Modelling Long-Term Clinical Outcomes of Patients With Transfusion-Dependent β-Thalassemia in the United States

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INTRODUCTION

- β-thalassemia is a rare hereditary blood disorder characterized by reduced or absent β-globin production that leads to ineffective erythropoiesis and chronic anemia[1-4]
- The most severe form of the disease is transfusion-dependent β-thalassemia (TDT), wherein patients require regular red blood cell transfusions (RBCTs) and iron chelation therapies (ICTs) for survival[1,2]
- Individuals with TDT experience significant clinical complications driven by ineffective erythropoiesis, hemolysis, hypercoagulability, anemia, and primary and secondary iron overload[3]
- Clinical complications impact all organ systems, particularly the hepatic, cardiac, endocrine, and skeletal systems
- A recent registry analysis estimated the median age of death among patients with TDT in the United States to be ~37 years; additional literature suggests that life expectancy has been improving in recent years, reflecting advances in treatments[5]
- The impact of TDT on chronic complications and long-term clinical outcomes, including life expectancy, has not been fully characterized

OBJECTIVE

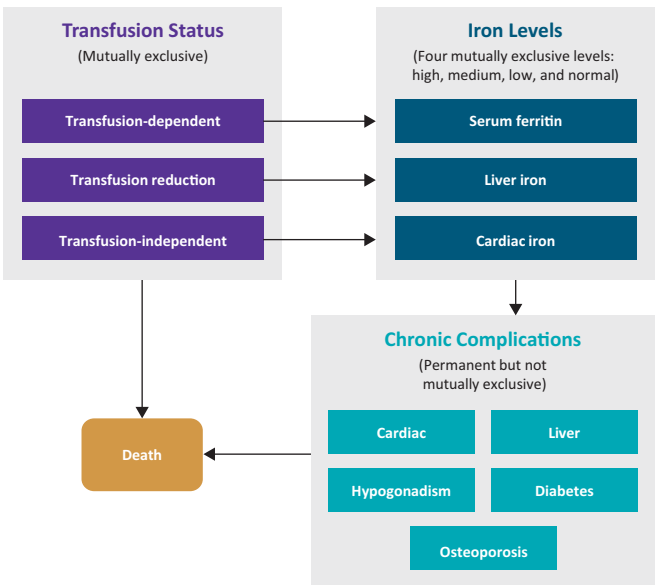
- To develop a health care decision analytic model that predicts long-term clinical outcomes in patients with TDT in the United States

METHODS

Model Overview

- A Markov cohort model was developed to estimate the life expectancy and lifetime prevalence of clinical complications in patients with TDT in the United States
  - The model framework is similar to those used in published models of patients with TDT[5-8] (**Figure 1**)
  - The Markov model structure was selected based on the results of previous analyses, which concluded that an individual-level microsimulation required significant additional complexity which was unnecessary when modelling TDT[5,8]

Figure 1. Schematic for TDT Markov Model



TDT, transfusion-dependent ß-thalassemia.

- All patients in the simulated TDT cohort were assumed to be transfusion-dependent at model start and to therefore have elevated iron levels (serum ferritin levels, cardiac iron content, and liver iron content), which result in an increased risk of developing chronic complications
  - Chronic complications, which were assumed to be permanent once developed, included cardiac complications, liver complications, diabetes, hypogonadism, and osteoporosis

Data Sources and Model Inputs

- A cohort of patients with TDT receiving standard of care (SoC) therapies (regular RBCTs and ICTs) were modelled from baseline (age 18 years; 50% female) and assumed to receive 17 RBCTs per year throughout their lifetimes[9]
  - SoC therapies were not assumed to change the need for RBCTs; all patients were assumed to be transfusion-dependent throughout the lifetime horizon and to therefore maintain the same rate of RBCT and iron chelator use for model horizon
- Patients were assumed to have no chronic complications at baseline
- Baseline iron levels were derived from published literature[10]
  - Serum ferritin levels: low (≤1,000 ng/mL): 23.0%; moderate (1,000 to 2,500 ng/mL): 38.8%; high (>2,500 ng/mL): 38.2%
  - Cardiac iron content: low (>20 ms): 79.5%; moderate (10 to 20 ms): 10.6%; high (<10 ms): 9.8%
  - Liver iron content: low (<7 mg/g): 60.5%; moderate (7 to 15 mg/g): 23.5%; high (≥15 mg/g): 16.0%

Data Sources and Model Inputs (Continued)

- The risk of developing TDT-related complications was based on iron levels and was informed by published literature (**Table 1**)
  - Patients could develop multiple TDT-related complications (not mutually exclusive), which were assumed to be permanent once developed

Table 1. Risk of Developing TDT-Related Complications

Complication	Risk of Developing Complication	Source
Cardiac	Annual risk by cardiac iron content: • Low: 1.1% • Moderate: 1.9% • High: 4.0%	Pepe, et al[12]
Liver	Annual risk by liver iron content: • Low: 0% • Moderate: 0% • High: 8.5%	Angelucci, et al[13]
Diabetes and hypogonadism	Annual risk equation based on: • Age • Serum ferritin levels • Cardiac iron content	Ang, et al[14]
Osteoporosis	Age-specific monthly incidence rate in the general US population with an increased risk associated with transfusion dependence (rate ratio: 22.50)	Hippisley-Cox, et al[15]; Vertex data on file

TDT, transfusion-dependent ß-thalassemia; US, United States.

