



## IN PROFILE

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

In this issue, we bring you a commentary from the co-editors of the 2023 Thalassaemia International Federation (TIF) Guidelines for the Management of Non-transfusion Dependent  $\beta$ -thalassaemia ( $\beta$ -NTDT), Prof Ali Taher, Dr. Khaled Musallam, and Prof Maria Domenica Cappellini.

We have dedicated the past few decades to furthering our understanding of NTDT. What started with 'unique' observations in our clinics of unpredictable and severe morbidity profiles in a disease we once thought was 'intermediate' and 'mild', quickly transformed to a research interest and career path.

We have conducted various observational studies in our regions to understand true disease burden and combined those with translational studies to identify risk factors responsible for such adverse clinical outcomes. Ineffective erythropoiesis and anemia, iron overload, and

hypercoagulability immediately stood out as the culprits for most complications. We subsequently started several collaborations with the industry to develop optimal therapies for these disease mechanisms.

We are pleased to have witnessed such swift evolution in available options for disease management and even more pleased to know that several others are in ongoing development.

The TIF Guidelines are our primary tool and resource to regularly communicate all these advances to our colleagues, who are involved in the care and research



of NTDT, and we hope they find the guidelines practical and applicable in their various contexts of practice.

The journey does not stop there for us, we are also making sure to engage in various education and awareness activities, through omnichannel approaches, to ensure optimal knowledge transfer to a global audience.

## IN-DEPTH : UPDATED GUIDELINES FOR THE MANAGEMENT OF $\beta$ -NTDT

### Providing an in-depth analysis of recent publications

As understanding of the disease processes involved in thalassemia and their impact on patient well-being grows and treatments improve, management strategies and treatment goals must evolve accordingly<sup>1</sup>.

Improving survival shifted the focus of treatment to the management of symptoms and comorbidities associated with thalassemia. This has helped highlight the disease burden of patients who do not undergo regular blood transfusions; a sub-population of thalassemia patients that has historically been overlooked.

TIF has recently revised their guidelines for the management of  $\beta$ -NTDT<sup>2</sup>. Unlike the previous version, which included both  $\alpha$ - and  $\beta$ -thalassemia, the updated version focuses specifically on  $\beta$ -thalassemia. Alpha-thalassemia is now considered a distinct condition requiring dedicated attention in an independent guideline.

A notable feature of the latest guideline is the structure of the recommendations. Extensive research into the disease processes at work in  $\beta$ -NTDT has clarified

the underlying pathophysiology of  $\beta$ -NTDT. The guideline is thus separated into sections according to pathophysiology rather than by the available treatment modalities (e.g. splenectomy, transfusion, iron chelation).

This article provides an overview of some of the key sections in the latest guideline.

### Ineffective Erythropoiesis and Anemia

Chronic anemia arises in  $\beta$ -NTDT due to an imbalance in the production of  $\alpha$ - and  $\beta$ -globin chains resulting in unstable globin chain tetramers. This causes cellular damage and the death of both developing red blood cells within the bone marrow (ineffective erythropoiesis), and mature blood cells in circulation (hemolysis). It is now clear that ineffective erythropoiesis and the resulting anemia can give rise to a number of complications affecting almost every organ system. Without appropriate



intervention, these can become more severe, and often irreversible, as the patient ages<sup>3</sup>.

### Treatment recommendations

Considerations for the management of  $\beta$ -NTDT are summarized in Figure 1 and discussed further below.

Extensive research has now demonstrated an association between hemoglobin levels  $<10$  g/dL and reduced survival, as well as an increased risk of complications such as leg ulcers, thrombosis, extramedullary hematopoiesis, liver disease, endocrine and bone diseases, and pulmonary hypertension<sup>4,5</sup>. Accordingly, intervention to raise hemoglobin by  $\geq 1$  g/dL is indicated for patients with hemoglobin levels  $<10$  mg/dL to reduce the risk of future serious complications.

A few pharmacological treatments are currently available for the management of anemia in  $\beta$ -NTDT and the pipeline of novel agents under investigation continues to expand. The different agents have distinct modes of action and may provide customized options to best meet individual patient needs as more treatments become

available. The guideline details the factors to be considered in choosing an appropriate treatment strategy.

Blood transfusion provides immediate improvement of hemoglobin level, however, long-term transfusion requires consideration of the risk of secondary iron overload and organ failure. Furthermore, dependence on transfusion can be detrimental to patient quality of life and mental well-being. However, carefully measured use can be beneficial in patients with  $\beta$ -NTDT, e.g. to address acute exacerbations in the event of infections, surgery, or pregnancy<sup>2</sup>.



