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Original article

# SARS-CoV-2 infection in patients with $\beta$ -thalassemia: The French experience



Estelle Jean-Mignard<sup>a,b</sup>, Gonzalo De Luna<sup>c</sup>, Laurent Pascal<sup>d,e</sup>, Imane Agouti<sup>b,\*</sup>,  
Isabelle Thuret<sup>b</sup>

<sup>a</sup> Département de médecine interne, hôpital de la Timone, Assistance Publique des hôpitaux de Marseille, Marseille, France

<sup>b</sup> Centre de référence des syndromes drépanocytaires majeurs, thalassémies et autres pathologies rares du globule rouge et de l'érythropoïèse, Assistance Publique des hôpitaux de Marseille, 264, rue Saint-Pierre, 13005 Marseille, France

<sup>c</sup> Service de médecine interne, centre de référence des syndromes drépanocytaires majeurs, thalassémies et autres pathologies rares du globule rouge et de l'Erythropoïèse, hôpital Henri Mondor, APHP, Paris, France

<sup>d</sup> Service d'onco-hématologie adulte, hôpital Saint-Vincent de Paul, GH de l'institut catholique de Lille, Lille, France

<sup>e</sup> Centre de référence des syndromes drépanocytaires majeurs, thalassémies et autres pathologies rares du globule rouge et de l'Erythropoïèse, CHRU de Lille, Lille, France

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## ABSTRACT

**Introduction.** – Because of iron overload complications, thrombosis and infectious predisposition, patients with severe forms of thalassemia are likely to be at increased risk of COVID-19 complications.

**Results.** – A national survey conducted during the year 2020 across the French reference centers for hemoglobinopathies identified 16 cases of COVID-19 confirmed by RT-PCR in beta-thalassemia patients. Their age ranged from 11 months to 60 years. 15 patients were transfusion-dependent and 6 were splenectomized. Concerning iron overload related complications, none had diabetes or cirrhosis and only one had experienced heart failure. All 4 pediatric patients were pauci-symptomatic during the viral episode. Three patients (41, 49 and 57 years old) developed COVID-19 pneumonia requiring oxygen therapy without the need for mechanical ventilation. Neutropenia (absolute neutrophils count  $< 0.5 \times 10^9/L$ ) was observed in 2 patients receiving long-term treatment with hydroxycarbamide and deferasiprone. No thrombosis event, organ failure or death occurred. All patients recovered.

**Conclusion.** – Severity of COVID-19 in this population of young and middle-aged patients appeared increased compared to the general population but remained mild to moderate as already described in the few series reported in the literature. Occurrence of adverse events related to chronic treatment administered in thalassemia disease may be favored by the infectious episode.

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## 1. Introduction

Since the first cases of Coronavirus Disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reported in China in December 2019, more than 140 million patients were infected across the world (April 20, 2021) [1]. During the year 2020, a total of 2,600,498 confirmed cases of COVID-19 and more than 64,000 deaths were recorded in France [2]. Although the majority of infected patients experienced moderate or asymptomatic disease, advanced age and the presence of comorbidities increase the risk for developing serious complica-

tions during COVID-19 for which there is currently no curative treatment [3].

Thalassemia is a hereditary disorder characterized by a decrease in the production of normal hemoglobin. In the most severe forms of beta-thalassemia (beta-thalassemia major or Transfusion-Dependent Thalassemia, TDT) the absent or decreased synthesis of beta-globin chains leads to profound anemia requiring long-term transfusion therapy since early infancy. The main consequence of transfusions is iron overload. Long-term iron chelation therapy is always associated to regular transfusion regimen [4,5]. In intermediate severity forms, rarer than TDT, anemia is less severe and transfusions are not indicated or only occasionally (non-transfusion-dependent beta-thalassemia, NTDT) but patients are exposed to the complications stemming from chronic hemolytic anemia, ineffective erythropoiesis, iron overload secondary to intestinal iron

\* Corresponding author.

E-mail address: imane.agouti@ap-hm.fr (I. Agouti).

hyperabsorption and predisposition to thromboembolic events [5,6].

