

Changing the treatment paradigm in beta thalassemia

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Abstract

Beta-thalassemia is a hereditary disease that affects the synthesis of β -globin, resulting in ineffective erythropoiesis, chronic anemia, and iron overload. Although the traditional treatment approach, which includes hypertransfusion and chelation therapy, has increased patient survival, it does not address the underlying disease mechanisms. Improving erythroid maturation, increasing fetal hemoglobin synthesis, lowering iron burden, and modifying the disease's genetic background are the goals that have resulted in the development of several therapeutic classes and treatment options. Erythroid maturation modifiers have been shown to significantly reduce transfusion requirements in patients with beta-thalassemia, and inducers of fetal hemoglobin and hepcidin agonists show promise in controlling ineffective erythropoiesis and secondary iron overload. Gene therapy using lentiviral vectors or CRISPR/Cas9 genome editing has the potential to provide a significant proportion of patients with long-term transfusion independence. These therapeutic advances could significantly improve the quality of life and long-term survival of patients with beta-thalassemia. However, long-term studies are still needed to establish their safety profiles, refine patient selection criteria, and ensure greater access to these innovative treatments.

Keywords

hemoglobin F synthesis inducers, hepcidine modifiers, genome editing, lentiviral gene therapy, luspatercept

Introduction

Need for change in treatment strategies for β -thalassemia

Beta-thalassemia is an autosomal recessive hemoglobinopathy caused by mutations in the β -globin gene, which impair the quantitative synthesis of β -chains in maturing erythroid precursors, resulting in their marked reduction or even complete absence. Because α -globin synthesis remains unaffected, the unbalanced α/β ratio leads to a relative excess of α -chains in erythroid cells. Acting as cytotoxic radicals, the unbound α -chains trigger premature apoptosis of erythroid precursors, driving ineffective

erythropoiesis and chronic hemolytic anemia. Over time, patients accumulate complications involving nearly all organs and systems, thus contributing to reduced patient survival. The clinical spectrum is heterogeneous, ranging from severe phenotypes with varying degrees of transfusion dependence to milder, transfusion-independent yet clinically meaningful forms. Even in the latter, complications similar to those in the severe phenotype gradually emerge and necessitate therapeutic intervention.

For decades, beta-thalassemia treatment remained largely unchanged, with the primary focus on reducing the disease's two main manifestations: ineffective erythropoiesis and secondary iron overload. The standard treatment approach, which included a hypertransfusion regimen and chelation therapy, enabled patients to reach adulthood

with a higher quality of life and the ability to participate in strenuous physical and social activities. However, as survival rates increased, many unmet needs emerged within the framework of this traditional treatment strategy. Despite excellent adherence, patients continue to develop a variety of complications, including endocrinopathies, liver fibrosis, cardiac complications, osteoporosis, and others.

Until recently, allogeneic stem cell transplantation was considered the only curative option, yet only a small proportion of patients have access to or are eligible for this therapy. Moreover, the procedure carries a mortality risk of approximately 5%, which further discourages many families from choosing it. Consequently, there is an increasing need to develop new therapeutic approaches capable of effectively targeting defective hematopoiesis. Such strategies should not only modify the underlying disease biology and reduce transfusion requirements but also prevent the progression of chronic complications and attenuate their adverse impact on quality of life and overall survival.

In recent years, advances in molecular biology have redirected attention toward new research avenues, from the molecular mechanisms of erythroid maturation and defective β -globin synthesis to the development of strategies aimed at correcting the underlying genetic abnormalities. These developments are reshaping the therapeutic landscape, offering increasingly realistic opportunities for a true paradigm shift in the management of the disease. In the pursuit of novel treatments for beta-thalassemia, a range of innovative approaches has emerged, extending far beyond traditional supportive therapies. Based on their primary mechanism of action, new therapies can be broadly categorized into the following groups (Fig. 1):

1. Erythropoiesis-stimulating agents (ESA)
 - 1.1. Luspatercept, sotatercept
 - 1.2. Mitapivat (indirect ESA agent, metabolic activator of pyruvate kinase enzyme)
2. Agents, influencing fetal hemoglobin synthesis
3. Therapies for iron overload
 - 3.1. Hepcidin modulation
 - 3.2. New chelators
4. Gene therapy
 - 4.1. Lentiviral gene addition
 - 4.2. CRISPR/Cas9 gene editing
5. New approaches to allogeneic hematopoietic stem cell transplantation (HSCT)

Erythropoiesis stimulation agents

Erythropoiesis stimulation agents represent a novel class of therapeutic agents acting on the differentiation and maturation pathways of erythroid precursors. Unlike erythropoietin, which primarily stimulates early stages of erythropoiesis, these agents target the later stages of red cell development. Their principal therapeutic effect is mediated through modulation of Smad signaling, a pathway that regulates late erythroid maturation.

