Arch Argent Pediatr 2023;121(3):e202202757

Immunization with messenger RNA vaccines against COVID-19 in adolescents with a history of multisystem inflammatory syndrome: a case series

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ABSTRACT

In most cases, children with SARS-CoV-2 have a mild infection. However, very rarely, some children may develop a severe disease called multisystem inflammatory syndrome in children temporally associated with COVID-19 (MIS-C). Given its recent emergence, some aspects of its pathophysiology are still unknown. The possibility of recurrence in case of reinfection or SARS-CoV-2 vaccination are new questions we are facing.

Here we report a case series of 4 adolescent patients who developed MIS-C and, months later, received the SARS-CoV-2 vaccine with messenger RNA (mRNA) platforms without disease recurrence or cardiac adverse events.

Key words: *SARS-CoV-2; COVID-19; multisystem inflammatory syndrome in children associated with COVID-19; COVID-19 vaccines; mRNA vaccines.*

doi: http://dx.doi.org/10.5546/aap.2022-02757.eng

To cite: Curtti T, Agrimbau Vázquez J, Yori S, Kantarovsky A, et al. Immunization with messenger RNA vaccines against COVID-19 in adolescents with a history of multisystem inflammatory syndrome: a case series. *Arch Argent Pediatr* 2023;121(3):e202202757.

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Funding*: Tamara Curtti, M.D., received a scholarship from Fundación Garrahan to conduct the research protocol "Post-Covid-19 PIMS".*
Silvana Cecilia Yori received a scholarship from Fundación Garrahan to conduct the research protocol "Multisystem inflammatory syndrome temporally associated with SARS-CoV-2 in patients seen at a tertiary care children's hospital in Argentina".
Jorge Agrimbau Vázquez, M.D., and Luis Urrutia, M.D., were the directors of the research scholarships granted to Tamara Curtti and Silvana Cecilia Yori, but received no compensation for such role.

Conflict of interest*: None.*

Received*: 6-29-2022*
Accepted*: 7-18-2022*

INTRODUCTION

The SARS-CoV-2 pandemic presented a new diagnostic and therapeutic challenge for pediatricians, given the emergence of a new entity called multisystem inflammatory syndrome in children and adolescents temporally associated to COVID-19 (MIS-C). Although the incidence of MIS-C is low (estimated at 1/100 000 children younger than 21 years),[1] it should be taken into consideration because of its potential severity and risk for myocarditis, myocardial dysfunction, and coronary artery involvement.

The clinical features of MIS-C usually occur 2–6 weeks after SARS-CoV-2 infection and include persistent fever and non-specific symptoms, including abdominal pain, vomiting, headache, and asthenia. MIS-C is frequently associated with conjunctival injection and rash resembling Kawasaki disease (KD). A proportion of patients develop a severe condition, including multiple organ failure and shock requiring inotropes.[2]

The pathophysiology of MIS-C has not been fully elucidated; a post-viral immune reaction has been proposed.[3] These patients usually present with lymphopenia, but with a highly increased T-cell response leading to the so-called "cytokine storm." The B-cell response also plays a role, given that the presence of autoantibodies against different tissues (endothelial, cardiac, and intestinal) has been demonstrated.[4] Endothelial damage plays a key role in the pathophysiology of MIS-C. An additional mechanism linked to the presence of a SARS-CoV-2 protein with superantigenic properties has also been proposed.[5]

Children who have had MIS-C may be exposed to the virus again due to the persistence of viral circulation in the community and the emergence of new variants. Receiving the SARS-CoV-2 vaccine in these children would imply re-exposure of their immune system to viral antigens related to the pathophysiology of the disease.

The low incidence of MIS-C and the lack of follow-up of patients after vaccination lead to a paucity of data in relation to vaccine tolerability in these children. To date, no reports have been published about the recurrence of MIS-C following vaccination.[6]

According to the guidance published by the United States Centers for Disease Control and Prevention (CDC), vaccination in these patients should be indicated taking into account both the benefit it confers in reducing severe SARS-CoV-2 infection and the risks, such as the possibility of recurrence of MIS-C and the risk of myocarditis. Clinical recovery after the acute episode, normalization of cardiac function, elapsed time greater than 90 days, presence of pre-existing conditions, and immunomodulatory therapy used in the treatment of MIS-C should be considered.[7]

CASE REPORTS

Here we describe 4 clinical cases of patients who have had MIS-C and subsequently received the SARS-CoV-2 vaccines with mRNA platforms: BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) with no evidence of recurrence of MIS-C. We opted for a case series due to the low incidence of MIS-C.

We included adolescent patients seen at Hospital Juan P. Garrahan and Hospital del Niño Jesús de Tucumán in the period between November 2020 and June 2021 who had inflammatory syndromes and fever that met World Health Organization (WHO) criteria for MIS-C.[8] During this period, a total of 25 patients with this diagnosis were admitted to Hospital Garrahan and 40, to Hospital del Niño Jesús de Tucumán.

During outpatient follow-up, vaccination against COVID-19 was suggested. The 4 cases reported here were the first patients to receive the vaccine, according to the risk-benefit assessment for each case.

The mRNA-1273 and BNT162b2 vaccines were those available and authorized by the National Ministry of Health of Argentina for administration in children older than 12 years at the time of treatment.

