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UPDATES IN CLINICAL TRIALS
FOR HEMATOLOGICAL DISEASES

2021 update on clinical trials in β-thalassemia

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Abstract

The treatment landscape for patients with β-thalassemia is witnessing a swift evolution, yet several unmet needs continue to persist. Patients with transfusion-dependent β-thalassemia (TDT) primarily rely on regular transfusion and iron chelation therapy, which can be associated with considerable treatment burden and cost. Patients with non-transfusion-dependent β-thalassemia (NTDT) are also at risk of significant morbidity due to the underlying anemia and iron overload, but treatment options in this patient subgroup are limited. In this review, we provide updates on clinical trials of novel therapies targeting the underlying pathology in β-thalassemia, including the α/non-α-globin chain imbalance, ineffective erythropoiesis, and iron dysregulation.

1 | INTRODUCTION

The β-thalassemias are a group of inherited disorders of hemoglobin (Hb) synthesis characterized by chronic anemia of varying severity. The degree of anemia relies on several genetic and environmental factors and determines the need for regular transfusion therapy. It is now common practice to classify patients as having transfusion-dependent β-thalassemia (TDT) or non-transfusion-dependent β-thalassemia (NTDT).[1]

The TDT patients (β-thalassemia major and severe forms of HbE/β-thalassemia) are those who commonly present in early childhood with severe anemia and require lifelong transfusion therapy for survival.[1] Although the introduction of transfusions improved survival in TDT patients, it did not come without its own side-effect, systemic iron overload leading to end-organ damage and increased mortality from cardiac or hepatic disease.[2–4] Advances in iron chelation therapy and the introduction of MRI techniques to detect organ-specific iron overload have led to improved management and patient outcomes.[5,6] Still, TDT comes with considerable burden to the patient, clinician, and overall healthcare system owing to persistent morbidity and high healthcare utilization, poor access to optimal care and high treatment cost especially in resource-limited countries, and several unmet needs in terms of efficacy, safety and adherence to conventional therapies.[7] Allogeneic hematopoietic stem-cell transplantation (HSCT) has been used successfully for the past few decades to offer curative therapy for patients with TDT, but is only available to a minority of patients with compatible donors.[1]

Patients with NTDT (β-thalassemia intermedia and mild–moderate forms of HbE/β-thalassemia) usually present later in childhood or even in adolescence with mild–moderate anemia that does not require immediate placement on a regular transfusion program.[1,8] Progress made over the past few decades has indicated that the diagnosis of NTDT carries greater morbidity than previously recognized. Ineffective erythropoiesis and anemia have been linked to an array of morbidities stemming from chronic hypoxia and an established hypercoagulable state.[1] Patients with Hb levels < 10 g/dl are at an increased risk of morbidity development, and variations of 1 g/dl can change a patient's morbidity risk.[9,10] There are currently no approved agents for the management of anemia in NTDT.[11] Transfusions are used in settings of expected drop in Hb such as pregnancy, infection or surgery; and some physicians also elect to use short courses of regular transfusions to promote growth in childhood or prevent/treat morbidity in adulthood in view of evidence of benefit from observational studies.[12–14] Even in the absence of transfusions, NTDT

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patients remain at risk of iron overload secondary to ineffective erythropoiesis, low hepcidin levels, and increased intestinal iron absorption.[1] Iron overload levels in NTDT patients can reach clinically significant thresholds and serum ferritin levels > 800 ng/ml or liver iron concentration (LIC) > 5 mg/g have been linked to higher morbidity risk.[15,16] Iron chelation therapy is now also recommended in NTDT patients older than 10 years of age who have iron overload.[17,18]

In this review, we highlight recent data from key clinical trials evaluating novel therapies for β-thalassemia at various stages of clinical development. We mainly focus on active programs, while we also reflect on key clinical trials that did not necessarily advance further or were prematurely terminated as they did not deliver on the promise of the scientific advances that led to their initiation. Updates are presented in the context of the specific β-thalassemia disease processes that individual agents target (Figure 1).

2 | CORRECTION OF THE α/NON-α-GLOBIN CHAIN IMBALANCE

2.1 | Approaches with curative intent

2.1.1 | Gene insertion

In β-thalassemia, mutations in the *HBB* gene and deficient production of β-globin chains lead to an imbalance in the α/non-α-globin chain ratio of adult Hb (HbA). Accumulation of unstable α-globin chain tetramers is toxic to erythroid precursors and remains the basis for ineffective erythropoiesis and premature red blood cell (RBC) death.[1] The use of autologous and genetically modified hematopoietic stem cells (HSCs) by gene insertion has emerged as a therapeutic strategy to correct and replace defective β-globin genes in β-thalassemia. Upon isolation of hematopoietic stem and progenitor cells (HSPCs), exogenous β-globin genes are then incorporated into the host-cell genome using a lentiviral vector. After full or partial myeloablation, these genetically modified autologous HSPCs are then returned to the patient where they repopulate in the hematopoietic compartment. For gene insertion to be successful, HSPC engraftment and gene transfer should occur at high efficiency and lead to high levels of gene expression with minimal to no risk of insertional mutagenesis.[19–24]

Following proof of concept that a lentiviral transfer of a marked β-globin (β^{A}-^{T87Q}) gene could substitute for long-term transfusions in a patient with β-thalassemia,[25,26] a clinical trials program was initiated using the LentiGlobin BB305 vector, which encodes HbA with such T87Q amino acid substitution (HbAT87Q). Results from two phase 1/2 studies (HGB-204 [NCT01745120] and HGB-205 [NCT02151526])[27] including 22 TDT patients (12–35 years of age) who were reinfused with cells transduced ex-vivo with the LentiGlobin BB305 vector have led to the conditional approval of the gene therapy product betibeglogene autotemcel (bluebird bio Inc.) in June 2019 in Europe. Twelve of the 13 patients who had a non-β^{0}/β^{0} genotype had stopped receiving RBC transfusions with levels of total Hb ranging

