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Short communication

mRNA vaccines for COVID-19 are safe and clinically effective in patients with cardiac amyloidosis

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ABSTRACT

Introduction: Amyloidosis is a rare disease in which malformed proteins are deposited in tissues occurring mostly commonly in older age. These deposits can lead to severe organ dysfunction e.g. in the myocardium with great impact on prognosis. The Covid-19 pandemic has caused excess mortality worldwide since 2020. Risk factors for a severe course include pre-existing cardiac diseases like heart failure and advanced age. Therefore, vaccination against Sars-CoV2 viruses is highly recommended for patients with cardiac amyloidosis. However, since there are no specific data on mRNA vaccines in patients with cardiac amyloidosis, some patients have concerns about cardiac adverse events following immunization (AEFI), such as myocarditis.

Purpose: The purpose of the study is to assess the safety and efficacy of mRNA vaccines in patients with cardiac amyloidosis.

Methods: Patients of the Amyloidosis Center Charité Berlin (ACCB) were assessed about the vaccination, its tolerability and clinical effectiveness. To date, we included 62 patients (54 men) with a median age of 82,5 years (range 37 to 92). 46 patients had wtATTR amyloidosis, ten patients had hATTR amyloidosis, and six patients had AL amyloidosis. The mean systolic left ventricular function was 51% (range 30 to 62) with a mean global strain of −11,5% (range −18,5 to −3,1). The mean NT-pro-BNP was 1145 ng/l (range 24 to 48297).

Results: 59 patients were triple vaccinated and three patients so far are double vaccinated. Three of the patients were unvaccinated. 171 of the vaccine doses administered were mRNA vaccines and eight doses were a viral vector-vaccine. None of the patients reported severe side effects. Thirteen patients reported feeling of pressure and pain at the injection site after vaccination and four patients had fever of maximum two days, eight patients reported lower general condition of maximum five days. One patient reported malaise for 14 days after each vaccination, which resolved spontaneously. There was no clinical or laboratory evidence of suspected vaccine-induced myocarditis. Five patients reported of a COVID-19 breakthrough infection, all of which with a mild course of disease. None of the patients had symptoms of worsening heart failure in temporal relation to the vaccination.

Most of the vaccinations (1 0 3) were performed at an official vaccination center, 59 were performed at a general practitioner.

Conclusion: In patients with cardiac amyloidosis, mRNA vaccines for COVID-19 are safe with respect to severe cardiac adverse events and show effective protection against clinically relevant SARS-CoV2 infection.

1. Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection and represents the greatest global health challenge of the 21st century to date, having claimed over 6.1 million lives since 2019 [1]. Epidemiologic

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studies have shown that older patients and those with pre-existing cardiac conditions, such as cardiac amyloidosis, are most at risk for severe or fatal outcomes [1]. In large-scale clinical trials, new mRNA vaccines for COVID-19 have reduced disease severity and improved outcomes. Nevertheless, there are reports of rare adverse cardiac events, such as myocarditis, with this new class of vaccines [2], leading some patients and physicians to reject vaccination. In studies using data from the United States Vaccine Adverse Event Reporting System (VAERS), 1626 cases of myocarditis, as defined by the CDC, were detected in over 354 million COVID-19 mRNA vaccinations given to 192 million individuals [2]. These patients were mostly younger patients under 30 years of age, with a median age of 21 years [2]. However, data on the tolerability of COVID-19 vaccination in patients with cardiac amyloidosis is limited. Consequently, this study evaluated the safety and effectiveness of mRNA vaccination in patients with cardiac amyloidosis from the amyloidosis center Charité Berlin (ACCB).

2. Materials and methods

2.1. Baseline characteristics

We screened 81 patients from the ACCB registry retrospectively who had visited the cardiology consultation in the last two years. The inclusion criteria were a confirmed diagnosis of amyloidosis and at least one vaccination for COVID-19. We did not include patients with unconfirmed diagnosis or carriers of a mutation in the TTR gene without manifestations of amyloidosis. Of these 81 patients, 15 could not be reached by phone. Three patients were unvaccinated at the time of the survey, and one patient declined to participate in our study. Thus, we included 62 patients (54 men and 8 women) in our survey. They were diagnosed with wildtype transthyretine- amyloidosis (ATTRwt, n = 46), hereditary ATTR amyloidosis (hATTR, n = 10), and light-chain amyloidosis (AL, n = 6).