Vaccine reactogenicity and the presence of signs of systemic inflammation were specifically assessed. Follow-up of each patient was carried out according to the guidelines of each hospital, with on-site control 1 month after vaccination. A telephone contact was available for patients in case of any contingency. A retrospective, electronic written survey was administered to each patient, which included the main symptoms reported by the CDC.[9]

Prior informed assent was obtained from the patients in accordance with current national regulations.

RESULTS

Vaccinated patients were aged 12 to 15 years; 2 were male and 2, female. Two of them had a pre-existing condition: type 1 diabetes and asthma.

All of them presented clinically with febrile syndrome and other symptoms of MIS-C. Three patients had cardiac involvement (as evidenced by changes in the echocardiogram and increased cardiac markers); 3 were admitted with clinical symptoms of shock and 2 required admission to the pediatric intensive care unit (PICU).

All patients showed a favorable course following treatment with intravenous immunoglobulin G (IVIG) and/or corticosteroids, with resolution of the clinical features and normalization of laboratory parameters and echocardiogram.

The time elapsed between the acute MIS-C episode and vaccination ranged between 6 weeks and 9 months. The difference in elapsed time is due to the time at which COVID-19 vaccines were authorized in the pediatric population in our country.

During the subsequent follow-up, no major adverse effects were observed. The follow-up period after vaccination was 3 months. Clinical controls were performed on-site 1 month after vaccination and then remotely, by telephone contact, with no evidence of disease recurrence.

Table 1 describes the main characteristics of each patient, the date of MIS-C onset, degree of involvement, treatment, and the time elapsed between MIS-C and vaccination.

DISCUSSION

MIS-C shares both clinical and pathophysiological features with KD; both entities are characterized by a severe inflammatory response. Articles have been published that describe cases of KD following vaccination, which has been proposed as a potential triggering factor, although an increased risk of KD due to vaccines could not be demonstrated.[10]

Both the mRNA-1273 and BT162b2 vaccines are composed of single-stranded mRNA encoding for the spike protein (protein S) of SARS-CoV-2, which has been proposed as a superantigen that would initiate the inflammatory cascade in MIS-C. A question arises about the risk that such exposure would have in terms of post-vaccination MIS-C recurrence.

Multisystem inflammatory syndrome has also been described, although less frequently, in adult patients (MIS-A). Recently, Nune et al., reported the case of an adult patient who met MIS-A criteria which developed within 48 hours of receiving the BNT162b2 vaccine and who was successfully treated with intravenous corticosteroids.[11] This has not been reported in the pediatric population.

Since May 2021, a few cases of myocarditis and pericarditis have been reported in young and adolescent patients who received vaccines with mRNA platforms. Most cases occurred within

Table 1. Description of patients

	Patient 1	Patient 2	Patient 3	Patient 4
Age	13 years	15 years	14 years	12 years
Sex	Female	Male	Female	Male
Pre-existing condition	Type 1 diabetes	None	None	Asthma
Date of MIS-C	June 2021	November 2020	May 2021	January 2021
Cardiac involvement	No	Yes	Yes	Yes
MIS-C severity				
PICU	No	5 days	5 days	No
Inotropes	No	2 days	4 days	No
MV	No	2 days	3 days	No
Treatment	IVIG	IVIG + methylprednisolone pulse for 48 hours	IVIG + methylprednisolone pulse for 48 hours	IVIG + dexamethasone for 7 days
Length of stay (days)	8	9	12	10
Time from MIS-C to vaccination	6 weeks	8 months	5 months	9 months
Vaccine administered	mRNA-1273	mRNA-1273	BNT162b2	BNT162b2

MIS-C: multisystem inflammatory syndrome in children associated with COVID-19; NT-ProBNP: N-terminal pro-B-type natriuretic peptide; MV: mechanical ventilation; IVIG: intravenous immunoglobulin G.

48 hours of the second dose.[12] However, there is no evidence of a causal relationship between these events and vaccination. Myocarditis is a form of presentation of MIS-C and its pathogenesis is associated with the presence of autoantibodies; therefore, a possible relationship between SARS-CoV-2 vaccines and MIS-C has been proposed. In our case series, there was no evidence of symptoms compatible with this adverse effect.

Wisniewski et al. conducted a retrospective study in 15 adolescents with an average age of 14.4 years (12 to 18 years) who developed MIS-C, received the BNT162b2 vaccine 90 days later, and were followed for an average of 9.5 months without recurrence of inflammatory syndrome or myocarditis.[13]

The study published by Levy et al. suggests that vaccination with 2 doses in adolescents may reduce the incidence of MIS-C in this population.[14]

Recently, a CDC report involving 24 hospitals in the United Stated included a total of 102 patients aged 12 to 18 years who were admitted with a diagnosis of MIS-C between July and December 2021, and reported that vaccination with 2 doses of the BNT162b2 vaccine in this population would be 91% effective in reducing the risk of MIS-C.[15]

CONCLUSION

Here we describe a series of 4 patients with a history of MIS-C who subsequently received mRNA vaccines without evidence of recurrence of the inflammatory syndrome or adverse cardiac effects. Further studies are required to assess the optimal vaccination strategy for these children. ■

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