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SHORT REPORT

Immune response and adverse events after vaccination against SARS-CoV-2 in adult patients with transfusion-dependent thalassaemia

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Summary

Patients with transfusion-dependent thalassaemia (TDT) are considered an at increased-risk population for severe and/or morbid coronavirus disease 2019 (COVID-19) infection. Timely vaccination is the main preventive method for severe COVID-19. Different adverse events and reactions after vaccination have been reported, with severe ones being extremely rare. Patients with TDT may have altered immunity due to chronic transfusions, iron overload and chelation therapy, and splenic dysfunction. Here, we show that adult patients with TDT following vaccination with the novel messenger RNA vaccines have mild adverse events and can produce protective antibodies comparable to the healthy population.

KEYWORDS
coronavirus disease 2019 (COVID-19), thalassaemia, vaccines

INTRODUCTION

Thalassaemia represents one of the most common genetic disorders with highest prevalence in the Eastern Mediterranean, Africa, and Southeast Asia.[1] Patients with transfusion-dependent thalassaemia (TDT) require lifelong packed red blood cell (PRBC) transfusions to survive, which eventually lead to severe iron overload requiring iron chelation therapy on a daily basis. The survival of patients with TDT has improved dramatically but most patients develop significant comorbidities.[2] Patients with TDT are at high risk of developing severe infections and show signs of immune impairment.[3] Increased susceptibility to infections has been attributed to alterations in the T- and natural killer-cell populations, impaired phagocytosis and impaired immunoglobulins (Igs) and complement system due to reasons like chronic transfusions, iron overload and chelation, endocrinological disorders, and splenectomy.[3]

Since the beginning of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic, vaccination against the virus represents a major goal for all organised healthcare systems as a means to prevent serious illness and death.[4] The BNT162b2 messenger RNA (mRNA) vaccine is the first anti-SARS-CoV-2 vaccine approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency.[5] The second mRNA vaccine approved, the mRNA-1273, showed comparable safety[6,7] and increased efficacy[8] in studies compared to the BNT162b2 mRNA vaccine. Both mRNA vaccines are delivered in two doses. Data on vaccine efficacy in patients with TDT has not been reported.

In this study, we examined the safety and efficacy of vaccination against COVID-19 in patients with TDT.

PATIENTS AND METHODS

This single-centre study was approved by the institutional Research Ethics Committee and was carried out in accordance with the Declaration of Helsinki and the International Conference on Harmonisation for Good Clinical Practice. All participants provided written informed consent.

The study's objectives were: (i) to report the adverse events (including changes in haematological parameters) following mRNA vaccinations in patients with TDT, and (ii) to assess the changes in the levels of neutralising antibodies (NAbs) and IgG Abs against the Spike-receptor binding domain (anti-S-RBD) against SARS-CoV-2 in patients with TDT in comparison with healthy volunteers.

Adult patients with TDT who received care at the University Thalassemia Unit, 'Aghia Sophia' Children's Hospital in Athens and received mRNA vaccination against COVID-19 according to national guidelines up to June 2021 were eligible, but patients who had active hepatitis B or C infection, active human immunodeficiency virus infection, or those who were on immunosuppressive therapy were excluded.

Participants' serum samples were collected at three predefined time points: just before the first dose (TP1), 3 weeks after the first dose (TP2) and 7 weeks after the first dose (TP3) of COVID-19 vaccination. Samples were stored at −80°C until measured. NAbs against SARS-CoV-2 and titres of anti-S-RBD IgG Abs were measured using FDA-approved methods (enzyme-linked immunosorbent assay; cPass SARS-CoV-2 Neutralising Antibody Detection Kit, GenScript, Piscataway, NJ, USA; and Elecsys Anti-SARS-CoV-2 S assay; Roche Diagnostics GmbH, Mannheim, Germany respectively), as previously described.[10,11] A total of 77 age-matched healthy volunteers (median [range] age 46 [24–64] years; 24 males/53 females) who received mRNA vaccines served as the control group for comparison of Ab response. The control group included individuals of similar gender and age as the patients in the TDT cohort, who were consented to participate in the study and were vaccinated at the Alexandra General Hospital in Athens during the same period of time. According to their medical history (taken at the time of vaccination) they had no medical problems and they were receiving no medications. Reference values for anti-S-RBD IgG Abs were used, as previously described.[10]

RESULTS

A total of 180 adult patients with TDT (median [range] 45 [18–61] years; male/female: 83/97) met the study criteria and were included in the safety study, of which 167 patients were vaccinated with the BNT162b2 vaccine and 13 with the mRNA-1273 vaccine. The incidence of adverse events after the first and second doses in patients with TDT was 41.1% (74/180) and 58.9% (106/180) respectively. Adverse events were reported according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.[9] There were no serious adverse events (Grade 4 or 5) or any anaphylaxis reaction to either the first or second doses of mRNA vaccine (Table 1).

