

Filling the gap in epidemiology, management and clinical course of COVID-19 vaccination-related pericarditis

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Coronavirus disease 2019 (COVID-19) is responsible for the ongoing pandemic associated with significant morbidity and mortality around the globe.^{1,2} Vaccines based on a broad range of different technologies have proven highly effective at preventing symptomatic disease and death and have played an essential role in flattening the epidemiology curve.^{1,2} Nevertheless, some concerns have been raised due to rare cases of myocarditis and pericarditis following the receipt of COVID-19 vaccine, especially mRNA vaccines.^{1,2} In the attempt to provide a nosological frame for clinical activity, the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) and the Italian Society of Cardiology (SIC) have defined ‘vaccine-associated myocarditis and pericarditis’ as myocarditis and/or pericarditis occurring within 15 days from administration of mRNA vaccine against COVID-19.^{3,4} Despite their large sample sizes, no safety issue concerning postvaccine myocarditis or pericarditis was reported in landmark studies on COVID-19 mRNA vaccine.⁵ Later, large registry-based studies suggested a possible relationship between mRNA vaccines and myocarditis/pericarditis. On July 2021, myocarditis and pericarditis were added to the list of adverse effects of both mRNA-based vaccines [BNT162b2 (Pfizer–BioNTech) and mRNA-1273 (Moderna)] against COVID-19 by the European Medicines Agency (EMA).^{3,4}

More than 10 billion doses have been administered since the outbreak of the COVID-19 pandemic² and postvaccine myocarditis and pericarditis have been reported as rare events with an estimated incidence of 0.5–2 cases in 100 000 individuals receiving one dose and two doses, respectively.^{6–9} Following two large European epidemiological studies, the Pharmacovigilance Risk Assessment Committee (PRAC) – the EMA committee responsible for assessing and monitoring the safety of human medicines – determined that postvaccine myocarditis and pericarditis are ‘very rare’, occur after a median time of 4–

5 days following vaccination, follow a mild clinical course and result in a complete resolution of symptoms in 95% of cases. The highest risk of postvaccine myocarditis was observed in men less than 30 years of age following the second dose of mRNA vaccine, especially in the event of heterologous vaccination.^{3,4,10–13} Finally, although major advances have been made in the epidemiology and clinical course of postvaccine myocarditis, further research is required to fill the knowledge-gap on pericarditis following administration of COVID-19 vaccine.

In the last issue of the Journal, Collini *et al.*¹⁴ provide real-world data of postvaccine pericarditis, with and without concomitant myocarditis (i.e. ‘myopericarditis’), defined according to the official recommendation by Italian and international health authorities.^{3,4} The Authors are to be congratulated on their efforts, as collecting populations of individuals with well characterized postvaccine (myo)pericarditis has been a hard task to pursue over the recent years, despite the consistent number of cases worldwide. Many studies included heterogeneous populations with ‘clinically suspected’ postvaccine pericarditis and myocarditis, even without further characterization by cardiac magnetic resonance^{15,16} or in the presence of chest pain following vaccination as the predominant (sometimes unique) feature supporting the suspicion of pericarditis. Conversely, the Authors applied stringent inclusion criteria in order to identify a homogenous population of consecutive patients with a clinical and – in cases with suspected associated myocarditis – CMR diagnosis of (myo)pericarditis who received at least a single dose of vaccine against COVID-19. Patients did not undergo endomyocardial biopsy in light of the low-risk presentation, according to the official recommendations.^{17,18} Although limited in size, the study population represents one of the few published series in which all individuals had a PCR test to assess for COVID-19 infection as the inclusion criteria. Of note, only those who tested negative for COVID-19 were included in the study cohort, thus making a strong case for the association for the development of (myo)pericarditis following vaccination.

Considering the small sample size, fairly addressed in the limitations by the Authors, the study by Collini *et al.*¹⁴ reports several interesting findings. First, their results provided evidence that the relative incidence of (myo)pericarditis is highest among individuals younger than

