ThalassemiaNEWS

A quarterly newsletter keeping the medical and patient community in touch with thalassemia developments

Summer 2022

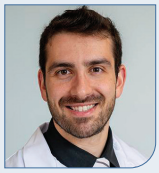
IN PROFILE

An in-depth view of an organization or individual involved in thalassemia

In this first issue, learn more about the thalassemia experts who are supporting ThalassemiaNEWS

This global group of experts have come together to generate ideas and facilitate initiatives that improve the care of patients with thalassemia. Their aim is to address critical gaps in knowledge, awareness, diagnosis, and management of the disease, including a special focus on unmet needs for alpha-thalassemia.

ThalassemiaNEWS is one of these initiatives and we hope that you find it interesting and useful.



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This newsletter is prepared in collaboration with Agios Pharmaceuticals. All of these experts serve as paid consultants for Agios.

IN-DEPTH

Providing an in-depth analysis of recent publications

Quantifying disease burden in NTDT

Non-transfusion-dependent β-thalassemia (NTDT) has historically been perceived as a milder condition compared to transfusion-dependent β-thalassemia (TDT). However it is now clear that NTDT can cause considerable morbidity.[1]

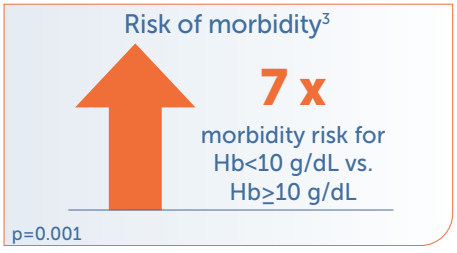
Hemolysis and ineffective erythropoiesis and subsequent chronic anemia, a key pathologic driver in NTDT, can impair organ function giving rise to long-term morbidity. Indeed, hemoglobin level (Hb) is now an accepted predictor of serious clinical sequelae developing in patients with NTDT. Patients with Hb<10 g/dL are at high risk of future morbidity.[2] Several recent publications have provided greater insight into morbidity and mortality risk as a function of Hb in NTDT.[3-6]

10-year morbidity-free survival[3]

Patients with NTDT showing no baseline morbidity were observed over 10 years for the development of thalassemia-related morbidities, such as:

No form of transfusion, iron chelation, or fetal hemoglobin induction therapy was administered throughout the study.

Almost three quarters of the 53 patients had Hb<10 g/dL on entry. The 10-year cumulative morbidity-free survival for these patients was significantly lower than in patients with Hb≥10 g/dL (13.2% vs 78.6%; p<0.001).[3] Indeed, Hb<10 g/dL was associated with a 7-fold increase in the risk of morbidity compared to patients with Hb≥10 g/dL (p = 0.001). The same was noted for multiple morbidity risk. An increase in baseline Hb of 1 g/dL was associated with a reduction in morbidity risk of 28% (hazard ratio [HR] 0.72, p=0.024).



KEY DATES

June 9-12 2022
European Hematology Association (EHA) – Vienna, Austria/hybrid

June 13-14 2022
World Congress of Hematology and Genetic Blood Disorders (WCHGD) – Prague, Czechia

July 15-17
Cooley's Anemia Foundation Patient-Family Conference, Rosemont, IL, USA

October 17-20
Eleventh Cooley's Anemia Symposium, New York, NY, USA

Oct 20-22
17th Annual Sickle Cell and Thalassemia Conference (ASCAT), London, UK

Dec 10-13
64th ASH Annual Meeting, New Orleans, LA, USA

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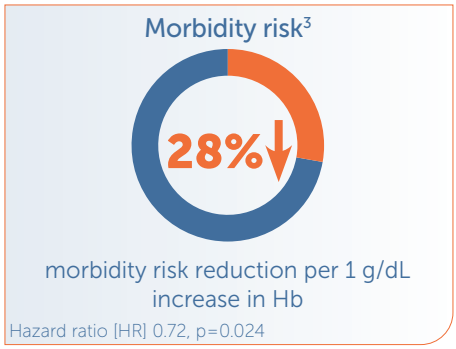


In accordance with current understanding, this study clearly showed that Hb<10 g/dL was associated with significantly compromised morbidity-free survival in patients with NTDT. Consequently, there is potential to reduce NTDT morbidity risk through interventions that elevate Hb.

Impact of hemoglobin level variations on morbidity risk[4]

A separate publication also supported the importance of Hb level in development of comorbidities in NTDT patients.

