

## Methotrexate and glucocorticoids, but not anticytokine therapy, impair the immunogenicity of a single dose of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic inflammatory arthritis

Strategies aimed at expediting immunisation campaigns against COVID-19 include providing single vaccine doses to individuals with previous exposure to SARS-CoV-2 and delaying second doses. While such approaches are effective at the population level, immunogenicity yielded by one dose of vaccines in immunocompromised patients may be alarmingly low.<sup>1,2</sup> Biological (b) and targeted synthetic (ts) disease-modifying antirheumatic drugs (DMARDs) interfere with the immune system at multiple levels and may variably reduce response to viral vaccines.<sup>3</sup> Limited data on small numbers of rheumatic patients with variable diagnoses and treatments hamper definitive conclusions on the possible impact of immune-mediated inflammatory diseases,

immunomodulatory drugs or both on the efficacy of the new generation of mRNA vaccines.<sup>4,5</sup>

Here we present interim data analysis on the immunogenicity of the BNT162b2 COVID-19 vaccine in 140 patients with chronic inflammatory arthritis all treated with b/tsDMARDs at the Division of Rheumatology of the IRCCS Policlinico San Matteo University Hospital of Pavia, receiving the first dose of vaccine between 24 and 31 March 2021. Patients were advised to discontinue both the b/tsDMARD and concomitant methotrexate around vaccination. In particular, the following suggestions were made: (1) for all the bDMARDs and methotrexate, withholding of therapy in the 7 days before and after vaccination; and (2) for tsDMARDs, withholding of therapy from the day before until day 7 after vaccination. For glucocorticoids and conventional synthetic DMARDs other than methotrexate, no modifications were advised. Blood samples were obtained immediately before vaccination and at day 21 after the first dose. Serum samples were tested using chemiluminescent immunoassay (LIAISON SARS-CoV-2 S1/S2 IgG; DiaSorin) for the quantitative characterisation of SARS-CoV-2 anti-S1 and anti-S2 IgG antibodies, with values >15 AU/mL indicating a positive

**Table 1** Demographic and clinical characteristics of the study population, stratified for response to the first dose of the BNT162b2 mRNA COVID-19 vaccine

	All n=140 patients	Responders n=85	Non-responders n=55	P value
Age, mean (SD), years	55.7 (14.4)	50.9 (13.9)	63.3 (11.6)	<0.001
Females, n (%)	95 (67.9)	53 (62.4)	42 (76.4)	0.12
BMI, mean (SD)	25.89 (5.24)	25.37 (5.31)	26.69 (5.09)	0.19
Smoking, n (%)	23 (16.4)	14 (16.5)	9 (16.4)	0.83
Hypertension, n (%)	47 (33.6)	23 (27.1)	24 (43.6)	0.07
Obesity, n (%)	26 (18.6)	15 (17.6)	11 (20)	0.89
CCI, mean (SD)	0.57 (0.92)	0.47 (0.91)	0.73 (0.93)	0.11
≥1 comorbidity*, n (%)	50 (35.7)	23 (27.1)	27 (49.1)	0.01
Previous COVID-19*, n (%)	20 (14.3)	19 (22.4)	1 (1.8)	0.002
Diagnosis, n (%):				
RA	83 (59.3)	40 (47.1)	43 (78.2)	<0.001
PsA	29 (20.7)	20 (23.5)	9 (16.4)	0.42
SpA	28 (20)	25 (29.4)	3 (5.5)	0.001
Disease duration, mean (SD), years	13.7 (8.2)	12.9 (8.7)	14.9 (7.2)	0.15
Active disease†, n (%)	34 (24.3)	22 (25.9)	12 (21.8)	0.73
Glucocorticoids, n (%)	53 (37.9)	26 (30.6)	27 (49.1)	0.04
Prednisone dose, mean (SD), mg/day	3.7 (1.8)	3.7 (1.5)	3.7 (2.1)	0.94
csDMARDs, n (%)	80 (57.1)	38 (44.7)	42 (76.4)	<0.001
MTX	66 (47.1)	27 (31.8)	39 (70.9)	<0.001
SSZ	12 (8.6)	10 (11.8)	2 (3.6)	0.17
LFN	5 (3.6)	3 (3.5)	2 (3.6)	0.67
CYA	1 (0.7)	0 (0)	1 (1.8)	0.83
MTX dose, mean (SD), mg/week	14.7 (5.2)	14.6 (5.3)	14.7 (5.2)	0.93
Days of MTX withholding, mean (SD)	16.4 (3.5)	16.1 (3.4)	16.6 (3.6)	0.65
Adherence to MTX withholding‡, n (%)	33 (50)	13 (48.1)	20 (51.3)	0.99
b/tsDMARDs, n (%)	140 (100)	85 (100)	55 (100)	
TNFi	61 (43.6)	39 (45.9)	22 (40)	0.61
IL-6Ri	14 (10)	8 (9.4)	6 (10.9)	0.99
IL-17/IL-23i	19 (13.6)	17 (20)	2 (3.6)	0.01
CTLA4Ig	30 (21.4)	9 (10.6)	21 (38.2)	<0.001
JAKi	12 (8.6)	9 (10.6)	3 (5.5)	0.46
PDE4i	4 (2.9)	3 (3.5)	1 (1.8)	0.94
Days of b/tsDMARD withholding, mean (SD)	22 (13.2)	23.7 (14.7)	19.4 (10.2)	0.06
Adherence to b/tsDMARDs withholding‡, n (%)	96 (68.6)	62 (72.9)	34 (61.8)	0.23

Bold indicates statistically significant values (p<0.05).

