

## Correspondence on 'Immunogenicity and safety of anti-SARS-CoV-2 mRNA vaccines in patients with chronic inflammatory conditions and immunosuppressive therapy in a monocentric cohort'

We read with interest the work by Geisen and colleagues<sup>1</sup> on the efficacy and safety of anti-SARS-CoV-2 mRNA vaccine in patients with rheumatic diseases. While substantial data on the efficacy and safety of SARS-CoV-2 vaccination have been created during the last months, it is currently unclear whether the vaccination is efficacious and safe in patients with autoinflammatory diseases (AIDs). These patients present with exacerbated innate immune responses associated with enhanced production of interleukin (IL)-1.<sup>2</sup>

Testing the immune response to SARS-CoV-2 vaccination in patients with AIDs is of interest, as IL-1 has been involved in the pathogenesis of COVID-19; thus, IL-1 expression is massively increased in patients with severe COVID-19.<sup>3-5</sup> Furthermore, COVID-19 has shown to trigger an increased inflammatory disease activity in patients with AIDs.<sup>6,7</sup> In addition, IL-1 inhibition has been applied in the treatment of COVID-19 and while initial uncontrolled studies revealed promising results,<sup>8</sup> a randomised controlled trial showed no improvement of COVID-19 on IL-1 blockade.<sup>9</sup> While current data suggest the immune response to SARS-CoV-2 vaccination may be reduced in certain diseases, such as rheumatoid arthritis,<sup>10</sup> and certain treatments such as methotrexate,<sup>11</sup> such data cannot be applied to AID or to IL-1 inhibitors as the underlying pathophysiology is fundamentally different. Hence, we aimed to investigate SARS-CoV-2 vaccination responses in patients with AIDs treated with IL-1 inhibitors and compared them with healthy controls (HCs).

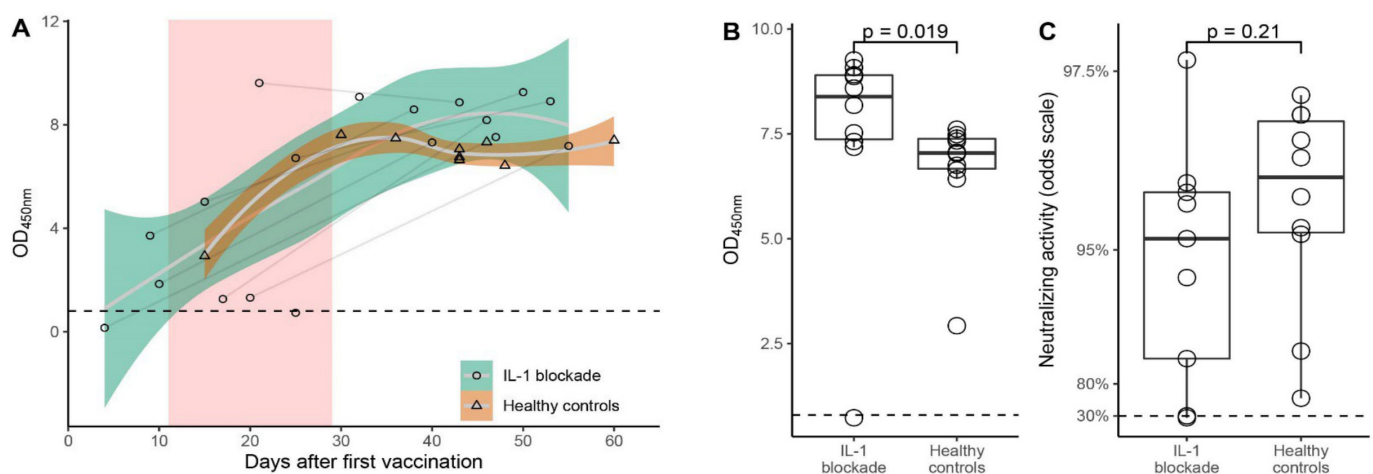
Ten patients with AIDs, four with adult-onset Still's disease, three with familial Mediterranean fever (FMF) and each one with gout, systemic AID and tumour necrosis factor receptor-associated periodical syndrome were investigated (online supplemental table 1). Their mean age was  $33 \pm 10$  years, eight were women and two men. All patients with AIDs were treated with

IL-1 inhibitors, eight with canakinumab and two with anakinra, administered regularly and at standard dosages of 150 mg/300 mg every 4 weeks and 100 mg/day, respectively. Two patients with FMF were additionally treated with 1 mg colchicine. None of the patients received glucocorticoids. In addition, 10 HCs were examined. All patients with AIDs and HCs received the BNT162b2 vaccine (Pfizer/BioNTech). None of the patients with AIDs and HCs did have COVID-19 before, nor did they have a positive anti-SARS-CoV-2 antibody test before vaccination.

