Myocarditis and Pericarditis in Adolescents after First and Second doses of mRNA COVID-19 Vaccines

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Introduction

While mRNA COVID-19 vaccines like Tozinameran (Pfizer-BioNTech BNT162b2) and Elasomeran (Moderna mRNA-1273) have shown a high level of efficacy and effectiveness in real-life, some concerns about vaccination-related pericarditis and/or myocarditis have raised.[1,2] After the initial signals from Israel, European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) alerted on the risk of pericarditis and/or myocarditis with mRNA COVID-19 vaccines.[2,3] In August 2021, the US Centers for Disease Control and Prevention (CDC) published data suggesting a higher rate of vaccination-related myocarditis in young men, but no stratification was made on adolescent age group.[4] Recently, 2 two observational studies from Israel estimated the incidence of myocarditis around 0.64 and 1.42 per 100,000 persons after the first dose of Tozinameran and 3.83 per 100,000 after the second dose.[5,6] The risk difference between the first and second doses of Tozinameran was evaluated to 1.76 per 100,000 persons, with a great difference among boys between 16 and 19 years.[6] To date no data were published in the young adolescent between 12 and 15 years. In addition, recent update from Canada (Ontario) and from European Nordic countries, suggest that Elasomeran have higher rates of post-vaccination myocarditis than Tozinameran in all male age groups.[7,8] Considering these cardiac risks, different vaccination policies have been decided in particular among adolescents. While the United States and several European countries (such France) recommend 2 doses of mRNA COVID-19 vaccines, the United Kingdom recommend one dose to low-risk adolescents against COVID-19.[9] The European Nordic countries (Norway, Denmark, Sweden and Finland) decided recently to limit the vaccination with Elasomeran in adolescent and/or young adults (<30 years).[10]

Since most of data came from drug agencies communications, mostly from US and Israel, there is an urgent need to provide additional data on pericarditis and/or myocarditis with mRNA COVID-19 vaccines in the age group of adolescents, particularly in 12 and 15

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years. It is also necessary to have more information on the risk of pericarditis and/or myocarditis between the 2 mRNA COVID-19 vaccines in this young population Thus, the objective of this study was to determine whether the risk of reporting pericarditis and/or myocarditis with mRNA COVID-19 vaccines varied according dose-vaccination, age, sex and type of pericarditis and/or myocarditis in adolescents between 12-17 years.

Methods

We performed a pharmacovigilance analysis reviewing all reports with mRNA COVID-19 vaccines recorded Vigibase®, the World Health Organization (WHO) Global Individual Case Safety Reports (ICSRs) database. Vigibase includes more than 25 million reports forwarded to the WHO Uppsala Monitoring Center (UMC) by national pharmacovigilance systems from over 148 countries. The Medical Dictionary for Regulatory Activities (MedDRA®) is used to code each adverse drug reaction. According to the clinical research French law, review from an ethics committee is not required for such observational studies. As all data from VigiBase® were deidentified, patient informed consent was not necessary.

We included all reports registered between January 1, 2021, and September 14, 2021, with age and sex known. All adolescents (12-17 years) who received mRNA COVID-19 vaccines were included. As the reports from US did not include dose information (first or second dose), we have excluded these data from the study. All reports were reviewed by authors (DF, CF, PDP) including one clinical cardiologist (DF) and were classified in reports related to first dose (D1), second dose (D2) or non-available information (NA). Performing disproportionality analyses, we compared the cases of pericarditis and/or myocarditis in patients exposed to the second dose of mRNA COVID-19 vaccines with those reported in