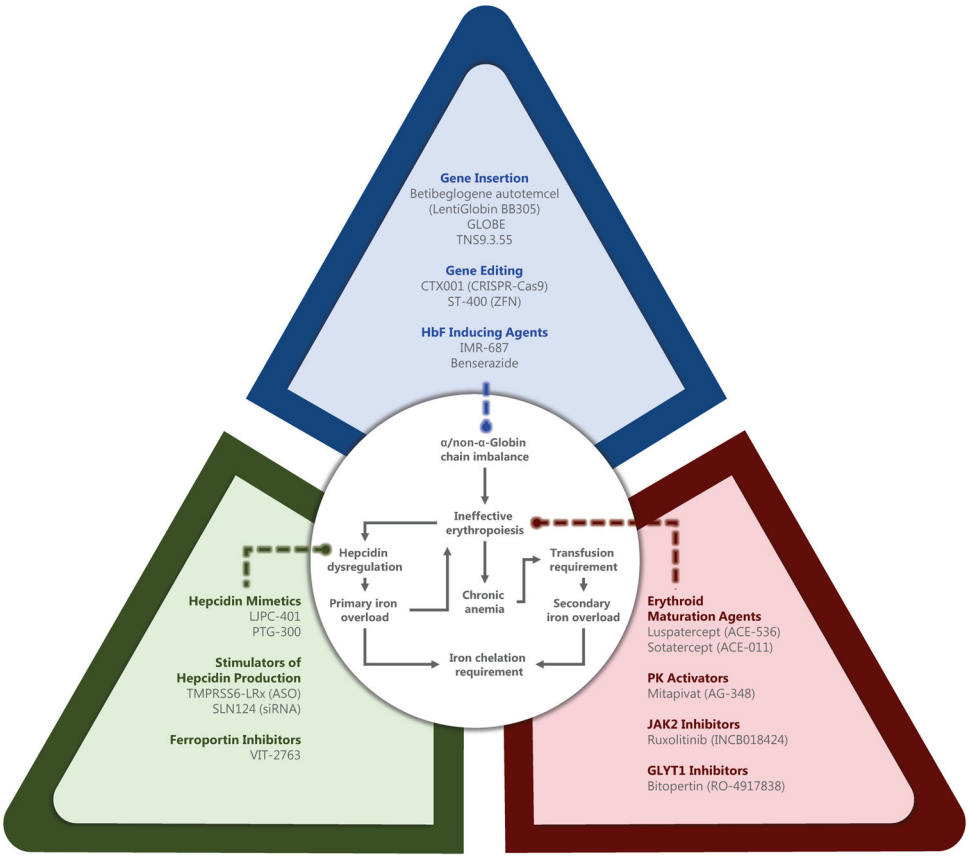

FIGURE 1 Novel agents with recently completed or ongoing clinical trials in β-thalassemia. ASO, anti-sense oligonucleotides; CRISPR-Cas9, clustered regularly interspaced short palindromic repeats linked to Cas9 nucleases (CRISPR-Cas9); GLYT1, Glycine Transporter 1; JAK2, janus kinase 2; PK, pyruvate kinase; siRNA, small interfering ribonucleic acid; TMPRSS, transmembrane serine protease; ZFN, zinc finger nucleases [Color figure can be viewed at wileyonlinelibrary.com]

from 8.2 to 13.7 g/dl. In nine patients with a β^0/β^0 genotype - an IVS1-110 (G>A) [HBB:c.93-21G>A] mutation was also considered with β^0 in this program - the median annualized transfusion volume was decreased by 73%, and transfusions were discontinued in three patients. No safety issues were attributed to the LentiGlobin BB305 vector in either study and treatment-related adverse events (AEs) were typical of those associated with autologous HSCT, including two episodes of veno-occlusive liver disease attributed to busulfan conditioning.[27] The conditional approval in Europe was thus limited to TDT patients who are non-β^0/β^0 and ≥ 12 years old, and who are transplant-eligible but do not have a matched sibling donor.

The phase 3 clinical trial program is using a refined transduction process compared with phase 1/2 studies, to evaluate the efficacy of betibeglogene autotemcel in achieving transfusion independence (defined as a weighted average Hb ≥ 9 g/dl without any transfusions for a continuous period of ≥ 12 months at any time during the study after drug product infusion). Final data from the HGB-207 study (Northstar-2, NCT02906202, 23 TDT subjects ≤ 50 years, non-β^0/β^0) and HGB-212 (Northstar-3, NCT03207009, 18 TDT subjects ≤ 50 years, β^0/β^0) are awaited. Interim data as of 30 November 2020 on 41 patients (12 β^0/β^0, 29 non-β^0/β^0) followed for a median of 24.3 months, showed transfusion independence in 30/34 (88.2%) evaluable patients (6/7 [85.7%] β^0/β^0 and 24/27 [88.9%] non-β^0/β^0) maintained for a median of 20.6 months. Weighted average Hb during transfusion independence was 11.5 g/dl. Adverse events in ≥ 2 patients considered by the investigator to be related or possibly related to betibeglogene autotemcel included abdominal pain ($n = 3$) and thrombocytopenia ($n = 3$; one serious event). There were no deaths and no evidence of clonal dominance or insertional oncogenesis in these studies.[28] These data included 27 pediatric patients who achieved a similar rate of transfusion independence (9/11 evaluable patients < 12 years, and 10/10 patients ≥ 12 to < 18 years) and showed a similar safety profile as with adults.[29]

Following two-years of observation in the phase 1/2 and 3 trials of betibeglogene autotemcel, patients could be enrolled in a 13-year long-term follow-up study, LTF-303 (NCT02633943). Interim results (November 30, 2020) from 44 patients enrolled in LTF-303 with a median follow-up of 45.6 months (range: 22.9–76.4) showed that transfusion independence was achieved and maintained in 15/22 (68.2%) patients treated in the phase 1/2 studies and in 20/22 (90.9%) of patients treated in the phase 3 studies. Weighted average Hb during transfusion independence was 10.3 and 11.8 g/dl in patients in phase 1/2 and phase 3 trials, respectively. This was driven by betibeglogene autotemcel HbAT87Q levels and remained stable from 24 to 36 months. Iron removal therapy was managed at the discretion of the investigator. While the LIC increased just after betibeglogene autotemcel, levels decreased over time in patients who achieved transfusion independence, particularly in those who had an elevated LIC at baseline. Serious AEs during LTF-303 included gonadotropic insufficiency, ectopic pregnancy, fetal death, gallbladder wall thickening/polyp, bacteremia with neutropenia, and major depression (all $n = 1$). No deaths, replication-competent lentivirus, or insertional oncogenesis were reported.[30]

On February 16, 2021, bluebird bio announced the temporary suspension of clinical trials and marketing of betibeglogene autotemcel following two reports of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) in sickle cell patients recruited in the HGB-206 trial.[31] On June 7, 2021, the company announced the lifting of FDA clinical hold for sickle cell disease and β-thalassemia studies, considering the AML case was found to be very unlikely related to the vector and the diagnosis of the MDS case was revised by the investigator to transfusion-dependent anemia.[32] Of note, an earlier case of MDS was also reported in a sickle cell patient but multiple independent assays demonstrated the absence of vector integration in the CD341 blasts and excluded lentiviral vector-mediated oncogenesis as the MDS cause.[33]

Several other gene insertion approaches and vectors have also been evaluated in animal models and validated for clinical investigation. A phase 1/2 trial (TIGET- BTHAL, NCT02453477) in TDT patients with β^0 or severe $\beta+$ mutations using an intrabone administration of HSCs transduced with the lentiviral vector GLOBE showed transfusion reduction in three adults and complete independence in 3/4 evaluated children.[34] Early data from the phase 1 TNS9 clinical trial (NCT01639690) on four adult TDT patients with β^0/β^+ and β^0/β^0 genotypes treated with autologous CD34+ HSPCs transduced with the TNS9.3.55 lentiviral vector showed durable and stable gene marking and no evidence of clonal dominance in all patients. One patient experienced a significant decrease in transfusion requirements that lasted for more than 5 years.[23,35]