2.2. Methods

This study was designed as a retrospective cohort survey. The results are based on the information from the patient survey or from the documentation in the vaccination record. Vaccinations did not take place in our amyloidosis center, so systematic monitoring was not possible. All patients were systematically interviewed after vaccination regarding the date, site (e.g. vaccination center, family doctor) and active ingredient of all COVID-19 vaccinations administered to date. Our survey focused on vaccination reactions and adverse events after vaccination (AEFI) as well as COVID-19 infections or cardiac events, such as hospitalization for heart failure, that occurred after vaccination. The exact questions of the query were local reaction at the injection site, fever, allergic reaction, deterioration of general condition, non-specific acute adverse events, gastrointestinal complaints, occurrence of thrombosis, hospitalization of any cause up to four weeks after vaccination and persistent long-term adverse events over 3 months Patients were asked about clinical symptoms related to clinically relevant myocarditis. The last NT-proBNP value before the first vaccination and after the respective vaccination dose, if available, as well as the mean global longitudinal strain (GLS) from the last echocardiographic findings were determined from our registry data. Standard transthoracic echocardiography was performed in the left decubitus position using an ultrasound scanner (Vivid 7, GE Medical Systems, Horton, Norway) with an M5S transducer from 1.5 to 4.5 MHz or a GE 4Vc-D 3D/4D phased array transducer from 1.4 MHz to 5.2 MHz. LVEF and GLS were determined according to ASE and EACVI 3 recommendations [3]. For our analysis, LVEF > 50% and GLS below −16% were considered normal. Laboratory chemistry and echocardiography results were taken from the clinical practice registry data.

Data was collected from February to October 2022. The survey was conducted at a single point in time and was therefore not necessarily related in time to the vaccinations. A follow-up survey was not conducted.

2.3. Statistics

Data were collected in an Excel spreadsheet and exported to SPSS 29 after completion of data collection. All statistical calculations were performed using SPSS 29.0 (SPSS, Inc., Chicago, IL, USA). Data were transformed as follows: All statements such as “fatigue,” “feeling of illness,” “malaise” were changed to ”Deterioration of general condition.“ If no further information was provided and long-term adverse events were denied, the duration of symptoms was assumed to be one day. All adverse events and reactions were considered together as ”event after vaccination“.

2.4. Ethics statement

The study complied with good clinical practice in accordance with the Declaration of Helsinki and the laws and regulations applicable in Germany. The local Ethics Committee of the Charité – Universitätsmedizin Berlin approved the study (Record number EA1/014/20).

3. Results

The 62 individuals surveyed were vaccinated 183 times. Of these, 59 patients (95.2%) were vaccinated at least thrice. Three (4.8 %) patients were vaccinated twice. Of the vaccine doses administered, 173 (93.4 %) were mRNA vaccines (n = 159 Comirnaty®/BioNTech/Pfizer, n = 14 Spikevax®/ Moderna), and eight vaccine doses (4.4%) were vector-based vaccines (Vaxzevria®/AstraZeneca) (Table 1). Data on the vaccines used were not available for two vaccine doses (1.1%). A total of 103 vaccine doses (56.3%) were administered at certified vaccination centers, and 59 vaccine doses (32.2%) were administered by primary care physicians. The remaining vaccine doses (11.5%) were administered at other sites, such as outpatient specialists, dialysis centers, or health insurance companies.

No severe AEFI’s were observed after any vaccination, there were no vaccination- associated hospitalizations. A total of 57 light events including vaccination reactions occurred during 183 vaccinations. Of these, 50 events after vaccination with Comirnaty (0.32 events/vaccination) and 7 events after Spikevax (0.54 events/vaccination). No events occurred after vaccination with Vaxzevria. In 30 vaccinations (16.4 %), local vaccination reactions occurred at the injection site (pain, redness, or feeling of pressure) (Table 2). Fifteen vaccinations (8.2 %) led to a deterioration in the general condition. Acute reactions occurred

Table 1
Patients characteristics.

		Patients n (%)
Gender	male	54 (87.1)
	female	8 (12.9)
	total	62(100)
Subtype	ATTRwt	46 (74.2)
	hATTR	10 (16.1)
	AL	6 (9.7)
Age	<70 years	8 (12.9)
	70–85 years	39 (62.9)
	>85 years	15 (24.2)
	median (range)	82.5 (37–62)
LVEF (%)	<40 %	5 (8.1)
	40–50 %	15 (24.1)
	>50%	35 (56.5)
	missing	7 (11.3)
	median (range)	51 (30–62)
NTpro BNP (ng/L)	median (range)	1145 (24–48297)
Global longitudinal strain (%)	median (range)	−11.5 (−18.5 to −3.1)

Table 2
Vaccinations and adverse events.

		Vaccinations n (%)
Vaccine	Comirnaty®	159 (86.9)
	Spikevax®	14 (7.7)
	Vaxzevria®	8 (4.3)
	unknown	2 (1.1)
	Total	**183(100)**
Place of vaccination	Certified vaccination Center	103 (56.3)
	General practitioner	59 (32.2)
	other	21 (11.5)
Events after vaccination per vaccine administered *(percentage per vaccine)*	Comirnaty®	50 (31.6)
	Spikevax®	7 (53.8)
	Vaxzevria®	0 (0)
Events after all vaccinations *(percentage of all vaccinations)*	All vaccines	57 (31.1)
Adverse reaction	Local reaction	30 (16.4)
	Worsening of general condition	15 (8.2)
	Acute reaction	6 (3.3)
	Fever	5 (2.7)
	Allergic reaction	1 (0.5)
	Cardiovascular hospitalization	0(0)
	Total	**57 (31.1)**