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patients exposed to the first dose of mRNA COVID-19 vaccines. Reporting Odds Ratios (ROR) with their 95% confidence interval (CI) were calculated to estimate the risk of reporting pericarditis and/or myocarditis. ROR is a ratio similar in concept to the odds ratio in case-control studies and corresponds to the exposure odds among reported cases of pericarditis or myocarditis over the exposure odds among reported non-case. Cases were reports containing any terms including the terminology "Non-infectious Pericarditis" or "Non-infectious Myocarditis" found in MedDRA dictionary. Non-cases were all other reports recorded in VigiBase® during the same period of interest for our population. Logistic regression model were performed for the disproportionality analysis to take into account the potential confounders including the following variables: age, sex, type of reporter (physician or other), completeness of individual case safety reports (high or low), and number of co-reported drugs when the headcount allowed it. As secondary objectives, we also evaluated the risk of reporting pericarditis and/or myocarditis according to age group (12-15 versus 16-17 years), sex, and type of mRNA COVID-19 vaccines (Elasomeran versus Tozinameran). Sensitivity analyses were performed including only physician reports.

Results

In total, we analyzed 4,942 reports with mRNA COVID-19 vaccines in adolescents aged 12 to 17 years old (Tozinameran = 4,659; Elasomeran = 283). We identified 242 pericarditis and/or myocarditis (49 pericarditis only, 191 myocarditis only, 2 myopericaditis) and 233 were reported with Tozinameran and 9 with Elasomeran (**Table**). Among these cases, patients were mostly boys (205, 85%) and with a mean 15.8±1.4 age of years. Most of reports were serious (229, 95%) including 191 (79%) leading to hospitalization. The evolution was fatal in only one case. Reports of pericarditis and/or myocarditis came mostly from Germany (59; 24 %), followed by France (40, 17 %) and Italy (24; 10%) and from physicians in 150

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cases (62%). The most frequent co-reported symptoms were chest pain, pyrexia or dyspnea. The time onset was 4 days for D1 and 3 days for D2 (3 days for NA) (**Figure 1**).

Compared with the first dose of mRNA COVID-19 vaccines, the second dose was associated with an increased risk of reporting pericarditis and/or myocarditis (ROR 4.95; 95%CI 3.14, 7.89) **(Figure 2)**. The ROR remained significant when analysis was limited to myocarditis only (ROR 4.98; 95%CI 3.05, 8.27) or pericarditis only (ROR 5.44; 95%CI 2.01, 16.10). No differences were found when we compared age group (12-15 versus 16-17 years) whatever the dose (except for the analyse with NA). The risk of reporting pericarditis and/or myocarditis was 10 times higher in boys than in girls at both the first dose (ROR 10.1; 95%CI 4.26, 29.6) and second dose (ROR 10.2; 95%CI 4.88, 25.0). No difference between the two types of vaccines could be demonstrated (D2; ROR 2.20; 95%CI 0.48, 7.61). Consistent results were observed in sensitivity analyses restricting data to reports made by physicians.

Discussion

This study evaluated more than 4,900 adverse effects of mRNA COVID-19 vaccines in adolescents mainly reported by European countries. We found that the second dose of vaccine was associated with a 5-fold increase in the reporting odds of myocarditis and/or pericarditis compared to first dose of vaccine. This risk was higher in boys particularly for myocarditis. Our results suggest no differences according age group or type of vaccine. As the US pharmacovigilance data did not include dose information (dose 1 or dose 2), we were unable to analyze the reports. This lack of information is a potential limitation of our study on the transferability of the results to the US vaccination context and may have limited the statistical power of our study, particularly when comparing the two vaccines. However, to our knowledge, this is the first investigation based on non-US data which provide additional data on vaccine safety in adolescents. Such pharmacovigilance analyses could be subject to

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reporting bias, but our results add new information relatively to young adolescents (12-15 years), the difference between age group and type of mRNA COVID-19 vaccines and corroborate the higher risk of second dose particular in boys.[5,6,11] While randomized clinical trials show that mRNA COVID-19 vaccines represent an effective method of preventing infection, our finding should be integrated as component of the vaccine strategy to limit the impact of cardiac adverse effects, in balance with the exceptional severe form of covid-19 in adolescent. Our study calls for corroboration in large real-world studies and evaluation of long-term consequences of this vaccine-associated pericarditis/myocarditis.