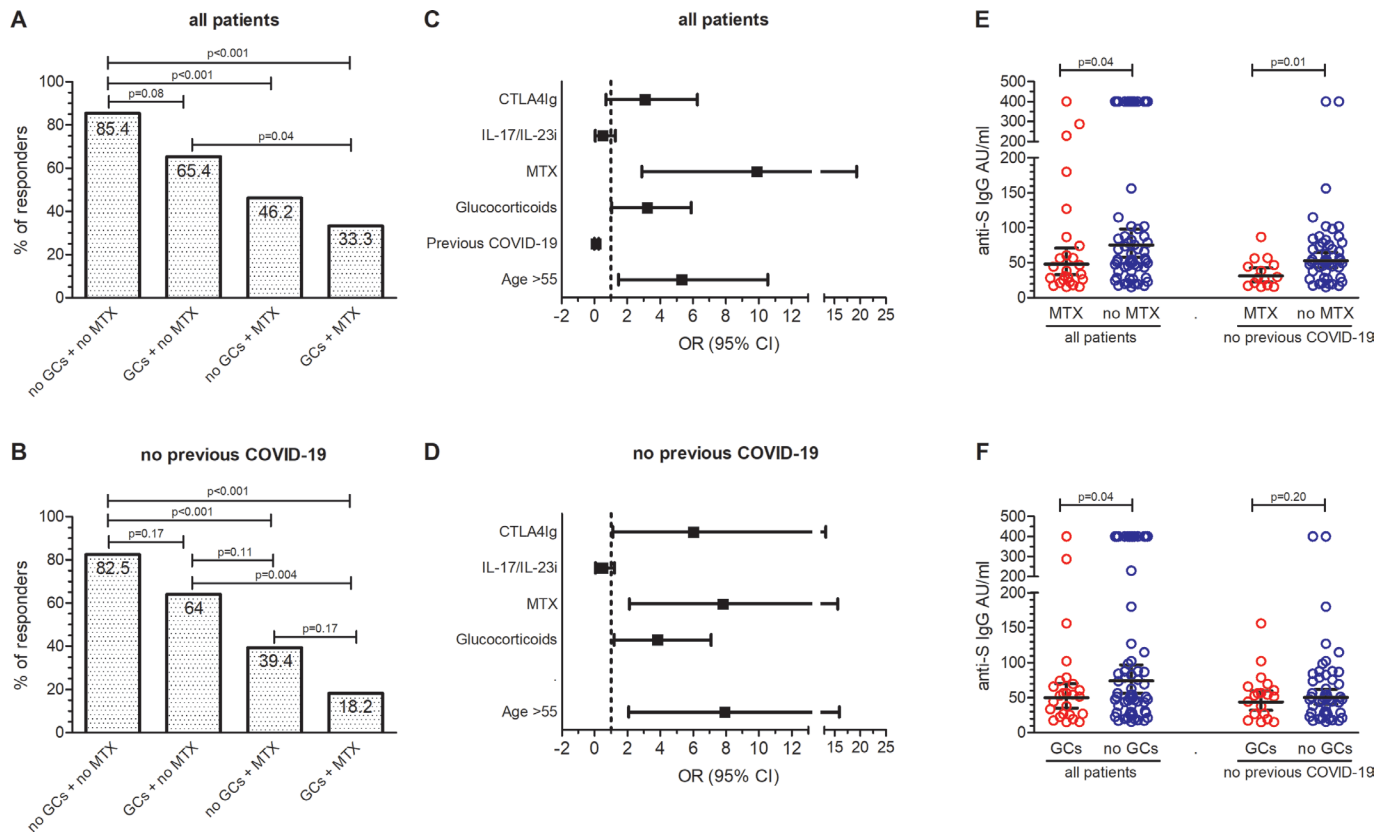
ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score calculated with C reactive protein; BMI, body mass index; b/ts, biological/targeted synthetic CCI, Charlson Comorbidity Index; cs, conventional synthetic; CTLA4Ig, cytotoxic T lymphocyte associated protein-4 immunoglobulin;

CYA, cyclosporine; DAPSA, Disease Activity in Psoriatic Arthritis; DAS28, Disease Activity Score on 28 joints; DMARD, disease-modifying antirheumatic drug; IL-17/IL-23i, interleukin-17/interleukin-23 inhibitor; IL-6Ri, interleukin-6 receptor inhibitor; JAKi, Janus kinase inhibitor; LFN,

leflunomide; MTX, methotrexate; PDE4i, phosphodiesterase-4 inhibitor; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SpA, spondyloarthritis; SSZ, sulphasalazine; TNFi, tumour necrosis factor inhibitor.

