CLINICAL AND ECONOMIC BURDEN OF TRANSFUSION-DEPENDENT BETA-THALASSEMIA IN FRANCE: A RETROSPECTIVE ANALYSIS OF THE FRENCH NATIONAL HEALTH DATA SYSTEM (SNDS)

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INTRODUCTION

- With an incidence of approximately 1 case for 100,000 in France, beta-thalassemia is a rare genetic hemoglobinopathy (Thuret I et al, 2010).
- Depending on severity and clinical management beta-thalassemia is classified into transfusion-dependent beta-thalassemia (TDT) or non-transfusion dependent beta-thalassemia (NTDT).
- Transfusion therapy is burdensome and many patients continue to experience TDT-related morbidities.
- Transfusion also leads to iron accumulation, which can cause serious complications, including organ damage. Hence, rigorous patient monitoring is needed together with life-long iron chelation therapy (ICT).
- Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potential curative treatment option (Porter J, 2018) for TDT patients with a matched donor.
- Recently, autologous CD34+ cells encoding $\beta^{A\text{-}T87Q}$-globin gene (LentiGlobin for beta-thalassemia), a gene therapy indicated for the treatment of patients 12 years and older with TDT who do not have a b0/b0 genotype, for whom HSCT is appropriate but a human leukocyte antigen (HLA)-matched related donor is not available, was approved by EMA.
- There are limited data available on the burden of disease and healthcare resource utilisation (HRU) of TDT patients in France.

OBJECTIVES

- Describe the clinical burden and HRU in patients with TDT in France.

METHODS

Study design

- Retrospective analysis of the French National Health Data System ("Système National des Données de Santé", SNDS), managed by the French National Health Insurance (CNAM), covering 99% of the French population (Figure 1).
- *Observation period*: 1st January 2007 – 31st December 2016.
- *Index date*: date of first blood transfusion (BT) recorded during observation period.
- *Follow-up period*: from index date to time of death, last record in the database (lost to follow-up), or 31st December 2016 (end of latest data cut), whichever occurred first.

Study population

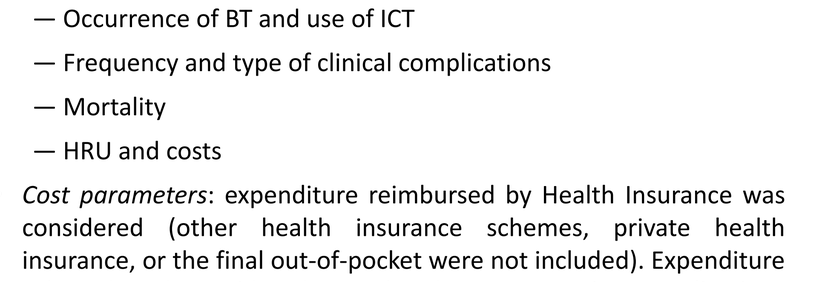
- Patients with TDT were defined as receiving at least 8 BT within any 12-month period, during the observation period.
- Inclusion criteria: ≥1 occurrence before age 50 of one of the ICD10 beta-thalassemia-related codes (D56.1, D56.8 or D56.9) in hospitalization records and in long-term sickness registration database ('ALD' database, D56 code); ≥8 BT within any 12-month period.

Study outcomes and statistical analysis

- Analysis was descriptive in nature and included:
  - — Patient demographics and clinical characteristics
  - — Occurrence of BT and use of ICT
  - — Frequency and type of clinical complications
  - — Mortality
  - — HRU and costs
- *Cost parameters*: expenditure reimbursed by Health Insurance was considered (other health insurance schemes, private health insurance, or the final out-of-pocket were not included). Expenditure selected and considered as related to TDT or its complications include:
  - — Hospital costs: Diagnostic Related Group (DRG) cost and supplements applied to the patient during hospitalization. All types of hospitalizations were considered: public hospitalisations (all), private hospitalisations (short-stay, psychiatry, other), community care institutions, rehabilitation centres and long-term care. From an economic model perspective, hospital production costs were estimated attributing the corresponding "Echelle Nationale des coûts" (ENC) costs to each specific DRG.
  - — Outpatient costs
    - Medical costs (including costs in private clinics)
    - Paramedical assistance
    - Pharmacy: ICT and drugs used to treat complications
    - Laboratory tests
    - Transportation
    - Sick leave benefits

The mean total cost per person per year (PPPY) of the recorded health resources was computed as follows: hospital costs + outpatient costs.

