Immunogenicity of the COVID-19 mRNA vaccine in adolescents with juvenile idiopathic arthritis on treatment with TNF inhibitors

Patients with rheumatic and musculoskeletal diseases (RMDs) on immunosuppressants are generally considered to be more prone to infections, and therefore, a vulnerable group for severe COVID-19 infection. However, current data are reassuring, indicating that immunosuppression, and especially, TNF inhibitor (TNF-i) treatment, is not a specific risk factor for severe or fatal disease.[1] On the other hand, treatment with rituximab is associated with more severe disease and less favourable outcome.[1] So far, adherence to personal protection measures and immunisation comprise the two available strategies for battling the COVID-19 pandemic.[2] In the adult population, it has been demonstrated that the vast majority of patients with RMDs using non-B-cell-depleting therapy who received two doses of the COVID-19 mRNA vaccine mounted a protective immune response.[3 4] Until recently, data regarding the immunogenicity of COVID-19 vaccination in adolescents with RMDs on immunosuppressants were lacking, since these individuals were excluded from the vaccine trials.[5] The purpose of this study was to evaluate the immunogenicity of the BNT162b2 COVID-19 vaccine in adolescents with juvenile idiopathic arthritis (JIA) on TNF-i treatment.

This single-centre study involved adolescents aged 16–21 years previously diagnosed with JIA (based on the International League of Associations for Rheumatology (ILAR) criteria)[6] and treated with TNF-i. All patients were in clinical remission (Juvenile Arthritis Disease Activity Score (JADAS) Score<2).[7 8] All participants received two doses of the COVID-19 vaccine (Pfizer-BioNTech) intramuscularly at 0 and 3 weeks from 15 April to 15 May 2021. COVID-19 vaccination was performed in the time intervals between the administrations of their immunosuppressive treatment. Follow-up visits were planned at 1 and 3 months. Blood samples for the evaluation of vaccine immunogenicity were collected from all of the subjects at the time of enrolment, as well as at 1 and 3 months after the second vaccine dose. Quantitative measurement of IgG antibodies to SARS-CoV-2 spike protein-1 was performed with a cut-off level of 100 rU/mL (Euroimmun Quantivac-Elisa-IgG assay). Data were analysed using SPSS V.28.0 software. Descriptive statistics were presented as counts/percentage for qualitative data and mean/SD or median/range for quantitative data. Groups were compared with Kruskal-Wallis test. A p value<0.05 was considered statistically significant.

A total of 21 adolescents (males: 5 (24%); females: 16 (76%)) were enrolled with a median age of 17 years (range:16–21 years). Eight (38%) patients had polyarticular JIA, 7 (33%) psoriatic JIA and six (29%) enthesitis-related arthritis. In particular, 10 (48%) were receiving adalimumab fortnightly; 11 (52%) were given etanercept once a week, whereas 15 patients (71%) were on concomitant weekly subcutaneous methotrexate (MTX). All patients were in clinical remission at the time of vaccinations. None of the participants discontinued TNF-i/MTX treatment at the time of vaccine administration or during the follow-up period. All subjects were seronegative at baseline. Seropositivity rate was 100%; all patients developed a sustained humoral response against SARS-CoV-2 at 1 and 3 months after vaccination (mean(±SD) anti-SARS-CoV-2 IgG levels 11 293 U/L±12 441 and 17 590 U/L±15400, respectively (p<0.05) (1 vs 3 months) (figure 1)). The type of JIA did not reveal any differences in the humoral response at 3 months post vaccination (p=0.894). Additionally, no statistically significant difference was detected on comparison of the immunogenicity between the different treatment arms (adalimumab vs etanercept) at 3 months (mean(±SD) anti-SARS-CoV-2-IgG level: 15 739 U/L±17 132 vs 19273 U/L±14270, (p=0.387)) or on comparison of TNF-i monotherapy versus combined therapy (TNF-i plus MTX) (mean(±SD) anti-SARS-CoV-2-IgG level: 16 480 U/L±14 602 vs 19393 U/L± 17496, (p=0.623)). None of the participants developed disease flare during the follow-up period.[9] None of the participants withdrew from the study due to vaccination adverse events.[9]