IgG antibodies against the S1 domain of the spike protein of SARS-CoV-2 were tested by CE-certified ELISA (Euroimmun, Lübeck, Germany).<sup>12</sup> To assess neutralisation activity of antibodies, a CE-certified SARS-CoV-2 surrogate virus neutralisation assay (cPASS, Medac, Wedel, Germany) was used. A cut-off of 30% inhibition was considered as positive, according to the manufacturer's instructions.<sup>13</sup> We compared binary response status of antibody levels and neutralising activity using Fisher's exact test. ODs and per cent neutralising activity of the antibodies were compared using Mann-Whitney U tests. Two-sided p values were considered significant when  $<0.05$ . Analyses were performed using the open-source R software V.4.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

Nine out of 10 patients with AIDs and all HCs developed SARS-CoV-2-specific IgG antibodies (OD  $>0.8$  units). The time course of the antibody response in patients and controls was very similar (figure 1A). SARS-CoV-2-specific IgG antibodies were even higher in patients with AIDs than in HCs (figure 1B). Respective median (IQR) ODs were 7.0 (6.6 to 7.4) in HCs and 8.4 (7.3 to 8.9) in patients with AIDs ( $p=0.0019$ , Wilcoxon rank-sum test). The neutralising activity of receptor-binding domain binding to ACE2 was 96.4% (95.4% to 97.2%) in HCs and 95.3% (87.2% to 96.2%) in patients with AIDs, respectively ( $p=0.21$ , Wilcoxon rank-sum test). Vaccination was tolerated well in all patients and controls.

These data show good responses to SARS-CoV-2 vaccination in patients with AIDs treated with IL-1 inhibitors. They support previous anecdotal reports that IL-1 inhibitors may not impair the immune response in the context of COVID-19.<sup>14</sup> Importantly, both IgG levels as well as neutralising capacity of the anti-SARS-CoV-2 antibodies were comparable in patients with AIDs



**Figure 1** (A) Time course of anti-SARS-CoV-2 antibody response in patients with autoinflammatory disease receiving interleukin (IL)-1 blockade and healthy controls. Horizontal dashed line indicates the cut-off at OD 0.8. Shaded area represents the period during which second vaccine dose was administered. Dots connected by lines indicate antibody measurements from the same participants after the first and second vaccine dose. (B) Optical densities after the second vaccination, horizontal dashed line indicates the OD cut-off of 0.8. P value by Wilcoxon rank-sum test. (C) Neutralising activity of the antibodies after second vaccination. Horizontal dashed line indicates the cut-off at 30%. P value by Wilcoxon rank-sum test.

and HCs. Only one patient with gout and chronic renal failure undergoing haemodialysis did not respond to SARS-CoV-2 vaccination. The data also showed that there is no overshooting inflammatory response to SARS-CoV-2 vaccination in patients with AID. Taken together, these data support the current American College of Rheumatology guidelines for SARS-CoV-2 vaccination in patients with rheumatic diseases, including AIDs.<sup>15</sup>

In summary, SARS-CoV-2 vaccination in patients with AIDs receiving IL-1 inhibition is efficacious and well tolerated.