‡Among those listed in the Charlson Comorbidity Index.

ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score calculated with C reactive protein; BMI, body mass index; b/ts, biological/targeted synthetic CCI, Charlson Comorbidity Index; cs, conventional synthetic; CTLA4Ig, cytotoxic T lymphocyte associated protein-4 immunoglobulin; CYA, cyclosporine; DAPSA, Disease Activity in Psoriatic Arthritis; DAS28, Disease Activity Score on 28 joints; DMARD, disease-modifying antirheumatic drug; IL-17/IL-23i, interleukin-17/interleukin-23 inhibitor; IL-6Ri, interleukin-6 receptor inhibitor; JAKi, Janus kinase inhibitor; LFN, leflunomide; MTX, methotrexate; PDE4i, phosphodiesterase-4 inhibitor; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SpA, spondyloarthritis; SSZ, sulphasalazine; TNFi, tumour necrosis factor inhibitor.





**Figure 1** Impaired immunogenicity of a single dose of the BNT162b2 mRNA COVID-19 vaccine associated with methotrexate and glucocorticoids. (A and B) Rates of response to the first dose of mRNA COVID-19 vaccine in patients on treatment with biological or targeted synthetic disease-modifying antirheumatic drugs ((A) overall population, n=140; (B) patients with previous exposure to SARS-CoV-2 infection excluded, n=120) stratified for concomitant therapy with glucocorticoids (GCs), methotrexate (MTX) or both. (C and D) Forest plots illustrating factors associated with non-response to the first dose of mRNA COVID-19 vaccine in the overall population (C) and after exclusion of patients with previous exposure to SARS-CoV-2 infection (D). (E and F) Comparisons of anti-S IgG antibody levels in patients achieving response to the first dose of mRNA COVID-19 vaccine (levels above the cut-off of 15 AU/mL at day 21) stratified for concomitant therapy with MTX (E) and GCs (F). Data are shown as geometric mean values with 95% CIs.

result. Demographic and clinical variables were retrieved from the last available rheumatological assessment (median (IQR) 14 (5–19) days before vaccination) (table 1). The b/tsDMARD was predominantly an anticytokine therapy (67.1%), followed by CTLA4Ig (21.4%) and Janus kinase inhibitors (8.6%). Treatment also included low-dose glucocorticoids (mean (SD) prednisone dose 3.8 (1.9) mg/day;  $\leq 5$  mg/day in 98.6% of the cases) in 38.5% of the patients and conventional synthetic DMARDs (mostly methotrexate) in 56.6%. Arthritis was on average well controlled, with 74.8% of the patients being in low disease activity.

Fifty-five patients (39.3%) were non-responders based on anti-S IgG levels at day 21. As shown in table 1, non-responders were more frequently on methotrexate and/or glucocorticoids; among the different b/tsDMARDs, CTLA4Ig was more common and interleukin-17/23 inhibitors were less common in non-responders. Results were confirmed when patients with a known history of swab-confirmed COVID-19 (n=9) or prevaccine antibody levels indicative of previous SARS-CoV-2 infection (n=11) were excluded (online supplemental table S1). Collectively, seroconversion decreased from 85.4% among patients not receiving neither methotrexate nor glucocorticoids to 33.3% among those on both therapies (figure 1A); such significant trend was confirmed after exclusion of patients with previous COVID-19 (figure 1B). At multivariable analysis, methotrexate and glucocorticoids independently predicted

failure to achieve immunogenicity with adjusted ORs (95% CI) of 7.46 (2.88 to 19.33) and 2.69 (1.04 to 5.89), even with the inclusion of patients with previous stimulation by SARS-CoV-2 (online supplemental figure 1S 1C, table S2). In contrast, the effect of CTLA4Ig was restricted to patients with no history of COVID-19 (figure 1C and D and online supplemental table S2). The lower rates of seroconversion observed in patients with RA compared with other arthritis were largely dependent on covariates such as age and type of immunomodulatory treatment. Of note, neither adherence to the recommendations on methotrexate withholding (followed by 50% of the patients) nor the interval of b/tsDMARD discontinuation significantly impacted on the results (online supplemental table S2). The negative impact of methotrexate and glucocorticoids was confirmed in the larger subgroup of patients on tumour necrosis factor inhibitors (online supplemental table S3). Importantly, both drugs also impaired the magnitude of the antibody response among patients who seroconverted (figure 1E and F). The negative association of methotrexate and glucocorticoids with antibody levels was dose dependent (online supplemental table S4). Although the vast majority of the patients was receiving prednisone doses  $\leq 5$  mg/day, differences were already seen between the group treated with  $>2.5$  mg/day and the group treated with  $\leq 2.5$  mg/day (geometric mean (95% CI) anti-S IgG levels 69.81 (150.95) vs 39.85 (83.82) AU/mL,  $p=0.07$ ).