Article information

Contributions

All authors conceived and designed the study. FM and CF acquired the data and did the statistical analyses. All authors analyzed and interpreted the data. DF wrote the manuscript, and all authors critically revised the manuscript. FM supervised the study and is the guarantor. All authors approved the final version of the manuscript and are accountable for its accuracy.

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Role of the funding source

NA

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Data availability

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

Conflict of Interest Disclosures: All authors have no conflicts to disclose.

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Table 1. Characteristics of Pericarditis and/or Myocarditis reports with mRNA COVID-19 vaccines in adolescents, in Vigibase.

	Myocarditis[a]	Pericarditis[a]
n (%)	193	51
Age (mean, sd / median)	15.9 (1.3) / 16	15.6 (1.5) / 16
Age		
[12-15]	50 (25.9)	19 (37.3)
[16-17]	143 (74.1)	32 (62.7)
Sex		
Men	172 (89.1)	35 (68.6)
Women	21 (10.9)	16 (31.4)
Country		
Germany	57 (29.5)	2 (3.9)
France	28 (14.5)	13 (25.5)
Spain	16 (8.3)	2 (3.9)
Austria	15 (7.8)	0
Italy	15 (7.8)	10 (19.6)
Denmark	12 (6.2)	4 (7.8)
Hungary	9 (4.7)	1 (2.0)
UK	8 (4.2)	2 (3.9)
Others	33 (17.1)	17 (33.3)
Reported by Physician	121 (62.7)	31 (60.8)
High Completeness[b]	178 (92.2)	41 (80.4)
Event-related dose number[c]		
D1	31 (16.1)	6 (11.8)
D2	58 (30.1)	10 (19.6)
NA	104 (53.9)	35 (68.6)
mRNA Vaccine		
Tozinameran	185 (95.9)	50 (98.0)
Elasomeran	8 (4.1)	1 (2.0)
Serious *(Yes)*	190 (98.5)	41 (80.4)
Hospitalization	172 (89.1)	21 (41.2)
Co-reported event		
Chest pain	50 (25.9)	13 (25.5)
Pyrexia	22 (11.4)	6 (11.8)
Headache	13 (6.7)	1 (2.0)

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	Myocarditis[a]	Pericarditis[a]
Time to Onset (days), median[d]	3 d	4 d

[a] Of the 242 reports mentioning Pericarditis and/or Myocarditis, 2 had both events (Pericarditis and Myocarditis).

[b] The Uppsala Center (manager of VigiBase) has developed a notification completeness score (VigiGrade). It is calculated by assigning penalties according to the availability of information and its clinical relevance. Here, high completeness was defined by a completeness score >= 0.6.

[c] Event-related dose number means the dose at which the event occurred (D1 for dose n°1, D2 for dose n°2 and NA when no information was found on the dose number).

[d] Based on 45 cases data for Pericarditis and 173 cases data for Myocarditis.

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Figure 1. Time to Onset of Pericarditis and/or Myocarditis after mRNA COVID-19 vaccines in adolescents (days)

