**Thalassemia**NEWS

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

### Winter 2023

## **IN PROFILE**

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

In this Issue, we bring you excerpts from an interview with thalassemia specialist **Dr. Vip Viprakasit**, Professor of Pediatrics and Director, Thalassemia Research, Siriaj Hospital, Thailand

One of the biggest misconceptions about thalassemia is how **common** it is, especially in Western countries. Sometimes physicians may confuse thalassemia with iron deficiency anemia because they share a common symptom such as anemia; a number of patients have been treated with iron supplementation because of this misunderstanding. Thalassemia is becoming a **global pandemic** as people migrate from areas with high incidence e.g., Southeast Asia to other parts of the world.

In term of genetic prevalence, alphathalassemia is much more common than beta-thalassemia. For example, in Southeast Asia such as Thailand, Vietnam, Cambodia, Laos, the incidence of alpha-thalassemia carriers is as high as 10-15% of the general population. Yet most physicians know more about betathalassemia due to its wide geographic distribution and variety in clinical presentation from mild disease to very severe.

Thalassemia has a tremendous impact on the patient and of course on family life. Most of the patients will suffer from chronic anemia and will feel tired, exhausted. The patient will often look jaundiced and this can be noticed by friends and people around you. If the anemia is severe, the patient will have a big liver and spleen and be very uncomfortable. Usually, they have satiety and cannot eat, especially children. Several complications can occur later on in the disease, including iron overload that may relate to the treatment we provide such as blood transfusion. Patients may have iron in the liver, causing liver cirrhosis, or iron in the heart leading to cardiac cirrhosis; this can affect the conductivity of the heart, causing fibrosis or heart failure.



Dr. Vip Viprakasit

I see three challenges facing the thalassemia community. **Healthcare policy makers** don't really understand the condition. Secondly, making the **correct diagnosis** is not easy. I have worked on alpha-thalassemia for 25 years and it is an amazing clinical syndrome, with a varied presentation affecting millions of people worldwide. Third, I would say getting the **patient community to speak out** to help overcome the taboos associated with genetic disease that exist in certain countries – many countries don't have a strong patient support group.

The full interview can be viewed here.



## **IN-DEPTH : SPOTLIGHT ON ALPHA-THALASSEMIA**

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

Medical advances have drastically improved survival among patients with thalassemia and a diagnosis of thalassemia can now be compatible with an average life expectancy<sup>1,2</sup>. However, although prolonging survival, current treatments cannot prevent many of the symptoms and comorbidities associated with thalassemia, such as fatigue, anemia, iron overload, and splenomegaly, which can limit physical capabilities and interfere with everyday activities. In addition, patients have the added burden of being dependent on treatment. Regardless of the treatment received, it becomes an integral part of a patient's life and is often associated with side effects that may require further medical management.

Alpha-thalassemia has been less well characterized than beta-thalassemia, and has historically been perceived as a more benign condition. This notwithstanding, many patients with alpha-thalassemia experience considerable disease burden. The extent of this burden is only now being quantified in robust clinical studies.

#### Clinical burden of alphathalassemia in real-world setting

Two recent publications have highlighted the clinical burden of alpha-thalassemia based on a systematic literature review and a retrospective analysis using data from medical insurance databases in the US<sup>34</sup>.

# Retrospective analysis of alpha thalassemia comorbidities<sup>3</sup>

This analysis included data for adult patients with entries in the Merative MarketScan® Commercial & Medicare and Multi-State Medicaid claims databases for thalassemia between January 2013 and June 2021. Patients with a diagnosis of trait/carrier were excluded from this analysis. All patients had at least 12 months of data recorded. Controls with no history of thalassemia or other hemolytic anemias were matched 5:1 to patients with thalassemia with respect to age, sex, payor, race and follow-up time. In the Medicaid cohort controls were also matched for ethnicity.