Splenectomy is becoming less common in the management of  $\beta$ -NTDT. Although it can effectively increase hemoglobin level and avoid transfusion, its use requires careful consideration due to increased morbidity risk<sup>2</sup>. Patients undergoing splenectomy are more susceptible to thrombotic and vascular events, iron-related organ morbidity and fatal infection and sepsis.



### Primary iron overload

Primary iron overload occurs in  $\beta$ -NTDT as a consequence of ineffective erythropoiesis and can ultimately lead to organ damage. Increased absorption of dietary iron due to low red blood cell counts, and occasional blood transfusion both increase iron levels.



Although iron overload occurs more slowly in  $\beta$ -NTDT than in transfusion-dependent thalassemia (TDT), it is a cumulative process and can give rise to iron-related morbidity from the age of 10 years. Liver disease is one of the leading causes of death in  $\beta$ -NTDT, and higher liver iron concentration has been associated with an increased risk of developing thrombosis, pulmonary hypertension, endocrinopathies, and osteoporosis. The increased risk of developing morbidity has been associated with serum ferritin >800 ng/mL, and so regular monitoring of iron levels and associated morbidities is recommended.

### Screening and treatment recommendations

Frequent assessment of iron overload status is recommended for all patients with  $\beta$ -NTDT from the age of 10 years

- Liver iron concentration should be measured by magnetic resonance every 12-24 months; more frequently if iron chelation therapy is being used
- Serum ferritin level should be assessed every 3 months and can be used as the primary index of iron overload when assessment of liver iron concentration is not feasible

Iron chelation therapy should be initiated in  $\beta$ -NTDT patients aged  $\geq 10$  years if the liver iron concentration is  $\geq 5$  mg/g dry weight or serum ferritin reaches

800 ng/mL. If liver iron concentration measurement is not possible, treatment is advised if the serum ferritin level exceeds 300 ng/mL and there are other clinical or laboratory measurements indicative of iron overload. The target of chelation therapy is to achieve a liver iron concentration of  $\leq 3$  mg/g dry weight or serum ferritin of  $\leq 300$  ng/mL. In addition, due to the potential for decreasing iron absorption from the gut, tea consumption should be encouraged.



Secondary iron overload in patients with  $\beta$ -NTDT who require long-term regular blood transfusions should be managed in accordance with treatment guidelines for patients with TDT.

### Optimizing care

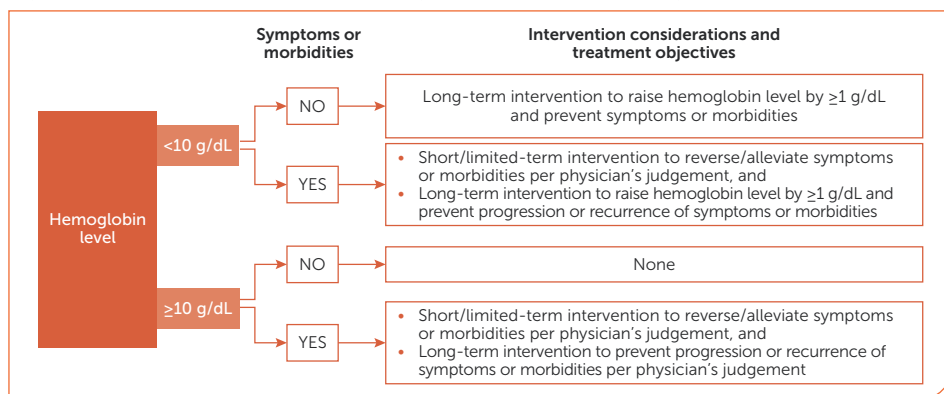
Globally, there is a huge unmet need for appropriate monitoring and medical care among patients with  $\beta$ -NTDT. In many cases, even patients who are receiving effective treatment have to make long journeys to access an expert center.

The provision of access to multidisciplinary care and expert review of clinical status for all patients is even more problematic. Thalassemia is associated with serious complications affecting several organs and systems, most notably the liver and cardiovascular system. The knowledge of specialists in several medical disciplines must therefore be pooled to identify the best management strategy for a patient with  $\beta$ -NTDT. This poses many significant challenges in the organization of integrated services, and coordination of monitoring for organ dysfunction.

There are ongoing efforts to improve the availability of holistic treatment for patients with thalassemia and it is important that patients are involved. Well-structured channels of patient involvement are important to minimizing gaps in care and fundamental to optimizing the treatment of  $\beta$ -NTDT.