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#### REFERENCES

- Geisen UM, Berner DK, Tran F, *et al.* Immunogenicity and safety of anti-SARS-CoV-2 mRNA vaccines in patients with chronic inflammatory conditions and immunosuppressive therapy in a monocentric cohort. *Ann Rheum Dis* 2021. doi:10.1136/annrheumdis-2021-220272. [Epub ahead of print: 24 Mar 2021].
- Dinareello CA, Simon A, van der Meer JWM. Treating inflammation by blocking interleukin-1 in a broad spectrum of diseases. *Nat Rev Drug Discov* 2012;11:633–52.
- Schett G, Sticherling M, Neurath MF. COVID-19: risk for cytokine targeting in chronic inflammatory diseases? *Nat Rev Immunol* 2020;20:271–2.
- Schett G, Manger B, Simon D, *et al.* COVID-19 revisiting inflammatory pathways of arthritis. *Nat Rev Rheumatol* 2020;16:465–70.
- Williamson EJ, Walker AJ, Bhaskaran K, *et al.* Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020;584:430–6.
- Welzel T, Samba SD, Klein R, *et al.* COVID-19 in autoinflammatory diseases with immunosuppressive treatment. *J Clin Med* 2021;10:605.
- Huang C, Wang Y, Li X, *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497–506.
- Cavalli G, Larcher A, Tomelleri A, *et al.* Interleukin-1 and interleukin-6 inhibition compared with standard management in patients with COVID-19 and hyperinflammation: a cohort study. *Lancet Rheumatol* 2021;3:e253–61.
- CORIMUNO-19 Collaborative group. Effect of anakinra versus usual care in adults in hospital with COVID-19 and mild-to-moderate pneumonia (CORIMUNO-ANA-1): a randomised controlled trial. *Lancet Respir Med* 2021;9:295–304.
- Simon D, Tascilar K, Fagni F, *et al.* SARS-CoV-2 vaccination responses in untreated, conventionally treated and anticytokine-treated patients with immune-mediated inflammatory diseases. *Ann Rheum Dis* 2021:annrheumdis-2021-220461. doi:10.1136/annrheumdis-2021-220461
- Haberman RH, Herati R, Simon D, *et al.* Methotrexate hampers immunogenicity to BNT162b2 mRNA COVID-19 vaccine in immune-mediated inflammatory disease. *Ann Rheum Dis* 2021. doi:10.1136/annrheumdis-2021-220597. [Epub ahead of print: 25 May 2021].
- Simon D, Tascilar K, Krönke G, *et al.* Patients with immune-mediated inflammatory diseases receiving cytokine inhibitors have low prevalence of SARS-CoV-2 seroconversion. *Nat Commun* 2020;11:3774.
- Taylor SC, Hurst B, Charlton CL, *et al.* A new SARS-CoV-2 dual-purpose serology test: highly accurate infection tracing and neutralizing antibody response detection. *J Clin Microbiol* 2021;59. doi:10.1128/JCM.02438-20. [Epub ahead of print: 19 Mar 2021].
- Başaran S, Şimşek-Yavuz S, Meşe S, *et al.* The effect of tocilizumab, anakinra and prednisolone on antibody response to SARS-CoV-2 in patients with COVID-19: a prospective cohort study with multivariate analysis of factors affecting the antibody response. *Int J Infect Dis* 2021;105:756–62.
- Curtis JR, Johnson SR, Anthony DD, *et al.* American College of rheumatology guidance for COVID-19 vaccination in patients with rheumatic and musculoskeletal diseases: version 1. *Arthritis Rheumatol* 2021. doi:10.1002/art.41734. [Epub ahead of print: 17 Mar 2021].

Number	Sex	Age	Diagnosis	Therapy	Duration of IL-1 inhibition (months)	SARS-CoV-2 IgG (OD) Pre-Vaccination	Days after 2nd vaccination	SARS-CoV-2 IgG (OD) post-Vaccination	Neutralizing activity (%)
Patient 1	F	52	AoSD	Canakinumab	17	0,048	47	7.180	17,972
Patient 2	F	22	FMF	Canakinumab	10	0,097	29	9.261	87,237
Patient 3	F	35	sAID	Anakinra	9	0,116	21	8.867	NA
Patient 4	F	30	TRAPS	Canakinumab	4	0,124	10	7.318	96,364
Patient 5	F	27	AoSD	Canakinumab	5	0,1	5	8.908	97,576
Patient 6	M	50	Gout	Canakinumab	4	ND	25	0.732	30,431
Patient 7	F	31	AoSD	Canakinumab	9	0,141	25	7.525	96,219
Patient 8	F	20	FMF	Canakinumab	3	0,127	16	8.592	94,085
Patient 9	M	47	AoSD	Anakinra	17	0,08	12	9.078	96,025
Patient 10	F	17	FMF	Canakinumab	24	0,079	18	8,18	95,297
Control 1	F	50	-	-	-	NA	ND*	2,926	70,642
Control 2	F	37	-	-	-	NA	22	6,640	96,146
Control 3	F	49	-	-	-	NA	47	7,030	95,553
Control 4	F	54	-	-	-	NA	22	7,060	97,152
Control 5	F	43	-	-	-	NA	22	7,330	95,403
Control 6	M	29	-	-	-	NA	27	6,426	97,32
Control 7	F	33	-	-	-	NA	25	7,400	96,902
Control 8	F	53	-	-	-	NA	36	7,480	96,702
Control 9	M	27	-	-	-	NA	21	6,750	97,151
Control 10	F	55	-	-	-	NA	30	7,611	88,483

**Table 1:** Characteristics of patients and controls. AoSD: Adult onset Still's disease, FMF: familial Mediterranean fever, sAID: systemic autoinflammatory disease, TRAPS: TNF receptor associated periodic syndrome; ND: not determined (\*only first short of vaccine)