As pointed out by the International Thalassemia Federation (TIF) [7], patients with severe forms of thalassemia should be considered as vulnerable to COVID-19. Several complications of this hereditary anemia may explain such a recommendation: immunosuppression mainly related to splenectomy which is often performed to reduce transfusion volumes, iron overload related organ damage such as heart or liver disease and diabetes as well as the risk of decompensation of unrecognized or partial endocrine insufficiency, in particular adrenal insufficiency [4,5,8–10]. In addition, both COVID-19 and thalassemia (due to the circulation of thalassemia pro-coagulant red blood cells and splenectomy often performed in thalassemia patients) increased risk of thromboembolism events [11–14]. In the United Kingdom, the NHSE (National-Health Service England) also identified in patients with hemoglobinopathies some specific risks during COVID-19. They resulted from a possible increase in the frequency and or severity of adverse effects (particularly renal or hematological side effects) related to long-term treatments prescribed in thalassemia patients mainly chelation therapy agents [15].

In order to better describe the frequency and manifestations of COVID-19 in thalassemia patients living in France, we report the cases of SARS-CoV-2 infection that occurred during the year 2020. Beta-thalassemia is widespread in the world but is a rare disease in France with an estimated prevalence of 12 per 1,000,000 for severe forms. According to Thalassemia National Registry, the current number of patients with beta-thalassemia major (TDT) or intermediate (TNDT) living and receiving regular treatment in France is estimated at around 600 patients. This number excludes “ex-thalassemia” patients who have been successfully treated with hematopoietic cell transplantation [16].

## 2. Patients and methods

All practitioners involved in the management of patients with hemoglobinopathies (belonging to MCGRE, the national French network of pediatric and adult reference centers for inherited Red Blood Cell and Erythropoiesis Disorders) were invited to report thalassemia patients with positive real-time PCR test for SARS-CoV-2. The information's collection concerned patients infected between 15 March 2020, date of the first case reported, and 31 December 2020. Data collection used a standardized questionnaire, gathering patient's characteristics (demographic data, co-morbidities, iron overload evaluation and thalassemia associated treatment) as well as information on the clinical course of COVID-19, its complications and therapeutic management.

## 3. Results

16 cases of COVID-19, documented by the detection of SARS-CoV-2 RNA by RT-PCR from nasopharyngeal swab, were diagnosed in thalassemia patients. Among the 16 patients, there were 4 children aged 11 months to 13 years and 12 adults aged 26 to 60 years (median age of 32 years). Fifteen patients had TDT and received regular monthly pRBC transfusions. The characteristics of 15 patients and details of their infection course are noted in Table 1. Additional clinical information could not be obtained for a 16th patient reported.

Iron overload was evaluated by a recent liver MRI, performed in the 12 previous months during their regular follow-up, for 12 patients, including 11 adults. Seven patients had mild liver iron overload (Liver Iron Content, LIC = 50–125  $\mu\text{mol}$  iron/g dry weight), 4 moderate iron overload (LIC = 150–270  $\mu\text{mol}$ /g) and only one patient severe iron overload (LIC > 270  $\mu\text{mol}$ /g) (Table 1). Two of

the 11 adults assessed by cardiac MRI demonstrated myocardial iron overload defined by a cardiac T2\* value < 20 ms. Median of the last ferritin levels was 500  $\mu\text{g/L}$ , ranging from 96 to 2881. Iron overload related endocrinopathies (hypothyroidism, hypoparathyroidism, adrenal insufficiency) were present in 6 patients, all adults. Three patients did not receive iron chelation therapy due to very young age, ongoing pregnancy, or NTDT. All the others were on long-term chelation therapy, deferasirox ( $n = 5$ ), deferiprone ( $n = 3$ ) or the association of 2 chelator agents ( $n = 4$ ).

Four adult patients were overweight (BMI between 25 and 29.99  $\text{kg/m}^2$ ) and none were obese (BMI  $\geq 30$   $\text{kg/m}^2$ ). Regarding the thrombotic risk, 2 patients had a history of thromboembolic events and six patients were splenectomized. Two patients were receiving long-term treatment with hydroxycarbamide (HC) for pre-transfusion bone pain related to thalassemia residual dyserythropoiesis.