Figure 1: Study design



RESULTS

Sample sizes and patient characteristics

- A total of 448 patients with TDT were identified (Population 1). Among them, 140 had their first documented diagnosis of beta-thalassemia during the study period (2007-2014) (Population 2).

Table 1: Patient characteristics

Patient characteristics	Population 1 TDT patients, all	Population 2 TDT patients, first documented diagnosis during the study period 2007-2016
Number of patients, N (%)	448 (100%)	140 (31%)
Gender, male, N (%)	220 (49%)	71 (51%)
Age at first occurrence of a documented diagnosis[1] of beta-thalassemia, years		
Mean (SD)	20 (15)	9 (11)
Median (min – max)	18 (0 – 54)	5 (0 – 44)
Follow-up time, years		
Mean (SD)	8 (3)	5 (3)
Median (min – max)	10 (1 – 10)	5 (1 – 10)
Age at first BT[2] recorded during the study period, years		
Mean (SD)	20 (14)	9 (11)
Median (min – max)	18 (0 – 54)	5 (0 – 41)
Number of episodes of BT per person per year (PPPY)		
Mean (SD)	11 (5)	10 (4)
Median (min – max)	11 (1 – 35)	10 (1 – 26)
Number of patients with ICT, N (%)	428 (96%)	132 (94%)
Age at first ICT[3] recorded during the study period, years		
Mean (SD)	21 (14)	6 (5)
Median (min – max)	19 (1 – 55)	5 (2 – 19)
Time period between first transfusion record and first ICT record, years		
Mean (SD)	0.8 (0.8)	0.8 (0.9)
Median (min – max)	1 (0 – 6)	0 (0 – 5)
Number of patients who had iron overload monitoring[4], N (%)	339 (76%)	101 (72%)
Number of patients who had HSCT, N (%)	39 (9%)	19 (14%)
Age at first HSCT[5] recorded during the study period, years		
Mean (SD)	11 (9)	6 (5)
Median (min – max)	8 (2 – 48)	5 (2 – 19)

[1] The earlier date BETWEEN the date of first inscription in the long-term illness database as a thalassemia patient AND the first ICD10 code for a documented beta-thalassemia diagnosis during hospitalization.

[2] Age at first occurrence of procedure code and/or ICD10 diagnosis code for BT.

[3] Age at first ICT recorded.

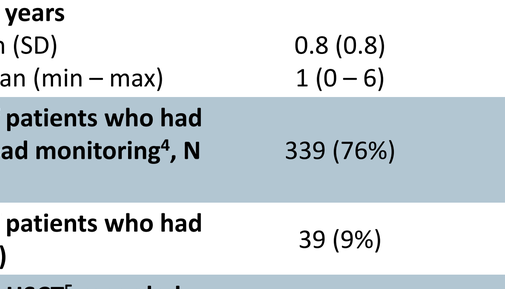
[4] Include cardiac MRI, iron-related laboratory tests (iron, ferritin, transferrin, and iron binding capacity) and liver biopsy.

[5] Age at first occurrence of HSCT.

Clinical burden

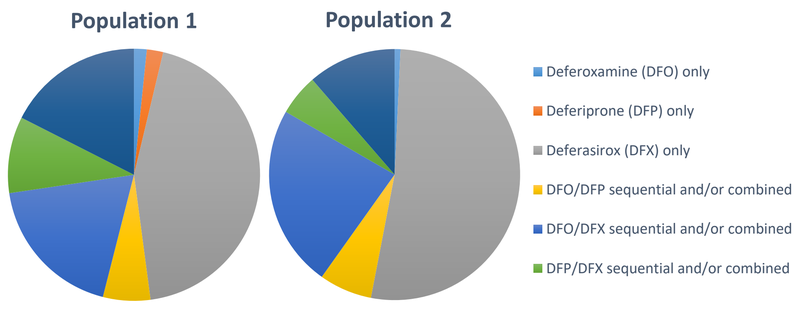
- During follow-up (mean duration of 8 years), mean number of episodes of BT PPPY was 11 for the Population 1 and 10 for the Population 2 (Table 1). Number of episodes of BT PPPY (Figure 2) was constant over the study period.