Deeper characterisation of memory B cell and T cell responses after each of the two doses of mRNA vaccines is needed to assist the optimal vaccination strategy in rheumatic patients on immunosuppressive treatments. Furthermore, the impact of specific medications, such as those interfering with interferon-driven responses, needs to be more extensively evaluated in larger patient cohorts. Equally important, strategies of methotrexate withholding, alone or in combination with b/tsDMARDs, should be established through randomised clinical trials. Notwithstanding these limitations, the high rate of response (>80%) following a single dose of mRNA COVID-19 vaccine among patients not receiving neither methotrexate nor glucocorticoids found here approaches the immunogenicity reported in registration trials of BNT162b<sup>6</sup> and confirms the low impact of most anticytokine therapies on vaccination.<sup>3</sup> However, impaired humoral responses associated with methotrexate and glucocorticoids, even at low doses, impose caution before endorsing delayed second dose boosts in rheumatic patients.

Serena Bugatti <sup>1,2</sup>, Ludovico De Stefano,<sup>1,2</sup> Silvia Balduzzi,<sup>1</sup> Maria Immacolata Greco,<sup>1</sup> Terenzj Luvaro,<sup>1</sup> Irene Cassaniti,<sup>3,4</sup> Laura Bogliolo,<sup>1</sup> Iolanda Mazzucchelli,<sup>2</sup> Bernardo D'Onofrio,<sup>1,2</sup> Michele di Lernia,<sup>1,2</sup> Eleonora Mauric,<sup>1,2</sup> Daniele Lillieri,<sup>3</sup> Fausto Baldanti,<sup>3,4</sup> Antonio Manzo,<sup>1,2</sup> Carlomaurizio Montecucco <sup>1,2</sup>

<sup>1</sup>Division of Rheumatology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

<sup>2</sup>Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy

<sup>3</sup>Microbiology and Virology Department, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

<sup>4</sup>Department of Clinical, Surgical, Diagnostic and Paediatric Sciences, University of Pavia, Pavia, Italy

**Correspondence to** Professor Serena Bugatti, Division of Rheumatology, Fondazione IRCCS Policlinico San Matteo, Pavia 27100, Italy; serena.bugatti@unipv.it

**Handling editor** Josef S Smolen

**Acknowledgements** We are grateful to our trainees Alessandra Milanese, Fabio Brandolino, Sofia Chiricolo and Clarissa Rocca for their precious help in recruiting patients and collecting clinical data. We are equally grateful to our nurses Laura Vecchio, Michela Milanese, Massimo Facchini, Marina Filippa Berlinese, Giovanna Strarostj, Maria Carmela Amoroso and Francesca Clarissa Lorato for their unconditioned assistance in the phases of vaccination and blood sampling. On top, we are grateful to our patients for their enthusiasm in the COVID-19 vaccination campaign.

**Contributors** SBU conceived the work, contributed to the analysis and interpretation of data and drafted the manuscript. LDS conceived the work, contributed to the analysis and interpretation of data, and drafted the manuscript. SBA contributed to the acquisition and interpretation of clinical and laboratory data and revised the manuscript critically. MIG, TL and IM contributed to the collection and handling of serum samples, to the interpretation of data and revised the manuscript critically. IC contributed to the analysis of serum samples, to the interpretation of the results and revised the manuscript critically. LB contributed to the acquisition and interpretation of data and revised the manuscript critically. BD, MdL and EM contributed to the acquisition of clinical data, to the collection of serum samples and revised the manuscript critically. DL contributed to the analysis of serum samples, to the interpretation of the results and revised the manuscript critically. FB contributed to the interpretation of data and revised the manuscript critically for important intellectual content. AM contributed to the analysis and interpretation of data and revised the manuscript critically for important intellectual content. CM conceived the work and revised the manuscript critically for important intellectual content. All the authors provided final approval of the version to be published.

**Funding** This study was supported in part by fundings from the IRCCS Policlinico San Matteo Foundation, Pavia, Italy.

**Competing interests** None declared.

**Patient and public involvement statement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not required.

**Ethics approval** The study was approved by the Local Ethical Committee of the IRCCS Policlinico San Matteo Foundation, Pavia, Italy.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** The authors confirm that the data supporting the findings of this study are available within the article. Raw data are available from the corresponding author (SBU) on reasonable request.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

This article is made freely available for use in accordance with BMJ's website terms and conditions for the duration of the covid-19 pandemic or until otherwise determined by BMJ. You may use, download and print the article for any lawful, non-commercial purpose (including text and data mining) provided that all copyright notices and trade marks are retained.

© Author(s) (or their employer(s)) 2021. No commercial re-use. See rights and permissions. Published by BMJ.

