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.[1 2] 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.[3] 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.[4 5]

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).
*Based on patient-reported history of swab-confirmed SARS-CoV-2 infection and/or on prevaccine anti-S IgG levels >15 AU/mL (LIAISON SARS-CoV-2 S1/S2 IgG; DiaSorin).
†Above the threshold of low disease activity according to the appropriate composite index: DAS28 >3.2; DAPSA >14; ASDAS-PCR >2.1.
‡Recommendations for timing of immunomodulatory therapies in relation to vaccination: (1) for all the bDMARDs and MTX, withholding of therapy in the 7 days before and after vaccination; (2) for tsDMARDs, withholding of therapy from the day before until day 7 after vaccination; and (3) for glucocorticoids and csDMARDs other than MTX, no modifications.
§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.

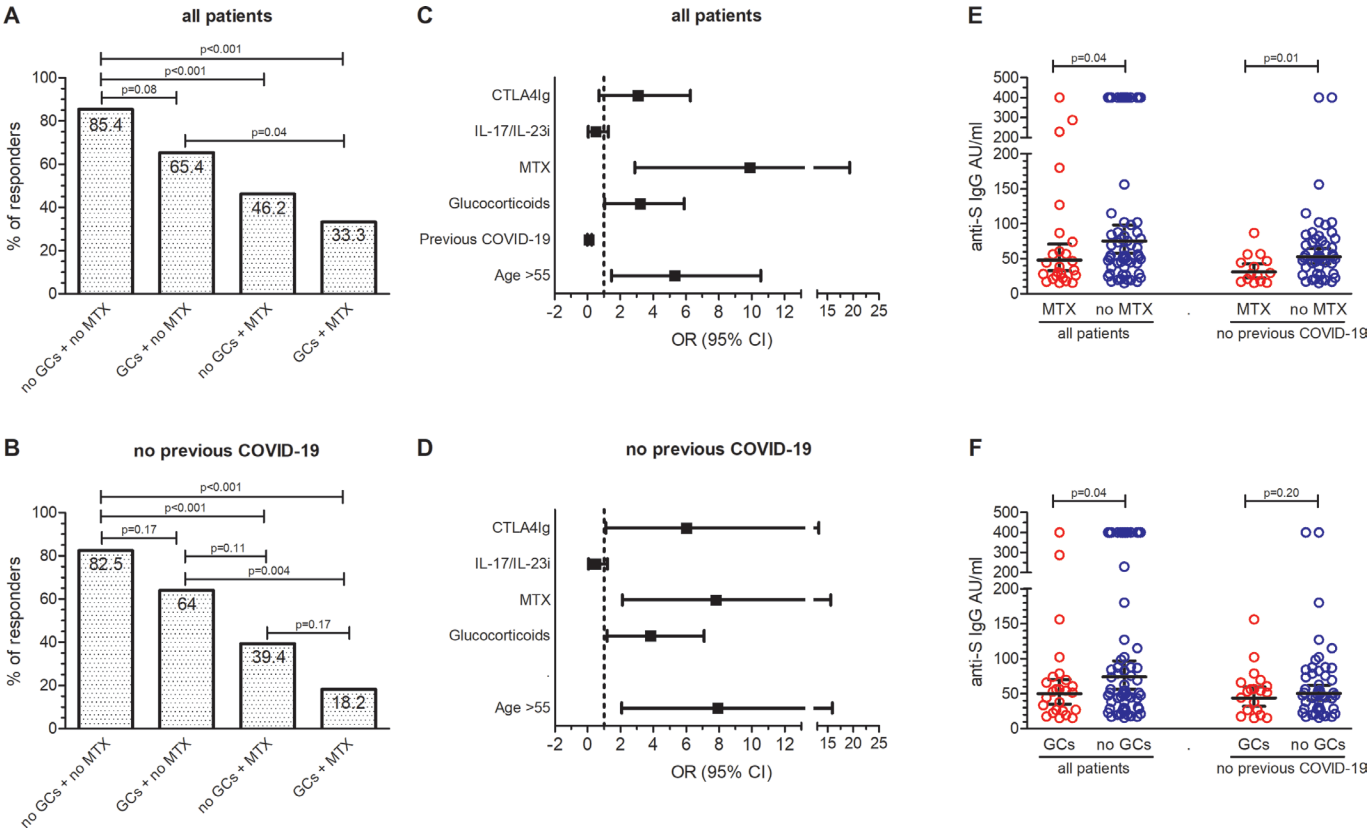

Figure 1 Impaired immunogenicity of a single dose of the BNT162b2 mRNA COVID-19 vaccine associated with methotrexate and glucocorticoids. (A and B) Rates of response to the first dose of mRNA COVID-19 vaccine in patients on treatment with biological or targeted synthetic disease-modifying antirheumatic 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; ≤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 ≤5 mg/day, differences were already seen between the group treated with >2.5 mg/day and the group treated with ≤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 BNT162b2[6] and confirms the low impact of most anticytokine therapies on vaccination.[3] However, impaired humoral responses associated with methotrexate and glucocorticoids, even at low doses, impose caution before endorsing delayed second dose boosts in rheumatic patients.

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