At the time of SARS-CoV-2 infection, all patients were symptomatic: fever was present in 6 patients, respiratory signs (cough, dyspnea) in 7 patients. Ageusia and/or anosmia was found in 4 patients, diarrhea in 3 patients. Three adult patients aged 41, 49 and 57 years developed typical COVID-19 pneumonia with a severe clinical course (oxygen saturation  $\leq 93\%$  at rest). Pneumonia was classified by chest computed tomography (CT) scan as moderate in 2 cases and severe in 1. Agranulocytosis occurred in 2 patients receiving a long-term treatment with deferiprone and hydroxycarbamide: the nadir of absolute neutrophil count was of 0.39 and 0.47  $10^9/\text{L}$ . This severe neutropenia as well as the associated moderate thrombocytopenia (platelet nadir at 98 and 120  $10^9/\text{L}$ ) were reversible in 48 hours.

Nine patients were isolated and followed-up at home. Among the six patients hospitalized, two were for less than 24 hours. The 3 patients who developed COVID-19 pneumonia required oxygen therapy with high-flow oxygen therapy in one case. None required intubation or mechanical ventilation. Cardiac, hepatic or endocrine decompensation or documented secondary bacterial infection did not occur. Finally, there was no new thrombosis event, even in the absence of systematic preventive anticoagulation in 2 patients with pneumonia due to rectal bleeding or hemoptysis. Chelation therapy and hydroxycarbamide were stopped due to severe neutropenia and/or diarrhea in 3 cases. Two hospitalized patients received pRBC transfusion in addition to their usual transfusion regimen. The details of the treatments administered during the SARS-CoV-2 infection are shown in Table 1. Six patients of which 5 splenectomized received or continued antibiotic therapy. Hydrocortisone therapy was adapted in the 2 patients with adrenal insufficiency.

The outcome was favorable for all patients. At 3–5 months of the infectious episode, the 3 patients who presented COVID-19 pneumonia were reevaluated. The follow-up chest CT scan showed complete regression of parenchymal involvement without sign of fibrosis in the 41 and 57-year-old patients and the persistence of very few linear ground glass infiltrations in the 49-year-old patient.

## 4. Discussion

We report 16 cases of SARS-CoV-2 infection that occurred in beta-thalassemia patients living in France during the 2 epidemic waves of the year 2020. All except one were TDT while the French cohort included around 600 patients (2/3 of TDT and 1/3 of NTDT) [16]. This over-representation is probably partly the consequence of a selection bias, TDT patients being more tested even for minimal symptoms due to their frequent visits to day hospitals for blood transfusion.

Our study presented low number of patients, as other published series concerning symptomatic thalassemia patients [15,17,18]. Indeed, current data from the literature reporting outcomes

