

Concise report

Immunogenicity 6 months post COVID-19 mRNA vaccination among adolescents with juvenile idiopathic arthritis on treatment with TNF inhibitors

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Abstract

Objectives. Mass vaccination is the most effective strategy for controlling the COVID-19 pandemic. This study aimed to evaluate the 6-month immunogenicity after BNT162b2-COVID-19 vaccination in adolescents with JIA on TNFi treatment.

Methods. This single-centre study included adolescents with JIA treated with TNFi for at least 18 months. Patients received two doses of COVID-19 vaccine (Pfizer-BioNTech) from 15 April to 15 May 2021. Quantitative measurement of IgG antibodies to SARS-CoV-2-spike-protein-1 was performed at 1, 3 and 6 months post-vaccination.

Results. Overall, 21 adolescents with JIA in clinical remission at the time of vaccinations were enrolled. None of them discontinued TNFi/MTX treatment at the time of vaccine administration or during the follow-up period. All patients developed a sustained humoral response against SARS-CoV-2 at 1 and 3 months after vaccination ($P < 0.05$). The antibody levels decreased significantly at 6 months post-vaccination ($P < 0.01$). The type of JIA did not reveal any differences in the humoral response at 3 ($P = 0.894$) or 6 months post-vaccination ($P = 0.72$). No difference was detected upon comparison of the immunogenicity between the different treatment arms (adalimumab vs etanercept) at 3 ($P = 0.387$) and 6 months ($P = 0.526$), or TNFi monotherapy vs combined therapy (TNFi plus methotrexate) at 3 ($P = 0.623$) and 6 months ($P = 0.885$).

Conclusions. Although mRNA vaccines develop satisfactory immunogenicity at 1 month and 3 months post-vaccination in adolescents with JIA on TNFi, SARS-CoV-2 antibody titres decrease significantly overtime, remaining at lower levels at 6 months. Further collaborative studies are required to determine long-term immunogenicity, real duration of immune protection and the need for a booster vaccine dose.

Key words: immunogenicity, COVID-19 mRNA vaccines, adolescents, juvenile RA, TNF inhibitors

Rheumatology key messages

- mRNA vaccines develop satisfactory immunogenicity at 1 and 3 months in adolescents with JIA on TNFi.
- SARS-CoV-2 antibody titres decrease significantly overtime, remaining at lower levels at 6 months post vaccination.
- Administration of a vaccine booster dose 6 months post second dose may be beneficial.

Introduction

Patients with rheumatic and musculoskeletal diseases (RMDs) on immunomodulating treatment were generally considered to have increased susceptibility to COVID-19 infection. However, current data are reassuring, indicating that immunosuppression and especially TNF inhibitor

(TNFi) treatment is not a specific risk factor for severe or fatal disease [1]. On the contrary, treatment with rituximab has been related to more severe disease and adverse outcome [1]. In addition, patients on rituximab failed to mount a sufficient immunogenic response to the two-dose immunization scheme with the mRNA vaccines, hence current guidelines suggest either

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postponing immunization or administering vaccines prior to initiation of treatment [2]. Adherence to personal protection measures and mass vaccination were shown to be the two most effective strategies for controlling the COVID-19 pandemic [3]. In the adult population of patients suffering from RMD, 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 an adequate immune response [4]. In addition, combination of TNFi with methotrexate resulted in an attenuated vaccine response as compared with TNFi monotherapy [4, 5].

To date, data regarding the long-term immunogenicity of COVID-19 vaccination in adolescents with RMDs on immunosuppressants are scarce, as these individuals were excluded from the vaccine trials [6]. In our previous studies, we presented the results about safety and immunogenicity of the COVID-19 mRNA vaccine in adolescents with juvenile idiopathic arthritis on treatment with TNFi at 3 months following immunization [7, 8]. The purpose of the present study was to evaluate the immunogenicity 6 months after BNT162b2-COVID-19 vaccination in this specific population.