- Mortality estimates were based on transfusion dependence status and the presence of TDT-related complications
  - Patients who were transfusion-dependent were assumed to have a 3.9-fold increased risk of mortality compared to age-matched individuals in the general population of the United States[5]
  - Two chronic complications were assumed to have an additional (multiplicative) impact on mortality: cardiac complications and diabetes
    - Patients who developed cardiac complications had an increased annual mortality risk of 13%[5]
    - Patients with diabetes were assumed to have a 1.2-fold increased risk of mortality[11]

Model Outcomes

- The following outcomes were projected by the model:
  - Mean life expectancy
  - Mean number of transfusions
  - Proportion of patients developing each chronic complication
- All outcomes were undiscounted

Sensitivity Analyses

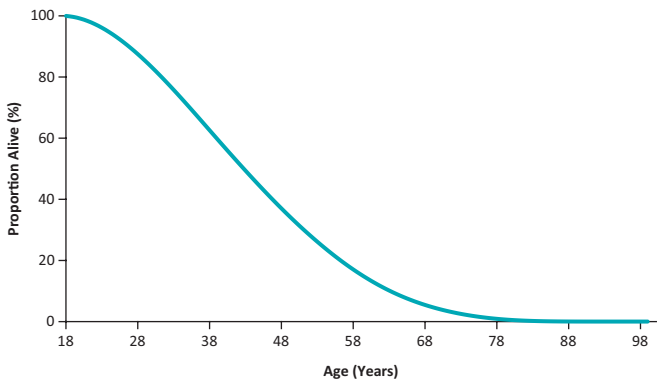
- Model parameters that were varied from the base case to evaluate the impact of TDT on patient life expectancy included:
  - Annual risk of developing each chronic complication increased/decreased by 20%
  - Mortality inputs increased/decreased by 20%
  - Assumed 20% increased risk in mortality associated with liver complications and hypogonadism (base case assumes no impact on mortality)

RESULTS

Base Case Results

- The cohort of patients with TDT were followed in the model for a mean of 26 years (**Figure 2**), during which time they received a mean of 442.5 transfusions
  - Mean life expectancy was 44.0 years
- The most common chronic complications that patients developed over the lifetime horizon were hypogonadism (65%) and diabetes (36%), followed by cardiac complications (31%), liver complications (29%), and osteoporosis (27%)

Figure 2. Survival for TDT Cohort Treated With SoC Therapies



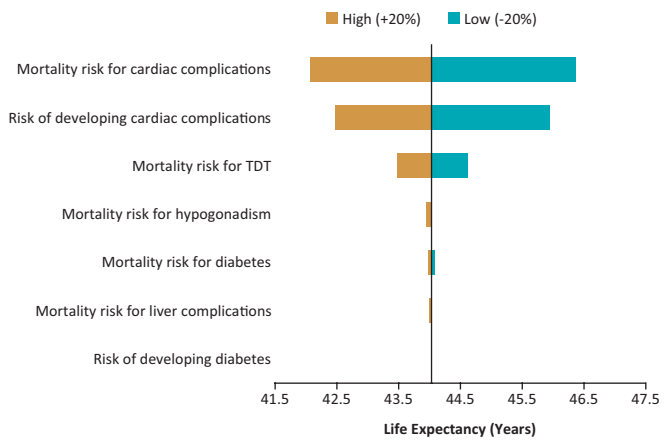
SoC, standard of care; TDT, transfusion-dependent ß-thalassemia.

Sensitivity Analyses Results

- Life expectancy estimates ranged from 42.1 to 46.4 years when the model input values for mortality and complication risk were varied (**Figure 3**)
- Survival estimates were most sensitive to the mortality and risk inputs for cardiac complications

Sensitivity Analyses Results (Continued)

Figure 3. Results of Sensitivity Analyses



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Model Structure Assessment

- The modelled prevalence of TDT-related complications in this study was broadly aligned with published literature estimates[16,17]
- The use of a Markov model structure is appropriate for predicting long-term clinical outcomes in patients with TDT; the additional complexity of using an individual-level simulation structure was unnecessary
- This model structure is conducive to modelling the benefits of novel non-curative and curative therapies that reduce or eliminate the need for RBCTs among patients with TDT

LIMITATIONS

- The model does not include all possible TDT-related complications; key complications were selected for inclusion based on clinician input and are consistent with those used in previous TDT economic models
- Health care decision analytic models may oversimplify the complex nature of TDT disease pathophysiology and interdependent nature of TDT-related complications
- The model did not estimate the impact of recently approved therapies for TDT on clinical outcomes; previous literature suggests that including these therapies in SoC treatment may lead to improvements in the projected clinical outcomes of patients with TDT

CONCLUSIONS

- Model projections demonstrate that patients with TDT who receive SoC therapies in the United States have a high risk of developing complications and a reduced life expectancy
- Innovative therapies that can remove the need for RBCTs and thus reduce the risk of developing complications could improve long-term clinical outcomes in this patient population
- The model structure used in this study could be leveraged to model long-term clinical and economic outcomes for future curative and non-curative TDT therapies that modify the need for RBCTs

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AUTHOR DISCLOSURES

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