Figure 2: Mean number of transfusions PPPY



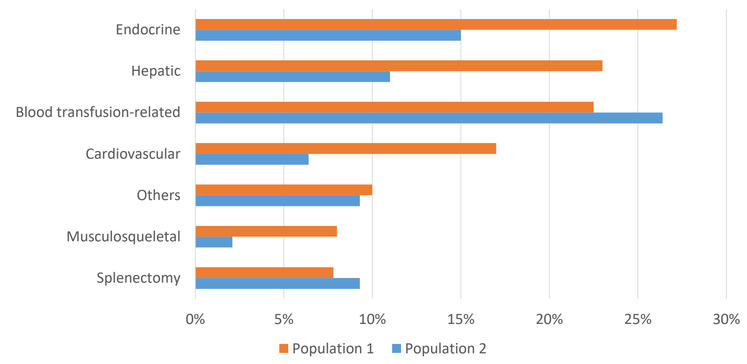
- Among Populations 1 and 2, 428/448 (96%) and 132/140 (94%) of patients with TDT had ≥1 prescription of ICT over the study period, respectively. Distribution of the different ICT used is described in Figure 3.

Figure 3: Distribution of ICT in Populations 1 and 2



- 83% (Population 1) and 75% (Population 2) of patients experienced complications. The most frequent were endocrine, hepatic, transfusion-related and cardiac complications (Figure 4).

Figure 4: Distribution of complications according to time of diagnosis documentation (ICD10 codes)



Mortality

- All-cause mortality rate was 7.1% (N = 32) over study period and median (min – max) age at death was 37 (5 – 55) years old.

HRU and Costs

- The median (min – max) number of hospitalizations PPPY (including both ambulatory and inpatient stays) was 13 (1 – 145). Hospitalizations for transfusions represented 89% of all hospitalizations.
- A total of 376 (84%) patients had ≥1 overnight hospitalization, with a median (min – max) length of stay of 7 (2 – 365) days.
- Almost all patients (99%) required ≥1 outpatient visit during the study period; 81% had ≥1 Emergency Room visit (with or without subsequent hospitalization).
- From an economic model perspective, the mean cost PPPY was estimated for a specific TDT subpopulation, including patients ≥12 years, not transplanted (N = 229). Clinical burden and HRU figures for this population were similar to the full TDT population presented here.
- In this population, the mean (SD) **total cost PPPY was €32,917** (18,032), including:
  - — Hospital cost PPPY[1] (mean (SD)): **€18,460** (10,735), including:
    - Hospitalizations for blood transfusion: €8,256 (3,134)
    - Cardiovascular complications: €5,182 (9,901)
    - Hepatic complications: €14,845 (23,506)
    - Endocrine complications: €2,496 (1,913)
  - — Outpatient cost PPPY[1] (mean (SD)): **€15,614** (13,552), including:
    - ICT: €15,359 (11,760)
    - Drugs related to TDT complications: €696 (2,388)
    - Transportations: €903 (1,174)
    - Outpatient visits: €3,402 (8,215)
    - Sick leave benefits: €1,755 (2,827)

[1] Among patients who have at least 1 cost recorded; as not all patients in the selected population had records for all tracked costs, costs do not add up.

Study limitations

- Potential study limitations include misclassification of patients, underreporting in medical records, missing data including costs not incurred by Health Insurance (*e.g.*, production costs for blood bags and social costs such as productivity at work for patients and for caregivers, loss of revenue from employee and Company contributions), and quality of life data.

CONCLUSIONS

- In France, TDT is associated with high clinical and economic burden.
- Costs for treatment of patients with TDT are mainly related to hospitalizations (including transfusions which represent most hospitalizations and management of comorbidities) and ICT.
- Given the extensive burden of TDT, a new therapy with a potential long-life efficacy could have a positive effect on patients and healthcare system over time.

REFERENCES

- Thuret I, Pondarre C, Loundou A, et al. Complications of patients with beta-thalassemia in France: results of the National Registry. Haematologica.2010;95:724-729
- Porter J. Beyond transfusion therapy: new therapies in thalassemia including drugs, alternate donor transplant, and gene therapy. Hematology Am Soc Hematol Educ Program. 2018 Nov 30;2018(1):361-370. doi: 10.1182/asheducation-2018.1.361

DISCLOSURES

This study is funded by bluebird bio and conducted independently by Certara Evidence & Access.

VB and CB received consulting fees from bluebird bio.

NQ and LQ are full-time employees of Certara, who received consulting fees from bluebird bio to conduct the study.

FG, CP and LU are full-time employees at bluebird bio.