Methods

A single-centre study was conducted including adolescents aged 16–21 years previously diagnosed with JIA according to the ILAR criteria [9] and treated with TNFi. All patients were in clinical remission (JADAS score <2 or 1.2 depending on the type of JIA) for at least three months prior to the initiation of this study [10]. All patients were on TNFi treatment for at least 18 months. The study was approved by the institution's Ethical and Research Committee; written informed consent was obtained at enrolment (approval number: 134/23.3.2021). All participants received two doses of the COVID-19 mRNA vaccine (Pfizer-BioNTech) intramuscularly at 0 and 3 weeks, during the period 15 April and 15 May 2021. COVID-19 vaccination was carried out at the time intervals between the administrations of their immunosuppressive treatment. None of the participants discontinued their immunosuppressive treatment during the vaccination and follow-up period. Follow-up visits were planned at 1, 3 and 6 months. Blood samples for the evaluation of vaccine immunogenicity were collected from all of subjects at the time of enrolment, as well as at 1, 3 and 6 months after the second vaccine dose [7, 8]. Blood samples were collected in specific containers, were centrifuged and quantitative measurement of IgG antibodies to SARS-CoV-2 spike protein-1 was performed in serums of the patients with a cut-off level of 100 rU/ml (Euroimmun Quantivac-Elisa-IgG assay). Disease flare was evaluated by using the Juvenile Arthritis Disease Activity Score (JADAS-27). Adverse reactions were defined as any reaction that lasted for >7 days after the vaccination and serious adverse reactions as any reaction requiring medical attention or hospitalization.

Data were analysed using SPSS 28.0 software. Descriptive statistics were presented as counts/percentage for qualitative data and mean/standard deviation or median/range for quantitative data. Groups were compared with Kruskal–Wallis test. A *P*-value < 0.05 was considered statistically significant.

Results

Demographics and clinical characteristics of adolescents with JIA on TNFi treatment who were immunized with the COVID-19 mRNA vaccine are shown in Table 1. 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, seven (33%) psoriatic JIA and six (29%) enthesitis-related arthritis (ERA). 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 MTX. All patients were in clinical remission at the time of vaccinations and none of them discontinued TNFi/MTX treatment at the time of vaccine administration or during the follow-up period. None of the participants was receiving steroids during vaccination.

All participants were seronegative at baseline. Seropositivity rate was 100% at 1, 3 and 6 months post second dose of vaccine; all patients developed a sustained humoral response against SARS-CoV-2 at 1 and 3 months after vaccination [mean (s.d.) anti-SARS-CoV-2 IgG levels 11 293 U/l (12 441) and 17 590 U/l (15 400), respectively (*P* < 0.05) (1 vs 3 months)] (Fig. 1). The antibody levels decreased significantly at 6 months post vaccination [mean (s.d.) anti-SARS-CoV-2 IgG levels 408 U/l (349)] as compared with the levels at 1 and 3 months after immunization (*P* < 0.01) (Fig. 1). The type of JIA did not reveal any differences in the humoral response at 3 months [polyarticular JIA vs psoriatic JIA vs ERA: mean (s.d.) anti-SARS-CoV-2-IgG level: 16 819 U/l (13 192) vs 12 738 U/l (14 933) vs 23 927 U/l (24 465), (*P* = 0.894)] and at 6 months post vaccination [polyarticular JIA vs psoriatic JIA vs ERA: mean (s.d.) anti-SARS-CoV-2-IgG level: 438 U/l (314) vs 230 U/l (269) vs 435 U/l (549), (*P* = 0.72)]. Additionally, no statistically significant difference was detected upon comparison of the immunogenicity between the different treatment arms (adalimumab vs etanercept) at 3 months [mean (s.d.) anti-SARS-CoV-2-IgG level: 15 739 U/l (17 132) vs 19 273 U/l (14 270), (*P* = 0.387)] and at 6 months [mean (s.d.) anti-SARS-CoV-2-IgG level: 507 U/l (406) vs 317 U/l (277), (*P* = 0.526)], or upon comparison of TNFi monotherapy vs combined therapy (TNFi plus methotrexate) at 3 months [mean (s.d.) anti-SARS-CoV-2-IgG level: 16 480 U/l (14 602) vs 19 393 U/l (17 496), (*P* = 0.623)] and at 6 months [mean (s.d.) anti-SARS-CoV-2-IgG level: 460 U/l (445) vs 376 U/l (292), (*P* = 0.885)].