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/annrheumdis-2021-220862>).



**To cite** Bugatti S, De Stefano L, Balduzzi S, *et al.* *Ann Rheum Dis* Epub ahead of print: [please include Day Month Year]. doi:10.1136/annrheumdis-2021-220862

Received 26 May 2021

Accepted 21 June 2021

*Ann Rheum Dis* 2021;**0**:1–3. doi:10.1136/annrheumdis-2021-220862

#### ORCID iDs

Serena Bugatti <http://orcid.org/0000-0002-5396-7077>

Carlomaurizio Montecucco <http://orcid.org/0000-0001-8263-3925>

#### REFERENCES

- 1 Boyarsky BJ, Werbel WA, Avery RK, *et al.* Immunogenicity of a single dose of SARS-CoV-2 messenger RNA vaccine in solid organ transplant recipients. *JAMA* 2021;325:1784–6.
- 2 Monin L, Laing AG, Muñoz-Ruiz M, *et al.* Safety and immunogenicity of one versus two doses of the COVID-19 vaccine BNT162b2 for patients with cancer: interim analysis of a prospective observational study. *Lancet Oncol* 2021;22:765–78.
- 3 Curtis JR, Johnson SR, Anthony DD. American College of rheumatology guidance for COVID-19 vaccination in patients with rheumatic and musculoskeletal diseases: version 1. *Arthritis Rheumatol* 2021. [Epub ahead of print: 17 Mar 2021]. doi:10.1002/art.41734
- 4 Simon D, Tascilar K, Fagni F. SARS-CoV-2 vaccination responses in untreated, conventionally treated and anticytokine-treated patients with immune-mediated inflammatory diseases. *Ann Rheum Dis* 2021. [Epub ahead of print: 06 May 2021]. [annrheumdis-2021-220461](https://doi.org/10.1136/annrheumdis-2021-220461). doi:10.1136/annrheumdis-2021-220461
- 5 Spiera R, Jinich S, Jannat-Khah D. Rituximab, but not other antirheumatic therapies, is associated with impaired serological response to SARS-CoV-2 vaccination in patients with rheumatic diseases. *Ann Rheum Dis* 2021.
- 6 Walsh EE, Frenck RW, Falsey AR, *et al.* Safety and immunogenicity of two RNA-based Covid-19 vaccine candidates. *N Engl J Med* 2020;383:2439–50.

**Supplementary Table S1.** Demographic and clinical characteristics of the study population with no previous exposure to SARS-CoV-2, stratified for response to the first dose of the BNT162b2 mRNA COVID-19 vaccine.

	All n=120 pts	Responders n=66	Non-responders n=54	p
Age, mean (SD), yrs	56.7 (14.0)	51.2 (13.4)	63.5 (11.6)	<b>&lt;0.001</b>
Females, n. (%)	81 (67.5)	40 (60.6)	41 (75.9)	0.11
BMI, mean (SD)	26.09 (5.22)	25.59 (5.33)	26.69 (5.09)	0.30
Smoking, n. (%)	20 (16.7)	11 (16.7)	9 (16.6)	0.82
Hypertension, n. (%)	42 (35)	18 (27.3)	24 (44.4)	0.08
Obesity, n. (%)	24 (20)	13 (19.7)	11 (20.4)	0.89
CCI, mean (SD)	0.53 (0.88)	0.39 (0.82)	0.70 (0.92)	0.05
≥1 comorbidity*, n. (%)	42 (35)	16 (24.2)	26 (48.1)	<b>0.01</b>
Diagnosis, n. (%):				
RA	69 (57.5)	27 (40.9)	42 (77.8)	<b>&lt;0.001</b>
PsA	26 (21.7)	17 (25.8)	9 (16.7)	0.33
SpA	25 (20.8)	22 (18.3)	3 (5.6)	0.07
Disease duration, median (IQR), yrs	13.8 (8.0)	13.2 (8.7)	14.6 (7.0)	0.34
Active disease <sup>§</sup> , n. (%)	27 (22.5)	15 (22.7)	12 (22.2)	0.88
Glucocorticoids, n. (%)	47 (39.2)	20 (30.3)	27 (50)	<b>0.04</b>
Prednisone dose, mean (SD), mg/d	3.6 (1.8)	3.5 (1.3)	3.7 (2.1)	0.69
csDMARDs, n. (%)	67 (55.8)	26 (39.4)	41 (75.9)	<b>&lt;0.001</b>
MTX	55 (45.8)	17 (25.8)	38 (70.4)	<b>&lt;0.001</b>
SSZ	11 (9.2)	9 (13.6)	2 (3.7)	0.12
LFN	3 (2.5)	1 (1.5)	2 (3.7)	0.86
CYA	1 (0.8)	0 (0)	1 (1.9)	0.90
MTX dose, mean (SD), mg/wk	14.8 (5.3)	15.3 (5.7)	14.6 (5.2)	0.66
Days of MTX withholding, mean (SD)	16.3 (3.5)	15.9 (3.5)	16.6 (3.6)	0.57
Adherence to MTX withholding <sup>^</sup> , n. (%)	26 (47.3)	6 (35.3)	20 (52.6)	0.37
b/tsDMARDs, n. (%)	120 (100)	66 (100)	54 (100)	
TNFi	53 (44.2)	33 (50)	20 (37)	0.21
IL-6Ri	12 (10)	6 (9.1)	6 (11.1)	0.95
IL-17/IL-23i	16 (13.3)	14 (21.2)	2 (3.7)	<b>0.01</b>
CTLA4Ig	25 (20.8)	4 (6.1)	21 (38.9)	<b>&lt;0.001</b>
JAKi	10 (8.3)	7 (10.6)	3 (5.6)	0.51
PDE4i	4 (3.3)	3 (4.5)	1 (1.9)	0.78
Days of b/tsDMARD withholding, mean (SD)	22 (13.8)	24.1 (15.9)	19.4 (10.2)	0.06
Adherence to b/tsDMARDs withholding <sup>^</sup> , n. (%)	80 (66.7)	47 (71.2)	33 (61.1)	0.33

