

Matthias H Busch <http://orcid.org/0000-0001-7324-2471>

Adâja Elisabeth Baars <http://orcid.org/0000-0001-7842-0871>

Theo Rispens <http://orcid.org/0000-0001-9600-1312>

REFERENCES

- 1 Wieske L, van Dam KPJ, Steenhuis M, *et al.* Humoral responses after second and third SARS-cov-2 vaccination in patients with immune-mediated inflammatory disorders on immunosuppressants: a cohort study. *Lancet Rheumatol* 2022;**4**:e338–50.
- 2 Vogelzang EH, Loeff FC, Derksen NIL, *et al.* Development of a SARS-cov-2 total antibody assay and the dynamics of antibody response over time in hospitalized and nonhospitalized patients with COVID-19. *J Immunol* 2020;**205**:3491–9.
- 3 Furer V, Eviatar T, Freund T, *et al.* Immunogenicity induced by two and three doses of the bnt162b2 mRNA vaccine in patients with autoimmune inflammatory rheumatic diseases and immunocompetent controls: a longitudinal multicentre study. *Ann Rheum Dis* 2022;**81**:1594–602.
- 4 Cassese G, Arce S, Hauser AE, *et al.* Plasma cell survival is mediated by synergistic effects of cytokines and adhesion-dependent signals. *J Immunol* 2003;**171**:1684–90.
- 5 Menni C, Valdes AM, Polidori L, *et al.* Symptom prevalence, duration, and risk of hospital admission in individuals infected with SARS-cov-2 during periods of omicron and delta variant dominance: a prospective observational study from the ZOE COVID study. *Lancet* 2022;**399**:1618–24.
- 6 Stalman EW, Wieske L, Van DK, *et al.* Breakthrough infections with the SARS-CoV-2 omicron (B.1.1.529) variant in patients with immune-mediated inflammatory diseases. *Ann Rheum Dis* 2022;**81**:1757–66.