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REVIEW

Profile of Luspatercept in the Treatment of Anemia in Adults with Non-Transfusion-Dependent β-Thalassemia (NTDT): Design, Development and Potential Place in Therapy

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Abstract: Over the past decade, evidence has been mounting on the detrimental clinical sequelae of untreated anemia in patients with non-transfusion-dependent β-thalassemia (NTDT). There are no pharmacologic agents that are specifically approved for the management of anemia in NTDT, and available options such as splenectomy, transfusion therapy, and hydroxyurea each come with their own shortcomings, especially for long-term use. Luspatercept is an erythroid maturation agent that has been evaluated in a Phase 2, randomized trial and showed a significant benefit in raising hemoglobin level by at least 1 g/dL in adults with NTDT and a baseline hemoglobin level ≤10 g/dL. These data led to luspatercept's approval by the European Commission for the treatment of anemia in adults with NTDT and presents the first evidence-based approach for a novel agent that is able to ameliorate anemia in this patient population.

Keywords: anemia, ineffective erythropoiesis, iron, management, thalassemia, transfusion

Introduction

The β-thalassemias are a group of inherited disorders of hemoglobin synthesis that are most prevalent in Southern Europe, Eastern Mediterranean, and Southeast Asia, although with increasing frequency in Northern Europe and the Americas due to population migrations.[1,2] The past few decades have witnessed considerable advances that transformed the management of patients with transfusion-dependent β-thalassemia (TDT), especially with regard to transfusion safety, secondary iron overload detection, and iron chelation therapy.[3,4] In contrast, our understanding of disease mechanisms in patients with non-transfusion-dependent β-thalassemia (NTDT) only recently started to unfold and paved the way for the development of new therapies. NTDT patients commonly inherit homozygous or compound heterozygous β-thalassemia mutations that are of mild-moderate severity, or inherit severe mutations with secondary modifiers (eg, α-thalassemia or increased capacity for γ-globin chain production) that alleviate the resulting ineffective erythropoiesis and anemia. Heterozygous carriers of β-thalassemia mutations can also develop NTDT when they co-inherit α-globin gene duplications. Most patients present later in childhood compared to patients with TDT and have mild-moderate anemia that does not stimulate a decision to start lifelong regular transfusion therapy.[5,6] Evidence over the past two decades, however, has established that when left untreated, ineffective erythropoiesis and anemia can lead to significant morbidity and mortality in patients with NTDT.[7]

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In this review, we further expand on the unmet need for managing anemia in NTDT and highlight the rationale and key data from a novel erythroid maturation agent, luspatercept, which has been developed to address such unmet needs in this patient population.

Anemia at the Core of Pathophysiology in NTDT

Ineffective erythropoiesis and anemia are the hallmark of pathophysiology in patients with NTDT, which can also give rise to other secondary mechanisms of disease including primary iron overload and hypercoagulability.[5–8] When left untreated, these pathologies can lead to serious and often irreversible clinical morbidity that manifests in every organ system, especially as patients advance in age (Figure 1).[9–12]

Ineffective erythropoiesis and medullary expansion can lead to skeletal deformity and osteoporosis as well as hepatosplenomegaly and extramedullary hematopoiesis.[5,6] When it comes to anemia, it is now established that a hemoglobin level of <10 g/dL is associated with a higher risk of morbidity (liver disease, extramedullary hematopoiesis, endocrine and bone disease, leg ulcers, thrombosis, pulmonary hypertension) and mortality in both cross-sectional and longitudinal studies with over 10 years follow up.[13–15] Variations by 1 g/dL of hemoglobin level are significantly associated with variation in morbidity risk.[16] In this instance, anemia can be regarded as a direct causal agent for clinical complications through chronic hypoxia or as a marker of the underlying ineffective erythropoiesis.

