SARS-CoV-2 vaccinations in children and adolescents with rheumatic diseases

Ethan S. Sen [1,2], Dalila Julandani [3], Athimalaipet V. Ramanan [3,4 †]

Authors:

[1] Department of Paediatric Rheumatology, Great North Children's Hospital, Newcastle upon Tyne, UK.
[2] Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK
[3] Department of Paediatric Rheumatology, Bristol Royal Hospital for Children, Upper Maudlin Street, Bristol, UK
[4] Translational Health Sciences, University of Bristol, Bristol, UK

[†] Corresponding author
Athimalaipet V. Ramanan
Department of Paediatric Rheumatology
Bristol Royal Hospital for Children
Upper Maudlin Street
Bristol BS2 8BJ
United Kingdom
Email: avramanan@hotmail.com

EDITORIAL

COVID-19 has had a significant impact on the lives of patients with autoimmune or inflammatory rheumatic diseases (AIIRD). A systemic review and meta-analysis of studies examining SARS-CoV-2 infection and COVID-19 outcomes in patients (mostly adults) with rheumatic diseases found a 52% higher relative risk of infection and a 74% increase in risk of death compared with the general population (1). Within a year of COVID-19 being declared a pandemic by the World Health Organisation, several vaccines had been developed, evaluated in clinical trials and approved for use. Although children and young people have, generally, been affected more mildly, there have been concerns that those receiving immunosuppression could be at greater risk. After the initial study of the BNT162b2 mRNA vaccine in adults (2), safety and efficacy were investigated in healthy children aged 12-18 years (3). Subsequent research has demonstrated that the BNT162b2 vaccine offers children and adolescents reasonable protection against the SARS-Cov-2 omicron variant (4).

Two articles in *Rheumatology* have examined the humoral response and safety of the BNT162b2 vaccine in adolescents with AIIRD. Akgün *et al.* conducted a prospective, observational study of the vaccine in children aged 12-18 years with AIIRD who were receiving conventional disease modifying rheumatic disease drugs (cDMARDs) and/or biologic DMARDs (bDMARDs) (5). The two-dose vaccination regimen led to markedly elevated antibody titres in all patients compared with baseline, however, levels were significantly lower in those on a combination of cDMARDs and bDMARDs compared with those on cDMARDs alone. The study did not examine the incidence of COVID-19 in the months following the vaccination, so was not able to report on efficacy, and the absence of a control group means that comparison with the humoral response in healthy subjects was not possible. Akgün *et al.* reported that no patients had a significant increase in disease activity

after vaccination, and the commonest side effects (localised pain and fatigue) were mild with no serious adverse events.

A second study, conducted by Heshin-Bekenstein *et al*., also sought to examine safety and immunogenicity of the BNT162b2 vaccine in adolescents with AIIRD (6). Their patient cohort was larger and included 91 subjects (80% on immunosuppression) aged 12-21 years, although a humoral response was assessed in only 37. They also recruited 40 healthy controls, of whom 22 were tested for humoral responses. Among the patients, 97% became seropositive after two vaccine doses compared with 100% of controls. However, the IgG antibody titres against SARS-CoV-2 spike protein were significantly lower in the adolescents with rheumatic diseases. Despite this, no patients or controls developed COVID-19 infection in the 3 months following vaccination.

Regarding BNT162b vaccine safety, Heshin-Bekenstein *et al*. found that mild, local side effects occurred with similar frequency in patients and controls (6). Fever, fatigue, myalgia and arthralgia were more common in patients, but the difference was not statistically significant. There was no change in disease activity in over 94% of patients following first or second vaccine doses.

Overall, these two studies do not highlight any new or serious safety signals in relation to adverse events or disease flare in adolescents with rheumatic diseases who are receiving immunosuppressive medications. Similar findings have been reported in two other studies which support the safety of the vaccine (7, 8). Disease flares appeared to be more frequent in another study of COVID-19 vaccination in adolescents in which the authors reported flare in 11% of 246 subjects within one month of vaccination (9). However, inclusion in this study

and outcome recording were via a web-based survey completed by patients and parents after invitations on social media platforms. There is, therefore, a significant risk of selection bias. Furthermore, of those patients with a suspected flare of disease, over half had FMF for whom symptoms of a flare (fever, arthralgia or chest or abdominal pain) may also be seen as side effects of the vaccine itself. Another study, also examining COVID-19 vaccination in adolescents and young adults, reported disease flare in 4.4% of 159 patients (10).

In all studies of COVID-19 vaccination in adolescents with AIIRD discussed above, immunosuppressive treatment was continued without interruption. A break in treatment is usually suggested only for live vaccines, balanced against the risk of flare of the underlying disease (11). However, being on DMARDs likely contributes to a decreased antibody response compared with controls following a range of different vaccinations, and this reduced response has been reported in up to one third of children and adolescents with AIIRD on immunosuppression (12). Lower immunogenicity of COVID-19 vaccines in immunosuppressed or immunocompromised patients led to WHO guidance recommending an additional vaccine dose as part of the primary vaccination series (13).

The accumulating data from observational cohort studies of COVID-19 mRNA vaccines in adolescents with AIIRD do not, as yet, highlight any specific safety concerns. The majority of patients become seropositive after two doses of the vaccine; however, antibody titres are significantly lower than healthy controls, hence the recommendation that patients on immunosuppression receive an additional dose of vaccine as part of the primary course. Some studies have reported a flare of the underlying disease with temporal association with vaccination in a minority of patients. Investigations of COVID-19 vaccinations in adolescents with AIIRD have focused on the humoral response but have not examined the specific T-cell

response, which is likely important for the longevity of vaccine protection. Studies of the T-cell response in adults receiving cDMARDs or bDMARDs found that it was significantly impaired in a proportion of patients (14).

The studies by Akgün *et al.* and Heshin-Bekenstein *et al*. both provide support for the current clinical practice of offering the BNT162b2 vaccine to adolescents with rheumatic diseases without stopping their immunosuppression. We do not yet know how long the protective effect of the vaccines will last in this population, and this will require follow-up studies. It is likely that adolescents with AIIRD will require booster doses of COVID-19 vaccines.

Looking to the future, uncertainty remains regarding the evolution of novel COVID-19 variants and the severity of subsequent disease in children and adolescents with AIIRD. It is also unclear how the role of vaccination in this group may change as an increasing proportion have immunity from previous infection. Most clinical trials of immunosuppressant drugs in children and adolescents with AIIRD will, in the coming years, include responsiveness to COVID-19 vaccines as part of their protocols. This may help to address some of the current uncertainty.

Subsequent to the trial of BNT162b2 vaccine in adolescents, a study has shown that two 10-µg doses given 21 days apart in children 5-11 years old are safe, immunogenic and efficacious (15). Additional research will be required, which includes children with AIIRD on immunosuppression in this age group, in order to confirm the vaccine profile in these younger patients.

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