**Table 1**  
Demographic data and clinical characteristics of  $\beta$ -thalassemia patients infected with SARS-CoV-2.

Patient-Gender, Age	Thal/SPT	Thalassemia related comorbidities (excluding hypogonadism) and History of TEC	Ferritin $\mu\text{g/L}$	LIC $\mu\text{mol/g}$	Cardiac T2* ms	Iron chelation	HC/Long-Term Anti-coagulant therapy	Date of positive SARS-CoV-2 PCR	Days of hospitalization	COVID-19 specific Symptoms	LMWH	Specific treatment	Antibiotic treatment
1–49 years, F	TDT/-	Osteoporosis	350	34	35	DFP	HC/-	Mar 15th	18	Severe pulmonary disease Severe neutropenia	Prophylactic-therapy during COVID	HCQ	Azithromycin
2–60 years, F	TDT/+	Paravertebral EMH, Osteoporosis, DVT	1116	86	> 20	DFX	-/-	Mar 20th	0	No	No	No	No
3–11 month, M	TDT/-	No	800	ND	ND	No	-/-	Mar 26th	1	No	No	No	No
4–26 years, M	TDT/-	No	300	39	38	DFX	-/-	Mar 31st	0	No	No	HCQ	No
5–32 years, F	TDT/+	No, (3rd trimester pregnancy), 2PE	990	231	45	No	-/LMWH	Apr 2nd	5	No	On long-term prophylaxis	HCQ	Amoxicillin
6–57 years, M	TDT/+	Adrenal insufficiency, Hypoparathyroidism, paravertebral EMH, Osteoporosis RA treated by MTX and CST, mixed ventilatory defect and OSAS	1450	205	45	DFP	HC/-	Apr 7th	9	Severe pulmonary disease	No	HCQ	Cefotaxime Azithromycin
7–39 month, M	TDT/+	No	500	ND	ND	DFX	-/-	Jul 15th	0	No	No	No	No
8–35 years, F	TDT/-	Hypothyroidism	229	39	45	DFX	-/-	Sep 16th	1	No	Prophylactic-therapy during COVID	No	No
9–41 years, M	TDT/+	Paravertebral EMH	486	66	> 20	DFO + DFX	-/-	Sep 30th	4 <sup>a</sup>	Severe pulmonary disease	No	Dexamethasone	Cefotaxime, spiramycin azithromycin
10–7 years, F	TDT/-	No	1618	116	ND	DFO + DFP	-/-	Nov 1st	0	No	No	No	No
11–24 years, M	TDT/-	Hypothyroidism, congenital encephalopathy	500	190	> 20	DFP	HC/-	Nov 2nd	0	Severe neutropenia	No	No	No
12–13 years, F	NTDT/-	Early epileptic encephalopathy	96	ND	ND	No	-/-	Nov 2nd	0	No	No	No	No
13–26 years, M	TDT/+	Hypothyroidism,	2231	88	11	DFO + DFX	-/-	Nov 11th	0	No	No	No	Amoxicillin
14–31 years, M	TDT/-	Osteoporosis, Hypoparathyroidism	478	266	20–25	DFX	-/-	Nov 18th	0	No	No	No	No
15–27 years, M	TDT/+	Osteoporosis, Dilated heart disease, adrenal insufficiency	2881	350	8	DFX + DFP	-/-	Dec 1st	0	No	No	No	Amoxicillin

F: Female, M: Male, TDT: transfusion-dependent thalassemia; NTDT: non-transfusion-dependent thalassemia; SPT: splenectomy, TEC: thromboembolic complications; RA: Rheumatoid Arthritis; MTX: Methotrexate; CST: Corticosteroid Therapy; OSAS: Obstructive Sleep Apnea Syndrome; DVT: Deep Vein Thrombosis; PE: pulmonary embolism; LIC: Liver Iron Concentration; HC: hydroxycarbamide; LMWH: Low-molecular-weight heparin, EMH: Extra-Medullary Hematopoiesis, PCR: polymerase chain reaction; LMWH: Low-molecular-weight heparin HCQ: hydroxychloroquine, DFP: Deferiprone, DFX: Deferasirox, Deferoxamine: DFO., ND: Not done.

<sup>a</sup> One day in intensive care unit.

of thalassemia patients with SARS-Cov-2 infection are limited. Between March 2020 and July 2020, 22 cases of SARS-Cov-2 infection (18 TDT and 4 NTDT) were reported in Italy for a national cohort including 6900 patients (5000 TDT and 1900 NTDT) [18]. In the United Kingdom, over a period of eight weeks between April 8th and May 6th 2020, 26 patients presented with SARS-Cov-2 infection (20 TDT and 6 NTDT), the English national registry listing more than 1500 patients [15].

Symptomatic cases in children with thalassemia were, in France and in the literature, rare and of very mild severity as reported in the general pediatric population [19,20].

