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Non-Transfusion-Dependent Thalassemia: An Image Gallery Worth a Thousand Words

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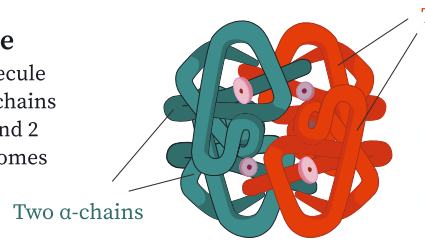
Our understanding of the molecular pathways and associated clinical presentations characterizing various thalassemia phenotypes has substantially improved over the years. Non-transfusion-dependent thalassemia (NTDT) refers to patients who present with mild–moderate anemia, which does not necessitate lifelong, regular transfusion therapy. This typically includes patients with β-thalassemia intermedia, mild–moderate hemoglobin E/β-thalassemia, and α-thalassemia intermedia (hemoglobin H disease) (Figure 1) [1–7]. The underlying α/non-α globin chain imbalance and subsequent ineffective erythropoiesis and peripheral hemolysis lead to chronic anemia, primary iron overload, and a hypercoagulable state. These, in turn, are associated with a range of clinical morbidities that can impact quality of life and lead to premature death (Figure 2) [2, 8–22]. In view of the growing evidence on the negative impact of untreated anemia in these patients, long-term management becomes key. However, the only options that have been available so far include transfusions which can worsen iron overload and introduce transfusion-dependence burden, off-label use of hydroxyurea based on data from small trials or observational studies, and splenectomy which is associated with increased risks of infections and thrombosis (Figure 3) [6, 9, 23, 24]. Beyond anemia, cumulative iron overload due to increased intestinal iron absorption needs to be regularly monitored and managed with iron chelation therapy. Multimorbidity in NTDT also requires close monitoring and early intervention through a multidisciplinary team approach (Figure 4) [2, 6, 25–27]. In the last decade, we have witnessed several novel agents being developed to manage anemia in NTDT. Agents targeting hepcidin dysregulation have not been successful in clinical trials, despite encouraging data in animal models. Luspatercept, an erythroid maturation agent, showed efficacy in improving hemoglobin level in adults with β-NTDT and is now approved in Europe (but not the United States). Mitapivat, a pyruvate kinase activator, has also shown efficacy in improving hemoglobin level and functional status in a recent phase 3 trials in adult patients with both α- and β-NTDT (Figure 5) [24, 28–30]. Clinical management guidelines are now available, but awareness of the various morbidities and treatment options in NTDT, especially among patients remains essential (a patient friendly summary is provided in the Appendix S1).

Thalassemia: molecular understanding and classification

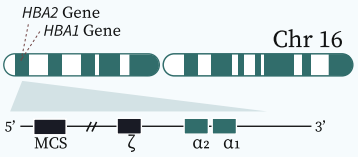
The Hemoglobin Molecule

The adult hemoglobin (HbA) molecule is made up of 2 α- and 2 β-globin chains coded by 4 α-globin genes (*HBA*) and 2 β-globin genes (*HBB*) on chromosomes 16 and 11, respectively.[1]



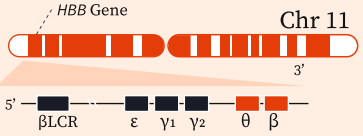
Inherited mutations in the α- or β-globin genes lead to deficient production of corresponding α- or β-globin chains, and a clinical manifestation of α- or β-thalassemia.[1]

α - Thalassemia



>370 different molecular defects are known to cause α-thalassemia including deletional (-) or nondeletional (α^T) mutations (qualitative change, phenotypically more severe) in the α-globin genes.[2]

β - Thalassemia



>350 mutations have been described in β-thalassemia, which can lead to complete absence (β^0) or relative reduction (β^+) of β-globin chain product.[3]

The magnitude of α/β-globin chain imbalance determines the severity of HbA deficiency (anemia), erythroid cell death in the bone marrow due to accumulation of unpaired chains (ineffective erythropoiesis), and premature red blood cell death in the peripheral circulation (hemolysis).[2,3]

Classification

Thalassemia phenotypes are defined based on clinical parameters, with variable genotype correlations.[2,3]