Ineffective erythropoiesis and anemia can also lead to increased intestinal iron absorption through downregulation of the hepatic hormone by erythroid factors.[14,17,18] Elevated serum ferritin and liver iron concentration (LIC) levels are common in adults with NTDT, and have been linked to hepatic, endocrine, renal, and vascular morbidity.[11,19–24] Moreover, early hemolysis exposes several thrombogenic markers on the surface of red cells which, combined with other abnormalities in platelets and the coagulation system, lead to a hypercoagulable state in NTDT.[25,26] High rates of thromboembolic events and pulmonary hypertension are noted especially in splenectomized adults, and these remain among the most common causes of mortality in this patient population.[27–33] In addition to increased risks of long-term

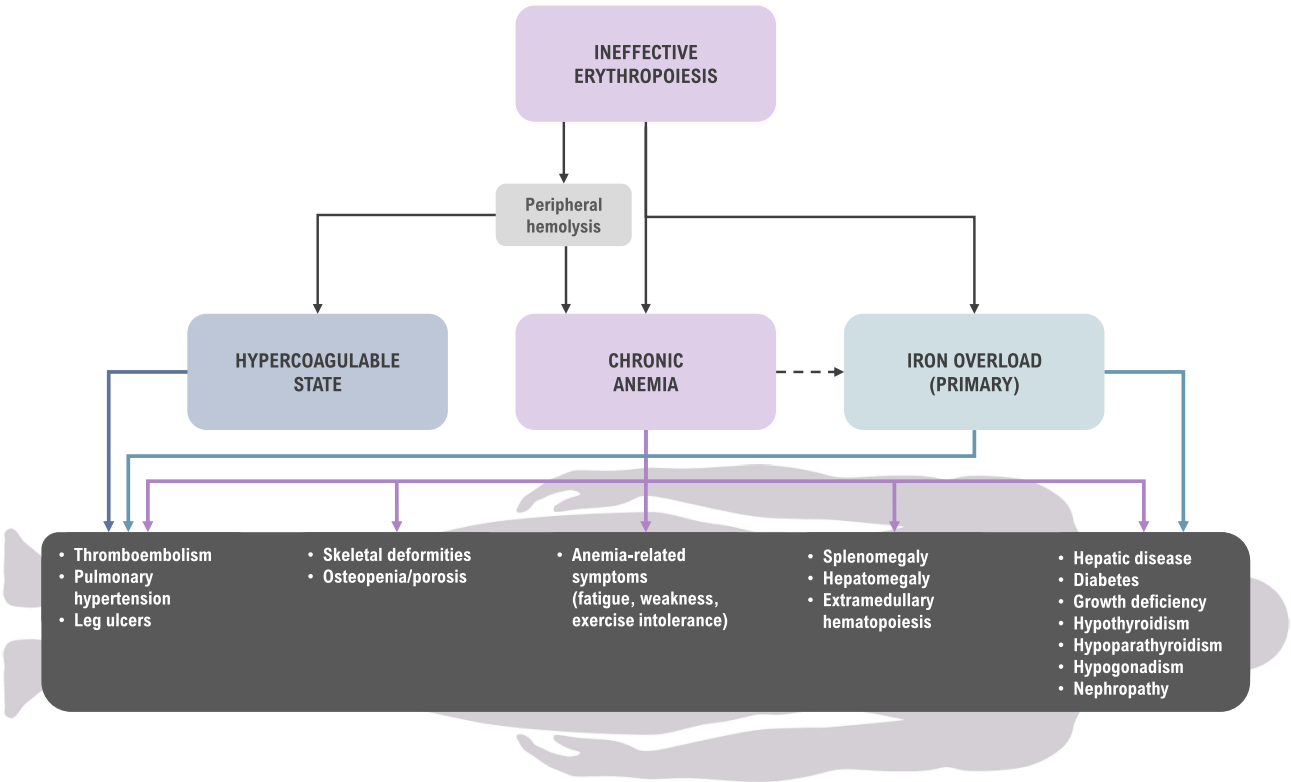


Figure 1 Key pathophysiologic drivers in non-transfusion-dependent β-thalassemia (NTDT).

morbidity and mortality, chronic anemia is also linked to short-term symptoms of fatigue as well as poor quality of life and mental health.[7,34–37]

Available Options for Managing Anemia in NTDT

Management of NTDT through evidence-based clinical trial data and international guidelines has been mostly restricted to iron chelation therapy for iron overloaded.[38,39] Until recently, there have been no pharmacologic agents specifically approved for the management of anemia in NTDT. Although the critical need to address anemia in patients with a hemoglobin level <10 g/dL has only recently been uncovered, health-care providers have already been resorting to various approaches to improve hemoglobin level for patients in clinical need; although these come with challenges.