NTDT-related morbidities that developed during a 10-year observation period were recorded for 150 patients with NTDT (mean age 35.7 years) from two chronic care centers according to baseline Hb.[4] Mean 6-month Hb at baseline was 9.0 g/dL and more than three quarters of participants had Hb<10 g/dL. At least one morbidity was recorded for 81% of patients.

Analysis of these data revealed a significant negative correlation between Hb level and the number of morbidities (p<0.001). Using a regression model including factors known to affect morbidity risk in NTDT (age, splenectomy, iron chelation, and liver iron concentration) a formula was created that described the extent of morbidity based on baseline characteristics (R^2 = 0.568, p<0.001):

It was demonstrated that each 1.5 g/dL increase/decrease in Hb was associated with a decrease/increase of one morbidity.

This research supports the targeting of anemia in patients with NTDT to improve patient outcomes. Data for novel therapies designed to combat hemolysis, ineffective erythropoiesis and anemia in NTDT are eagerly awaited.[5]

Cause of death in patients with NTDT[6]

Mortality data from an International Health Repository were analyzed for over 2000 patients with NTDT from 13 centers of excellence for thalassemia in the US, Europe, Middle East, and Asia.[6]

This is the first study to provide mortality estimates for a large cohort of NTDT patients. The median follow-up time was 33.9 years and 5.6% of the patients had died. The median age at death was 46.3 years.

Estimations of cumulative survival for the study population were lower than survival probability estimates for the general population of Italy (2019): 93.4 vs 98.5% at age 50 years; 81.8 vs 94.0% at 65 years; 66.2 vs 82.9% at 75 years.

The leading cause of early death among patients with NTDT was cardiovascular disease (36.3%, at a median age of 34.2 years; mostly non-iron-mediated). Among older patients, death was most commonly due to hepatic disease (20.4%, at a median age of 55.4 years).

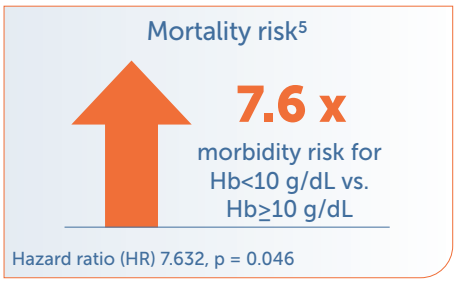
All-cause mortality was significantly higher (log-rank test Chi-square: 13.298, p<0.001) among patients continuing to receive no or limited transfusions compared with patients who transitioned to receiving regular transfusions. Regular transfusion therapy was found to reduce mortality by around 80% for both all-cause (HR 0.202, p=0.001) and cardiovascular (HR 0.199, p=0.032) deaths.[6]

Iron chelation was used concomitantly in all patients undergoing transfusion and did not impact rates of all-cause mortality or death from cardiovascular disease. In contrast, iron chelation therapy reduced the risk of mortality from hepatic disease by 73% (HR 0.277, p=0.022).

Overall, cardiovascular disease was the leading cause of death in patients with NTDT. This is likely to be a consequence of vascular disease arising due to the chronic anemia and hypercoagulability associated with NTDT.[2] Although long-term transfusion could reduce cardiovascular mortality in NTDT, the value of such intervention may be offset by the risk of siderosis secondary to transfusion and the associated need for iron chelation therapy.[6]

Since NTDT often results in iron overload requiring iron chelation therapy,[7] mortality rates were studied not only by Hb level but also by serum ferritin level.[5] Data from 415 patients with NTDT who had not transitioned to regular transfusions and had Hb and serum ferritin measurements were analyzed. Iron chelation therapy was being used in >90% of patients.

The analysis confirmed the increased mortality risk of low Hb; patients with Hb ≤10 g/dL had a 7.6-fold higher risk of mortality than patients with higher Hb (HR 7.632, p=0.046).[5]



Mortality risk was found to be almost 10-fold higher in patients with serum ferritin >800 ng/mL compared with patients having lower serum ferritin levels (HR: 9.755, p<0.001).[5]

Occurrence of the two risk factors simultaneously was found to have a cumulative detrimental effect on survival. Survival was significantly worse among patients having both Hb ≤10 g/dL and serum ferritin >800 ng/mL (n=185) than those with either of these risk factors alone (Log-rank test Chi-square 33.728, p<0.001).[5]

Take home messages

- Regression modelling has demonstrated a significant correlation between Hb and the number of comorbidities in NTDT[4]
- In adults with NTDT, Hb <10 mg/dL is significantly associated with shorter morbidity- and mortality-free survival[3,5]
- A 1 g/dL increase in Hb is associated with a significant reduction in morbidity[2-4]

References

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PATIENT COMMUNITY RESOURCES

Discover new resources for the thalassemia patient community and their caregivers

Living with thalassemia often involves a steep learning curve to understand the disease and the different management approaches. Sharing experiences, practical lifestyle tips, and the latest research findings can provide invaluable support and reassurance between clinic visits.