We also examined whether vaccination had any effect on haemoglobin levels and transfusion requirements in patients with TDT. The mean total PRBC volume transfused in the 3-month period following the first dose of the vaccination did not differ compared to the 3-month period preceding vaccination (3223 vs. 3200 ml, $p = 0.28$; Figure 1A). When the two periods were compared, the mean pre-transfusion haemoglobin levels were lower by >10% as compared to the baseline pre-transfusion haemoglobin in 12 patients (12/185, 6.5%; mean [SD] 99 [6.3] vs. 98.1 [6.4] g/l, $p = 0.05$). Of note, two male patients (aged 51 and 45 years) presented with acute haemolytic events with haemoglobinuria on the third and 20th day after the second dose of the BNT162b2 vaccine respectively. They were treated with corticosteroids with partial response. Both patients had a history of acute haemolytic events within the last 3 years.

Of the 180 patients who participated in the study, 72 (median [range] age 46 [22–63] years; 31 males, 41 females), were further evaluated for their immune response to vaccination, and their response was compared to those of the 77 healthy volunteers (median [range] age 46 [24–64] years; 24 males). Of the 72 patients, 25 were splenectomised, 59 received the BNT162b2 vaccine, and 13 received the mRNA-1273 vaccine. All patients were on iron chelation therapy (Table 2).

Based on our results, NAbs were at the level of non-immunity at baseline (TP1) in all the patients and showed a significant increase after the first dose (TP2) and further increase after the second dose (TP3) ($p < 0.0001$). There were no significant differences between patients and controls at any of the time points ($p = 0.09$, $p = 0.08$ and $p = 0.28$, for TP1, TP2 and TP3 respectively; Figure 1B). According to the manufacturer, the scale of NAbs titre is 0–100%, with ≥30% to be considered as positive and ≥50% as clinically relevant viral inhibition.[11] Patients had similar mean titres of NAbs compared to controls at TP2 (mean [SD] 51.26 [27.6]% vs. 57.7 [16.55]%, $p = 0.08$), which was above the threshold of 50% that is considered protective. The NAbs titre levels at TP3 had increased significantly compared to levels at TP2.

TABLE 1 The incidence of adverse events after first and second dose of vaccination in patients with transfusion-dependent thalassaemia

Adverse events after vaccination	After first dose, % (*n*)	After second dose, % (*n*)
Pain at injection site	26.7 (48)	16.1 (29)
Fatigue	9.4 (17)	17.8 (32)
Fever	5.0 (9)	28.9 (52)
Headaches	4.4 (8)	8.9 (16)
Arthralgia and myalgia	2.2 (4)	11.7 (21)
Lymphadenopathy	0.5 (1)	3.3 (6)
Dizziness		0.6 (1)
Tachycardia		0.6 (1)
Diarrhoea/vomiting		0.6 (1)
Amaurosis fugax		0.6 (1)