Luspatercept (trade name: Reblozyl) is a recombinant fusion protein consisting of the Fc portion of IgG linked to a modified receptor for members of the transforming growth factor-beta (TGF- β) superfamily. It functions as a ligand "trap" for specific molecules (e.g., growth differentiation factor 11, activins) involved in the late stages of erythropoiesis. By inhibiting Smad2/3 signaling, luspatercept effec-

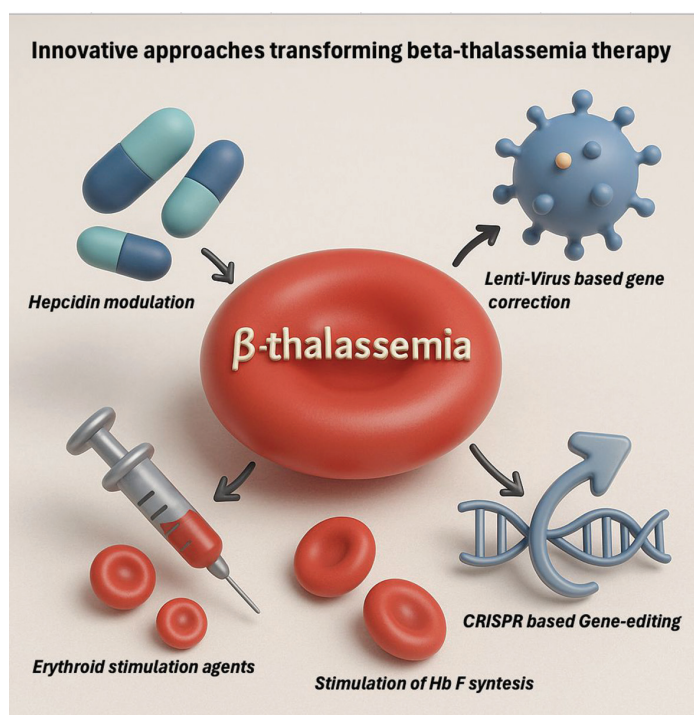


Figure 1. New classes of emerging therapies for beta-thalassemia.

tively “releases the brake” on terminal erythroid maturation and promotes the differentiation of erythroid precursors in the bone marrow, thereby reducing ineffective erythropoiesis.^[1-3] Clinically, this results in decreased transfusion requirements in β -thalassemia: in transfusion-dependent thalassemia (TDT) patients, transfusion burden is reduced, while in non-transfusion-dependent thalassemia (NTDT) patients, hemoglobin levels increase. Following positive preclinical findings, the drug was evaluated in clinical trials that led to its regulatory approval. The BELIEVE study, conducted in patients with transfusion-dependent β -thalassemia, demonstrated a $\geq 33\%$ reduction in transfusion requirements by week 24 of treatment.^[4] Moreover, long-term follow-up (over 3 years) confirmed sustained efficacy together with a favorable safety profile.^[5] Most adverse effects were mild to moderate, supporting the suitability of luspatercept as a long-term treatment option for patients with β -thalassemia.^[6] The drug has also been evaluated in NTDT β -thalassemia in the BEYOND trial, where it demonstrated a sustained increase in hemoglobin levels.^[7] Since November 2019, Reblozyl has been approved for the treatment of patients with TDT beta-thalassemia.^[8] In addition, in 2023 its indication was expanded to patients with NTDT. Importantly, luspatercept also addresses disease-related complications, particularly those associated with iron overload. Treated patients not only experience hemoglobin improvement but also a reduction in iron burden while maintaining a favorable safety profile.^[9,10] Beyond monotherapy, ongoing studies are assessing the safety and efficacy of combination regimens that include luspatercept and erythropoietin (EPO). Biologically, these agents may act synergistically: EPO stimulates earlier stages of erythropoiesis, whereas luspatercept enhances late-stage maturation, together yielding a more robust erythropoietic response.^[9,11] This combination therapy has shown promising results in preclinical models and early-phase clinical trials. Studies in cohorts of patients with myelodysplastic syndrome (MDS) demonstrate that the concurrent administration of luspatercept and EPO redirects erythropoiesis from the proliferation of early precursors toward enhanced late-stage maturation, resulting in more substantial hemoglobin improvements compared with EPO alone.^[12-14] These findings highlight the value of a combined therapeutic strategy aimed at optimizing erythropoiesis and improving the quality of life of patients with anemia.^[3,15] Extrapolating these data from MDS, the rationale for such a combination can be logically extended to the field of thalassemia. In a study using mouse models of β -thalassemia, luspatercept was shown to enhance the sensitivity of early erythroid precursors to endogenous EPO, suggesting that combining EPO with luspatercept may yield superior therapeutic outcomes.^[16] However, their concurrent use still requires validation in clinical settings. At present, a clear scientific gap persists in this area, as no dedicated clinical trial has systematically evaluated the impact of this combination therapy in β -thalassemia cohorts.

