Impact of COVID-19 and COVID-19 vaccination on high-risk patients with Antiphospholipid Syndrome: a nationwide survey

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Running Head: COVID-19 & vaccination in APS

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ABSTRACT

Objectives: Patients with antiphospholipid syndrome (APS) and triple-positive for antiphospholipid antibodies (aPL) are at high-risk of recurrent events. As COVID-19 and COVID-19 vaccination may induce thrombotic complications, the objective of the study was to assess the course of COVID-19 and adverse events after vaccination in these patients.

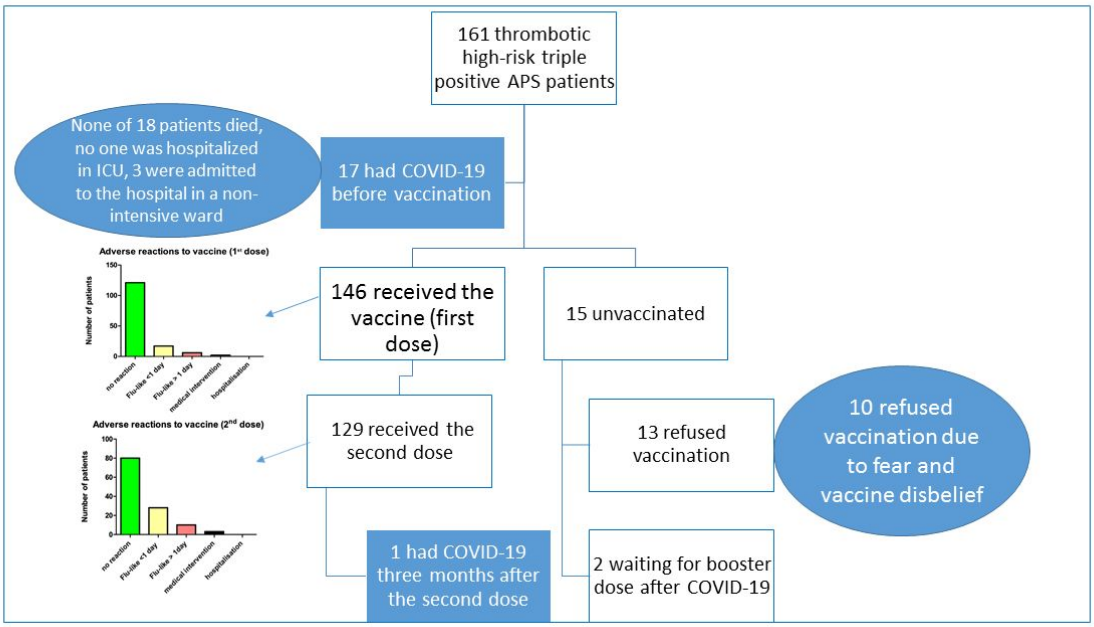
Methods: This is a nationwide multicentre survey conducted in nine APS referral centres by means of a questionnaire. Included patients are thrombotic APS with triple-positive aPL confirmed 12 weeks apart. Reference specialist physicians used a four-graded scale of severity for COVID-19 [from 0 (asymptomatic) to 3 (hospitalization in intensive care unit)] and a six-graded scale for adverse reactions to vaccination [from 0 (transient local injection site sign/symptoms) to 5 (potentially life-threatening reactions)]. Outcomes were considered within a 30-days period.

Results: Out of 161 patients interviewed, 18 (11%) had COVID-19. All of them fully recovered without any progression to severe disease nor thromboembolic event. One-hundred-forty-six patients received the first (92%) and 129 (80%) the second dose of vaccine; side effects were minimal and, in most cases, (83% after the first and 68% after the second shot) limited to a sore arm. Fifteen patients (9%) were unvaccinated. Most of them raised doubts on the need for vaccination, complained for poor safety and in general were reluctant on COVID-19 vaccination.

Conclusion: Patients with triple-positive thrombotic APS did not suffer from severe COVID-19 outcomes. Importantly, COVID-19 vaccination was well tolerated. These data may reassure patients and physicians and contribute in reducing hesitancy in unvaccinated patients.

Key words: Antiphospholipd Syndrome, COVID-19, Vaccination, Thrombosis

Visual abstract



Rheumatology key messages

- Physicians and patients with APS are concerned about the impact of COVID-19 and COVID-19 vaccination.
- High-risk thrombotic APS patients at did not develop thrombotic events and vaccination was well tolerated.
- These data reassure APS patients and caregivers, and contribute to reducing hesitancy in unvaccinated patients.