2.1.2 | Gene editing

The degree of α/non-α-globin chain imbalance can also be ameliorated by the effective synthesis of γ-globin chains and fetal Hb (HbF) after birth. Genome-wide association studies examining common variations in HbF levels identified the multi-zinc finger containing transcriptional regulator, BCL11A, as a key regulator of the fetal-to-adult Hb switch and HbF silencing.[36,37] Genetic variation in the expression of *BCL11A* and persistence of HbF production was shown to reduce clinical severity in β-thalassemia.[38,39]

Gene editing, or in-situ manipulation of genes by specific nucleases, represents a novel strategy that has been developed to directly correct genetic mutations in the endogenous DNA of the cell or to disrupt specific DNA sequences in the genome. Genome editing approaches to inhibit *BCL11A* have been possible through the identification of several enzymes, including clustered regularly interspaced short palindromic repeats linked to Cas9 nucleases (CRISPR-Cas9), transcription activator-like effector nucleases (TALENS), and zinc finger nucleases (ZFN).[40–42] Clinical application involves mobilization and collection of a patient's autologous CD34+ HSPCs using granulocyte colony-stimulating factor (G-CSF) and plerixafor, and these are then edited ex-vivo using guide RNAs specific for the erythroid specific enhancer region of *BCL11A*. The product is then infused following myeloablative busulfan conditioning.

Note, CLIMB THAL-111 (NCT03655678) is a phase 1/2 trial evaluating the safety and efficacy of CTX001 (CRISPR-Cas9) in 45 patients

with TDT (12–35 years). Efficacy is being determined through transfusion reduction and independence ≥ 6 months. Changes in iron overload indices and iron chelation therapy as well as quality of life are also being investigated. Interim results from 10 TDT patients (four with β^0 or IVS1-110 mutations) who received CTX001 infusion are now available (mean follow-up 9.8 months, range: 4.3–23.8). Patients achieved engraftment of neutrophils and platelets at medians of 30 and 38.5 days, respectively; and all demonstrated increases in total Hb, HbF, and F-cell pancellularity over time (mean total Hb at baseline 10.6 g/dl including 0.2 g/dl HbF, mean total Hb at 21 months 13.3 g/dl including 12.5 g/dl HbF). Patients also stopped transfusions within 2 months after CTX001 infusion and were transfusion-free up to 23.8 months of follow-up. The safety profile was also generally consistent with busulfan myeloablation and autologous HSCT. One patient had four serious AEs considered related or possibly related to CTX001: headache, hemophagocytic lymphohistiocytosis (HLH), acute respiratory distress syndrome, and idiopathic pneumonia syndrome, all in the context of HLH and all of which have resolved.[43,44]

A CRISPR-Cas9 trial with CTX001 in patients with severe sickle cell disease is also ongoing (CLIMB SCD-121, NCT03745287).[43] A CRISPR-edited red cell therapy (CRISPR_SCD001) intended to directly correct the mutation in the β-globin will also be evaluated in a phase 1/2 clinical trial in patients with severe sickle cell disease (NCT03432364). Other approaches using CRISPR-Cas9 nucleases are also being evaluated, some that are looking at dual targets and a combined effect on the α/non-α-globin chain imbalance: α-globin downregulation by deleting the *HBA2* gene to recreate an α-thalassemia trait, alongside an increase in β-globin expression by targeted integration of a β-globin transgene downstream the *HBA2* promoter.[45]

So, THALES (NCT03432364) is a phase 1/2 clinical trial evaluating the safety and efficacy of the ST-400 (ZFN) in reducing transfusion requirement (frequency and volume) in six adults (18–40 years) with TDT. Preliminary results from two patients showed prompt hematopoietic reconstitution and increase of HbF levels, with one patient eligible for clinical assessment showing transfusion independence for 6 weeks followed by intermittent transfusions. The safety profile was generally consistent with busulfan myeloablation and autologous HSCT.[46]

2.2 | Fetal hemoglobin inducing agents

There has also been a considerable effort to stimulate γ-globin and HbF production through various pharmacological agents. In general, data in β-thalassemia were never as encouraging as in sickle cell disease. Several agents have been evaluated mostly off-label, as monotherapy or in combination, including DNA-methylation inhibitors, cytotoxic agents, short-chain fatty acids, erythropoietic-stimulating agents, and immunomodulatory imide drugs. The key challenge in interpreting overall results is that data on these compounds mostly stem from case series or small clinical trials and are often limited to patients from single centers or specific regions. For instance, hydroxyurea use has been associated with durable hematologic responses in both TDT and NTDT patients, but this was mostly observed in patients from India or Iran, especially those with homozygosity for the *Xmn*I polymorphism. Studies from Italy have conversely shown limited durability of response.[47] Thalidomide has also been associated with hematologic responses in both NTDT and TDT patients in observational studies and small trials from India or China.[48–55] Polymorphisms in *HBG2* and *HBS1L-MYB* contributed significantly to thalidomide response in these patients.[56] Larger clinical trials with thalidomide in TDT patients are ongoing in Pakistan (NCT03651102) and China. More novel and targeted agents are now also being evaluated for their ability to induce HbF in β-thalassemia patients.

Note, IMR-687 is a potent, specific, and highly selective small molecule inhibitor of phosphodiesterase (PDE) 9, which mediates cellular signaling pathways by degrading cyclic guanosine monophosphate (cGMP) to its inactive or monophosphate form. By inhibiting PDE9, IMR-687 increases intracellular cGMP levels and stimulates the production of HbF, as mostly evident in pre-clinical models of sickle cell disease.[57] A phase 2, randomized, double-blind, placebo-controlled study is currently underway to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of IMR-687 administered once daily for 36 weeks in two populations of 120 adult subjects with β-thalassemia (NCT04411082). The primary objective of this study is to assess the safety and tolerability of IMR-687 in adult subjects with TDT and NTDT. Secondary objectives in the TDT patients include reduction in transfusion burden, iron load rate, iron chelation dose requirements, and serum ferritin levels. Secondary objectives in NTDT patients include increase in Hb and HbF levels and in the absence of a transfusion. Of note, interim data from the phase 2 study of IMR-687 in patients with sickle cell disease showed a mean absolute change of +1.9 and +7.3 in HbF (%) and F-cells (%) at 4 months, respectively, with minimal changes in Hb.[58]

Benserazide is a peripheral decarboxylase inhibitor used in patients with Parkinson's disease.[59] It was recently shown to activate *HBG* gene transcription in a high throughput screen, and subsequent studies confirmed HbF induction in erythroid progenitors from hemoglobinopathy patients, transgenic mice, and anemic baboons.[60–62] A phase 1b sequential, open-label, dose-ranging study is currently evaluating the safety, pharmacokinetics, and preliminary activity of benserazide in 36 adult patients with NTDT and a baseline Hb of 6–10 g/dl.