Splenectomy has the ability to raise hemoglobin level by 1–2 g/dL but the procedure is associated with a considerable risk of infection and thrombosis, that it is now mainly reserved for cases of symptomatic splenomegaly or hypersplenism.[38] Hydroxyurea has also shown some effect in case series and small trial in NTDT patients, but long-term safety and durability of response were concerning.[40,41] Transfusions are occasionally used in clinical settings that require immediate improvement (or "protection") of hemoglobin level such as during acute infection, pregnancy, and surgery.[5,6,38] Observational studies have also highlighted that NTDT patients that transitioned to regular transfusion therapy had lower rates of morbidity and mortality.[30,42] Although this further reinforces the need to treat anemia in NTDT, it cannot widely reinforce transitioning patients to regular transfusion program, owing to risks of secondary iron overload and related morbidity and burden.[43,44]

Luspatercept for β-Thalassemia

Luspatercept (ACE-536) is a recombinant fusion protein comprising a modified extracellular domain of the human activin receptor type IIB fused to the Fc domain of human IgG1. The domains bind to select transforming growth factor β (TGF-β) superfamily ligands, block SMAD2/3 signaling, and enhance erythroid maturation during late-stage erythropoiesis.[45,46] RAP-536 (a murine analog of luspatercept) was shown to enhance erythroid maturation by restoring nuclear levels of the transcription factor GATA-1 in erythroid precursors.[47] In β-thalassemia mouse models, treatment with RAP-536 reduced α-globin chain aggregation and subsequent hemolysis, while increasing erythrocyte life span and improving iron overload.[46] RAP-536 also increased red-blood cell parameters, as well as reduced the decrease in bone mineral density and splenomegaly.[45] The exact mechanisms by which luspatercept exerts its full effects in patients with β-thalassemia are yet to be fully understood.[48]

In a Phase 1 trial of 32 healthy volunteers (NCT01432717), a dose-dependent increase in hemoglobin level was observed one week after initiation of luspatercept, and was maintained for several weeks after cessation of therapy; while treatment was well tolerated.[49] A multicenter, open-label, dose-ranging, phase 2 trial of luspatercept in adults with β-thalassemia (NCT01749540) followed, with a 5-year extension (NCT02268409). Sixty-four patients were enrolled including 33 NTDT and 31 TDT. Patients received 0.2 to 1.25 mg/kg luspatercept subcutaneously every 21 days for ≥5 cycles (dose-finding stage) and 0.8 to 1.25 mg/kg (expansion cohort and 5-year extension). The primary endpoint was erythroid response, defined as a hemoglobin increase of ≥1.5 g/dL from baseline for ≥14 consecutive days (without transfusions) for NTDT patients. Eighteen NTDT patients (58%) receiving higher dose levels of luspatercept (0.6–1.25 mg/kg) achieved a mean hemoglobin increase of ≥1.5 g/dL over ≥14 days compared with baseline. The most common grade 1 to 2 adverse events were bone pain, headache, and myalgia. Luspatercept also reduced LIC and improved quality of life among patients with NTDT. Some NTDT patients on the trial that had morbidities like leg ulcers experienced full healing.[50] Long-term safety data for up to five years of treatment on this trial are now also available. Median duration of luspatercept exposure for NTDT patients was 910 days and 17/31 (54.8%) NTDT patients achieved a mean hemoglobin increase of ≥1.5 g/dL with a median cumulative duration of response of 1126 days. The most common treatment-related adverse events of any grade were bone pain, headache, and myalgia.[51]

Luspatercept was further developed in a Phase 3, randomized trial (NCT02604433, BELIEVE) in adult TDT patients which met its primary endpoint of transfusion reduction by at least 33% from baseline during weeks 13 through 24 plus a reduction of at least 2 red-cell units over this 12-week interval.[52] This led to luspatercept's approval for the treatment of

anemia associated with TDT in both the USA and Europe. A trial in pediatric patients with TDT is also ongoing (NCT04143724). Further development in NTDT patients was pursued through the BEYOND trial.[53]

The BEYOND Trial

BEYOND (NCT03342404) was a phase 2, double-blind, randomized (2:1), placebo-controlled, multicenter trial evaluating the efficacy and safety of luspatercept in 145 adults (≥18 years) patients with NTDT conducted at 12 centers in Thailand, Lebanon, Greece, Italy, the UK, and the USA (Figure 2).[53] Eligible patients had a baseline hemoglobin level of ≤10 g/dL. Luspatercept was given once subcutaneously every 3 weeks for 48 weeks in the double-blind treatment period and started at 1.0 mg/kg with titration up to 1.25 mg/kg, or reduction in the event of toxicity or excessive hemoglobin increase. The primary endpoint was achievement of an increase from baseline of ≥1.0 g/dL in mean hemoglobin level over a continuous 12-week interval during weeks 13–24, in the absence of transfusions.

