Flares of mixed cryoglobulinaemia vasculitis after vaccination against SARS-CoV-2

Studies on the safety and immunogenicity of SARS-CoV-2 vaccination in patients with inflammatory rheumatic diseases

Table 1 Demographic, clinical and immunological features of patients who had flare of stable MC vasculitis bona fide caused by vaccination against SARS-CoV-2

Patient	Age (years)/ sex	MC type	SVR (months)	Last active symptoms and RTX before vaccination (months)		Vaccine	Symptoms after first dose	Symptoms after second dose	Cryocrit, %		SARS-CoV-2 Antibody titre (Binding Antibody Units;/ mL)
				Symptoms	RTX				Prevaccination	Flare	
1	70/male	EMC	N/A	P (40)	N/T	AstraZeneca	Diffuse P (day 3)	Second dose refused	1	6	N/A
2	41/female	EMC	N/A	P (20)	20	Pfizer	None	Diffuse P (day 1)	0	0	900
3	76/female	EMC	N/A	P (27)	N/T	Pfizer	None	Diffuse P (day 5)	0	0	2961
4	57/female	HCV-MC	67	PN (42)	N/T	Pfizer	None	Moderate P, PN (day 10)	Traces	Traces	694
5	66/female	HCV-MC	62	P, PN (48)	N/T	Pfizer	None	Moderate P, PN (day 7)	Traces	0	3115
6	63/female	HCV-MC	30	P, PN (26)	N/T	Pfizer	None	Moderate P (day 7)	0	10	2430

EMC, essential mixed cryoglobulinaemia; HCV-MC, hepatitis C virus-related mixed cryoglobulinaemia; MC, mixed cryoglobulinaemia; N/A, not applicable; N/T, never treated; P, purpura; PN, peripheral neuropathy; RTX, rituximab therapy; SVR, sustained virological response after antiviral therapy.

have so far not included mixed cryoglobulinaemia (MC) vasculitis.[1–3] We report a prospective observational multicentre study on this disorder.

Participants were followed at four tertiary referral centres and were instructed to promptly inform the attending physicians about unusual events felt as possibly related to vaccination. Seventy-one patients were recruited: they had infection-cured hepatitis C virus (HCV)-related MC, either uncomplicated (HCV-MC, n=50) or complicated by low-grade non-Hodgkin's lymphoma (MC-NHL, n=8), or essential MC (EMC, n=13). The characteristics of the patients, exclusion criteria and definition of bona fide vaccination-related flare are described in online supplemental methods.

Overall, 9 of 71 (12.7%) patients had postvaccination MC vasculitis flare. However, 8 of 71 patients had experienced within 12 months before vaccination spontaneous flares, where 7 cases required rituximab and 3 of them (37.5%) had postvaccination flare (see online supplemental information). Thus, to exclude the confounding effects of high proneness to spontaneous flare as the facilitator and of rituximab as the preventor, we further restricted the evaluation of postvaccination flare rate to 63 patients off-therapy and without spontaneous flares for 20–48 months before vaccination (see online supplemental information). In none of them rituximab was postponed in view of vaccination.

Six of the 63 patients (9.5%) with stable MC had bona fide vaccination-related flares (table 1). Flares were more frequent in patients with EMC (3 of 8, 37%) than with HCV-cured HCV-MC or MC-NHL (3 of 55, 5.4%) (p=0.023). Flares were characterised by purpura, new onset in one case, which subsided within 1–2 weeks; in three cases the purpura was so diffuse (online supplemental figure 1) that one patient defined it as 'never experienced before' and another refused the second dose. Two patients also had flare of peripheral neuropathy that had remained stable for several months. Cryoglobulins (online supplemental figure 2A) increased in 2 of 6 patients with and in 0 of 25 patients without flare tested (p=0.032).

Anti-SARS-CoV-2 IgG responses were measured 8–14 days after the second dose of vaccine in 50 patients. Five of 43 (11.6%) rituximab-free and 5 of 7 (71%) rituximab-treated patients (p=0.002) proved seronegative (<7 binding antibody units /mL) (online supplemental figure 2B). Seronegativity was more frequent (p=0.04) among patients with EMC (2 of 5) than with HCV-MC (1 of 33) (online supplemental figure 2C), suggesting lower immune dysregulation in HCV-MC due to reversion of B cell abnormalities after clearance of infection.[4] Among rituximab-treated patients, seronegativity correlated with B cell count <5 cells/µL (online supplemental table 2). No correlations were found between seronegativity and vasculitis flare or cryocrit level (online supplemental figure 2D,E).

Concerning possible mechanism(s) of post-vaccination flare, it is interesting that pathogenic rheumatoid factor-specific B cells expanded in MC are unresponsive to the stimulation of the B cell receptor and of toll-like receptors (TLR) 7 and 9, but can be activated by the simultaneous engagement of these receptors[5]; thus, vaccination-induced immune complexes acting as autoantigen for rheumatoid factor-specific B cells and vaccine nucleic acids acting as TLR 7/9 ligands could work together in activating pathogenic B cells in vivo.

The overall rate of postvaccination flare observed in patients with MC is similar to that reported in other autoimmune rheumatic diseases[1–3]; importantly, flares did not endanger patients and subsided spontaneously. This reassures the safety of SARS-CoV-2 vaccination in patients with MC.

While in other inflammatory rheumatic diseases lack of immunogenicity of the SARS-CoV-2 vaccine was mostly attributed to immunosuppression especially with rituximab,[1 2] the 11.6% seronegativity rate in treatment-free patients with MC suggests that disease-related factors may impair vaccine immunogenicity in this disorder. Two patients contracted mild COVID-19, one (rituximab-treated, seronegative) 3 weeks after and one (rituximab-untreated, seropositive) 17 weeks after the second dose of vaccine (see online supplemental information). Our observations encourage administering vaccine booster[6] to patients with MC and postponing vaccination of rituximab-treated patients after B cell repopulation.

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