Introduction

COronaVIrus Disease 19 (COVID-19) caused by the acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a global pandemic associated with a remarkably high rate of morbidity and mortality(1, 2). There is strong evidence supporting a major pathogenic role of a procoagulant state associated with mortality in severe COVID-19(3) and autopsy studies have extensively reported the presence of macro- and micro-embolism(4). This clinical phenotype has similarities with thrombotic antiphospholipid syndrome (APS) and its catastrophic variant(5, 6). Indeed, there are reports that at least three patients with infection caused by SARS-CoV-2 had cerebral infarcts associated with the presence of antibodies to β2-Glycoprorein I (β2GPI) and cardiolipin(7). Moreover, some authors detected Lupus Anticoagulant (LAC), a risk factor for thromboembolic events, in 45% of 56 patients with COVID- 19(8). Thus, hypothetically, COVID-19 patients may develop thrombotic APS, although detected antibodies are apparently different from those of genuine APS(9). Patients with thrombotic APS are at high-risk of thrombosis recurrence both in arterial and venous circulation when positive in all the three tests for antiphospholipid antibodies (aPL)(10). Secondary prevention with warfarin is mandatory while direct oral anticoagulants are not recommended(11) as they failed to provide non-inferiority versus warfarin in randomized clinical trials(12-14). However, thromboembolic events may occur despite anticoagulation(10). In the same way, the risk of thromboembolism remains high in hospitalized COVID-19 patients despite anticoagulation prophylaxis. Indeed, the incidence of thrombotic events in COVD-19 complications is 9.5%(15), but in those requiring intensive care, thrombosis rates can be remarkably high (31%)(16). In March 2021, concerns developed regarding the occurrence of a feared complication, the Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT) mainly related to the use of ChAdOx1 nCoV-19 (Oxford– AstraZeneca) vaccine(17). Some authors raised concerns that COVID-19 vaccines, at least theoretically from a pathophysiologic point of view,

could induce full-blown APS in aPL carriers(18). However, to our knowledge, there is no patient-involving study assessing the impact of SARS-CoV-2 infection or vaccination against SARS-CoV-2 in high-risk thrombotic APS. Despite the general advice to undergo vaccination, some physicians may be reluctant on vaccination due to fear of thrombotic events in this high-risk group of patients. Based on these premises, we sought to answer the widespread concern among patients and physicians on the impact of SARS-CoV-2 infection and vaccination in APS patients. We performed a survey on the occurrence of COVID-19 and adverse reactions following vaccination against SARS-CoV-2 in APS patients at high-risk of thromboembolic events.

Materials and Methods

Study design and survey questionnaire

This survey was conducted in centres participating in the TRAPS trial (12) where high-risk triple-positive thrombotic APS patients agreed to be followed up for trial extension outcomes (19). All thrombotic APS patients were positive for Lupus Anticoagulant (LA), anti-cardiolipin (aCL) and anti β2-Glycoprotein I (aβGPI) antibodies confirmed 12 weeks apart. All participants gave written informed consent and the study was performed in accordance with the principles of the Declaration of Helsinki. Research ethics approval was not required: the information was obtained as part of routine clinical management in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects. In order to ensure respect for data protection and privacy, data were completely anonymized. Patients were interviewed in person during on-site follow-up visits or by means of a phone call. A dedicated physician completed the survey questionnaire. All patients agreed to be interviewed (absence of nonresponse bias). General questions exploring demographics and clinical status were routinely collected or retrieved from the TRAPS database (12); mandatory items were the past APS clinical

history, the index thrombotic event (arterial, venous, catastrophic) and the presence of associated autoimmune disease. We specifically collected data on possible prior SARS-CoV-2 infection, date, type of diagnosis and on vaccination status and possible side effects or established thrombotic events within a 30-day period. Patients were required to indicate the clinical evolution of previous SARS-CoV-2 infection using a four-graded scale of severity: 0= asymptomatic; 1=mild symptoms treated at home; 2= hospitalization in non-intensive ward; 3=hospitalization in intensive care unit (ICU). We specifically collected data on the type of vaccine administered (Pfizer/BioNTech, Moderna and AstraZeneca), the timing and number of administrations given. Adverse events included all local and systemic reactions in the first month following the injection. Local adverse reactions included injection-site pain or inflammation. Systemic adverse reactions comprised flu-like symptoms (fever, chills, headache, cough, muscle pain and body aches, fatigue and weakness, nausea or vomiting, diarrhoea). Allergic reactions such as angioedema, urticaria, wheezing, and skin rash were also assessed. The severity of adverse reactions was graded according to the following criteria: 0=no adverse reaction apart from transient local injection site signs/symptoms; 1=flu-like signs/symptoms of less than one-day duration; 2=flu/like sign/symptoms of more than one-day duration; 3=symptoms requiring medical intervention; 4= hospitalization; 5=potentially life-threatening reaction requiring assessment in the emergency department. In case patients did not get vaccination, the reason was noted, even if this was related to disbelief towards vaccines, fear, hesitancy, and advice from relatives or their general practitioner.