The trial met its primary endpoint with 74/96 (77.1%) of patients in the luspatercept arm vs 0/49 placebo patients achieving erythroid response. Fifty (52.1%) patients in the luspatercept group actually had a mean hemoglobin increase of at least ≥1.5 g/dL. Response was observed across all evaluated subgroups by age, gender, region, baseline hemoglobin level, and genotype.[53] Increasing proportions of patients treated with luspatercept achieved a hemoglobin level >10.0 g/dL, from 55.2% (n = 53/96) at week 12, 63.0% (n = 58/92) at week 24, 67.0% (n = 61/91) at week 36, to 69.7% (n = 62/89) at week 48.[54] The key secondary endpoint was a change in a patient-reported outcome measure of tiredness/weakness specifically developed and validated for patients with NTDT (NTDT-PRO T/W).[55,56] Improvement in NTDT-PRO T/W during weeks 13–24 favored luspatercept over placebo, although the difference was not statistically significant. This may be attributed to the inclusion of asymptomatic patients and the short duration before assessment. In fact, the difference was more pronounced at later timepoints (weeks 37–48) and in patients who were symptomatic at baseline. Improvement in NTDT-PRO T/W also correlated with improvement in hemoglobin level. Serum ferritin and LIC did not show significant changes from baseline during treatment. The proportion of patients with serious adverse events was lower in the luspatercept group than in the placebo