The clinical impact of COVID-19 in beta-thalassemia patients is not yet well defined. Despite their age, patients were often hospitalized: 4 out of 11 adult patients for 4 to 19 days, 3 experiencing an oxygen-dependent pneumonia. These patients were relatively young, without diabetes, hypertension, or obesity, highlighting the vulnerability of this population to COVID-19. However, there were no deaths and only one admission to the intensive care unit. Likewise, in the Italian series, half of the patients were hospitalized (one in intensive care unit) and the outcome was favorable for all. In the UK, among the 26 patients reported by Telfer et al., 45% were hospitalized, one patient received mechanical ventilation, and two deaths occurred in a 53-year-old diabetic patient with severe hemochromatosis and an NTDT patient of 92 years old with neoplastic disease [15]. Finally, in Iran, where the number of TDT and NTDT patients is estimated to be 15,950 and 2,400 respectively, Karimi et al. reported 23 cases of COVID-19 (18 TDT). With six deaths, the infection was more often fatal in this series which probably selected the most severe cases. Comorbidities such as diabetes, heart disease or pulmonary hypertension were found in all deceased patients [21].

In June 2020, the TIF published recommendations relating to thalassemia patients management during COVID-19 pandemics [7]. A general classification in 3 groups (low to moderate risk, high risk and very high risk), according to the level of COVID-19 severity risks, was proposed. The patients at low/moderate risk are well transfused (pre-transfusion hemoglobin >9 gr/dL), receive optimal chelation, had intact spleen and no co-morbidities. Patients are considered to be at high or very high risk depending on their age (> 50 years), the presence of co-morbidities, the degree of iron overload and a history of splenectomy. According to the TIF classification, half of the patients of our cohort are at mild/moderate risk, 4 patients at high risk and 3 at very high risk of severe infection. It should be noted that the most severe thalassemia complications were absent in our population (diabetes, cirrhosis, pulmonary hypertension or decompensated heart disease). Indeed, iron overload evaluated by MRI was generally well controlled with only one patient with severe hepatic iron overload and 2 subjects with cardiac iron overload. We also note that the 3 patients who developed pneumonia fell into each of the 3 risk categories, illustrating the need for large international studies to validate the classification proposed by the TIF. All patients were over 40 years old, a relatively advanced age for patients suffering from TDT, whose current life expectancy is estimated to be around 50 years [22]. Two subjects were overweight and none had hypertension. All three progressed favorably with pulmonary evaluation, at 2–3 months post infection, in favor of the absence of respiratory sequelae.

There are key challenges related to the prompt management of chronic treatments, especially chelation therapy, during COVID-19 in thalassemia patients. While chelation therapy is most often continued during infection, its suspension should be discussed in patients with severe disease. The renal toxicity of deferasirox may be favored by COVID-19 gastro-intestinal symptoms or the administration of NSAIDs [23]. This chelation agent should be suspended in case of renal insufficiency. Treatment with deferoxamine can be complicated by drug-induced agranulocytosis: neutropenia should

always be sought in the event of fever or infection and, if present, lead to immediate discontinuation of treatment [24]. The occurrence of agranulocytosis in 2 patients treated with both deferoxamine and hydroxycarbamide illustrates the need for closely monitoring the blood count during COVID-19 in thalassemia patients receiving deferoxamine and/or hydroxycarbamide which is also a potentially myelotoxic drug in thalassemia patients. Of note, except for 2 patients, no increase in blood requirement was observed. Inversely, the introduction of continuous parenteral chelation with deferoxamine could be discussed in cases of acute cardiac decompensation [25]. Overall, the long-term thalassemia treatment must be systematically evaluated and sometimes adapted. Finally, despite the lack of specific data available among thalassemia patient population, 3 additional risks of severe infection should also be systematically evaluated and/or prevented:

- the risk of latent or existing iron-overload adrenal insufficiency decompensation;
- the increased thromboembolic risk with the recommendation of prophylactic anticoagulation for patients with severe COVID-19;
- the risk of secondary bacterial infection particularly in splenectomized patients.

## 5. Conclusion

In our cohort, as in the literature, COVID-19 in thalassemia patients was associated with a high rate of hospitalization and complications for a relatively young population. The majority of cases reported in France had a favorable outcome probably due to the rarity of the most severe hemochromatosis complications such as diabetes, heart failure or cirrhosis and a level of iron overload assessed by MRI most often moderate. When managing COVID-19, specific risks related to both thalassemia related co-morbidities and long-term treatments should be taken into account.

## Disclosure of interest

The authors declare that they have no competing interest.

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