None of the participants withdrew from the study due to vaccination adverse events [12]. In addition, none of the participants developed disease flare in between the two

TABLE 1 Demographics and clinical characteristics of adolescents with JIA on TNF inhibitors treatment who were immunized with COVID-19 mRNA vaccine

Characteristics	<i>n</i> = 21 patients
Age in years [median (range)]	17 (16–21)
Sex (male/female)	5 (24%)/16 (76%)
Poly-articular JIA	8/21 (38%)
Psoriatic JIA	7/21 (33%)
ERA	6/21 (29%)
Treatment	
TNF inhibitors	
<i>Adalimumab</i>	10/21 (48%)
<i>Etanercept</i>	11/21 (52%)
Other concurrent treatment	
<i>Methotrexate</i>	15/21 (71%)
Vaccination characteristics	<i>n</i> = 21 patients
Seropositivity rate	21/21 (100%)
Anti-SARS-CoV-2 IgG levels (mean [s.d.])	
1 month post-vaccination	11 293 U/L (12 441)
3 months post-vaccination	17 590 U/L (15 400)
6 months post-vaccination	408 U/L (349)
<i>Adalimumab</i> and 3 months post vaccination	15 739 U/L (17 132)
<i>Adalimumab</i> and 6 months post vaccination	507 U/L (406)
<i>Etanercept</i> and 3 months post vaccination	19 273 U/L (14 270)
<i>Etanercept</i> and 6 months post vaccination	317 U/L (277)
<i>TNFi</i> monotherapy and 3 months post vaccination	16 480 U/L (14 602)
<i>TNFi</i> monotherapy and 6 months post vaccination	460 U/L (445)
<i>TNFi</i> plus <i>Methotrexate</i> and 3 months post vaccination	19 393 U/L (17 496)
<i>TNFi</i> plus <i>Methotrexate</i> and 6 months post vaccination	376 U/L (292)
Post-vaccination AE	<i>n</i> = 42 doses
Local	31/42 (74%)
Systemic	8/42 (19%)
Exacerbation of JIA	0/42 (0%)
Serious AE	0/42 (0%)

AE: adverse events; ERA: enthesitis-related arthritis; TNFi: TNF inhibitors.

doses or within four weeks from the second dose. Six participants developed a flare during the follow-up period and only four of them required a short course of steroids. Disease flare was reported between 3 and 6 months post-vaccination [mean (s.d.) days after immunization: 123.2 (16.7)]. No significant difference in antibody levels was detected between those who flared and those who remained in remission ($P = 0.09$). Finally, five patients experienced COVID-19 disease following completion of the two-dose scheme [mean (s.d.) days after immunization: 136 (32)]. Diagnosis was confirmed by RT-PCR in all individuals. They were diagnosed during the surge of the delta variant. Two were asymptomatic, none required

hospitalization, none flared post-infection. We measured anti-SARS-CoV-2-IgG at diagnosis, all were above the cut-off seroconversion level.