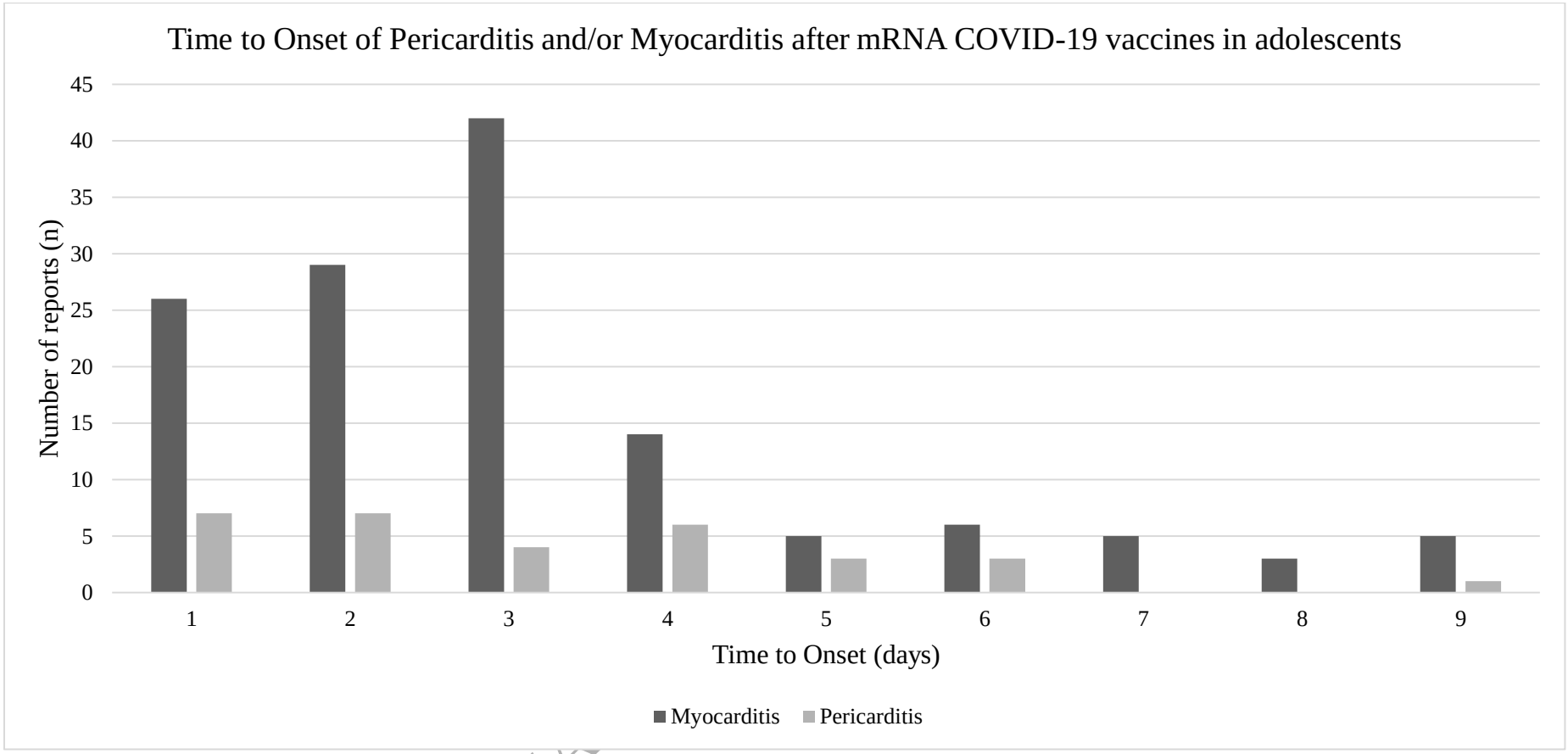

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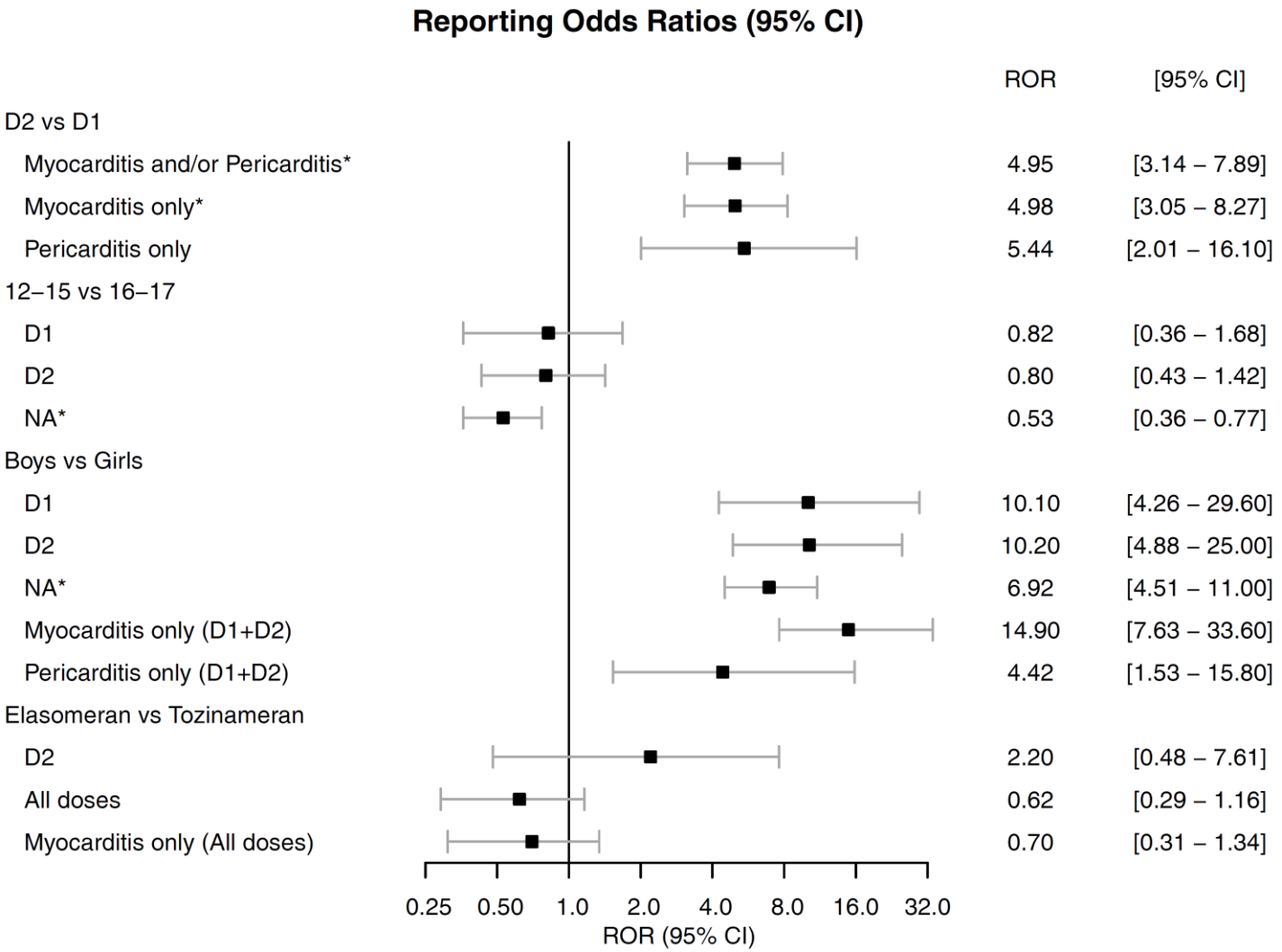
Figure 2: Reporting Odds Ratios for the Association between Reports of Non Infectious Myocarditis and/or Non Infectious Pericarditis and the Use of Tozinameran and Elasomeran[†]



Abbreviations: CI, confidence interval; ROR, reporting odds ratio. D1, first dose, D2, second dose, NA, information relative to the dose not available

[†]We used the case non-case method which is similar to case-control studies but adapted for pharmacovigilance studies. We used reporting odds ratios (ROR) and their 95% confidence interval (95% CI) to calculate disproportionality. ROR is a ratio similar in concept to the odds ratio in case-control studies and corresponds to the exposure odds

among reported cases of myocarditis/pericarditis over the exposure odds among reported non-case. Cases were reports containing any terms including the terminology “Non-infectious Pericarditis” or “Non-infectious Myocarditis” found in MedDRA dictionary. Non-cases were all other reports recorded in VigiBase® during the same period of interest for our population. The logistic regression model performed for the disproportionality analysis was adjusted for 5 variables: age, sex, type of reporter (physician or other), completeness of individual case safety reports (high or low), and number of co-reported drugs (none, one or two, or more than two) when the headcount allowed it.

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