A total of 1675 eligible patients with  $\alpha$ -thalassemia were identified on the Commercial/Medicare database. Of these, only 2 (0.1%) were transfusion-dependent, requiring  $\geq 8$  transfusions within the 12-month follow-up. Data for 590 patients with  $\alpha$ -thalassemia, none of whom were transfusion-dependent, were

included from the Medicaid database. In both databases,  $\alpha$ -thalassemia accounted for about 40% of all patients with thalassemia.

Similar to observations in  $\beta$ -thalassemia, comorbidities associated with thalassemia were significantly more common among patients with  $\alpha$ -thalassemia than in the matched controls (Figure 1). Other comorbidities not necessarily linked with thalassemia, including hypertension and diabetes, were also significantly (p<0.001) more common among patients with  $\alpha$ -thalassemia than the matched controls in both study populations (Figure 2). In addition, the mean Charlson Comorbidity Index that predicts 10-year mortality was significantly higher for patients with  $\alpha$ -thalassemia than for matched controls.

#### Systematic literature review of the disease burden of alphathalassemia

A systematic literature review of publications (January 2010 to September 2021) identified eight studies reporting disease burden for patients with a-thalassemia<sup>4</sup>. Of these studies, only three focused solely on a-thalassemia.

This paucity of publications on disease burden in this population highlights an urgent unmet need.

Patients with hemoglobin H (HbH) disease, the most severe non-fatal form of  $\alpha$ -thalassemia arising when three of the four alpha globin genes have mutations, had a high clinical burden. The most prevalent complications included iron overload (31% to 66%), hyperuricemia (60%), and cholelithiasis (28% to 52%).



# Health-related quality of life as an indicator of disease burden

Unsurprisingly, a diagnosis of thalassemia is known to be detrimental to a patient's quality of life<sup>5.6</sup>. Thalassemia is associated with a range of factors that can negatively impact a patient's life choices, such as fatigue, comorbidities, and regular monitoring visits. Assessments of health-related quality of life (HRQoL), which incorporate a patient's perspective on their ability to function physically, mentally, and socially and the impact the disease and its treatment has on their life, are used to provide a holistic view of disease burden<sup>7,8</sup>. Few studies evaluating HRQoL in thalassemia have been published and these are often limited to  $\beta$ -thalassemia<sup>9,10,11</sup>.

#### **HRQoL** in alpha-thalassemia

The previously described systematic literature review identified only two publications that evaluated HRQoL for patients with  $\alpha$ -thalassemia<sup>4</sup>. HRQoL in patients with HbH disease was found to be similar to that in patients with  $\beta$ -thalassemia, with the exception of physical functioning that was significantly worse for patients with HbH disease compared to homozygous  $\beta$ -thalassemia in one of the studies.

HRQoL data were only available for children and adolescents but they indicate that disease burden with  $\alpha$ -thalassemia is greater than had been assumed. HRQoL studies in adults with  $\alpha$ -thalassemia are needed to improve understanding of unmet needs in this patient population.

Figure 1. Comorbidities in patients with  $\alpha$ -thalassemia in US medical insurance databases



Figure 2. Other complications and comorbidities in patients with  $\alpha\mbox{-}thalassemia$  in US medical insurance databases



#### Take home messages

- There are limited data on the disease burden of α-thalassemia
- Although historically alpha-thalassemia has been considered less severe than beta-thalassemia, many patients experience symptoms and serious comorbidities, such as iron overload and cardiovascular disease
- The impact of α-thalassemia on quality of life is comparable to that reported for β-thalassemia in pediatric populations; further work is required to understand the impact on adults
- Unmet needs persist for patients with  $\alpha\mbox{-thalassemia}$