Genotype		Conventional Phenotype	Clinical Presentation		Clinical Presentation	Conventional Phenotype	Genotype
$\alpha^T\alpha/\alpha\alpha$; $\alpha\alpha^T/\alpha\alpha$	Carrier status	silent carrier or α-thalassemia minima	Normal or mild decrease in MCH/MCV	transfusions not or rarely required	Microcytic, hypochromic, borderline asymptomatic anemia (hemoglobin >10 g/dL)	β-Thalassemia carrier state (trait/minor) or HbE trait	β/β^+, β/β^0 or β/β^E
$--/\alpha\alpha$; $-\alpha/-\alpha$; $-\alpha/\alpha^T\alpha$; $-\alpha^T/\alpha\alpha$	Carrier status	α-thalassemia trait or α-thalassemia minor	Normal or borderline anemia RBC microcytic and hypochromic	occasional transfusions required	Delayed presentation (>2 years), mild-moderate anemia and clinical symptoms	β-Thalassemia intermedia or mild-moderate HbE/β-thalassemia	β^+/β^+ or β^E/β^+
$--/-\alpha$ (deletional)	Clinically relevant forms	HbH disease (α-thalassemia intermedia)	Clinical severity variable normal or borderline anemia RBC microcytic and hypochromic	occasional transfusions required	Early presentation (≤2 years), severe anemia and clinical symptoms	β-Thalassaemia major or severe HbE/β-thalassemia	β^+/β^0 or β^E/β^0
$--/\alpha^T\alpha$; $-\alpha^T/-\alpha$; $-\alpha^T/\alpha^T\alpha$; $\alpha^T\alpha/\alpha^T\alpha$ (nondeletional)	Clinically relevant forms	HbH disease (α-thalassemia intermedia)	More severe anemia RBC markedly microcytic and hypochromic	occasional transfusions required	Early presentation (≤2 years), severe anemia and clinical symptoms	β-Thalassaemia major or severe HbE/β-thalassemia	β^0/β^0
Any combination of – or α^T resulting in deletion or inactivation of all 4 genes	Clinically relevant forms	Hb Barts hydrops fetalis syndrome (α-thalassemia major)	Often die in utero or shortly after birth	regular transfusions required	Early presentation (≤2 years), severe anemia and clinical symptoms	β-Thalassaemia major or severe HbE/β-thalassemia	β^0/β^0

α-duplication; α-thalassemia → HbF production; α-duplication

Recently, transfusion dependence is more commonly used to classify patients as having transfusion-dependent thalassemia (TDT) or non-transfusion-dependent thalassemia (NTDT), mostly based on regular transfusion requirement in the past 6-12 months. This may be a reflection of disease severity and management needs or driven by patient/physician choice. This classification is dynamic and patients can move between these two transfusional phenotypes.[4–7]

FIGURE 1 | Thalassemia: Molecular understanding and classification [1–7].