Sotatercept (ACE-011) is a ligand trap for activins and related ligands of the TGF- β superfamily, utilizing the extracellular domain of the activin receptor IIA fused to an IgG1 Fc fragment.^[17] Its mechanism of action suggests that by reducing inhibitory signaling in late erythropoiesis, it promotes the maturation of erythroid precursors.^[18] In a phase II study by Cappellini and colleagues, sotatercept was assessed for its efficacy in patients with β -thalassemia and related conditions. The results demonstrated significant hemoglobin increases and a reduction in transfusion requirements.^[17] Despite these encouraging phase II data, no large randomized phase III trials of sotatercept in β -thalassemia have been conducted to date.^[19] A 2023 review by Zehao et al. reports that a planned phase III study had been discontinued in favor of advancing the luspatercept development program.^[20] Potential off-target effects, including bleeding and hypertension, may also have contributed to redirecting resources away from sotatercept. Its future inclusion in treatment regimens would require robust phase III randomized studies with long-term safety data, as well as a clearer definition of target patient subgroups (e.g., specific genotypes, TDT vs. NTDT) and a formal risk-benefit assessment.

Mitapivat (AG-348) is the first therapeutic agent designed to target the underlying metabolic defect rather than erythropoiesis itself. It functions as an activator of pyruvate kinase (PK), specifically its erythrocyte isoforms (PKR/PYK-R).^[21] In contrast to pyruvate kinase deficiency, where mitapivat directly restores pyruvate kinase activity, in thalassemia the drug enhances erythroid energy metabolism without correcting an underlying enzymatic defect. Evidence confirms markedly reduced ATP levels and increased oxidative stress in β -thalassemia, contributing to shortened red blood cell survival. Mitapivat stabilizes the active conformation of PKR, thereby enhancing ATP synthesis in red blood cells. The expected therapeutic outcomes include reduced hemolysis and improved red blood cell survival.^[22-25] Preclinical data shows that mitapivat not only reduces transfusion dependence but is also well tolerated, supporting its potential for long-term use.^[21] In addition, evidence suggests complementary activity when mitapivat is used in combination with luspatercept, offering a potentially innovative therapeutic strategy for beta-thalassemia.^[26] Early-phase clinical trials (phase II) show that mitapivat improves hematological parameters.^[27] Several active clinical studies are currently underway, with preliminary but as yet unpublished data. The ENERGIZE-T trial (NCT04770779), a phase II study, reports a $\geq 30\%$ reduction in transfusion burden with sustained transfusion independence at 36 weeks and a rate of serious adverse events comparable to placebo. Another study, NCT04770753, evaluates mitapivat in NTDT patients. Initial data show a significant increase in hemoglobin level and reduced fatigue in NTDT (α -/ β -thalassemia), alongside an acceptable safety profile.^[28] The phase II open-label study NCT03692052 in NTDT enrolled 15 patients with β -thalassemia and demonstrated a substantial hemoglobin response rate.^[29]

Overall, phase III clinical trials are essential to fully assess the long-term safety, durability of response, and broader clinical utility of mitapivat.

Increasing fetal hemoglobin expression

Studies of small molecules capable of inducing fetal hemoglobin (HbF) production have yielded promising early results, offering the possibility of an accessible therapeutic strategy without the risks related to stem cell transplantation. The well-established effect of hydroxyurea on HbF levels is widely recognized, particularly in patients with NTDT, and in TDT there is evidence supporting a reduction in transfusion requirements.^[30-32] More recently, additional molecules with HbF-inducing potential have been identified. Most of these agents remain in the preclinical or early clinical trial phase in β -thalassemia.