Results

The survey included 161 eligible patients and all accepted to answer the questionnaire. Patients' characteristics are reported in Table 1. Mean age was 47.1 years and the majority were females (68%). All the patients experienced venous and /or arterial thromboembolic events that were catastrophic in 2 cases and 60 (37%) had associated autoimmune diseases. The study flow is

depicted in Figure 1. Eighteen patients (11%) had SARS-CoV-2 infection confirmed by reverse transcriptase polymerase chain reaction (RT-PCR) assay. Seventeen had the infection before vaccination while one patient (female, 37 years old, with associated celiac disease) had the infection 3 months after her second dose of BNT162b2 Pfizer/BioNTech vaccine. Six of the eighteen patients had associated autoimmune diseases. No patient died, no one was hospitalized in ICU, 3 were admitted to the hospital in a non-intensive ward with fever and flu sign and symptoms without pneumonia and were discharged in a few days, 12 were treated at home by their General Practitioners and 3 were asymptomatic. One of the three hospitalized patients was a 70-year-old obese (BMI 32.9) woman with associated autoimmune disease (Hashimoto thyroiditis). The other two patients were a 51-year-old obese (BMI 30.8) man with cardiovascular risk factors (hypertension, diabetes and hyperlipidaemia) and a 57-year-old woman, both without associated autoimmune diseases. There was no difference in age, sex, type of past thromboembolic events and associated autoimmune diseases among patients who had SARS-CoV-2 infection and those who did not.

Of 161 patients included in the survey, 146 (91%) received the first dose of vaccine between January and September 2021: 121 the mRNA-based vaccine Pfizer-BioNTech (BNT162b2), 20 the mRNA-based vaccine Moderna (mRNA-1273) and five the adenovirus-vectored vaccine Oxford-AstraZeneca (ChAdOx1 nCoV-19). Of the 15 (9%) unvaccinated patients, 13 refused vaccination and two were waiting for the booster dose as recently affected by SARS-CoV-2 infection. Among the 13 patients who did not underwent vaccination, 10 refused vaccination due to fear and vaccine disbelief, one patient with associated SLE followed the treating physician recommendation against vaccination, one refused vaccination because of high titre positivity for IgM anti spike protein of SARS-CoV-2 despite having never got the infection, and one because of onset of a serious illness.

Vaccination was generally well tolerated as shown in Figure 2. One-hundred twenty-one (83%) had no adverse reaction or minimal signs/symptoms at the site of injection, 17 (12%) had flu-like symptoms lasting less than 1 day, six (4%) had these symptoms for more than 1 day, and two (1%) asked for medical intervention/counselling. No patient had severe adverse events that needed hospitalization. No case of VITT was reported during the 30 days following the first dose.

One-hundred twenty-nine patients (80%) received the second dose after a mean of 24 days from the first one. Of these, 88 (68%) had minimal transient reaction at the injection site. Twenty-eight (22%) had flu-like signs/symptoms lasting less than one day. Ten (8%) had flu-like signs/symptoms lasting more than one day. Three (2%) asked for the intervention of General Practitioner and one of them had a deep vein thrombosis 39 days after the second shot. Thirty patients with no or minimal local adverse reaction after the first shot had a worse reaction after the second shot. On the other hand, of 19 patients with some reaction after the first shot, nine had better, six no change and four a worse reaction after the second dose. No patients were hospitalized nor had severe allergic reactions after both shots.

Discussion

Procoagulant mechanisms are up-regulated in COVID-19(20) and could contribute to the occurrence of thromboembolic events in patients with acquired thrombophilia, namely aPL antibodies. Besides, the infection itself may generate circulating aPL antibodies(21), although they are different from those found in APS(9). Vaccination is a further problem as adenoviral vector-based COVID-19 vaccines are associated with a rare thromboembolic manifestation, namely VITT(17, 22). Many APS patients and even physicians pondered on the thromboembolic risk associated with eventual SARS-CoV-2 infection and vaccination. Given these premises, we sought to answer these questions by means of a survey among APS patients at high-risk of

thromboembolic events (*triple-positive* thrombotic APS patients). The rate of infection (11%) was close to that of the general population in our country(23). Indeed, cross-sectional studies indicated that autoimmune disease patients had a similar rate of infection with SARS-CoV-2 as compared with that in the general population(24).