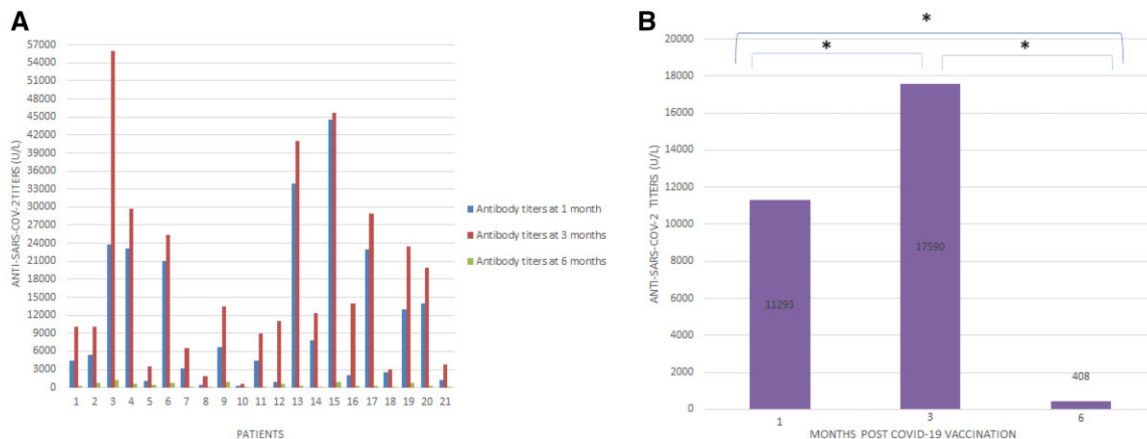
Discussion

To our knowledge, this is the first study demonstrating that the BNT162b2 mRNA vaccines initially develop and continue to accrue satisfactory immunogenicity at 1, 3 and 6 months post immunization in adolescents with JIA on TNFi. However, SARS-CoV-2 antibody titres decrease significantly overtime. Although patients with RMDs mount a significant anti-spike-SARS-COV-2-IgG antibody response to the mRNA vaccine [11], infection (even asymptomatic) is not fully avoidable. Anti-spike-SARS-COV-2-IgG antibody levels showed a strong negative correlation with the time since complete mRNA-vaccination and T cellular response may play an important role in inducing protection against COVID-19 in these patients [12]. Measurement of SARS-COV-2-IgG neutralizing antibodies or an explicit analysis of cellular immunity, which were not available at our site, may reveal more clinically significant information in terms of actual protection.

Current data suggest that severely immunocompromised patients need three doses of the mRNA vaccine followed by a booster dose [13]. At present, patients with RMDs are not included in this recommendation, but they should be considered candidates for early booster vaccination, because of the pronounced decline in humoral response at 6 months post vaccination [13, 14]. Furthermore, it was reported that although rituximab impairs immunogenicity after COVID-19 vaccination, a third booster dose might induce not only the humoral response, but also the T cellular immune response [15]. 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 a satisfactory humoral response against SARS-CoV-2, but antibody levels reduce over time, suggesting that the administration of a COVID-19 vaccine booster to these patients 6 months following the second vaccine dose may be beneficial.

Only 62% of patients with RMDs on treatment with MTX achieved adequate antibody production post immunization, whereas those on TNFi demonstrated an immune response similar to that of the healthy controls (>90%) [2, 5]. In addition, it was found that not only humoral immunity, but cellular immunity is important for protection against COVID-19 [16]. Temporary immunosuppressant discontinuation and especially MTX, rituximab and abatacept treatment is suggested as a strategy to increase vaccine immunogenicity in patients with RMDs [17]. Previously, it was also demonstrated that the discontinuation of MTX up to 2 weeks after annual influenza vaccination resulted in increased immunogenicity with minimal risk of disease flare in patients with rheumatoid arthritis [18]. However, our study indicated that it is not necessary to discontinue TNFi/MTX before and after the COVID-19 vaccination, as all the patients were

Fig. 1 Humoral response against SARS-CoV-2 after vaccination in adolescents with juvenile idiopathic arthritis on TNF inhibitor treatment



Humoral response against SARS-CoV-2 at 1, 3 and 6 months after vaccination (A) and mean anti-SARS-CoV-2 titres at 1, 3 and 6 months post-vaccination (B). *Statistically significant difference ($P < 0.05$).

shown to have adequate humoral response against COVID-19.

COVID-19 infection may trigger flares of rheumatic diseases. Furthermore, there is a theoretical risk for RMDs flare post COVID-19 vaccination; however, the estimated risks and benefits clearly favour vaccination and it is currently recommended COVID-19 vaccination for patients with rheumatic diseases [19]. No disease flare was observed at 1 month and 3 months follow-up post immunization in our cohort [8]. This is in accordance with other reports, showing that immunization does not provoke flares of underlying RMDs [20]. In addition, our study demonstrated that JIA flares were reported between 3 months and 6 months post vaccination, which were considered as events unrelated to prior immunization, supporting that vaccines are safe and their benefits outweigh the risks of RMDs relapse.

The longevity of vaccine-elicited antibody responses is unknown in this population. If the third dose would have rendered these patients fully shielded against SARS-CoV-2, or whether previous vaccination warranted protection against a more severe COVID-19 disease course are questions that remain to be answered. Further collaborative studies are required to determine long-term immunogenicity, real duration of immune protection and the need for a booster vaccine dose.

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Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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