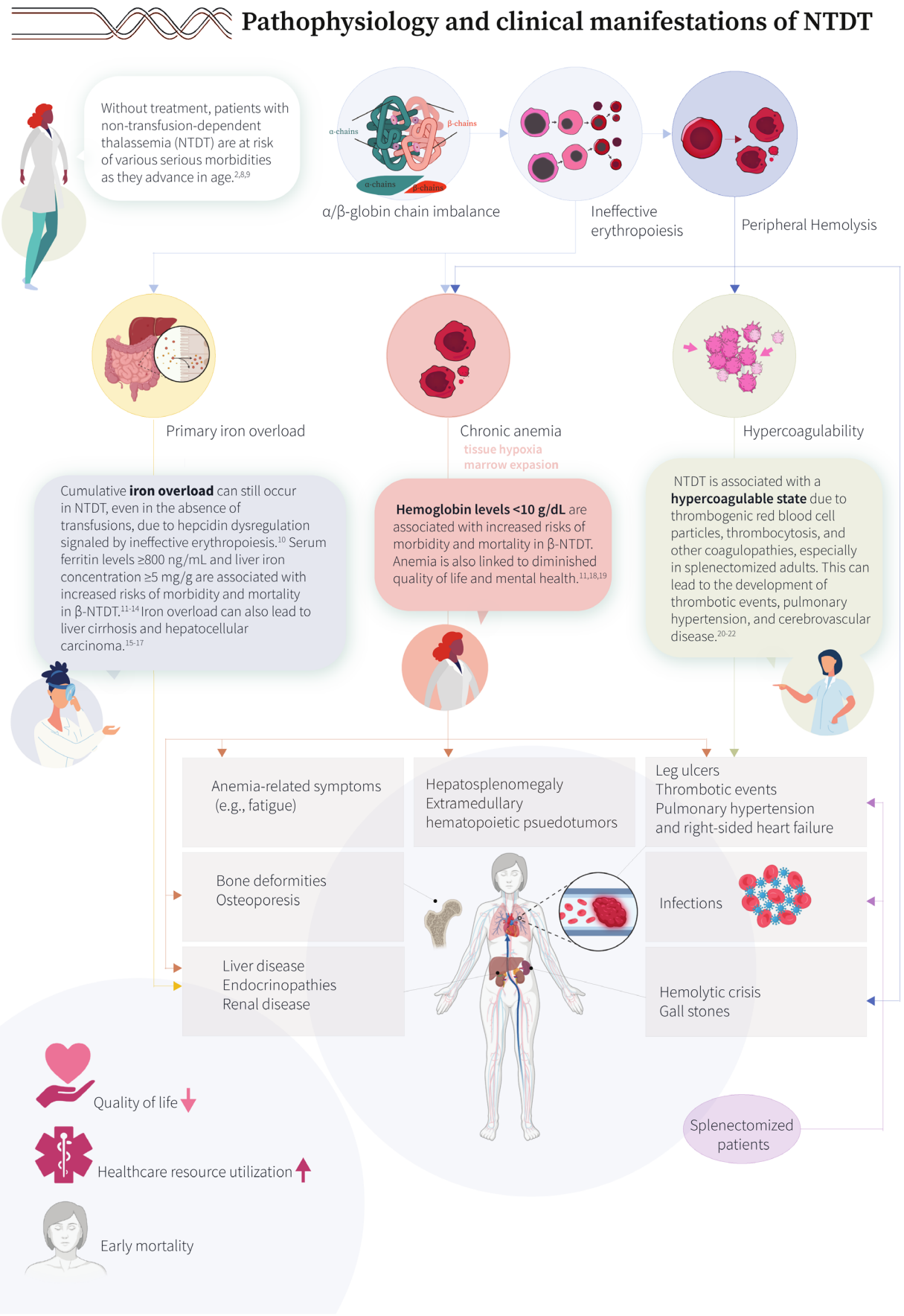


FIGURE 2 | Pathophysiology and clinical manifestations of NTDT [2, 8–22].