Despite the high prothrombotic state of APS and a triple positive antiphospholipid profile, patients with SARS-CoV-2 infection in this survey did not suffer thromboembolic events. Of eighteen patients experiencing SARS-CoV-2 infection, three were admitted to the hospital but did not suffer progression to more severe disease.

At the time of database lock (October 2021), 15 patients (9%) choose not to vaccinate. Most of them doubted the need of vaccines, complained for poor safety, and in general feared vaccination and its side effects. Vaccine hesitancy is a major healthcare burden as it compromises the achievement of herd immunity(25).

Vaccination side effects were minimal and, in most cases, limited to injection site pain. No serious safety problems were reported and no patient was hospitalized. In particular, the 2 patients with previous CAPS and the 5 patients receiving the Astra-Zeneca vaccine did not report thrombotic complications or VITT. Indeed, this complication was observed in young individuals, likewise the participants in this survey, and particularly in those having the Astra-Zeneca vaccine(17, 22, 26, 27).

At the time of survey, all patients were on oral anticoagulant treatment with warfarin (except two patients who refused to switch from rivaroxaban to warfarin after the premature closure of the TRAPS trial)(12). Whether prior oral anticoagulant treatment may protect patients from severe COVID 19 complications is still a matter of debate(28-30).

Limitations of the study. In this retrospective survey, recollection and perceptions of symptoms

may be variable among responders. The psychological status due to the perception of COVID-19 pandemic may have influenced data reporting. Nevertheless, investigators reported no severe impact. Different intervals between vaccination and survey questions may have influenced the patients' responses. However, it is unlikely that symptoms might have been missed given the social and mediatic entity of the problem and the mean interval between the first dose and survey administration was 3 months (range 2-8 months). Finally, to account for eventual missed hospitalisations or COVID-19 disease, a cross check with General Practitioners regarding patients' hospitalisation was done.

In conclusion, COVID-19 and COVID-19 vaccination did not result in severe adverse events in high-risk triple positive APS patients. A recent survey in patients with aPL at lower risk of thromboembolic events showed that mRNA COVID-19 vaccines have an acceptable safety and tolerability profile(31). These results should reassure patients and caregivers especially on the safety of COVID-19 vaccination. Moreover, the results of this survey may also be translated to lower risk APS patients with incomplete positive aPL profile (double and single positivity).

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Verification, analysis and interpretation of data: Gentian Denas (GD), LA, Angela Tincani (AG), PG, AH.

Drafting of the manuscript: VP, LA, PG, GD.

All authors had full access to all the data in the study and accepted responsibility to submit for publication. All authors approved the final version of the manuscript.

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Data availability statement

Data that support the findings of this study are available from the corresponding author, [VP], upon reasonable request.

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Table 1. Characteristics of 161 triple-positive APS patients

Age – yr	47.1± 4.2
Female sex – n. (%)	109 (68)
Caucasian – n. (%)	159 (98)
Type of thromboembolic event – n. (%)	
Venous	80 (50)
Arterial	49 (30)
Venous and Arterial	30 (19)
Catastrophic	2 (1)
Associated autoimmune disease – n. (%)	60 (37)
SLE	34
Lupus-Like	7
Hashimoto's thyroiditis	7
Sjögren's Syndrome	3
UCTD	3
Celiac disease	1
Immune thrombocytopenia	1
Myasthenia Gravis	1
Multiple Sclerosis	1
Psoriasis	1
Devic's Disease	1

Plus–minus value is mean ±SD. Abbreviations: SLE=Systemic Lupus Erythematosus, UCTD=Undifferentiated Connective Tissue Disease