Histone deacetylase inhibitors (e.g. trichostatin A and butyrate), induce HbF synthesis by activating the γ -globin gene through modulation of the p38 mitogen-activated protein kinase (MAPK) pathway.^[33] Resveratrol and its analogues have also demonstrated HbF-inducing potential, as shown in a study by Theodorou et al.^[34] Another emerging class of agents includes newly synthesized isoxazole derivatives.^[35] This represents a promising direction for the development of oral, affordable HbF inducers that could potentially replace hydroxyurea in the future.

Innovative approaches to enhancing traditional therapies for reducing iron overload

The treatment of beta-thalassemia also encompasses strategies aimed at managing complications arising from chronic transfusion therapy. Iron overload necessitates effective chelation approaches. Novel agents targeting the transferrin receptor (TFR2) are currently under evaluation for their capacity to reduce iron accumulation.^[36] In addition, ongoing research on Janus Kinase 2 (JAK2) inhibitors and hepcidin agonists offers promising avenues for correcting the dysregulated iron metabolism in beta-thalassemia.^[37] Chronic ineffective erythropoiesis leads to sustained activation of the JAK2/STAT signaling pathway, promoting excessive proliferation of erythroid precursors and contributing to massive extramedullary erythropoiesis and splenomegaly. This mechanism plays a role in multiple pathological processes, including accelerated atherosclerosis requiring interventional treatment.^[38,39]

This makes JAK2 a plausible therapeutic target that theoretically may decrease pathological hyperplasia, limit extramedullary erythropoiesis, and improve the efficiency of erythroid maturation.^[40] Studies of JAK2 inhibitors in β -thalassemia models have shown reductions in splenomegaly, decreased extramedullary erythropoiesis, and

partial restoration of erythroid cell morphology and function.^[41] Early phase IIa clinical data in humans demonstrate symptomatic improvement and spleen size reduction. However, the effect on anemia remains limited.^[42] The modest impact of JAK2 inhibition on anemia in thalassemia is explained by its primary action on inflammatory and proliferative signaling pathways, while the fundamental imbalance between globin synthesis and ineffective erythropoiesis remains uncorrected. To the present, JAK2 inhibitors have not received regulatory approval for use in patients with beta-thalassemia, and their application remains limited to scientific and early clinical research.

Hepcidin synthesis modifiers

Growing evidence highlights the role of hepcidin synthesis modifiers as potential therapeutic approaches for beta-thalassemia. Hepcidin is essential for maintaining iron homeostasis. One promising strategy involves targeting transmembrane serine protease 6 (TMPRSS6), a negative regulator of hepcidin expression. In mouse models of beta-thalassemia, TMPRSS6 inhibition resulted in a marked reduction in serum transferrin saturation and hepatic iron accumulation, accompanied by significant improvements in hemoglobin levels and erythropoiesis.^[43] Casu et al. demonstrated that treatment with minihepcidin (synthetic functional analogue of hepcidin) effectively alleviates anemia and iron accumulation in a mouse model of thalassemia intermedia. Furthermore, hepcidin expression and function can be influenced by external factors, including inflammation and erythropoietic activity.^[44] Studies have shown that down-regulation of hepcidin occurs in response to elevated erythropoietin levels, reflecting the attempt to maintain iron availability during increased red blood cell production.^[45] The development of small molecules that modulate hepcidin synthesis shows promise for controlling iron overload. SLN124 is a subcutaneously administered TMPRSS6 suppressor, leading to increasing hepcidin levels. In a phase I study among healthy volunteers, Porter et al. demonstrated a dose-dependent rise in hepcidin accompanied by a reduction in serum iron. Further clinical development includes evaluation in β -thalassemia and other iron overload conditions.^[46] Vamifeport (VIT-2763) is an oral ferroportin inhibitor with hepcidin-mimetic activity. By blocking ferroportin, it restricts iron export from enterocytes and macrophages, thereby reducing intestinal absorption of iron. In mouse models of beta-thalassemia, VIT-2763 improves anemia, reduces ineffective erythropoiesis, and diminishes iron overload.^[47] Phase I studies in healthy volunteers demonstrate good tolerability and predictable pharmacodynamic effects, and further clinical evaluation in NTDT beta-thalassemia is planned.^[48] Erythroferrone and growth differentiation factor 15 (GDF15) are additional modulators of hepcidin with therapeutic potential. Elevated GDF15 levels are associated with suppressed hepcidin expression, contributing to increased iron absorption.^[49] Moreover, monoclonal antibodies targeting matriptase-2 have been shown to

increase hepcidin levels, reduce iron overload, and improve erythropoiesis in preclinical models.^[50]