Table 1 summarizes key completed or ongoing clinical trials of discussed agents aiming for correction of the α/non-α-globin chain imbalance.

3 | TARGETING INEFFECTIVE ERYTHROPOIESIS AND RED BLOOD CELL PATHOLOGY

3.1 | Erythroid maturation agents

Luspatercept (ACE-536) is a recombinant fusion protein comprising a modified extracellular domain of the human activin receptor type IIB

TABLE 1 Key completed or ongoing clinical trials of novel therapies in β-thalassemia aiming for correction of the α/non-α-globin chain imbalance

Agent	Clinical trials[a]	Design	*n*[b], population, age	Key efficacy measures
Gene insertion (curative intent)				
Betibeglogene autotemcel (LentiGlobin BB305)	● HGB-204 ● NCT01745120 ● Completed[c]	● Phase 1/2 ● Open-label	● *n* = 19 ● TDT ● 12–35 years	● HbAT87Q ≥2 g/dl[d] ● Transfusion independence[d] ● Transfusion requirement ● Hb
	● HGB-205 ● NCT02151526 ● Completed[c]	● Phase 1/2 ● Open-label	● *n* = 7 ● TDT or severe SCD with no HLA-matched donor ● 5–35 years	● Transfusion independence ● Hb, HbAT87Q ● Transfusion requirement
	● HGB-207, Northstar-2 ● NCT02906202 ● Active, not recruiting[c]	● Phase 3 ● Open-label	● *n* = 23 ● TDT with non-$\beta^0\beta^0$, no HLA-matched donor ● ≤50 years	● Transfusion independence[d] ● Transfusion requirement
	● HGB-212, Northstar-3 ● NCT03207009 ● Active, not recruiting[c]	● Phase 3 ● Open-label	● *n* = 18 ● TDT with $\beta^0\beta^0$, no HLA-matched donor ● ≤50 years	● Transfusion independence[d]/ reduction ● Transfusion requirement
	● LTF-303 ● NCT02633943 ● Enrollment by invitation[c]	● Prospective long-term follow up	● *n* = 94 ●TDT or SCD enrolled in phase 1–3 studies	● Transfusion requirement[d] ● HbAT87Q[d] ● LIC[d], MIC[d]
GLOBE	● TIGET- BTHAL ● NCT02453477 ● Active, not recruiting[c]	● Phase 1/2 ● Open-label	● *n* = 10 ● TDT ● 3–64 years	● Transfusion requirement[d] ● Transfusion independence ● Hb ● HR-QoL
TNS9.3.55	● NCT01639690 ● Active, not recruiting[c]	● Phase 1 ● Open-label	● *n* = 10 ● TDT with no HLA-matched donor ● ≥18 years	● Transfusion requirement
Gene editing (curative intent)				
CTX001 (CRISPR-Cas9)	● CLIMB THAL-111 ● NCT03655678 ● Recruiting[c]	● Phase 1/2 ● Open-label	● *n* = 45 ● TDT with no HLA-matched donor ● 12–35 years	● Transfusion reduction[d]/ independence ● Hb, HbF ● HR-QoL, PRO ● SF, LIC, MIC, ICT use
ST-400 (ZFN)	● THALES ● NCT03432364 ● Active, not recruiting[c]	● Phase 1/2 ● Open-label	● *n* = 6 ● TDT ● 18–40 years	● Transfusion requirement ● Hb, HbF
HbF inducing agents				
IMR-687	● NCT04411082 ● Recruiting	● Phase 2 ● Randomized, placebo-controlled, double-blind	● *n* = 120 ● TDT, NTDT ● 18–65 years	● TDT: Transfusion reduction (≥20%, ≥33%), SF, ICT use ● NTDT: Hb, HbF, HbF increase ≥3%
Benserazide	● BENeFiTS ● NCT04432623 ● Recruiting	● Phase 1b ● Open-label	● *n* = 36 ● NTDT with Hb 6–10 g/dl ● ≥18 years	● HbF, F-cells, Hb ● LDH, sTfR

Abbreviations: CRISPR-Cas9, clustered regularly interspaced short palindromic repeats linked to Cas9 nucleases; Hb, hemoglobin; HbF, fetal hemoglobin; HLA, human leukocyte antigen; HR-QoL, health-related quality of life; ICT, iron chelation therapy; LDH, lactate dehydrogenase; LIC, liver iron concentration; MIC, myocardial iron concentration; NTDT, non-transfusion-dependent β-thalassemia; PRO, patient-reported outcomes; SCD, sickle cell disease; SF, serum ferritin; sTfR, soluble transferrin receptor; TDT, transfusion-dependent β-thalassemia; ZFN, zinc finger nucleases.

[a]Status per clinicaltrials.gov on June 28, 2021.

[b]Actual or estimated, per clinicaltrials.gov on June 28, 2021.

[c]Available interim or final results summarized in the main manuscript text.

[d]Primary endpoint.

fused to the Fc domain of human IgG1. Together, the domains bind to select transforming growth factor (TGF) β superfamily ligands, block SMAD2/3 signaling, and enhance erythroid maturation.[63,64] The murine analog of luspatercept, RAP-536, was shown to enhance erythroid maturation by restoring nuclear levels of the transcription factor GATA-1 in erythroid precursors.[65] In β-thalassemia mouse models, treatment with RAP-536 reduced α-globin chain aggregation and hemolysis, while increasing erythrocyte life span and improving iron overload.[64] Additionally, RAP-536 increased red-blood cell parameters, as well reduced comorbidities associated with β-thalassemia, such as decreased bone mineral density and splenomegaly.[63] A multicenter, open-label, dose-ranging phase 2 study of luspatercept in adults with β-thalassemia (NCT01749540, with 5-year extension NCT02268409) confirmed its safety and effectiveness in reducing transfusion requirement in TDT and improving Hb level in NTDT, paving the way for subsequent randomized trials.[66]

The BELIEVE study (NCT02604433) was a randomized, double-blind, placebo-controlled trial that included 336 adult TDT patients (>18 years) with no transfusion-free period of > 35 days within the 24 weeks before randomization. Patients were randomized in a 2:1 ratio to receive luspatercept (1.0 mg/kg, titration up to 1.25 mg/kg) or placebo every 3 weeks for ≥ 48 weeks.[67] All patients also received best supportive care, including transfusion and iron-chelation therapy, according to local guidelines. A significantly greater percentage of patients receiving luspatercept achieved the primary endpoint of a ≥ 33% reduction in transfusion burden from baseline during weeks 13–24 compared with placebo (21.4% vs. 4.5%). Secondary endpoints of a ≥ 33% reduction in transfusion burden versus baseline from weeks 37–48 and over any 12-week or 24-week rolling periods also favored treatment with luspatercept over placebo. The percentage of patients achieving a ≥ 50% reduction in transfusion burden versus baseline was greater in the luspatercept than the placebo group, at all given time points. Response was observed across all evaluated patient subgroups stratified per age, gender, region, and baseline transfusion burden. Although response rates were lower in patients with most severe disease (β^0/β^0), clinically meaningful reductions in transfusion burden were observed across all genotypes.[67] Patients responding to luspatercept were more likely to achieve clinically meaningful improvements in health-related quality of life compared with placebo.[68] The AEs consisting of transient bone pain, arthralgia, dizziness, hypertension, and hyperuricemia were more common with luspatercept than with placebo. Higher rates of thrombosis were noted in the luspatercept-treated patients, although these thrombotic events occurred mainly in patients with known risk factors.[67] Based on these findings, luspatercept (REBLOZYL, Celgene Corporation) in now approved in the US (2019) and Europe (2020) for the treatment of anemia in adult patients with β-thalassemia who require regular RBC transfusions.

