Letters to the Editors

Humoral and T-cell immune response following three doses of SARS-CoV-2 mRNA vaccine in giant cell arteritis: analysis of a prospective cohort

Sirs,

The present study describes SARS-CoV-2-specific humoral and cellular response in patients with giant cell arteritis (GCA) receiving three mRNA vaccine doses.

GCA patients followed up at the Rheumatology Clinic of Policlinico San Matteo, Pavia, Italy, were assessed for their immune status before (T2) and after (T3) the third anti-SARS-CoV-2 mRNA vaccine (BNT162b2 Pfizer/BioNtech or mRNA-1273 Moderna). Anti-SARS-CoV-2 trimeric spike (S-IgG) and neutralising (NtAbs) antibodies were measured (cut-off 33.8 Binding Antibody Units (BAU)/mL and 1:10 dilutions, respectively). T cell response was estimated via enzyme-linked immunospot assay (cut-off 10 IFN-γ spot-forming units [SFU]/10^6 PBMC). Patients contracting COVID-19 between the onset of the pandemic and T3 were excluded. Healthy controls were used as a comparison.

Forty-two patients were enrolled (Table I), 31 (73.8%) were females, median age 73 years (IQR 69-82). Thirty-three (78.6%) were on glucocorticoids (GCs) at a median dose of 3.8 mg/day prednisone-equivalents (IQR 1.3–5.0). Methotrexate (MTX) was the additional immunosuppressant in 17 (40.5%) patients, while six (14.3%) were treated with subcutaneous tocilizumab 162 mg/week (TCZ). At T2, 95.2% patients retained S-IgGs, 69.0% NtAbs, and 76.2% cellular response. Seroconversion rates at T3 were 97.6% for S-IgGs and 95.2% for NtAbs, median antibody titres rose from 138 BAU/mL (IQR 85-320) to 2080 BAU/mL (IQR 1863–2080) and from 10 (IQR 5-40) to 320 dilutions (IQR 160–640) respectively (p<0.0001). T3 cellular response was detectable in 80.5%, median 30 IFN-γ SFU/10^6 PBMC (IQR 10-80) (*vs*. 15 IFN-γ SFU/10^6 PBMC IQR 10-39 at T2, p=0.007). S-IgG and NtAbs levels, as well as T-cell response at T3 remained significantly lower than healthy controls.

Patients not developing NtAbs were more likely on medium-high GC doses (29.4 mg/day IQR 19.1–39.7 *vs*. 3.8 mg/day IQR 1.3–5.0, p=0.03) and were all taking MTX. GC ≥7.5 mg/day prednisone-equivalents were associated to lower seroconversion rates for both S-IgGs (83.3% *vs*. 100%, p=0.01) and NtAbs (66.7% *vs*. 100%, p=0.0005). Lower antibody levels were found in patients taking MTX: S-IgGs were 2040 BAU/mL (IQR 1590–2040) *vs*. 2080 BAU/mL (IQR 2080–2080) (p=0.03), while NtAbs dilutions were 160 (IQR 80–320) *vs*. 320 (IQR 160–640) (p=0.01). The combination GCs+MTX was associated to lower seroconversion rates and titres of both S-IgGs (92.9% *vs*. 100%, p=0.2–2060 BAU/mL IQR 645–2080 *vs*. 2080 BAU/mL IQR 2080–2080, p=0.02) and NtAbs (85.7% *vs*. 100%, p=0.04–120 dilutions IQR 80–280 *vs*. 480 dilutions IQR 160–640, p=0.003). MTX was associated to a reduced cellular response: 64.7% *vs*. 91.7% (p=0.03) with median 15 IFN-γ SFU/10^6 PBMC IQR 5–20 *vs*. 45 IFN-γ SFU/10^6 PBMC IQR 19–90 (p=0.04). Similarly, GC≥5 mg/day impaired the cellular response (20 IFN-γ SFU/10^6 PBMC IQR 0–35 *vs*. 55 IFN-γ SFU/10^6 PBMC IQR 10–106, p=0.02). The association GC+MTX again resulted in a poorer T-cell response: only eight patients taking GC+MTX (57.1%) had a detectable cellular response *vs*. 25 (92.6%) of the non-GC+MTX group (p=0.007). TCZ did not alter vaccine immunogenicity (p>0.05).

Three patients (7.1%) experienced a GCA flare 24±5 days after the third dose. Nine (21.4%) had COVID-19 at a median of 3.1 months (IQR 2.0-6.3) after the vaccine, none of them requiring hospitalisation.

To conclude, three vaccine doses conferred excellent seroconversion rates in a cohort of elderly patients receiving immunosuppressants. Nevertheless, immunosuppressive treatment reduced S-IgGs and NtAbs titres and influenced the cellular response. As experienced with the first immunisation round, GC partially contribution in decreasing the cellular immune response to the third dose (1). MTX significantly impaired humoral immune response and it might contribute to decreasing the cellular one, especially when combined with GCs, while TCZ did not (2, 3). Patients who contracted COVID-19 had a favourable outcome, in accordance with the previous literature evidence (4).

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Table I. SARS-CoV-2-specific immune response 6 months after the second vaccine dose (T2), and three weeks after the third (T3) compared to healthy controls. Humoral and cellular response in patients treated with MTX was weaker to those who were not.

	Overall T2 (n=42)	Overall T3 (n=42)	p	Controls T3 (n=59)	p	GC≥7.5 mg/die T3 (n=6)	GC<7.5 mg/die T3 (n=36)	p	MTX T3 (n=17)	No MTX T3 (n=25)	p	TCZ T3 (n=6)	No TCZ T3 (n=36)	p
S-IgG+, n (%)	40 (95.2)	41 (97.6)	0.6	59 (100.0)	0.2	5 (83.3)	36 (100.0)	0.01	16 (94.1)	25 (100.0)	0.2	6 (100.0)	35 (97.2)	0.7
S-IgG titre, BAU/mL, median (IQR)	138 (85-320)	2080 (1863-2080)	<0.0001	2080 (2080-2080)	0.002	2080 (730-2080)	2080 (1988-2080)	0.5	2040 (1590-2040)	2080 (2080-2080)	0.04	2080 (2080-2080)	2080 (1810-2080)	0.7
NtAbs+, n (%)	29 (69.0)	40 (95.2)	0.002	59 (100.0)	0.09	4 (66.7)	36 (100.0)	0.0005	15 (88.2)	25 (100.0)	0.08	6 (100.0)	34 (94.4)	0.6
NtAbs titre, 1:10 dilutions, median (IQR)	10 (5-40)	320 (160-640)	<0.0001	640 (320-640)	0.003	320 (84-560)	320 (160-640)	0.7	160 (80-320)	320 (160-640)	0.01	160 (100-520)	320 (160-640)	0.3
T cell responders, n (%)	32 (76.2)	33 (80.5)	0.6	59 (100.0)	0.0004	4 (66.7)	29 (82.9)	0.4	11 (64.7)	22 (91.7)	0.03	6 (100.0)	27 (77.1)	0.2
T cell response, IFN-γ SFU/10^6 PBMC, median (IQR)	15 (10-39)	30 (10-80)	0.007	110 (68-228)	0.02	15 (4-30)	35 (10-93)	0.1	15 (5-20)	45 (19-90)	0.02	50 (38-93)	20 (10-73)	0.3