Development of new chelating molecules

Iron overload remains one of the most serious complications in patients with beta-thalassemia. Although three iron chelators (deferoxamine, deferasirox, and deferiprone) are currently approved, achieving optimal control of iron burden continues to be challenging due to limited efficacy in specific clinical contexts, adverse drug reactions, and issues with long-term adherence. These limitations accentuate the need for a new generation of chelators that are safer, more effective, and more convenient for patients. Intensive research over the past decade has led to the development of novel chelating agents such as SP-420 and FBS0701, which show promise for enhancing chelation efficacy through more selective iron binding and extended half-life. A phase I study of SP-420 demonstrated a favorable pharmacokinetic profile and effective iron-chelating potential; however, the trial was discontinued due to renal adverse events.^[51] Subsequently, a new phase I/II study (THAL-01) was launched in 2022 to evaluate SP-420 at lower and presumably safer doses, with rigorous monitoring of renal function. Thus, SP-420 remains a viable candidate for future clinical development, particularly for patients who are unable to tolerate currently available chelators.^[52] FBS0701 (trial number NCT01186419) has progressed further in clinical development than SP-420, with successful completion of phase I and short-term phase II studies. However, the program was discontinued due to insufficient chelation efficacy. Despite this limitation, the molecule demonstrates excellent oral bioavailability, a long plasma half-life, and an absence of se-

rious toxicity during short-term administration. For these reasons, efforts to structurally optimize FBS0701 to enhance its long-term chelation efficacy are ongoing.^[53]

Gene therapy for beta-thalassemia

Gene therapy represents one of the most significant advances in the treatment of beta-thalassemia over the past decade. It marks a shift from supportive care to potentially curative strategies by addressing the underlying genetic defect. Through the development of viral vectors, genome-editing technologies, and ex vivo modification of hematopoietic stem cells (HSCs), gene therapy aims to restore endogenous production of functional hemoglobin, thereby eliminating or substantially reducing the need for transfusions.

At present, two main gene therapy approaches predominate:

1. Gene supplementation using lentiviral vectors, and
2. Genome editing techniques such as CRISPR/Cas9

Gene supplementation via lentiviral vectors

This approach introduces a functional beta-globin gene (HBB) gene or a modified, functionally active beta globin gene into autologous CD34+ cells using a lentiviral vector. Following conditioning therapy, the modified cells are reinfused, enabling long-term production of therapeutic hemoglobin (Fig. 2). Among the most notable results are those reported by Thompson et al. (2018) with betibeglogene