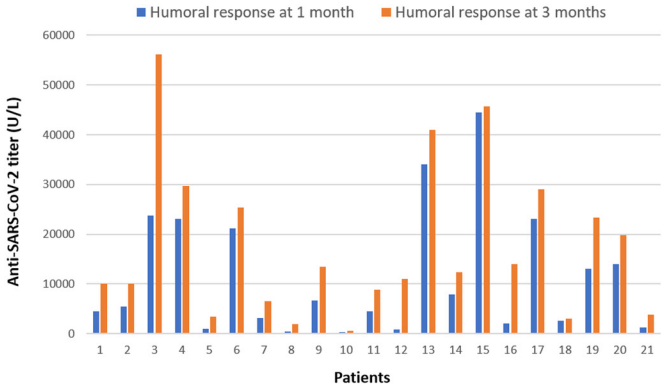

Figure 1 Humoral response against SARS-CoV-2 at 1 and 3 months after vaccination in adolescents with juvenile idiopathic arthritis on TNF inhibitor treatment.

This is a novel study demonstrating that mRNA vaccines develop and continue to accrue satisfactory immunogenicity at 1 and 3 months post immunisation in adolescents with JIA on TNF-i. Although our sample size was small and a restricted number of patients were included within each JIA type and treatment groups, it may be concluded that the vaccine assures an adequate humoral response against SARS-CoV-2, comparable with the immunogenicity of other vaccines studied in this specific population.[10 11] Likewise, this study indicated that it is not necessary to discontinue TNF-i/MTX before and after the vaccination. Further collaborative studies are required to determine long-term immunogenicity, real duration of immune protection and perhaps the need for a booster vaccine dose.

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REFERENCES

1 Regierer AC, Hasseli R, Schäfer M, *et al*. TNFi is associated with positive outcome, but JAKi and rituximab are associated with negative outcome of SARS-CoV-2 infection in patients with RMD. *RMD Open* 2021;7:e001896.
2 Schulze-Koops H, Specker C, Skapenko A. Vaccination of patients with inflammatory rheumatic diseases against SARS-CoV-2: considerations before widespread availability of the vaccines. *RMD Open* 2021;7:e001553.
3 Braun-Moscovici Y, Kaplan M, Braun M, *et al*. Disease activity and humoral response in patients with inflammatory rheumatic diseases after two doses of the pfizer mRNA vaccine against SARS-CoV-2. *Ann Rheum Dis* 2021;80:1317–21.
4 Furer V, Eviatar T, Zisman D, *et al*. Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and in the general population: a multicentre study. *Ann Rheum Dis* 2021;80:1330–8.
5 Furer V, Rondaan C, Agmon-Levin N, *et al*. Point of view on the vaccination against COVID-19 in patients with autoimmune inflammatory rheumatic diseases. *RMD Open* 2021;7:e001594.
6 Petty RE, Southwood TR, Manners P, *et al*. International League of associations for rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* 2004;31:390–2.
7 Consolaro A, Ruperto N, Bazso A, *et al*. Development and validation of a composite disease activity score for juvenile idiopathic arthritis. *Arthritis Rheum* 2009;61:658–66.
8 Trincianti C, Van Dijkhuizen EHP, Alongi A, *et al*. Definition and Validation of the American College of Rheumatology 2021 Juvenile Arthritis Disease Activity Score Cutoffs for Disease Activity States in Juvenile Idiopathic Arthritis. *Arthritis Rheumatol* 2021;73:1966–75.
9 Dimopoulou D, Spyridis N, Vartzelis G, *et al*. Safety and tolerability of the COVID-19 mRNA-vaccine in adolescents with juvenile idiopathic arthritis on treatment with TNF-inhibitors. *Arthritis Rheumatol* 2021. doi:10.1002/art.41977. [Epub ahead of print: 07 Sep 2021].
10 Esposito S, Corona F, Barzon L, *et al*. Immunogenicity, safety and tolerability of a bivalent human papillomavirus vaccine in adolescents with juvenile idiopathic arthritis. *Expert Rev Vaccines* 2014;13:1387–93.
11 Maritsi DN, Coffin SE, Argyri I, *et al*. Immunogenicity and safety of the inactivated hepatitis a vaccine in children with juvenile idiopathic arthritis on methotrexate treatment: a matched case-control study. *Clin Exp Rheumatol* 2017;35:711–5.