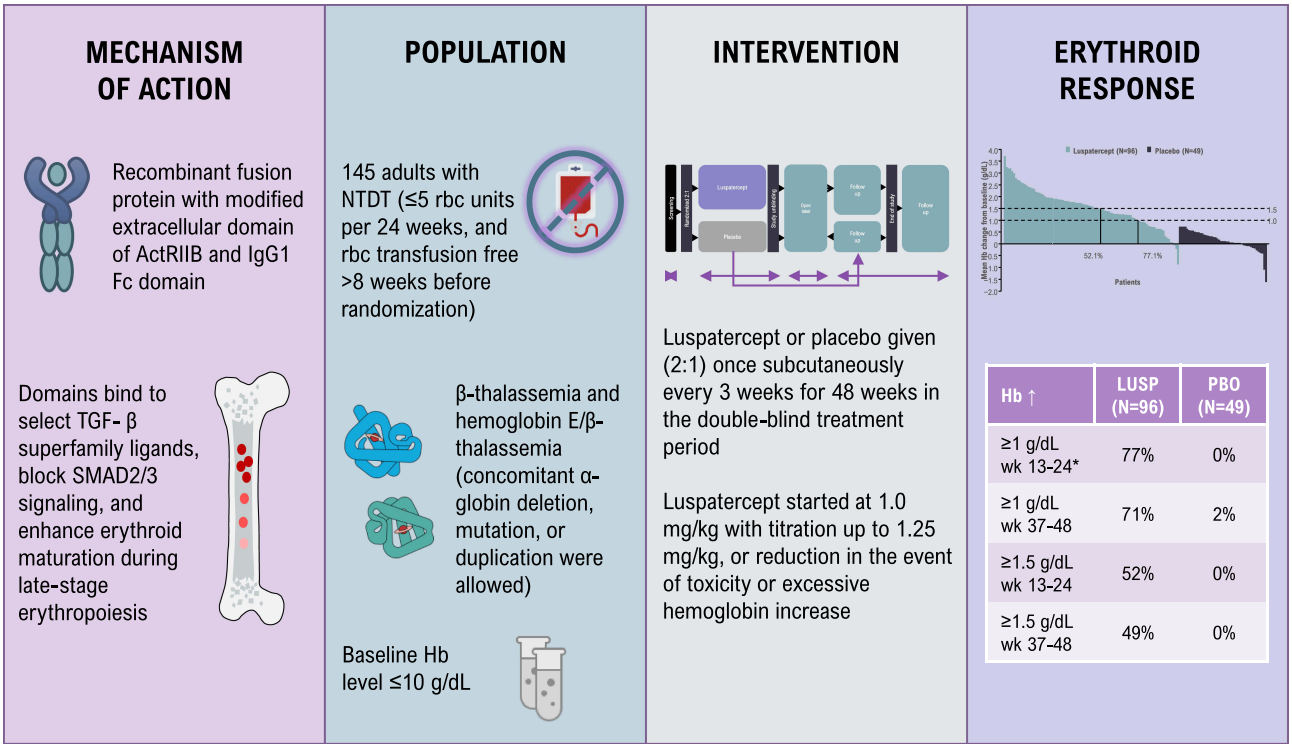


Figure 2 Summary of the BEYOND trial. The BEYOND trial was a phase 2, double-blind, randomized (2:1), placebo-controlled, multicenter trial evaluating the efficacy and safety of luspatercept in NTDT. *Primary endpoint.

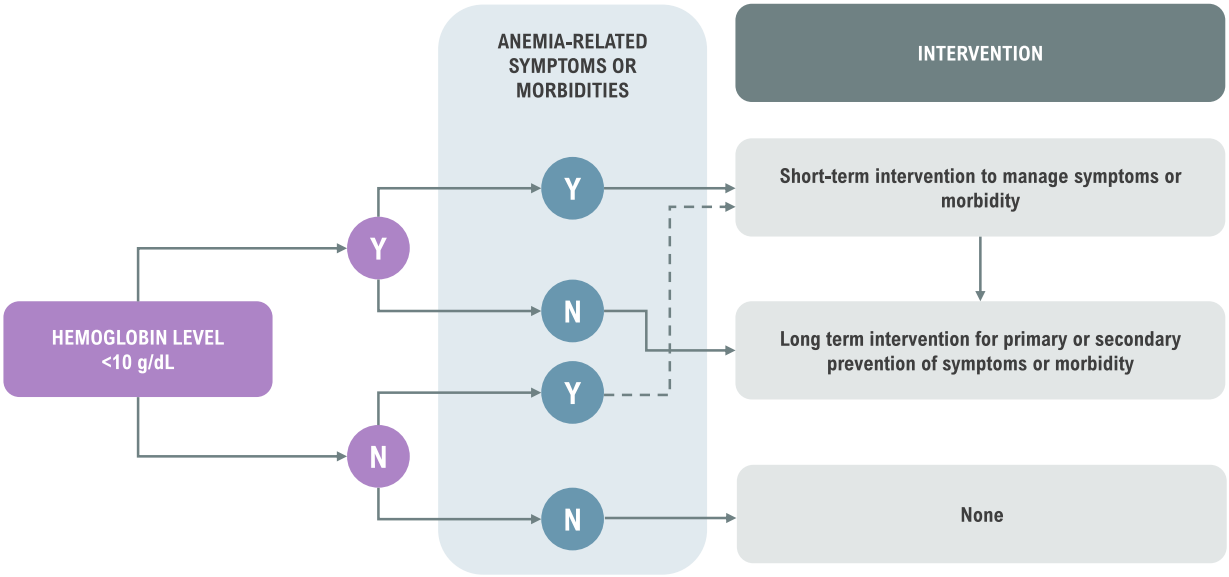
Abbreviations: NTDT, non-transfusion-dependent β-thalassemia; ActRIIB, activin receptor type IIB; IgG1, immunoglobulin G1; TGF-β, transforming growth factor-β; rbc, red blood cell; wk, week; hb, hemoglobin; LUSP, luspatercept; PBO, placebo.

group (12% vs 25%). Treatment-emergent adverse events most commonly reported with luspatercept were bone pain (37%), headache (30%), and arthralgia (29%). No thromboembolic events or deaths were reported during the study.[53] The latter may further support that thromboembolic events occurring in some TDT patients in the BELIEVE trial were most likely attributed to pre-existing risk factors rather than luspatercept therapy itself.[52]

The application for regulatory approval in the USA (Food and Drug Administration) for luspatercept as a treatment of anemia in NTDT was withdrawn in June 2022 for lack of agreement on benefit/risk.[57] However, luspatercept received European Commission approval in March 2023 as a treatment for adult patients with anemia associated with NTDT.[58]