The thalassemia podcast—*Thal Pals: The Alpha Beta Revolution™* launching later this year will enable ongoing collaboration between patients, caregivers, and medical experts. The monthly broadcasts will feature members of the thalassemia community from around the world discussing currents topics relevant to both α- and β-thalassemia ranging from management approaches to individual patient journeys. It will provide a forum for patients with thalassemia, or their caregivers, to tell their stories, and for experts in the field to explain different aspects of the disease, various management approaches, and the practical impact of recent advances in thalassemia.

CLINICAL TRIALS UPDATE

Sharing the latest news on clinical trials in thalassemia

Mitapivat (AG-348) is an oral, small-molecule allosteric activator of red blood cell (RBC) pyruvate kinase (PK) that increases RBC energy metabolism through elevated adenosine triphosphate (ATP) production, which in turn may lead to improvements in RBC maturation, survival, and function. It is in clinical development across a range of hemolytic anemias, including both α-thalassemia and β-thalassemia.

Data from an ongoing, proof of concept phase II trial in non-transfusion-dependent α- or β-thalassemia (NTDT) showed an increase in hemoglobin level (Hb) from baseline in 80.0% (16/20) of patients between Weeks 4 and 12.[1] The mean increase in Hb from baseline was 1.3 g/dL.[1]

Phase III studies evaluating the efficacy and safety of mitapivat in patients with α- or β-thalassemia are now underway (NCT04770753, NCT04770779).

Phase III ENERGIZE trial (NCT04770753)

ENERGIZE

Design

ENERGIZE is a phase III, randomized, double-blind trial evaluating the efficacy and safety of mitapivat relative to placebo in patients with NTDT.[2] Eligible patients will have α- or β-thalassemia, have received ≤5 RBC units during the previous 24 weeks and not needed RBC transfusions for ≤8 weeks, be aged ≥ 18 years, and have Hb ≤10.0 g/dL (estimated N=171).

Mitapivat 100 mg or matching placebo (2:1 randomization) will be administered twice daily for 24 weeks. Patients completing the 24-week study period can continue in the open-label extension to receive mitapivat for up to an additional 5 years.

The primary endpoint of the ENERGIZE trial is the proportion of patients in whom Hb increases by ≥1.0 g/dL from baseline between Week 12 and Week 24. Secondary endpoints include change from baseline in mean Hb, change from baseline in mean fatigue subscale score of the Functional Assessment of Chronic Illness Therapy (FACIT-Fatigue) scale from Week 12 to Week 24, and markers of hemolysis and erythropoiesis.

Latest trial status

This global trial recently enrolled its first patient and is estimated to complete in December 2023.

Phase III ENERGIZE-T trial (NCT04770779)

ENERGIZE-T

Design

ENERGIZE-T is a phase III, randomized, double-blind trial evaluating the impact of mitapivat on transfusion burden compared with placebo in patients (estimated N=240) with transfusion-dependent thalassemia (TDT).[3] Eligible patients will be ≥18 years old and have α- or β-thalassemia requiring transfusion of 6 to 20 RBC units and a ≤6-week transfusion-free period during the 24 weeks prior to enrolling

Mitapivat 100 mg or matching placebo (2:1 randomization) will be administered twice daily for 48 weeks. Patients completing the 48-week double-blind intervention phase can continue in the open-label extension phase to receive mitapivat for up to an additional 5 years.

The primary endpoint of the ENERGIZE-T trial is the proportion of patients who achieved a ≥50% reduction in transfused RBC units during any consecutive 12-week period. Secondary endpoints include the proportion of patients with ≥50% reduction from baseline in transfused RBC units during any consecutive 24-week period and change from baseline in number of RBC units transfused from Week 13 to Week 48.

Latest trial status

The first patient was recently enrolled into this global trial which is estimated to complete in June 2024.