b/ts = Biologic/Targeted Synthetic; BMI = Body Mass Index; CCI = Charlson Comorbidity Index; cs = Conventional Synthetic; CTLA4Ig = Cytotoxic T-lymphocyte Associated Protein-4 Immunoglobulin; CYA = Cyclosporine; DMARD = Disease Modifying Anti-Rheumatic Drug; IL-6Ri = Interleukin-6 Receptor Inhibitor; IL-17/IL-23i = Interleukin-17/Interleukin-23 Inhibitor; JAKi = Janus Kinase Inhibitor; LFN = Leflunomide; MTX = Methotrexate; PDE4i = Phosphodiesterase-4 inhibitor; RA = Rheumatoid Arthritis; PsA = Psoriatic Arthritis; SpA = Spondyloarthritis; SSZ = Sulphasalazine; TNFi = Tumor Necrosis Factor Inhibitor.

\*among those listed in the Charlson Comorbidity Index

<sup>§</sup>above the threshold of low disease activity according to the appropriate composite index: DAS28 >3.2; DAPSA >14; ASDAS-PCR >2.1. DAS28 = Disease Activity Score on 28 joints; DAPSA = Disease Activity in Psoriatic Arthritis; ASDAS-CRP = Ankylosing Spondylitis Disease Activity Score calculated with C-Reactive Protein.

<sup>^</sup>recommendations for timing of immunomodulatory therapies in relation to vaccination: (i) for all the bDMARDs and MTX, withholding of therapy in the 7 days before and after vaccination; (ii) for tsDMARDs, withholding of therapy from the day before until day 7 after vaccination; (iii) for glucocorticoids and csDMARDs other than MTX, no modifications.

**Supplementary Table S2.** Demographic and clinical factors associated with non-response to the first dose of the BNT162b2 mRNA COVID-19 vaccine. Univariable and multivariable analysis.