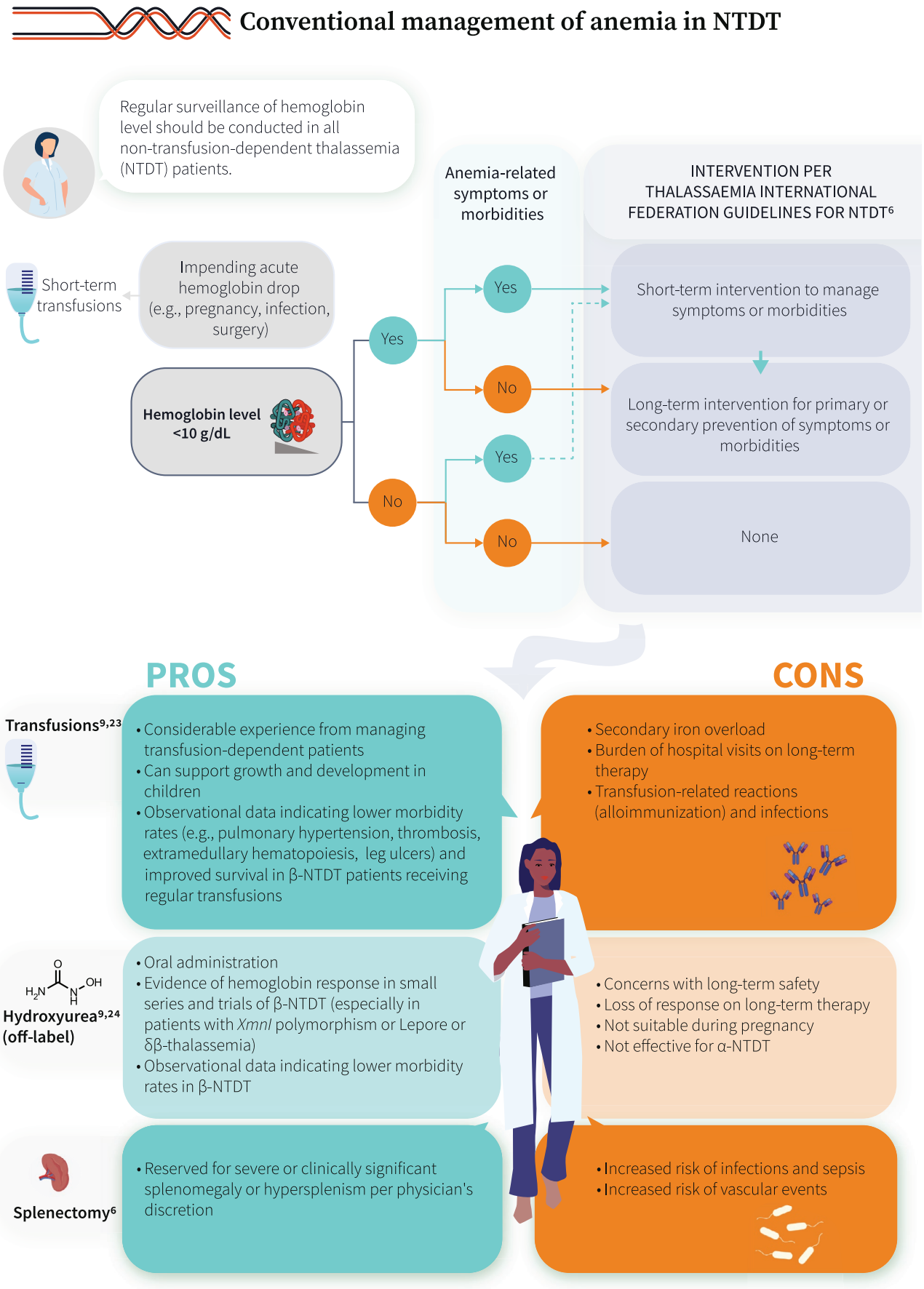
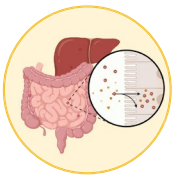


FIGURE 3 | Conventional management of anemia in NTDT [6, 9, 23, 24].

Monitoring and management of complications in NTDT

Iron overload



Deferoxamine (subcutaneous) has broad label indication for chronic iron overload management, but has not been specifically evaluated in non-transfusion-dependent thalassemia (NTDT)[2,6]

Deferiprone (oral, 3x daily) showed comparable reduction of serum ferritin to deferoxamine in a randomized trial of β-NTDT patients ≥13 years, but it is not currently approved for NTDT[25]

Deferasirox (oral, 1x daily) is indicated in NTDT patients ≥10 years, based on data from the randomized, phase 2 THALASSA trial (including α- and β-NTDT) showing significant reductions in liver iron concentration (LIC) and serum ferritin (SF)[26]

β-NTDT **≥ 10 years**
(or ≥15 years α-NTDT)

LIC Q12-24 months (or SF Q3 months)

LIC **<** 5 mg/g
(or SF **<** 800 ng/mL)

LIC **≥** 5 mg/g
(or SF **≥** 800 ng/mL)

Iron chelation therapy per local prescribing information for dose adjustment and adverse events monitoring[1,2]

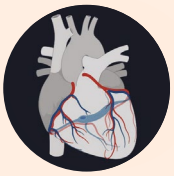
LIC Q6-12 months
(or SF Q3 months)

Interrupt chelation when
LIC ≤3 mg/g
(or SF ≤300 ng/mL)

Liver
- Liver function and bilirubin every 3 months
- Liver ultrasound annually
- Transient elastography every 2 years if available

Morbidities

Patients should be regularly monitored for symptoms and signs of morbidity from adolescence or earlier if feasible. Tests should be performed more frequently with abnormal findings along with prompt referral to specialist care.[2,6,27]