A 5-year open-label extension phase of the BELIEVE trial is under way to provide long-term data on the safety of luspatercept and its effects on transfusion burden and iron overload outcomes. Initial data show that patients on luspatercept continue to experience reductions in transfusion burden and events over 2 years of therapy.[69] A higher proportion of luspatercept-treated patients also shifted to lower serum ferritin, LIC, and myocardial iron levels during the first 48 weeks, with long-term luspatercept treatment leading to an increased proportion of patients with serum ferritin levels < 1000 ng/ml and decreasing trends of overall iron chelation use.[70] Luspatercept is now also being evaluated in pediatric TDT patients between the ages of 6 months and 18 years (NCT04143724).

So, BEYOND (NCT03342404) is a phase 2, double-blind, randomized (2:1), placebo-controlled, multicenter study evaluating the efficacy and safety of luspatercept in 145 adult patients with NTDT patients and a Hb level ≤ 10 g/dl. The trial met its primary endpoint with 74 (77.1%) of patients in the luspatercept arm versus zero placebo patients achieving a mean Hb increase of ≥ 1.0 g/dl from baseline over a continuous 12-week interval during weeks 13–24 in the absence of transfusions (52.1% of patients on luspatercept actually had ≥ 1.5 g/dl increase).[71] 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).[72,73] Improvement in NTDT-PRO T/W favored lupspatercept, and correlated with improvement in Hb level.[71]

It is worth noting that the development of luspatercept was preceded by another ligand-trap fusion protein containing the modified extracellular domain of activin receptor type IIA, sotatercept (ACE-011). Although sotatercept was evaluated in up to a phase 2 trial (NCT01571635) in β-thalassemia adults with positive findings, the sponsor made a decision not to advance trials of sotatercept in β-thalassemia and only proceed with the luspatercept clinical development program, considering the latter has a similar mode of action to sotatercept but does not bind to other members of the TGF-β superfamily, such as activin A.[74]

3.2 | Pyruvate kinase activators

The enzyme pyruvate kinase (PK) has recently become of interest in thalassemia. Preclinical studies on PK-deficient mice have indicated that the metabolic disturbance in PK deficiency alters not only the survival of RBCs but also the maturation of erythroid progenitors, resulting in ineffective erythropoiesis. Adenosine triphosphate (ATP) supply appears to be insufficient in thalassemic RBCs to maintain membrane fitness and clearance of globin precipitates.[75] Mitapivat (AG-348) is a first-in-class oral, small-molecule, allosteric activator of the RBC-specific form of PK (PK-R). Mitapivat has already shown efficacy and safety in clinical trials of patients with PK deficiency.[76,77] In mouse models of β-thalassemia, mitapivat increased ATP levels, reduced markers of ineffective erythropoiesis, and improved anemia, RBC survival, and indexes of iron overload.[78] An ongoing phase 2, open-label, multicenter study (NCT03692052) is evaluating mitapivat in 20 NTDT (including α-thalassemia) adults with a Hb level ≤ 10 g/dl, and assessing safety and efficacy in achieving Hb increase ≥ 1.0 g/dl and changes in markers of hemolysis and ineffective erythropoiesis. Interim data for β-thalassemia showed a Hb increase of ≥ 1.0 g/dl in 11 of 15 patients at 12 weeks with favorable changes in markers of

erythropoiesis and hemolysis. The most common non-serious AEs occurring in ≥ 25% of patients were initial insomnia, dizziness, and headache (5/20). There was one serious grade 3 unrelated AE of renal impairment which led to treatment discontinuation.[79] ENERGIZE-T (NCT04770779) is a phase 3, double-blind, randomized, placebo-controlled, multicenter study evaluating the efficacy and safety of mitapivat (100 mg orally, twice daily) in adult patients with TDT (α-thalassemia and β-thalassemia) due to start recruitment in 2021. The study plans to enroll 240 patients over 48 weeks with an open-label extension for 5 years. The primary endpoint is transfusion reduction response defined as ≥ 50% reduction in transfused RBC units with a reduction of ≥ 2 units of transfused RBCs in any consecutive 12-week period through week 48 compared with baseline. ENERGIZE (NCT04770753) is another phase 3 trial with a similar design to be conducted in adult patients with NTDT (α- and β-thalassemia). The study plans to enroll 171 patients over 24 weeks with an open-label extension for 5 years. The primary endpoint is Hb response defined as a ≥ 1.0 g/dl increase in average Hb concentration from week 12 through week 24 compared with baseline. Changes in Functional Assessment of Chronic Illness Therapy (FACIT) - Fatigue Subscale will also be assessed.[80]

3.3 | Janus kinase 2 inhibitors

Janus kinase 2 (JAK2) is another signaling molecule that regulates proliferation, differentiation, and survival of erythroid progenitors in response to erythropoietin. Studies in mouse models of β-thalassemia major and intermedia indicated that a short treatment with a JAK2 inhibitor can ameliorate ineffective erythropoiesis and decrease spleen size.[81,82] A single-arm, phase 2A study to evaluate the efficacy and safety of the JAK2 inhibitor ruxolitinib (INCB018424; INC424) administered orally at a starting dose of 10 mg twice daily among 30 adults with TDT and splenomegaly has been conducted (NCT02049450). Ruxolitinib was associated with a slight increase in pre-transfusion Hb levels (by 0.05 g/dl) and a trend towards reduced transfusion requirements (by 45 ml of hematocrit-adjusted RBC volume per 4 weeks) following 30 weeks of treatment. Mean spleen volume also decreased during ruxolitinib treatment. Treatment was tolerated with the most commonly reported AEs being upper respiratory tract infection, nausea, upper abdominal pain, anemia, diarrhea, and weight increase.[83] Thus, reduction in spleen size was the only clinical benefit seen with ruxolitinib treatment, which is primarily relevant to TDT patients with splenomegaly. However, since the major purpose of reducing spleen size in patients with TDT is to improve pretransfusion hemoglobin and reduce transfusion requirement, the limited effect of the drug on these parameters did not make an attractive candidate to advance for further phase 3 studies.[83]

