COVID-19 vaccine post-marketing surveillance: Cardiovascular doctors have a role to play!

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Several vaccines against SARS-CoV-2 have been authorized by various regulatory authorities since the beginning of the coronavirus pandemic. The four vaccines currently available in Europe are mRNA-based vaccines (Moderna mRNA-1273, Pfizer-BioNTech BNT162b2) and recombinant adenoviral vector vaccines encoding the spike protein of SARS-CoV-2 (AstraZeneca and Janssen).

Some of the adverse effects reported during the vaccination campaign were expected, as per the preliminary data collected through the vaccine trials (e.g. influenza-like illness, myalgia, and arthralgia). However, no cardiovascular adverse effects were mentioned in the summaries of product characteristics in December 2020, at the start of the vaccination campaign. The national pharmacovigilance systems have been highly solicited for the purpose of analysing and recording the numerous adverse events reported by healthcare professionals and patients [1]. Indeed, the objective of this process was to identify as soon as possible serious and/or unexpected adverse effects and detect potential safety signals to monitor the benefit-risk balance of these vaccines.

In this article we describe the cardiovascular signals emerging after this post-marketing surveillance.

Vaccine-induced immune thrombotic thrombocytopenia

Vaccine-induced immune thrombotic thrombocytopenia (VITT) has been highly publicized in the media, leading to temporary suspension of the AstraZeneca vaccine in March 2021 in some European countries. In most of these, the AstraZeneca vaccine has been reauthorized in an older population following a European assessment of that risk. Nonetheless, some countries, including Denmark and Norway, have permanently suspended use of this vaccine. The literature analysis of the 40 initial cases showed that VITT occurred primarily in women aged between 21 and 77 years [2]. Subsequently, 142 VITT were identified by the European Medicines Agency [3]. Most cases of thrombosis were cerebral venous thrombosis [4]. Additionally to the associated thrombocytopenia, other biological disorders were also reported: increases in D-dimer concentrations (up to 100 N), decreased international normalized ratio and decreases in fibrinogen concentrations. Several cases associated with disseminated intravascular coagulation were also reported. Antiplatelet factor 4/heparin antibodies were detected in all these cases of VITT, suggesting platelet activation despite no recent exposure to heparin. The mechanism is still hypothetical, but the authors suggest a similarity with autoimmune heparin-induced thrombocytopenia. It suggests that platelet factor 4 binds to

endogenous polyanions (such as hypersulphated chondroitin sulphate, DNA, RNA, polyphosphate, etc.), which may change the platelet factor 4 configuration and thus reveal the antigenic epitope [3]. Following those reports, VITT was added to the AstraZeneca and Janssen vaccine summaries of product characteristics, on 19 March and 15 April 2021, respectively. Regarding diagnosis and management, documents were published by the International Society on Thrombosis and Haemostasis [5] and the American Society of Hematology [6]. Hence, it was recommended that non-replicating viral vector vaccines should be avoided in patients affected by VITT after the first vaccination.

Myocarditis and pericarditis following mRNA COVID-19 vaccination

More recently, cases of myocarditis and pericarditis have been reported following mRNA-based vaccination (i.e. Pfizer-BioNTech and Moderna vaccines). The first cases of myocarditis described with the Pfizer-BioNTech vaccine were published by an Israeli team: patients were young (median age 23 years), and were treated with a non-steroidal anti-inflammatory drug and colchicine and discharged 4−8 days after admission [7]. Using the World Health Organization (WHO) Global Pharmacovigilance Database for Individual Case Safety Reports (VigiBase), cases of myocarditis associated with vaccines were analysed [8]. A total of 214 cases were associated with mRNA-based vaccines; the median age was 35 years, 63.9% were male, associated pericarditis was reported in 22% cases, and median time to onset between the last dose of vaccine and the adverse event was 3 days. According to the Centers for Disease Control and Prevention [9], “most patients who received care responded well to treatment and rest and quickly felt better”. On 14 July 2021, the Pharmacovigilance Risk Assessment Committee recommended listing myocarditis and pericarditis as new side-effects in the product information for these mRNA COVID-19 vaccines [10]. After the Moderna and Pfizer-BioNTech vaccine summaries of product characteristics were modified, recommendations were published on the 7 August 2021 in the Official Journal of the French Republic (*Journal Officiel de la République Française*) [11]: the second dose should not be administered after severe adverse effects such as myocarditis.

Hypertension

Hypertension is the first cardiovascular adverse event to be detected during the French vaccination campaign, initially occurring after Pfizer-BioNTech vaccination. These hypertension cases can be symptomatic and can occur independently of any history of hypertension. They occur either within minutes (probably via an adrenergic reaction induced by pain or stress) or days after the vaccination (via an unknown mechanism). Some cases were severe and/or required antihypertensive treatment [12]. According to the French Society of Hypertension, there is currently no reason to discontinue or postpone vaccination for patients with hypertension (with a high risk of severe COVID-19) or in subjects who experienced a blood-pressure modification after the first dose [13]. According to the French Pharmacovigilance Centers network, hypertension is a “confirmed” pharmacovigilance signal for mRNA-based vaccine and a “potential” signal for recombinant adenoviral vector encoding spike protein of SARS-CoV-2 vaccine [12]. Reports of cases in Switzerland and Greece have also been published [14,15], without leading to a European or international signal.

Thrombosis

The Global Pharmacovigilance Database attests that cases of venous and arterial thrombosis have been reported with all commercialized COVID-19 vaccines [16]. So far, these events do not constitute a confirmed safety signal. Currently, no special recommendation is available regarding patients affected by a thromboembolic event after the first dose as well as in patients with risk factors for thrombosis. Indeed, such events do not constitute a contraindication, and the decision to vaccinate or revaccinate is still based on case-by-case medical evaluation, including the risk of severe COVID-19.

Conclusion

During the current vaccination campaign, national and global pharmacovigilance systems are highly focused on the detection of COVID-19 vaccine safety signals. As potential reporters, all clinicians should be aware of the crucial role they play in the pharmacovigilance organization to assess and clarify the safety profile of new drugs such as COVID-19 vaccines and to evaluate their risk/benefit balance, even more so in a crisis context. In case of a possible drug/vaccine adverse effect, the main message is to report the case to the pharmacovigilance national system with sufficient data (including chronology, accurate description of event and investigation) to ensure the quality of the case report.

This quality is a major factor to adequately assess the drug causality and thus contribute to an efficient surveillance of drug safety.

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