in six vaccinations (3.3 %) and fever in five (2.7 %). One vaccination (0.5 %) was accompanied by an allergic reaction (a neurodermatitis episode) after a second vaccination with Spikevax. Of these 57 events, 14 occurred after the first vaccination, 26 after the second dose and 17 after the third vaccination. No other adverse events were reported. None of the patients reported long-lasting adverse events or hospitalizations 4 weeks after vaccination related to the vaccination. Five patients (8.1%) reported COVID-19 infection after vaccination. All courses were mild and did not require medical consultation or hospitalization. Of these five patients 4 patients had wtATTR amyloidosis and one patient had hATTR amyloidosis.

Concordantly, there were no significant changes in NT-proBNP levels at the baseline. None of the patients reported hospitalization due to heart failure events temporally related to vaccination (data not shown).

4. Discussion

This study investigated the safety and clinical effectiveness of vaccination against SARS-CoV2 in patients with amyloidosis. As expected, the new class of mRNA vaccines was used in over 93% of vaccinations. We could demonstrate that the incidence of adverse events was very low in patients with amyloidosis. Importantly, no serious adverse events occurred, and they were mainly local reactions. Interestingly, the rate of local reactions in our patients with amyloidosis was consistently lower than that described in the phase III vaccine trials. For Comirnaty, the occurrence of injection site pain in elderly patients (>55 years) is reported to be 71% after the first dose and 66% after the second dose. Fever occurred in 11% of the elderly patients [4]. With Spikevax, local reactions occurred in 84.2% at the first dose and 88.6% at the second dose [5].

Regarding the efficacy of COVID-19 vaccination in patients with amyloidosis, only one study has been conducted in Greece. In this study, antibody titers were investigated after vaccination with Comirnaty in patients with AL and ATTR amyloidosis [6]. Significantly lower antibody titers were found in patients with AL amyloidosis. In patients with ATTR amyloidosis, there was no difference in the levels of antibodies formed compared with the control group. This finding suggests an attenuated effect of vaccination in patients with AL amyloidosis. The authors of the study explained this effect mainly by the active immunosuppression that the patients received as a result of the therapy and not by the amyloidosis itself [6].

Our study population predominantly included patients with ATTR amyloidosis (90.3%). This is in contrast with the frequency of cardiac amyloidosis subtypes, as AL amyloidosis is still the most common cause of cardiac amyloidosis. This subtype distribution may also play a role in determining the vaccine against COVID-19 was so clinically effective. Only five patients (8.1%) reported COVID-19 infection after vaccination, all of whom had a mild course. Surprisingly, none of the 6 patients with AL amyloidosis in our cohort reported COVID-19 infection after vaccination. Given the results of the aforementioned study, it could be assumed that the COVID infections that occurred would have been detected mainly in patients with AL amyloidosis. We cannot verify this in this survey. However, this number of patients is too small to conclude causality. Nevertheless, given the high risk of COVID infections during this time and the fact that these patients have a high risk of severe progression, we believe that none of them had a noticed infection would strengthen the perception that even these patients with B-cell dyscrasia had antibodies that protected them from a highly symptomatic disease and therefore underlines the efficacy of the vaccination. Although we did not perform antibody testing in our patients to determine whether subclinical SARS-CoV2 infection existed, the clinical statement that no severe course had occurred is critical in this high-risk population.

5. Limitations

A major limitation of our study was the small cohort size, which was too small to detect rare adverse events after vaccination against COVID-19. However, cardiac amyloidoses are rare diseases, so much larger patient numbers, as in pivotal studies of vaccines, cannot be achieved. In particular, the distribution of vaccines allowed us to draw only confident conclusions about the Comirnaty mRNA vaccine. Another limitation is the retrospective study design. Some patients were interviewed several months after vaccination, so some of the reported adverse events may not have been related to vaccination or some adverse events that occurred may have been forgotten. However, there were no persistent or severe adverse events, which are crucial for evaluating tolerability. As this study was a single observational study, the clinical outcomes of the patients before and after the procedure were not systematically analyzed.

6. Conclusion

In conclusion, our study showed good tolerability and no evidence of increased adverse events of mRNA vaccines against SARS-Cov2 in patients with cardiac amyloidosis compared with the overall population. Based on our data, we also demonstrated that vaccination against SARS-

CoV2 was clinically effective in our patients. Based on the available evidence, COVID-19 vaccines are safe and effective in patients with amyloidosis in the same way as with other risk groups.

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Data availability statement

The included patients from our amyloidosis consultation agreed with their written consent that their data would be pseudo-anonymized and included in the ACCB registry. Contact information and consent were kept separate from the research data. The data are stored securely on the server of Charité - Universitätsmedizin Berlin.

Clinical Trials Registry

https://drks.de/search/de/trial/DRKS00032002, identifier DRKS00032002.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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