Figure 1. Considerations for the management of ineffective erythropoiesis and anemia



### Take home messages

- Patients with  $\beta$ -NTDT should be considered for interventions targeting ineffective erythropoiesis and anemia when Hb levels are <10g/dL
  - This may be short- or long-term depending on patient status
- Blood transfusions can be considered to manage anticipated drop in hemoglobin count in acute clinical settings such as during acute infection, pregnancy, blood loss, or surgery
- Iron overload should be monitored and promptly treated to decrease morbidity risk and improve patient quality of life
- Long term complications can affect multiple organ systems in  $\beta$ -NTDT and require close monitoring by a multi-disciplinary team of specialists
- Engaging patients with  $\beta$ -NTDT will contribute significantly to the identification of care components that require improvement, and help shape new initiatives to positively impact patient care and improve their overall quality of life.

### References

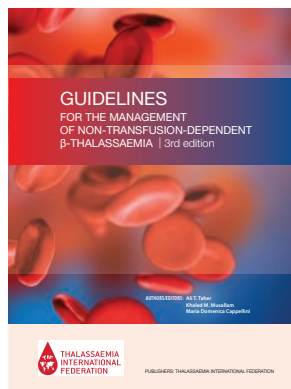
1. Kattamis A, Kwiakowski JL, Aydinok Y. Thalassemia. Lancet 2022;399(10343):2310-2324;
2. Thalassemia International Federation. Guidelines for the Management of Non-Transfusion-Dependent  $\beta$ -Thalassemia 2023. 3rd edition. Eds. Ali T. Taher, Khaled M. Musallam, Maria Domenica Cappellini. Available at <https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-non-transfusion-dependent-%CE%B2-thalassemia-3rd-edition-2023/>;
3. Musallam KM, Taher AT, Cappellini MD, et al. Hemasphere 2022;6(12):e806;
4. Musallam KM, Cappellini MD, Daar S, et al. Ann Hematol 2022;101(1):203-204;
5. Musallam KM, Vitran A, Meloni A, et al. Am J Hematol 2022;97(2):E78-E80.

# COMMUNITY RESOURCES

Discover new resources for the thalassemia patient community and their caregivers

## TIF $\beta$ -NTDT Guidelines

Thalassaemia International Federation (TIF) Guidelines for the Management of Non-transfusion-dependent  $\beta$ -thalassaemia (3rd Edition – 2023) are available to download on the TIF website.

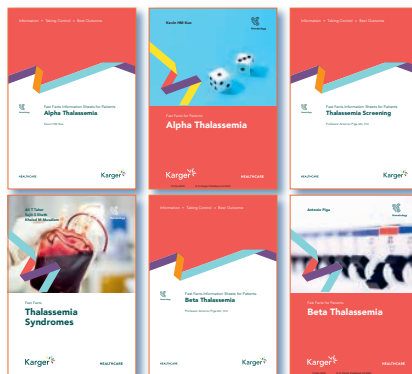


You can download the TIF Guidelines here:



## Fast Facts

A series of educational booklets and information sheets written by experts for patients, families, and healthcare providers on the key topics of thalassemia screening,  $\alpha$ -thalassaemia and  $\beta$ -thalassaemia.



You can access and download the Fast Facts resources here:



## Thal Pals Podcasts



The thalassemia podcasts *Thal Pals: The Alpha Beta Revolution™* aims to facilitate ongoing collaboration between patients, caregivers, and medical experts. The monthly broadcasts feature members of the thalassemia community from around the world discussing current topics relevant to both  $\alpha$ - and  $\beta$ -thalassaemia.

Twelve episodes are available and can be accessed here:



# 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  $\alpha$ -thalassaemia and  $\beta$ -thalassaemia. Data from a proof-of-concept phase II trial in non-transfusion-dependent  $\alpha$ - or  $\beta$ -thalassaemia (NTDT) showed an increase in hemoglobin level (Hb) from baseline in 80.0% (16/20) of patients between Weeks 4 and 12.<sup>1</sup> The average increase in Hb from baseline was 1.3 g/dL.<sup>1</sup>

Phase III studies evaluating the efficacy and safety of mitapivat in patients with  $\alpha$ - or  $\beta$ -thalassaemia are now underway ([NCT04770753](https://www.clinicaltrials.gov/ct2/show/study?term=NCT04770753&rank=1), [NCT04770779](https://www.clinicaltrials.gov/ct2/show/study?term=NCT04770779&rank=1)).