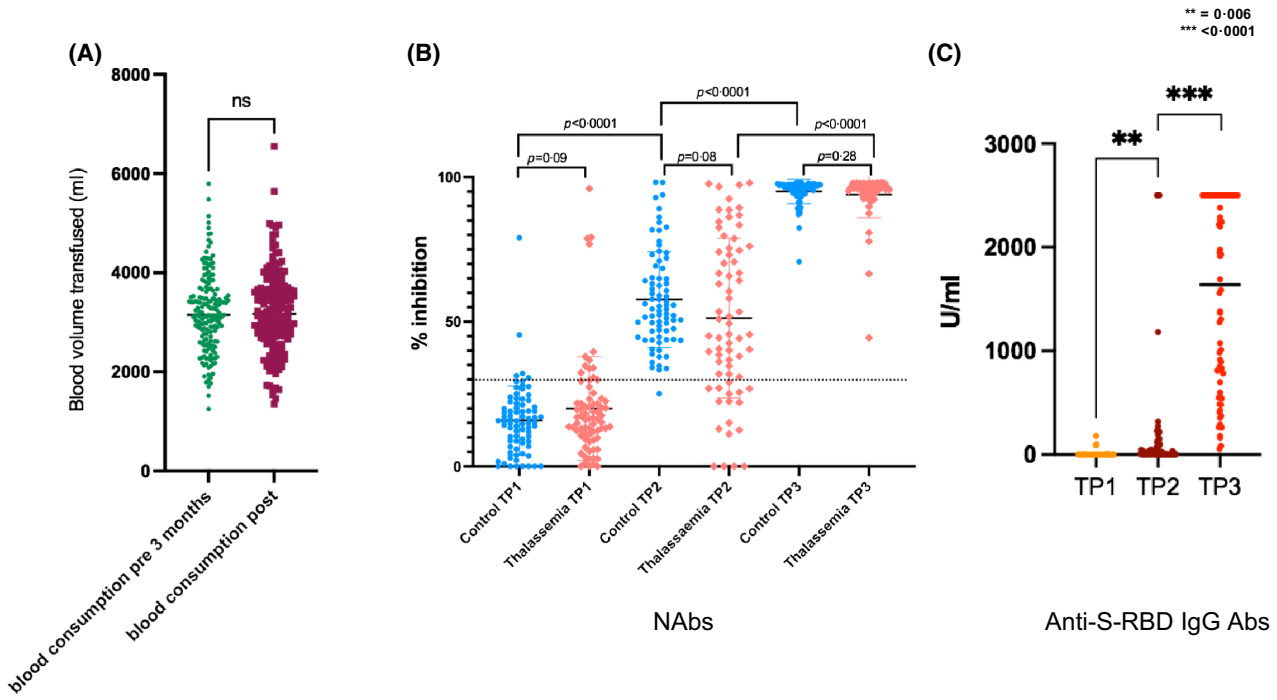

FIGURE 1 (A) Mean total packed red blood cell (PRBC) volume transfused in patients with transfusion-dependent thalassaemia in the 3-month period starting with the first dose of the vaccination did not differ compared to the 3-month period preceding vaccination. ns, non-significant. (B) Neutralising antibodies (NAbs) against severe acute respiratory syndrome coronavirus-2 were measured just before the first dose (TP1), 3 weeks after the first dose (TP2) and 7 weeks after the first dose (TP3). None of the patients had detectable Abs before vaccination, as a result of regular testing and isolation of patients. (C) Titres of anti-Spike-receptor binding domain (S-RBD) immunoglobulin G (IgG) Abs were measured at the same three time points as NAbs (TP1, TP2, TP3)

TABLE 2 Iron chelation treatment of patients evaluated in regard to their immune response to vaccination

	Patients examined for immune response to vaccination, *n* (%), (*N* = 72)
Splenectomy	25 (34.7)
Chelation treatment	All patients
Deferoxamine	10 (13.9)
Deferiprone	4 (5.5)
Deferasirox	19 (26.4)
Combined therapy	39 (54.2)

This increase was comparable between the patients with TDT and the controls (mean [SD] 93.94 [8.01]% vs. 95.05 [4.16]%, p = 0.289). Similarly, the spike Abs significantly increased on TP2 and further on TP3 compared to TP1 (p = 0.006 and p <0.0001 respectively; Figure 1C). There was no statistically significant difference in NAbs levels between splenectomised patients (n = 25) and patients with an intact spleen (n = 47) at either TP2 (mean [SD] 58.99 [28.96]% vs. 47.39 [26.36]%, p = 0.10) or TP3 (mean [SD] 94.77 [6.64]% vs.93.54 [8.63]%, p = 0.567). Similarly, there was no difference in the NAbs between female and male patients at both TP2 (mean [SD] 49.31 [26.98]% vs. 53.94 [28.68]%, p = 0.495) and TP3 (mean [SD] 93.84 [9.71]% vs. 94.07 [4.88]%, p = 0.908).

DISCUSSION

Patients with TDT are considered at high risk of developing severe infection with SARS-CoV-2 due altered immunity and frequent comorbidities.[3,13] While vaccination is essential for optimal protection against COVID-19 infection in healthy individuals,[12] it is not clear whether they are effective in patients with TDT, given the possibility of an altered ability to produce Abs (especially in patients who have undergone splenectomy) due to a possible imbalance between Th17 and regulatory T cells.[13,14] In our study, patients with TDT showed a similar ability to produce NAbs and IgG Abs against the S-RBD of SARS-CoV-2 after the first and second doses of the BNT162b2 and mRNA-1273 vaccines compared to healthy controls.

The safety profile of vaccination in the general population has revealed some serious side-effects, including Bell's palsy, myocarditis/pericarditis, cerebral venous sinus thrombosis, stroke, and thrombocytopenia.[15] Although there are reports on the safety and efficacy of mRNA vaccines in other at-risk populations[16,17], this has not been studied in the TDT population to date. While our patients did not experience any severe adverse events during the study period, two cases of haemolytic events were noted. Patients with TDT frequently develop haemolytic episodes, which may be exacerbated after antigenic stimulation. Thus, close post-vaccination haematological follow-up for these patients is recommended.

In conclusion, vaccination against COVID-19 infection using mRNA vaccines appears to be safe and effective in

inducing protective immunogenic response in this vulnerable population. There are some limitations in our study: only 180 patients were included in the study and the efficacy was assessed by means of measuring immune response rather than true protection (decreased number of actual infections). Further studies are required to reveal the effect of vaccination for COVID-19 in patients with TDT, especially after the current recommendation for a booster dose in all adults. Follow-up of the present study is ongoing in regard to long-term safety and efficacy in immune response and protection from infection.

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CONFLICT OF INTEREST

All authors declare no relevant conflicts of interest for this paper.

AUTHOR CONTRIBUTIONS

Antonis Kattamis, Evangelos Terpos, Meletios A. Dimopoulos, Ioannis Papassotiriou, Polyxeni Delaporta designed the research, performed the research, analysed the data, and wrote the paper. Elena E. Solomou analysed the data and wrote the paper. Sentiljana Gumeni, Evangelia Nitsa, Filia Apostolakou, Dimitra Kyriakopoulou, Ioannis Ntanasis-Stathopoulos, Ioannis P. Trougakos performed the research and analysed the data.

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