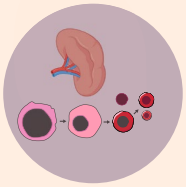


Heart
- Transthoracic echocardiography annually
- Electrocardiogram annually

Endocrine and bone
- Growth and pubertal development regularly
- Thyroid function, fasting glucose, oral glucose tolerance, calcium, phosphate, vitamin D, and parathyroid hormone annually
- Sex hormones with signs of abnormal sexual development or to assess fertility
- Bone mineral density annually

Quality of life
- Detailed history for signs of fatigue or poor mental health regularly

Leg ulcers
- Skin inspection regularly



Extramedullary hematopoiesis
- Spleen/liver size and neurologic assessment on physical exam regularly

FIGURE 4 | Monitoring and management of complications in NTDT [2, 6, 25–27].

Novel therapies for NTDT

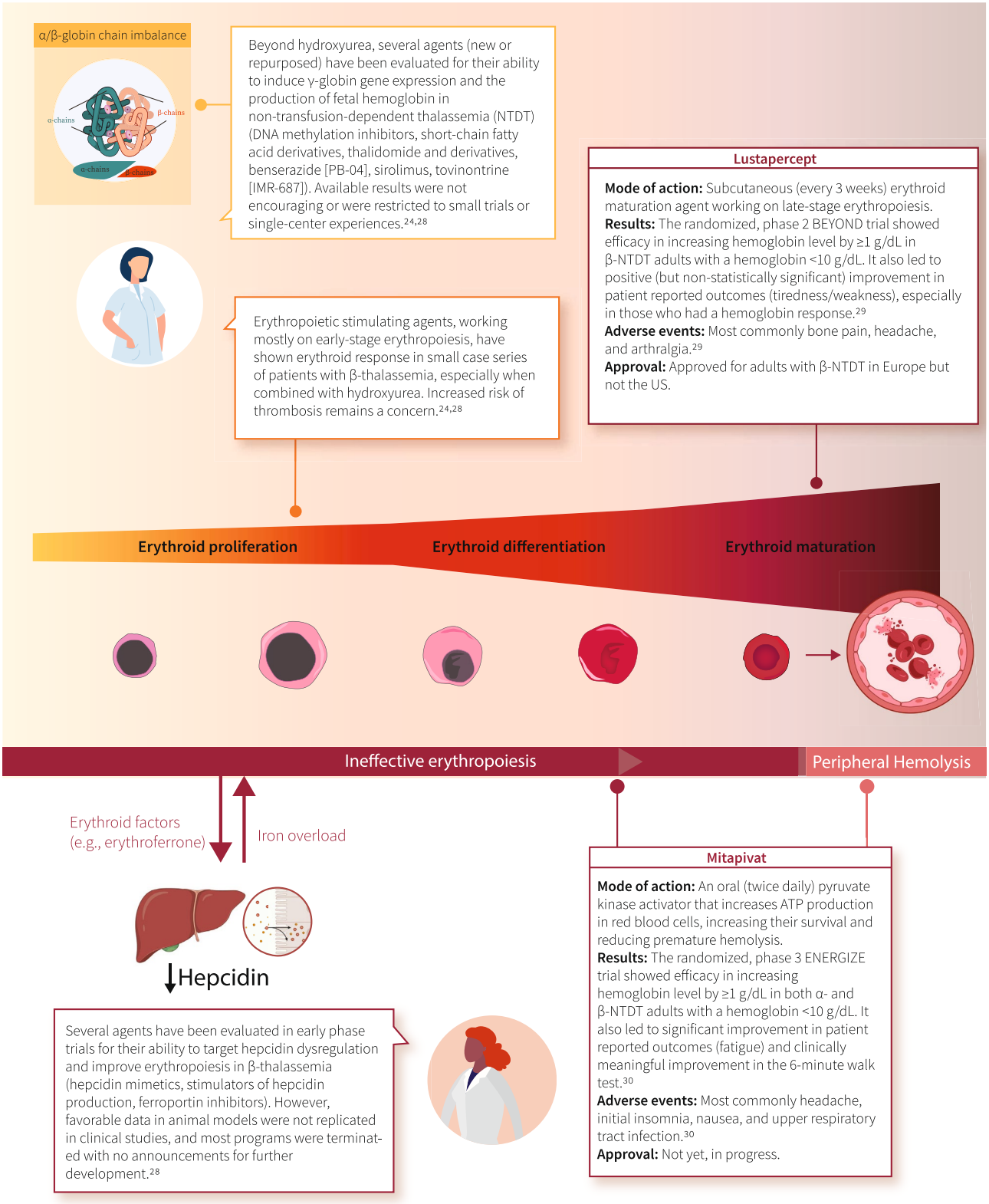
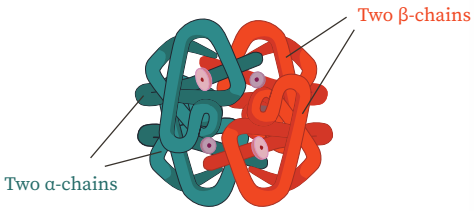
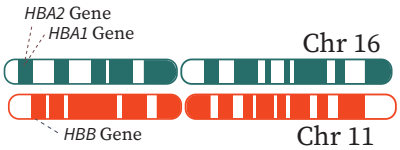