More information can be found at <https://www.energizeclinicaltrials.com/hcp/energize-t> (website for healthcare professionals) and <https://www.energizeclinicaltrials.com/> (website for patients).

## Phase III ENERGIZE trial (NCT04770753; 2021-000211-23)



### Design

ENERGIZE is a phase III, randomized, double-blind trial evaluating the efficacy and safety of mitapivat relative to placebo in patients with NTDT.<sup>2</sup> Eligible patients will have  $\alpha$ - or  $\beta$ -thalassaemia, have received  $\leq 5$  RBC units during the previous 24 weeks and not needed RBC transfusions for  $\leq 8$  weeks, be aged  $\geq 18$  years, and have Hb  $\leq 10.0$  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  $\geq 1.0$  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

As of June 2023, the 79 international study sites have completed enrollment. First data are anticipated to report in the first half of 2024.

## Phase III ENERGIZE-T trial (NCT04770779; 2021-000212-34)



### 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).<sup>3</sup> Eligible patients will be  $\geq 18$  years old and have  $\alpha$ - or  $\beta$ -thalassaemia requiring transfusion of 6 to 20 RBC units and a  $\leq 6$ -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

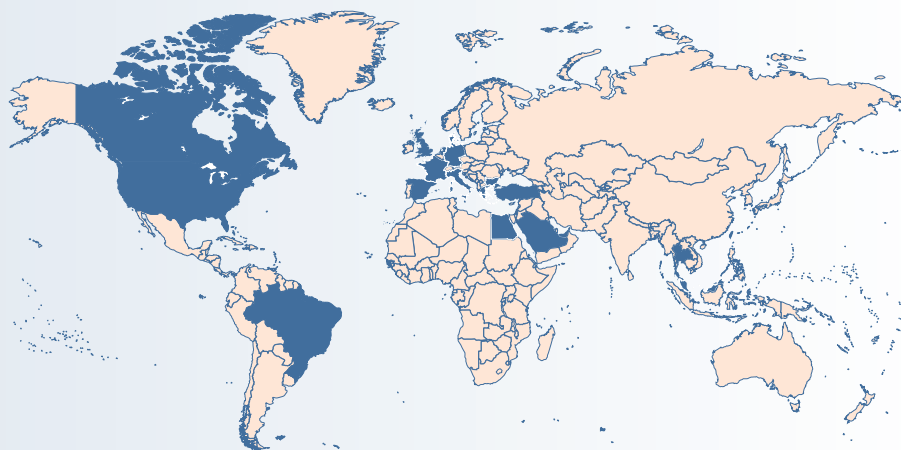
48-week double-blind intervention phase can continue in the open-label extension phase to receive mitapivat for up to an additional 5 years.

The primary endpoint of the ENERGIZE-T trial is the proportion of patients who achieved a  $\geq 50\%$  reduction in transfused RBC units during any consecutive 12-week period. Secondary endpoints include the proportion of patients with  $\geq 50\%$  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

As of June 2023, study recruitment from the 82 global sites has completed. Preliminary data are anticipated in the second half of 2024.

### Study sites for ENERGIZE and ENERGIZE-T



### References

1. Kuo KH, et al. Safety and efficacy of mitapivat, an oral pyruvate kinase activator, in adults with non-transfusion dependent  $\alpha$ -thalassaemia or  $\beta$ -thalassaemia: an open-label, multicentre, phase 2 study. Lancet 2022;400:493-501.
2. A Study Evaluating the Efficacy and Safety of Mitapivat in Participants with Non-Transfusion-Dependent Alpha- or Beta-Thalassemia ( $\alpha$ - or  $\beta$ -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 ( $\alpha$ - or  $\beta$ -TDT) (ENERGIZE-T). ClinicalTrials.gov Identifier: NCT04770779.

## KEY DATES

### October 12-14, 2023

EHA-SWG Scientific Meeting on Red Cell and Iron Metabolism Defects  
Budapest, Hungary

### October 25-28, 2023

Annual Scientific Conference on Sickle Cell and Thalassemia (ASCAT)  
London UK

### October 26-27, 2023

International Conference on Clinical Hematology and Transfusion Medicine  
Osaka, Japan

### November 3-5, 2023

Thalassaemia International Federation (TIF) International Conference  
Kuala Lumpur - Malaysia

### December 9-12, 2023

American Society of Hematology (ASH)  
San Diego - USA

## 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 as paid consultants for Agios Pharmaceuticals.

The following experts are involved in this initiative

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

Contact:  
ThalassemiaNews@agios.com

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