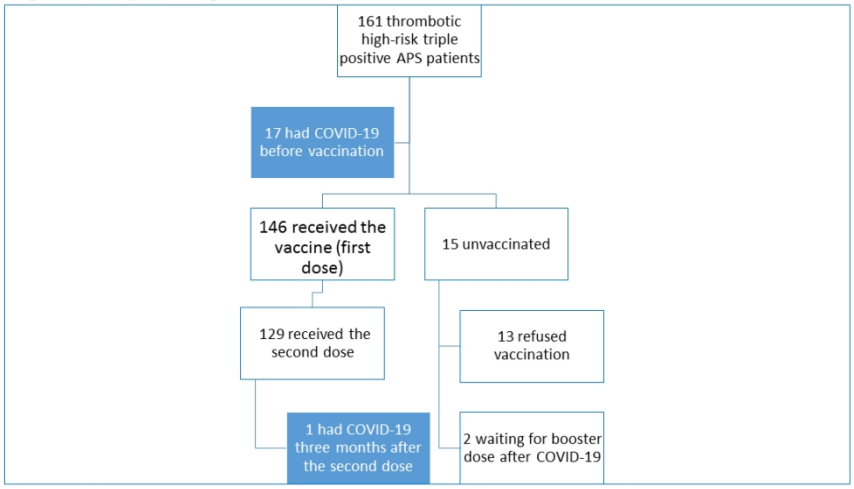
Legend to Figures

Figure 1. Study flow diagram

Figure 2. Adverse reactions to COVID-19 vaccination

Side effects after the first (Panel A) and second (Panel B) dose of COVID-19 vaccination. Most of patients had no adverse reaction or minimal transient reaction at the injection site. A few had flu-like symptoms lasting less 1 or 2 days while only and two (1%) after the first dose and 3 (2%) after the second dose asked for medical intervention/counselling. No patient had severe adverse events that needed hospitalization.

Figure 1. Study flow diagram



Study flow diagram

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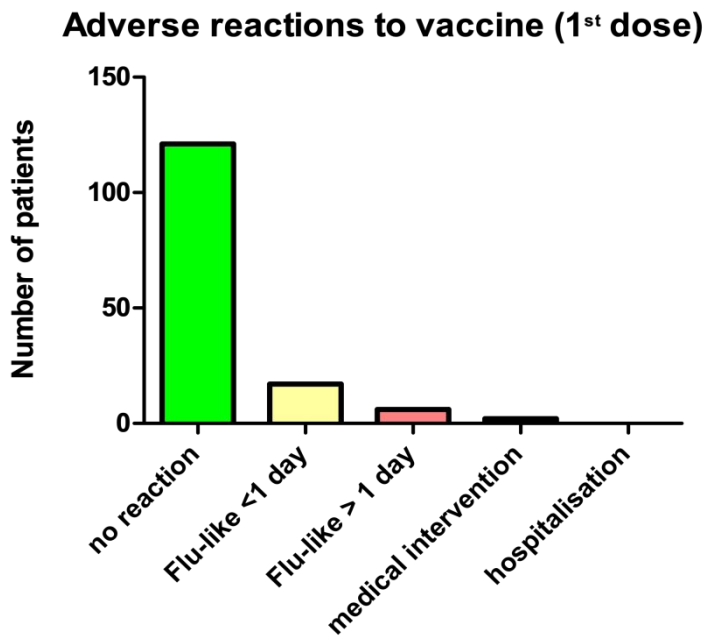
A)


Adverse reactions to vaccine (1st dose)
Number of patients
150
100
50
0
no reaction
Flu-like <1 day
Flu-like > 1 day
medical intervention
hospitalisation

B)

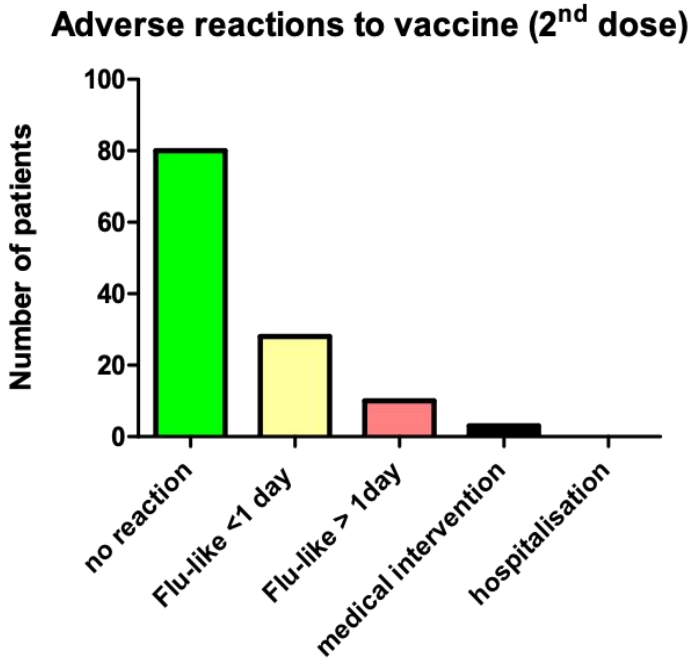

Adverse reactions to vaccine (2nd dose)
Number of patients
100
80
60
40
20
0
no reaction
Flu-like <1 day
Flu-like > 1day
medical intervention
hospitalisation

Figure 2.