3.4 | Glycine transporter 1 inhibitors

Glycine is a key initial substrate for heme and globin synthesis. Oral administration of bitopertin (RO-4917838), a potent and selective glycine transporter 1 (GLYT1) inhibitor, resulted in reduced anemia and hemolysis, enhanced in vivo survival of erythrocytes, and diminished ineffective erythropoiesis in β-thalassemia mice.[84] It was hypothesized that reduced heme synthesis down-regulates globin production and as such diminishes the α-chain excess, driving the observed improvements in Hb, hemolysis and RBC survival. A proof-of-mechanism phase 2 study of bitopertin in adults with NTDT (NCT03271541) was prematurely terminated. The first eight patients assessed at an eight-week preliminary efficacy analysis showed a mean total Hb reduction. Even when the dose was reduced to decrease excessive inhibition of heme biosynthesis and/or globin chain production, results remain unchanged. Thus, data from animal models did not necessarily translate to similar effects in humans and bitopertin treatment may have resulted in a greater reduction in all globin chain synthesis at any given dose.[85]

Table 2 summarizes key completed or ongoing clinical trials of discussed agents targeting ineffective erythropoiesis and red blood cell pathology.

4 | TARGETING IRON DYSREGULATION

4.1 | hepcidin mimetics

In β-thalassemia, ineffective erythropoiesis and hypoxia lead to decreased production of the hepatic hormone hepcidin which in turn results in increased intestinal iron absorption and its release from macrophages in the reticuloendothelial system, contributing to a state of iron overload with preferential hepatic iron storage. Erythroferrone, a hormone secreted by erythroblasts as a consequence of EPOR/JAK2/STAT5 pathway activation, has been identified as the main erythroid regulator of this process although other factors have also been proposed.[86,87] In β-thalassemia mouse models, moderate transgenic hepcidin expression decreased iron loading in the liver, and resulted in prolonged red cell life span, increased Hb levels and amelioration of splenomegaly suggesting a bidirectional relationship between ineffective erythropoiesis and iron overload.[88] Several pre-clinical studies have suggested that synthetic long-acting hepcidin analogues (often called minihepcidins) may be beneficial to restrict iron absorption and utilization in the setting of iron overload, with beneficial effects on ineffective erythropoiesis, anemia, and splenomegaly.[89–91] Thus, although initial interest in the hepcidin pathway was to ameliorate iron dysregulation, it prompted the initiation of several clinical trials targeting both hematologic improvement and iron overload in β-thalassemia.

However, clinical trial data were not as encouraging. LJPC-401, a synthetic human hepcidin given as a subcutaneous injection, was being evaluated in a phase 2, multicenter, randomized, open-label study (NCT03381833) in adult patients with TDT and a primary endpoint of improvement in myocardial iron overload detected by MRI. The trial was prematurely terminated, as an interim analysis showed absence of efficacy thus indicating an unfavorable risk–benefit profile.[92] The TRANSCEND study (NCT03802201) was another

TABLE 2 Key completed or ongoing clinical trials of novel therapies in β-thalassemia targeting ineffective erythropoiesis and red blood cell pathology

Agent	Clinical trials[a]	Design	*n*[b], population, age	Key efficacy measures
Erythroid maturation agents				
Luspatercept (ACE-536)	● NCT01749540 ● Completed[c]	● Phase 2 ● Open-label	● *n* = 64 ● TDT, NTDT with Hb <10 g/dl ● ≥18 years	● TDT: Transfusion reduction (≥20%)[d] ● NTDT: Hb increase ≥1.5 g/dl[d], Hb ● Biomarkers of erythropoiesis, hemolysis, iron metabolism, bone metabolism
	● NCT02268409 ● Completed	● Phase 2 extension	● n = 51 ● TDT, NTDT included in phase 2	● TDT: Transfusion reduction (any, ≥20%, ≥50%), Hb ● NTDT: Hb increase ≥1.5 g/dl, Hb ● Reticulocytes, EPO, nRBC, sTfR, SF, TIBC, TSAT, NTBI ● HR-QoL
	● BELIEVE ● NCT02604433 ● Active, not recruiting[c]	● Phase 3 ● Randomized, placebo-controlled, double-blind	● *n* = 336 ● TDT ● ≥18 years	● Transfusion reduction (≥33%[d], ≥50%) ● Transfusion requirement ● Transfusion independence ● SF, LIC, MIC, ICT use ● BMD ● HR-QoL, healthcare resource utilization
	● NCT04143724 ● Not yet recruiting	● Phase 2 ● Open-label	● *n* = 46 ● TDT ● 6 months-18 years	● Transfusion reduction ● Hb
	● BEYOND ● NCT03342404 ● Active, not recruiting[c]	● Phase 2 ● Randomized, placebo-controlled, double-blind	● *n* = 145 ● NTDT with Hb ≤10 g/dl ● ≥18 years	● Hb increase (any, ≥1 g/dl[d], ≥1.5 g/dl) ● Transfusion requirement ● PRO, HR-QoL, 6MWT ● SF, LIC, ICT use
Sotatercept (ACE-011)	● NCT01571635 ● Active, not recruiting[c]	● Phase 2 ● Open-label	● *n* = 46 ●TDT, NTDT ● ≥18 years	● Transfusion reduction (any, ≥20%) ● Hb
PK activators				
Mitapivat (AG-348)	● NCT03692052 ● Active, not recruiting[c]	● Phase 2 ● Open-label	● *n* = 20 ● NTDT (including α-thalassemia) with Hb ≤10 g/dl ● ≥18 years	● Hb increase ≥1 g/dl[d] ● Hb, Reticulocytes, bilirubin, LDH, haptoglobin, ● EPO, nRBC, sTfR
	● ENERGIZE-T ● NCT04770779 ● Not yet recruiting	● Phase 3 ● Randomized, placebo-controlled, double-blind	● *n* = 240 ● TDT (including α-thalassemia) ● ≥18 years	● Transfusion reduction (≥50%[d], ≥33%) / ● independence ● Transfusion requirement ● SF, TSAT, TIBC
	● ENERGIZE ● NCT04770753 ● Not yet recruiting	● Phase 3 ● Randomized, placebo-controlled, double-blind	● *n* = 171 ● NTDT (including α-thalassemia) with Hb ≤10 g/dl ● ≥18 years	● Hb increase ≥1 g/dl[d] ● PRO ● Hb, Hb increase ≥1.5 g/dl ● Reticulocytes, bilirubin, LDH, haptoglobin, EPO, ● SF, TSAT

(Continues)

TABLE 2 (Continued)