#### References

1. Cappellini MD, et al. Blood Rev. 2018;32(4):300-311; 2. Forni GL et al. Am J Hematol. 2023 Jan 1. doi: 10.1002/ajh.26798; 3. Langer AL, et al. Poster 2351 presented at the 64th ASH Annual Meeting and Exposition, December 10-13, 2022, New Orleans, LA, US; 4. Musallam KM, et al. Poster 1036 presented at the 64th ASH Annual Meeting and Exposition, December 10-13, 2022, New Orleans, LA, US; 4. Musallam KM, et al. Poster 1036 presented at the 64th ASH Annual Meeting and Exposition, December 10-13, 2022, New Orleans, LA, US; 5. Telfer P, et al. Ann N Y Acad Sci. 2005;1054(1):273–282; 6. Rodigari F, et al. Front Pediatr. 2022 Aug 25;10:886674; 7. Leplege A, Hunt S. JAMA. 1997, 278: 47-50; 8. Centers for Disease Control and Prevention. 2000. Available at https://www.cdc.gov/hrqol; 9. Tuysuz G, Tayfun F. J Pediatr Hematol Oncol. 2017 Jul;39(5):332-336; 10. Musallam KM, et al. Eur J Haematol. 2011 Jul;87(1):73-9; 11. Arian M, et al. Qual. Life Res. 2019, 28, 321–334.

#### THA-ALL-0052 / Date of preparation: March 2023

The newsletter content is prepared by thalassemia experts in collaboration with Agios Pharmaceuticals. Medical writing support provided by GK Pharmacomm is funded by Agios.

# PATIENT COMMUNITY RESOURCES

Discover new resources for the thalassemia patient community and their caregivers



The thalassemia podcasts *Thal Pals: The Alpha Beta Revolution*<sup>TM</sup> 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 currents topics relevant to both  $\alpha$ - and  $\beta$ -thalassemia.

 $\mathcal{T}_{\mathcal{T}}$ 

Four episodes are already available and can be accessed here

und

You can access and download the Fast Facts resources here:

Now available! : Fast Facts

thalassemia screening,  $\alpha$ -thalassemia and  $\beta$ -thalassemia.

A series of educational booklets and information sheets written by

experts for patients, families, and caregivers on the key topics of

Sector Sector

# 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  $\alpha$ -thalassemia and  $\beta$ -thalassemia.

Data from a proof-of-concept phase II trial in non-transfusion-dependent  $\alpha$ - or  $\beta$ -thalassemia (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  $\beta$ -thalassemia are now underway (<u>NCT04770753</u>, <u>NCT04770779</u>).

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

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

# C 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.<sup>2</sup> Eligible patients will have  $\alpha$ - or  $\beta$ -thalassemia, 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 <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 December 12 2022, this global study has 86 study sites open and is estimated to complete in December 2023.

### 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  $\beta$ -thalassemia requiring

transfusion of 6 to 20 RBC units and a  $\leq$ 6week 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 January 18 2023, this trial has 92 study sites open for recruitment and is estimated to complete in June 2024.

THA-ALL-0052 / Date of preparation: March 2023

The newsletter content is prepared by thalassemia experts in collaboration with Agios Pharmaceuticals. Medical writing support provided by GK Pharmacomm is funded by Agios.



#### 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.
- 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 Alphaor Beta-Thalassemia ( $\alpha$  or  $\beta$ -TDT) (ENERGIZE-T). ClinicalTrials.gov Identifier: NCT04770779.

## **KEY DATES**

#### February 20-21, 2023

World Hematology Congress Madrid, Spain

#### April 27-29, 2023

International Summit on Hematology and Blood disorders - Orlando, FL, USA

May 8, 2023 12:00 AM - May 9, 2023 12:00 AM World Thalassemia Day

#### June 8-11, 2023 European Hematology Association (EHA) Congress, Hybrid and Frankfurt, Germany

October 26-28, 2023

Annual Scientific Conference on Sickle Cell and Thalassaemia (ASCAT) - London, UK

**November 3-5, 2023** Thalassemia International Federation (TIF) International Conference - Malaysia

## **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

- 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

Contact: ThalassemiaNews@agios.com 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.

THA-ALL-0052 / Date of preparation: March 2023

The newsletter content is prepared by thalassemia experts in collaboration with Agios Pharmaceuticals. Medical writing support provided by GK Pharmacomm is funded by Agios.