Integration of Luspatercept in Contemporary Management Approaches

Data from the BEYOND trial was unequivocal with regard to luspatercept's ability to improve hemoglobin level in NTDT patients who are at highest risk of long-term morbidity and mortality associated with ineffective erythropoiesis and chronic anemia.[53] In fact, over half of patients already transitioned to safer hemoglobin levels (>10 g/dL) after only three months of therapy.[54] Since treatment was well tolerated over long-term exposure,[51] luspatercept can now be considered a safe and effective intervention for long-term treatment of NTDT patients with hemoglobin levels ≤10 g/dL with the aim of improving hemoglobin level by at least 1 g/dL, and ideally achieving a steady-state target hemoglobin level of >10 g/dL. Such treatment objective revolving around "prevention" of long-term morbidity is now "more feasible", since the only alternative up until now was introduction of lifelong regular transfusion therapy (or hydroxyurea in some cases) – a benefit/risk dilemma that many physicians were faced with in the real-life clinical setting. Data from extension studies and real-world evidence of luspatercept would still be needed to confirm its ability to reduce long-term morbidity risk, especially since it was not possible to assess such effects during the short course of the core clinical trial. The same applies to effects on iron overload, since



INTERVENTION	POSITIVE ATTRIBUTES	CHALLENGES
Transfusion	▪ Considerable experience from managing transfusion-dependent patients ▪ Observational data on management and prevention of morbidity and improved survival	▪ Secondary iron overload ▪ Transfusion-related reactions (alloimmunization) and infections ▪ Burden of administration and visit schedule
Hydroxyurea	▪ Evidence of erythroid response in small series and trials ▪ Oral administration ▪ Observational data on management and prevention of morbidity	▪ Concerns with long-term safety ▪ Loss of response on long-term therapy ▪ Not suitable during pregnancy
Luspatercept	▪ Evidence of erythroid response from a randomized clinical trial ▪ Improvement of morbidity (e.g., leg ulcers) in some patients included in the trials	▪ Absence of long-term data on clinical benefit ▪ Subcutaneous administration ▪ Not suitable during pregnancy

Figure 3 Contemporary management of anemia in non-transfusion-dependent β-thalassemia (NTDT).

improvement in erythropoiesis is expected to ameliorate cumulative iron loading from intestinal absorption and to mobilize existing tissue iron.[18] This may eventually decrease the dose or need for iron chelation therapy, although overt changes in clinical iron indices will take some time to be observed. This also calls for data on earlier intervention with luspatercept in children with NTDT.

The need for intervention becomes more apparent in NTDT patients with symptomatic anemia. Although data from the BEYOND trial did not show significant benefit in the NTDT-PRO T/W domains, improvement was still apparent especially in symptomatic patients. In patients with co-existing clinical complications, there is currently no evidence from clinical trials on the benefit of any intervention in reversing the pathology, although some anecdotal evidence from case series and observational studies suggests a role for transfusion and hydroxyurea (± erythropoietin) for managing growth delay, extramedullary hematopoiesis, pulmonary hypertension, and leg ulcers.[38] Figure 3 illustrates projected treatment landscape for anemia in NTDT.[59]

Other agents are also in development for the treatment of anemia in adults with NTDT. Mitapivat (AG-348) is a first-in-class oral, small-molecule, allosteric activator of the red blood cell-specific form of pyruvate kinase (PK).[60,61] Data have recently become available from an open-label, multicentre, phase 2 study of mitapivat in 20 adults with NTDT and a hemoglobin level of ≤10 g/dL evaluating safety and efficacy in achieving a hemoglobin increase by ≥1.0 g/dL. Sixteen (80%) patients had an erythroid response (5/5 in α-thalassemia and 11/15 in β-thalassemia).[62] Mitapivat is currently being evaluated in two phase 3, randomized trials in NTDT (ENERGIZE) and TDT (ENERGIZE-T), including α-thalassemia.[63,64]

Treatment of anemia in NTDT will always need to be individualized based on clinical and patient needs, and data from real-world evidence will also be key to identify patient profiles that could benefit the most from such novel interventions which may not necessarily be affordable or accessible to all NTDT patients globally, considering the majority of patients live in resource-limited countries.

Conclusion

Our understanding of the detrimental role of untreated anemia in patients with NTDT continues to expand. The availability of a new treatment option specifically developed to raise hemoglobin level in this patient population will enable our new management approach aimed at disease modification and prevention of long-term morbidity and mortality. Real-world evidence will be imperative to understand how data from clinical trials translate to clinical practice.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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