FIGURE 5 | Novel therapies for NTDT [24, 28–30].

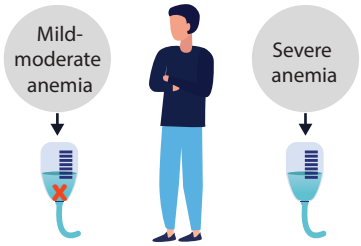
Non-transfusion-dependent thalassemia



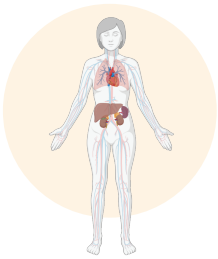
Thalassemia is an inherited disorder of hemoglobin, a molecule found in our red blood cells that is composed of four protein (globin) chains (2 α and 2 β), essential for oxygen delivery throughout the body.[1]



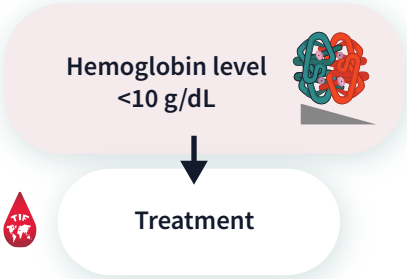
Patients who inherit genetic mutations affecting the α-globin chain have α-thalassemia and those with deficient β-globin chains have β-thalassemia.[1,2]



Thalassemia patients who were initially diagnosed with mild-moderate anemia and not placed on regular transfusion programs are known to have non-transfusion-dependent thalassemia (NTDT, which includes patients with β-thalassemia intermedia, mild/moderate hemoglobin E/β-thalassemia, and hemoglobin H disease).[3,4]



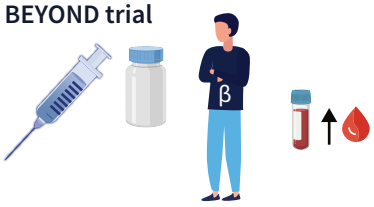
Recent studies have shown that, without treatment, patients with NTDT are at risk of various clinical complications and diminished quality of life, especially as they advance in age.[2,5,6]



Specifically, patients with hemoglobin levels <10 g/dL are at an increased risk of complications and early death.[7-9] The Thalassaemia International Federation (TIF) now recommends treatment for patients with a hemoglobin level <10 g/dL, especially those who are symptomatic.[10]

Until recently, transfusions were the only means to manage anemia in patients with NTDT. Although these may be effective, they increase the risk of iron overload and associated complications.[6,10,11]

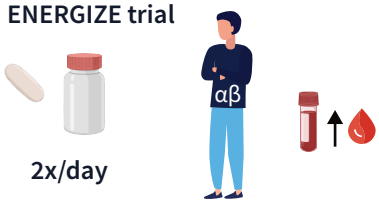
BEYOND trial



every 3 weeks

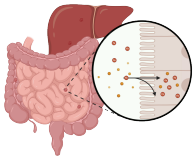
A clinical trial (BEYOND) has recently shown that **luspatercept,** a subcutaneous drug taken every three weeks, can improve hemoglobin level in adults with NTDT (β-thalassemia only), and the drug is now approved in Europe (but not the US).[12]