	All n=140			No previous COVID-19 n=120		
<b>Univariable analysis</b>						
	<b>OR</b>	<b>95% CI</b>	<b>p</b>	<b>OR</b>	<b>95% CI</b>	<b>p</b>
Age>55	6.30	2.86 to 13.91	<0.001	6.77	2.91 to 15.77	<0.001
Female gender	1.95	0.91 to 4.18	0.09	2.05	0.93 to 4.54	0.08
BMI	1.05	0.98 to 1.13	0.19	1.04	0.96 to 1.13	0.30
Smoking	1.07	0.41 to 2.82	0.89	1.09	0.40 to 3.03	0.86
CCI	1.35	0.93 to 1.95	0.11	1.52	0.98 to 2.36	0.06
≥1 comorbidity*	2.60	1.27 to 5.30	<b>0.009</b>	2.90	1.34 to 6.30	<b>0.007</b>
Previous COVID-19 <sup>#</sup>	0.06	0.01 to 0.50	<b>0.009</b>	--	--	--
Diagnosis						
RA	Reference			Reference		
PsA	0.42	0.17 to 1.03	0.06	0.34	0.13 to 0.87	<b>0.02</b>
SpA	0.11	0.03 to 0.40	<0.001	0.09	0.02 to 0.32	<0.001
Disease duration	1.03	0.99 to 1.08	0.16	1.02	0.98 to 1.07	0.34
Active disease <sup>§</sup>	1.27	0.39 to 4.17	0.69	1.07	0.30 to 3.79	0.92
Glucocorticoids	2.19	1.08 to 4.41	<b>0.03</b>	2.30	1.09 to 4.86	<b>0.03</b>
Prednisone dose	1.16	0.99 to 1.36	0.07	1.21	1.01 to 1.45	<b>0.04</b>
MTX	5.24	2.50 to 10.97	<0.001	6.85	3.07 to 15.29	<0.001
MTX dose	1.09	1.04 to 1.14	<0.001	1.10	1.05 to 1.16	<0.001
Days of MTX withholding	1.04	0.88 to 1.24	0.64	1.05	0.86 to 1.27	0.65
Adherence to MTX withholding <sup>^</sup>	1.20	0.37 to 3.92	0.76	1.98	0.49 to 7.94	0.34
b/tsDMARD						
TNFi	Reference			Reference		
IL-6Ri	1.39	0.43 to 4.55	0.58	1.60	0.45 to 5.65	0.47
IL17/IL-23i	0.22	0.05 to 1.04	0.06	0.23	0.05 to 1.11	0.07
CTLA4Ig	4.33	1.69 to 11.14	<b>0.002</b>	8.40	2.51 to 28.07	<0.001
JAKi	0.62	0.15 to 2.54	0.51	0.69	0.16 to 2.96	0.61
PDE4i	0.62	0.06 to 6.33	0.69	0.53	0.05 to 5.49	0.60
Days of b/tsDMARD withholding	0.97	0.94 to 1.00	0.06	0.97	0.94 to 0.99	<b>0.04</b>
Adherence to b/tsDMARDs withholding <sup>^</sup>	0.58	0.28 to 1.20	0.14	0.60	0.27 to 1.29	0.19
<b>Multivariable analysis</b>						
	<b>OR</b>	<b>95% CI</b>	<b>p</b>	<b>OR</b>	<b>95% CI</b>	<b>p</b>
Age>55	3.93	1.46 to 10.55	<b>0.006</b>	5.74	2.07 to 15.93	<0.001
Female gender	--	--	--	--	--	--
≥1 comorbidity*	--	--	--	--	--	--
Previous COVID-19 <sup>#</sup>	0.03	0.00 to 0.25	<b>0.002</b>			
RA	--	--	--	--	--	--
Glucocorticoids	2.69	1.04 to 5.89	<b>0.04</b>	3.17	1.18 to 7.09	<b>0.03</b>
MTX	7.46	2.88 to 19.33	<0.001	5.73	2.11 to 15.58	<0.001
b/tsDMARD						
anti-IL17/IL-23	0.20	0.04 to 1.27	0.10	0.21	0.04 to 1.21	0.08
CTLA4Ig	2.28	0.69 to 6.26	0.19	3.64	1.11 to 13.28	<b>0.04</b>
Days of b/tsDMARD withholding	--	--	--	--	--	--



b/ts = Biologic/Targeted Synthetic; BMI = Body Mass Index; CCI = Charlson Comorbidity Index; CTLA4Ig = Cytotoxic T-lymphocyte Associated Protein-4 Immunoglobulin; DMARD = Disease Modifying Anti-Rheumatic Drug; IL-6Ri = Interleukin-6 Receptor Inhibitor; IL-17/IL-23i = Interleukin-17/Interleukin-23 Inhibitor; JAKi = Janus Kinase Inhibitor; MTX = Methotrexate; PDE4i = Phosphodiesterase-4 inhibitor; RA = Rheumatoid Arthritis; PsA = Psoriatic Arthritis; SpA = Spondyloarthritis; TNFi = Tumor Necrosis Factor Inhibitor.

\*among those listed in the Charlson Comorbidity Index

#based on patient-reported history of swab-confirmed SARS-CoV-2 infection and/or on pre-vaccine anti-S IgG levels >15 AU/mL (LIAISON<sup>®</sup> SARS-CoV-2 S1/S2 IgG; DiaSorin)

<sup>§</sup>above the threshold of low disease activity according to the appropriate composite index: DAS28 >3.2; DAPSA >14; ASDAS-PCR >2.1. DAS28 = Disease Activity Score on 28 joints; DAPSA = Disease Activity in Psoriatic Arthritis; ASDAS-CRP = Ankylosing Spondylitis Disease Activity Score calculated with C-Reactive Protein.

<sup>^</sup>recommendations for timing of immunomodulatory therapies in relation to vaccination: (i) for all the bDMARDs and MTX, withholding of therapy in the 7 days before and after vaccination; (ii) for tsDMARDs, withholding of therapy from the day before until day 7 after vaccination; (iii) for glucocorticoids and csDMARDs other than MTX, no modifications.

**Supplementary Table S3.** Demographic and clinical factors associated with non-response to the first dose of the BNT162b2 mRNA COVID-19 vaccine in the subgroup of patients treated with tumor necrosis factor inhibitors. Univariable and multivariable analysis.