Agent	Clinical trials[a]	Design	*n*[b], population, age	Key efficacy measures
JAK2 inhibitors				
Ruxolitinib (INCB018424)	● NCT02049450 ● Completed[c]	● Phase 2 ● Open-label	● $n = 30$ ● TDT with spleen enlargement ● ≥18 years	● Transfusion requirement[d] ● Spleen volume, length Hb
GLYT1 inhibitors				
Bitopertin (RO-4917838)	● NCT03271541 ● Completed [prematurely terminated][c]	● Phase 2 ● Open-label	● $n = 12$ ● NTDT with Hb >7.5 to <9.5 g/dl ● 18–55 years	● Hb[d] ● Reticulocytes, LDH, bilirubin, RBC count

Abbreviations: BMD, bone mineral density; EPO, erythropoietin; GLYT1, Glycine Transporter 1; Hb, hemoglobin; HR-QoL, health-related quality of life; ICT, iron chelation therapy; JAK2, janus kinase 2; LDH, lactate dehydrogenase; LIC, liver iron concentration; MIC, myocardial iron concentration; nRBC, nucleated RBC; NTDT, non-transfusion-dependent β-thalassemia; NTBI, non-transferrin-bound iron; PK, pyruvate kinase; PRO, patient-reported outcomes; RBC, red blood cells; SF, serum ferritin; sTfR, soluble transferrin receptor; TDT, transfusion-dependent β-thalassemia; TIBC, total iron binding capacity; TSAT, transferrin saturation; 6MWT, 6-minute walk test.

[a]Status per clinicaltrials.gov on June 28, 2021.

[c]Available interim or final results summarized in the main manuscript text.

[b]Actual or estimated, per clinicaltrials.gov on June 28, 2021.

[d]Primary endpoint.

phase 2, open-label, single-arm, dose-escalation study evaluating another injectable hepcidin mimetic PTG-300, in adult patients with NTDT (to increase Hb level) and TDT (to decrease transfusion burden). No data have been publicly shared, and the further plans with the clinical development program remain unknown.

4.2 | Stimulators of hepcidin production

Hepcidin production can also be endogenously stimulated. One effective way to accomplish this is through the downregulation of a metalloprotease, transmembrane serine protease 6 (TMPRSS6), which plays a key role in hepcidin expression from the liver, and its inactivation leads to increased hepcidin levels, ameliorated iron overload, and improved ineffective erythropoiesis.[93,94] Anti-sense oligonucleotides (ASO) and small interfering RNA (siRNA) targeting TMPRSS6 have been effectively used to stimulate hepcidin, reduce iron burden, and improve ineffective erythropoiesis and RBC survival in mouse models of β-thalassemia intermedia.[95,96] Both approaches have now progressed to clinical trials in patients with β-thalassemia.

Note, TMPRSS6-LRx is a generation 2+ ligand-conjugated ASO targeting TMPRSS6. It is delivered as a subcutaneous drug (given every 4 weeks) and is now being evaluated in a randomized, open-label, phase 2 trial (NCT04059406) in 36 adults with NTDT and baseline Hb ≤ 10 g/dl for its effect on increasing Hb level by ≥ 1.0 g/dl and decreasing LIC. SLN124 is a GalNAc conjugated double-stranded fully modified siRNA targetting TMPRSS6 messenger RNA. It is now being evaluated in a phase 1, randomized, single-blind, placebo-controlled, single-ascending and multiple-dose study (NCT04718844) in 112 adults with NTDT (α- and β-thalassemia) and MDS to investigate safety and measure effects on hepcidin, iron parameters, and Hb. No interim data have yet been published from either study.

4.3 | Ferroportin inhibitors

The inappropriately low levels of hepcidin in β-thalassemia enable excessive iron absorption by ferroportin, the unique cellular iron exporter in mammals. Thus, VIT-2763 is a small molecular weight oral ferroportin inhibitor which competes with hepcidin for binding to ferroportin, displaces hepcidin bound to recombinant ferroportin, and reducing cellular iron efflux. In β-thalassemia intermedia mouse models, it restricted iron availability, ameliorated anemia, and reversed the dysregulated iron homeostasis.[97] It reduced the percentages of early erythroid precursors in the bone marrow and spleen, and increased the percentage of mature erythrocytes, providing evidence of improved ineffective erythropoiesis; while extending the lifespan of RBCs, thereby improving anemia and tissue oxygenation. Its effects were also shown to be independent and do not interfere with oral iron chelation therapy.[98] In a phase 1 study in 72 healthy adult volunteers, VIT-2763 administered at single oral doses up to 240 mg or multiple oral doses up to 120 mg twice daily was well tolerated compared with placebo. There were no serious or severe AEs or discontinuations due to AEs. Following VIT-2763, a rapid, temporary decrease in serum iron levels was observed.[99]

So, VITHAL (NCT04364269) is an ongoing randomized, double-blind, placebo-controlled, phase 2 trial evaluating the efficacy of VIT-2763 in improving Hb and iron indices in 36 NTDT patients aged ≥ 12 years with a baseline Hb ≤ 11 g/dl. No interim data have yet been published.

TABLE 3 Key completed or ongoing clinical trials of novel therapies in β-thalassemia targeting iron dysregulation

Agent	Clinical trials[a]	Design	*n*[b], population, age	Key efficacy measures
Hepcidin mimetics				
LJPC-401	● NCT03381833 ● Unknown [prematurely terminated][c]	● Phase 2 ● Randomized, open-label	● $n = 100$ ● TDT with high TSAT and MIC ● ≥18 years	● MIC[d] ● TSAT ● Hematology, Chemistry, Endocrine labs
PTG-300	● TRANSCEND ● NCT03802201 ● Completed	● Phase 2 ● Open-label	● $n = 63$ ● TDT, NTDT with Hb <10 g/dl ● 12–65 years	● NTDT: Hb[d] ●TDT: Transfusion reduction[d]
Stimulators of hepcidin production				
TMPRSS6-LRx (ASO)	● NCT04059406 ● Recruiting	● Phase 2 ● Randomized, open-label	● $n = 36$ ● NTDT with Hb 6–10 g/dl and LIC 3–20 mg/g ● 18–65 years	● Hb increase (≥1 g/dl[d], ≥1.5 g/dl) ● LIC decrease ≥1 mg/g
SLN124 (siRNA)	● NCT04718844 ● Recruiting	● Phase 1 ● Randomized, placebo-controlled, single-blind	● $n = 112$ ● NTDT (including α-thalassemia) or very low/low-risk MDS with Hb 5–11 g/dl and (SF >250 ng/ml or LIC >3 mg/g or TSAT >40%) ● ≥18 years	● TSAT, hepcidin ● Hb
Ferroportin inhibitors				
VIT-2763	● VITHAL ● NCT04364269 ● Recruiting	● Phase 2 ● Randomized, placebo-controlled, double-blind	● $n = 36$ ● NTDT with Hb ≤11 g/dl ● 12–65 years	● Hb[d] ● SF, serum transferrin, TSAT

Abbreviations: ASO, anti-sense oligonucleotides; Hb, hemoglobin; LIC, liver iron concentration; MDS, myelodysplastic syndromes; MIC, myocardial iron concentration; NTDT, non-transfusion-dependent β-thalassemia; SF, serum ferritin; siRNA, small interfering ribonucleic acid; TDT, transfusion-dependent β-thalassemia; TMPRSS, transmembrane serine protease; TSAT, transferrin saturation.