40 years after a second or third dose. As recently reported at the national Italian level, the age at a higher risk for postvaccine pericarditis ranges from 17 to 49 years compared with that of postvaccine myocarditis ranging from 12 to 29 years.⁴ Second, there was no sex difference between individuals with pericarditis and myopericarditis in this study cohort. Although male predominance has been reported in postvaccine myocarditis (the mechanism of which is not fully elucidated),¹³ data on sex in pericarditis are missing. In this perspective, the study by Collini *et al.*¹⁴ provides further insights into this field, in line with recent reports from AIFA⁴ on similar frequency of postvaccine pericarditis in both sexes. Third, clinical presentation of postvaccine pericarditis was similar to that of forms unrelated to vaccination with chest pain as the predominant symptom (83% of cases) and typical findings on surface ECG such as widespread ST-segment elevation with PR depression, with a clinical onset at a median time of 7 days from vaccination. Fourth, the average number of pericarditis observed every 3 months during the vaccine period was significantly higher than during the prevaccination period (12.3 vs. 6.2, $P < 0.001$). This finding is consistent with a lower threshold for undertaking second- and third-level diagnostic tests in individuals reporting symptoms of possible pericarditis and myocarditis in the pandemic era. As expected, this approach resulted in a higher number of individuals diagnosed with pericarditis, as outlined in other reports, but this did not translate into poorer outcome in larger studies. Finally, 21% of individuals had a previous pericarditis (one viral pericarditis due to COVID-19 in the previous 12 months and four idiopathic pericarditis in the previous 24 months) and they all were diagnosed with postvaccine myopericarditis. This is a remarkable finding, as identification of individuals at a higher risk of developing postvaccine pericarditis and myocarditis is crucial to addressing patient-tailored strategies for COVID-19 vaccination. Although the study does not have enough statistical power to derive a solid conclusion, it raises intriguing hypotheses to be investigated in larger cohorts. The current approach for risk stratification is based on age, sex and number of doses administered, but more parameters are likely to be associated with the development of postvaccine myopericarditis. The presence of a previous infection with SARS-CoV-2 presenting as pericarditis or myocarditis might predispose to myocardial injury. This possibility has been recently proposed by Bellos *et al.*¹⁹ who reported that myocarditis after the first dose of vaccine was significantly associated with prior COVID-19 infection. In this study, individuals received vaccines based on RNA technology, viral vectors, recombinant protein and inactivated virus; however, myopericarditis was diagnosed only in those receiving mRNA vaccines. Therefore, prior COVID-19 infection and use of mRNA vaccine might be additional parameters to consider when estimating the risk of myopericarditis following vaccination. Larger studies on well

characterized cohorts are required to investigate this hypothesis.

Patients with postvaccine (myo)pericarditis were managed in accordance with the 2015 European Society of Cardiology guidelines for the diagnosis and management of pericardial diseases.²⁰ In this study cohort, anti-inflammatory therapy was effective in controlling symptoms and treating postvaccine pericarditis with 92% of patients receiving one or two anti-inflammatory drugs, mostly ibuprofen.¹⁴ In light of the predominant pericarditis component, patients with myopericarditis (presenting with systolic dysfunction in $\approx 30\%$ of cases) were treated with colchicine, NSAIDs or corticosteroids as in acute pericarditis. Although potential concerns of toxicity have been raised in animal models of viral myocarditis treated with colchicine, no adverse drug-related effect occurred.

Interestingly, the evidence-based therapeutic approach for pericarditis unrelated to vaccination was also effective in vaccine-associated pericarditis, providing a rationale for further studies of therapy in this cohort. Myopericarditis unrelated to vaccination has a long-term benign outcome, especially in the presence of preserved global longitudinal strain.^{21–23} In this study,¹⁴ most patients were only briefly admitted to hospital and responded well to standard therapy. Short-term clinical outcomes have been favourable, without relevant arrhythmias and with rapid complete recovery. Although long-term outcome has to be confirmed in future analyses, the findings of the present study confirm the mild clinical course of postvaccine (myo)pericarditis and support the effectiveness of evidence-based therapy for this condition.

Further dedicated research is needed to investigate the natural history, management and long-term outcome of patients with postvaccine (myo)pericarditis. Long-term population analyses demonstrated that the cardiovascular risk conferred by COVID-19 extends beyond the acute phase, representing the rationale for implementing prevention strategies for SARS-CoV-2 infection and vaccination campaign.^{24–26}

In conclusion, the study by Collini *et al.*¹⁴ increases current knowledge on postvaccine pericarditis and has the ability to raise, explicitly or implicitly, a series of stimulating clinical and pathophysiological questions, to be addressed in future dedicated analyses. Meanwhile, the benefit-risk assessment for COVID-19 vaccination continues to show a favourable balance.

Conflicts of interest

There are no conflicts of interest.

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