	All n=61			No previous COVID-19 n=53		
<b>Univariable analysis</b>						
	<b>OR</b>	<b>95% CI</b>	<b>p</b>	<b>OR</b>	<b>95% CI</b>	<b>p</b>
Age>55	7.23	2.01 to 25.96	<b>0.002</b>	8.08	1.95 to 33.40	<b>0.004</b>
Female gender	0.91	0.30 to 2.80	0.87	0.97	0.30 to 3.14	0.96
BMI	1.05	0.95 to 1.17	0.34	1.04	0.93 to 1.15	0.51
Smoking	0.32	0.04 to 2.87	0.31	0.33	0.04 to 3.05	0.33
CCI	1.57	0.83 to 2.95	0.16	1.48	0.75 to 2.90	0.26
≥1 comorbidity*	3.71	1.13 to 12.16	<b>0.03</b>	3.73	1.04 to 13.45	<b>0.04</b>
Previous COVID-19 <sup>#</sup>	0.27	0.03 to 2.37	0.24	--	--	--
Diagnosis						
RA	Reference			Reference		
PsA	0.71	0.17 to 3.03	0.65	0.67	0.15 to 3.04	0.60
SpA	0.20	0.05 to 0.83	<b>0.03</b>	0.18	0.04 to 0.78	<b>0.02</b>
Disease duration	1.06	0.99 to 1.12	0.07	1.06	0.99 to 1.13	0.10
Active disease <sup>§</sup>	1.06	0.08 to 13.52	0.96	0.81	0.06 to 10.48	0.87
Glucocorticoids	3.71	1.13 to 12.16	<b>0.03</b>	3.86	1.11 to 13.37	<b>0.03</b>
Prednisone dose	1.36	1.01 to 1.83	<b>0.04</b>	1.35	0.99 to 1.83	0.06
MTX	8.40	2.43 to 29.04	<b>&lt;0.001</b>	7.14	1.97 to 25.94	<b>0.003</b>
MTX dose	1.12	1.04 to 1.21	<b>0.002</b>	1.11	1.03 to 1.20	<b>0.006</b>
Days of MTX withholding, mean (SD)	1.05	0.80 to 1.38	0.73	1.06	0.79 to 1.42	0.71
Adherence to MTX withholding <sup>^</sup>	0.90	0.13 to 6.08	0.91	1.50	0.17 to 13.23	0.72
Days of TNFi withholding, mean (SD)	0.98	0.94 to 1.03	0.41	0.97	0.93 to 1.02	0.26
Adherence to TNFi withholding <sup>^</sup>	1.10	0.37 to 3.29	0.87	1.11	0.35 to 3.49	0.86
<b>Multivariable analysis</b>						
	<b>OR</b>	<b>95% CI</b>	<b>p</b>	<b>OR</b>	<b>95% CI</b>	<b>p</b>
Age>55	6.86	1.02 to 46.19	<b>0.04</b>	11.38	1.64 to 78.80	<b>0.01</b>
≥1 comorbidity*	3.68	0.59 to 22.98	0.16	--	--	--
SpA	--	--	--	--	--	--
Disease duration	--	--	--	--	--	--
Glucocorticoids	7.66	1.29 to 45.61	<b>0.03</b>	6.44	1.16 to 35.71	<b>0.03</b>
MTX	23.26	3.37 to 160.42	<b>0.001</b>	14.94	2.34 to 95.30	<b>0.004</b>

BMI = Body Mass Index; CCI = Charlson Comorbidity Index; MTX = Methotrexate; RA = Rheumatoid Arthritis; PsA = Psoriatic Arthritis; SpA = Spondyloarthritis; TNFi = Tumor Necrosis Factor Inhibitor.

\*among those listed in the Charlson Comorbidity Index

<sup>#</sup>based on patient-reported history of swab-confirmed SARS-CoV-2 infection and/or on pre-vaccine anti-S IgG levels >15 AU/mL (LIAISON<sup>®</sup> SARS-CoV-2 S1/S2 IgG; DiaSorin)

<sup>§</sup>above the threshold of low disease activity according to the appropriate composite index: DAS28 >3.2; DAPSA >14; ASDAS-PCR >2.1. DAS28 = Disease Activity Score on 28 joints; DAPSA = Disease Activity in Psoriatic Arthritis; ASDAS-CRP = Ankylosing Spondylitis Disease Activity Score calculated with C-Reactive Protein.

<sup>^</sup>recommendations for timing of immunomodulatory therapies in relation to vaccination: (i) for all the bDMARDs and MTX, withholding of therapy in the 7 days before and after vaccination; (ii) for tsDMARDs,

withholding of therapy from the day before until day 7 after vaccination; (iii) for glucocorticoids and csDMARDs other than MTX, no modifications



**Supplementary Table S4.** Association of methotrexate and glucocorticoids with anti-S IgG levels in responders to the first dose of the BNT162b2 mRNA COVID-19 vaccine. Multivariable analysis.

	All n=85		No previous COVID-19 n=66	
	Stand $\beta$	p	Stand $\beta$	p
Age	--	--	--	--
Pre-vaccine anti-S IgG levels	0.56	<b>&lt;0.001</b>	--	--
Prednisone dose	-0.17	<b>0.04</b>	-0.16	<b>0.04</b>
Methotrexate dose	-0.15	0.05	-0.18	<b>0.04</b>