[a]Status per clinicaltrials.gov on June 28, 2021.

[b]Actual or estimated, per clinicaltrials.gov on June 28, 2021.

[c]Available interim or final results summarized in the main manuscript text.

[d]Primary endpoint.

Table 3 summarizes key completed or ongoing clinical trials of discussed agents targeting iron dysregulation.

5 | EXPERT COMMENTARY

The treatment landscape for β-thalassemia is swiftly evolving, so it remains of utmost importance to pause and reflect on successes and failures to inform gradual integration of such advances into routine clinical practice over the next decade. The promise for offering cure beyond bone marrow transplant in TDT seems to be on the horizon with encouraging data from gene insertion trials. Reports of malignant transformation have surely hampered excitement, but initial safety reviews have so far been reassuring and continued monitoring would mitigate any remaining concerns. Interim data from the phase 3 program of betibeglogene autotemcel indicate that therapy will likely be a viable option for all age groups and genotypes. That said, the key challenges to wide implementation are likely to be cost and the need for specialized centers and clinical expertise for application, especially in resource-limited countries. Although a recent economic evaluation using US data concluded that betibeglogene autotemcel is cost-effective for TDT patients compared to standard of care, the case may not be the same in non-Western countries where conventional therapy may be more affordable.[100] Cost-effectiveness analysis will also be particularly important for patients who only show transfusion reduction but do not achieve complete transfusion independence, even if they experience improvement in quality of life.[101] Thus, the expectation is that further information are still needed to be able to accurately predict, based on molecular and clinical parameters, ideal candidates for gene insertion that are most likely to achieve complete cure; and regional recommendations are starting to emerge.[102] Management of patients who achieve sustained transfusion independence will likely follow that of post-bone marrow transplant patients; for which ample experience is available.[1] Importantly, the long-term impact of persisting anemia in such now transfusion-independent patients should also be evaluated, considering the known morbidity associated with NTDT.

The same considerations are probably applicable to gene editing approaches. One additional challenge here is that the clinical benefit of pharmacological stimulation of HbF in β-thalassemia has not been as successful as it has been in sickle cell disease. High levels of circulating HbF could be associated with higher erythropoietin activity and

expansion of erythropoiesis,[103,104] but the exact mechanisms that explain such an association are not fully understood. Continued advances in understanding HbF expression in β-thalassemia could help further refine HbF stimulation approaches through gene editing and pharmacologic agents. Combined gene insertion and editing strategies are also emerging and would hopefully show synergistic effects that could better guarantee the desired hematologic response. For example, a new approach is currently being evaluated based on the inclusion of a short hairpin RNA targeting *BCL11A* into a β-globin expressing vector to allow concurrent synthesis of curative adult and fetal Hb.[105]

Despite the large array of pharmacologic agents in development, the goals of therapy remain the same: transfusion reduction in TDT and improvement of Hb level in NTDT. The first lesson learned from recent trials is that observations in animal models do not always translate to similar effects in humans, as exemplified by data from ruxolitinib and bitopertin. This further strengthens the importance of relying on data from multicenter, large clinical trials representative of the global patient population; and more importantly, the need for continued data generation through real-world evidence. Clinical trial endpoints should resonate with expected clinical benefits as perceived by patients and clinicians. For example, transfusion reduction achieved by luspatercept or potentially by mitapivat in future trials should be associated with improvements in quality of life, decreases in iron burden and related morbidity. But the reality is that such benefits are not easy to establish in the context of clinical trials. Improvement in quality of life is typically secondary to reduction in time lost to transfusion events, but this cannot be experienced during a clinical trial with a demanding visit schedule. Clinically meaningful reductions in iron overload and morbidity risk also require a long period of observation to be realized and should be evaluated in the context of concomitant iron chelation.[12] Almost all novel pharmacologic agents are being evaluated in adult patients who may already have considerable iron overload and manifested morbidities. The expectation is that patients would continue to require adequate iron chelation to rid the body of pre-existing iron overload, although with a potential of higher efficiency in view of decreased ongoing iron intake. This would ideally be followed by a gradual decline in dosing requirements with sustained reductions in transfusion burden. Available iron chelators have established efficacy and safety,[1] which may partly explain the absence of novel iron chelators in development, but there is still much to do to optimize access and adherence to iron chelation in many parts of the world. Extending such novel treatment advances to the pediatric population would also be of essential if the intention is to prevent iron accumulation and clinical complications early on.

In patients with NTDT, improvement in Hb level should also lead to short-term and long-term benefits in patient reported outcomes and morbidity risk, respectively. Luspatercept now has available clinical evidence for its ability to achieve hematologic responses in patients with NTDT, and long-term data on durability of such effects would be of merit. Mitapivat has also shown proof-of-concept and being evaluated in a randomized trial. Clinical data on TMPRSS6-LRx, SLN124, and VIT-2763 are awaited, especially following failure of hepcidin mimetics to achieve desired hematologic benefits through targeting hepcidin-related pathways. The challenge with NTDT would be to decide on the appropriate agent, if all come through, in the absence of head-to-head comparative studies. Combinations between such agents may also need to be evaluated post approvals.[106] Similar to patients with TDT, the impact of such therapies on iron overload prevention versus reduction, in the context of iron chelation therapy, will need to be carefully analyzed and interpreted as more trial data become available. At least data from animal models indicate that effects can be synergistic with the use of iron chelation therapy.[107–110]

Lastly, all novel developments need to go in parallel with programs that ensure access to patients in resource-limited countries, since the majority of β-thalassemia patients live in such regions.

CONFLICT OF INTEREST

K.M.M. has been or is a consultant for Novartis, Celgene Corp (Bristol Myers Squibb), Agios Pharmaceuticals, CRISPR Therapeutics and Vifor Pharma. R.B. reports no conflicts of interest. M.D.C. has been or is a consultant for Novartis, Celgene Corp (Bristol Myers Squibb), Vifor Pharma and Ionis Pharmaceuticals; and received research funding from Novartis, Celgene Corp (Bristol Myers Squibb), La Jolla Pharmaceutical Company, Roche, Protagonist Therapeutics and CRISPR Therapeutics. A.T.T. has been or is consultant for Novartis, Celgene Corp (Bristol Myers Squibb), Vifor Pharma, Silence Therapeutics and Ionis Pharmaceuticals; and received research funding from Novartis, Celgene Corp (Bristol Myers Squibb), La Jolla Pharmaceutical Company, Roche, Protagonist Therapeutics and Agios Pharmaceuticals.

AUTHOR CONTRIBUTIONS

All authors contributed to manuscript drafting or critical review and final approval for submission.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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