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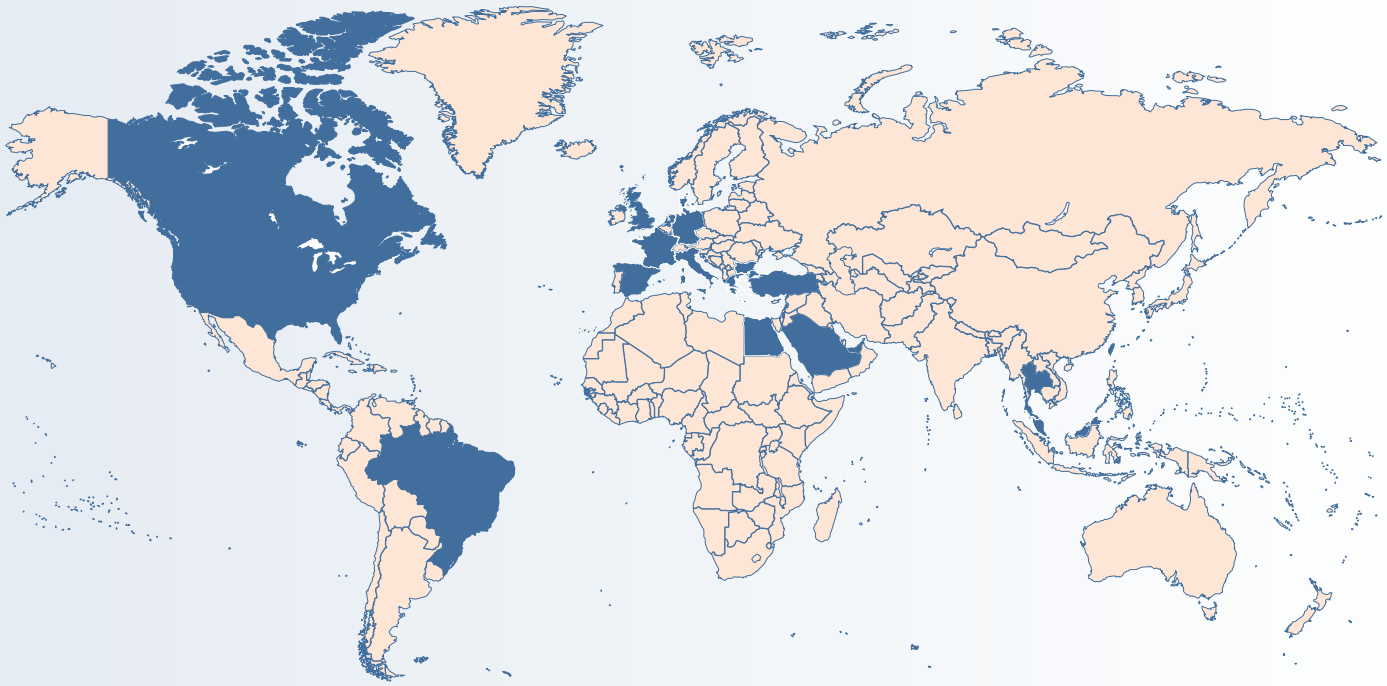
Planned study sites for ENERGIZE and ENERGIZE-T



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2. A Study Evaluating the Efficacy and Safety of Mitapivat in Participants with Non-Transfusion-Dependent Alpha- or Beta-Thalassemia (α- or -NTDT) (ENERGIZE). ClinicalTrials.gov Identifier: NCT04770753.
3. A Study Evaluating the Efficacy and Safety of Mitapivat in Participants with Transfusion-Dependent Alpha- or Beta-Thalassemia (α- or β-TDT) (ENERGIZE-T). ClinicalTrials.gov Identifier: NCT04770779.

EDITORIAL POLICIES & TEAM

The objective of this newsletter is to provide updates on new scientific information, resources, and activities of interest to the thalassemia medical and patient community. The newsletter content is prepared by thalassemia experts in collaboration with Agios Pharmaceuticals. All of these experts serve serve as paid consultants for Agios Pharmaceuticals.

The following experts are involved in this initiative

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- Sujit Sheth, MD
- Thomas Coates, MD
- Vip Viprakasit, MD, DPhil
- Ali Taher, MD, PhD
- Hanny Al-Samkari, MD
- Kevin Kuo, MD
- Maria Dominica Capellini, MD

Mitapivat is not approved for the treatment of thalassemia by any health authority. The safety and efficacy of mitapivat in thalassemia are under investigation and have not been established. There is no guarantee that mitapivat will receive health authority approvals or become commercially available in any country for the uses under investigation.

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