ENERGIZE trial



2x/day

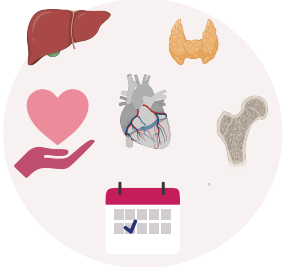
Mitapivat, which is taken orally twice per day, was also recently shown to improve hemoglobin level as well as functional status (fatigue) in adults with NTDT (both α- and β-thalassemia) in the ENERGIZE trial, and is now being reviewed for approval by regulatory agencies in Europe and the US.[13]



High serum ferritin
High liver iron

Iron overload can still occur in NTDT without transfusions, due to increased gut absorption.[14] Patients who have serum ferritin ≥800 ng/mL or liver iron concentration ≥5 mg/g have increased risks of complications and early death.[8,15-17] NTDT patients should be regularly monitored for iron overload and receive iron chelation if they reach these levels.[2,10,18,19]

NTDT patients should be regularly monitored for symptoms and signs of complications of the heart, blood vessels, liver, endocrine glands, bone, and other relevant body systems from adolescence or earlier if feasible. Tests should be performed more frequently with abnormal findings and patients should be referred to specialist care for management.[2,10,20]



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Author Contributions

All authors contributed to conceptualization and manuscript drafting or critical review. K.M.M. was also involved in the creation of visualizations. All authors validated the manuscript and gave final approval for submission.

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Ethics Statement

Ethics approval not applicable as no patients were involved in this work.

Conflicts of Interest

K.M.M. reports consultancy fees from Novartis, Bristol Myers Squibb (Celgene Corp), Agios Pharmaceuticals, CRISPR Therapeutics, Vifor Pharma, Novo Nordisk, and Pharmacosmos; and research funding from Agios Pharmaceuticals and Pharmacosmos. S.S. reports consultancy fees from Agios Pharmaceuticals, Bristol Myers Squibb, and Novo Nordisk; being a member of a clinical trial steering committee for Vertex Pharmaceuticals; and research funding (for clinical trials) from Agios Pharmaceuticals, Bristol Myers Squibb, Novo Nordisk, and Regeneron. T.D.C. reports advisory support to Agios Pharmaceuticals, Bristol Myers Squibb, and Chiesi. H.A.-S. reports consultancy fees from Agios Pharmaceuticals, Alnylam, Alpine, Amgen, argenx, Novartis, Pharmacosmos, and Sobi; and research funding to institution from Agios Pharmaceuticals, Amgen, Novartis, Sobi, and Vaderis. M.D.C. reports consultancy fees from Novartis, Bristol Myers Squibb (Celgene Corp), Vifor Pharma, and Vertex Pharmaceuticals; and research funding from Novartis, Bristol Myers Squibb (Celgene Corp), La Jolla Pharmaceutical Company, Roche, Protagonist Therapeutics, and CRISPR Therapeutics. K.H.M.K. reports grants from Agios Pharmaceuticals and Pfizer; consulting fees from Agios Pharmaceuticals, Alexion Pharmaceuticals, Biossil, Bristol Myers Squibb, Forma, Novo Nordisk, Pfizer, and Vertex Therapeutics; honoraria from Agios Pharmaceuticals and Bristol Myers Squibb; and being on a data safety monitoring board/advisory board for Sangamo. V.V. reports grants from Agios Pharmaceuticals, Bristol Myers Squibb (Celgene Corp), DisperSol Technologies, IONIS Pharmaceuticals, Novartis, Pharmacosmos, The Government Pharmaceutical Organisation, and Vifor; and consulting fees from Agios Pharmaceuticals, Bristol Myers Squibb (Celgene Corp), DisperSol Technologies, IONIS Pharmaceuticals, Novartis, Pharmacosmos, and Vifor. A.T.T. reports consultancy fees from Novo Nordisk, Bristol Myers Squibb (Celgene Corp), Agios Pharmaceuticals, Pharmacosmos, and Roche; and research funding from Novo Nordisk, Bristol Myers Squibb (Celgene Corp), Agios Pharmaceuticals, Pharmacosmos, and Roche.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.