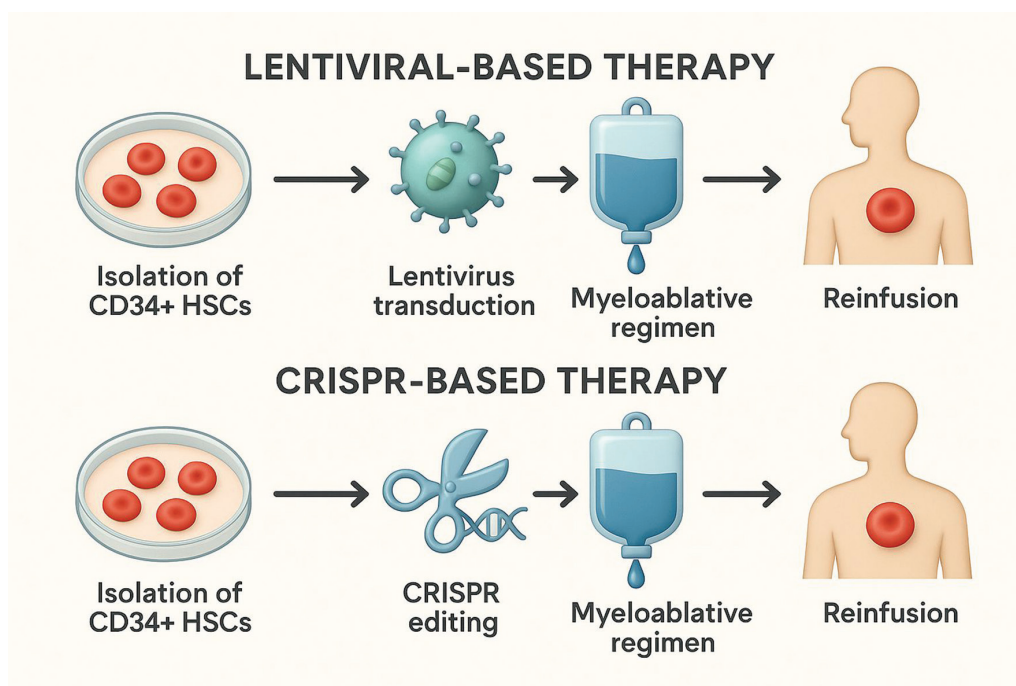


Figure 2. Schematical overview of gene-based therapies.

autotemcel (LentiGlobin BB305) in phase I/II and phase III studies. Betibeglogene autotemcel utilizes autologous CD34+ hematopoietic stem cells transduced with a lentiviral vector encoding a modified β -globin gene (β^A -T87Q). The first clinical evidence from phase I/II studies demonstrated highly encouraging outcomes, showing both sustained expression of therapeutic β -globin and a favorable safety profile. More than 90% of patients outside the β^0/β^0 group achieved transfusion independence, maintaining hemoglobin levels between 8 and 13 g/dL. In the most severe subgroup (β^0/β^0), approximately a 70% reduction in annual transfusion requirements was observed, with isolated cases of complete transfusion independence. Importantly, these responses have proven durable over several years, with no evidence of clonal evolution or oncogenicity.^[54] Locatelli et al. (2022) present phase III data on betibeglogene autotemcel, expanding the study population to children and patients with non- β^0/β^0 genotypes. A total of 91% of treated patients achieved sustained transfusion independence. The safety profile remained favorable, with adverse events primarily related to the myeloablative conditioning regimen and no reported cases of vector-related oncogenesis.^[55] This evidence supports the emergence of a new treatment paradigm in which correction of the underlying genetic defect offers an alternative to lifelong transfusions and iron chelation therapy.

Precision editing techniques

Precision editing techniques using CRISPR/Cas9 are gaining considerable attention as a potential therapeutic strategy for β -thalassemia. These genome-editing approaches aim to correct the underlying genetic defect at the DNA level. By precisely targeting the β -globin locus, the ultimate goal is to restore normal hemoglobin production. Exagamglogene autotemcel (exa-cel/CTX001, Casgevy) is an autologous gene therapy based on CRISPR/Cas9 editing, in which the erythroid enhancer of *BCL11A* is disrupted (“cut out”), thereby releasing the block on γ -globin synthesis. The resulting increase in fetal hemoglobin production improves the α /non- α globin balance, enhances erythropoiesis, and leads to higher total hemoglobin levels. In the CLIMB THAL-111 study (NCT03655678), treatment with exa-cel following myeloablative conditioning resulted in transfusion independence in approximately 91% of patients after a single treatment course.^[56] These outcomes formed the basis for the approval of Casgevy in January 2024 for the treatment of patients with TDT aged ≥ 12 years. Despite the impressive clinical results, access to this therapy remains limited due to its high cost. In the United Kingdom, the National Health Service and the National Institute for Health and Care Excellence have initiated a program to introduce Casgevy as a “life-changing gene therapy” for eligible patients with TDT.^[57] Following this breakthrough success, other nucleases, such as AsCas12a, are being explored for their ability to target alternative genomic sites, including direct editing of the hemoglobin gamma 1/gamma 2

(*HBG1/HBG2*) promoters, as well as combined editing of *BCL11A* and additional HbF regulatory elements. Several of these platforms are being evaluated simultaneously in TDT and sickle cell disease. One example is the ongoing phase III trial NCT05477563, assessing the safety and efficacy of autologous CRISPR–Cas9-modified CD34+ human hematopoietic stem and progenitor cells (hHSPCs) using the CTX001 platform. The study is being conducted at only five leading centers worldwide.

Despite the rapid progress of gene therapy, its availability remains limited due to the complexity of the procedure, the extremely high cost, and the requirement for myeloablative conditioning, which necessitates strict selection of suitable patients.

Allogeneic hematopoietic stem cell transplantation in TDT

Allogeneic HSCT remains a potential curative treatment option for beta-thalassemia, but its applicability is often constrained by the limited availability of compatible donors and by the risks inherent to the procedure. Traditionally, HSCT is performed using a myeloablative conditioning regimen that includes busulfan and cyclophosphamide.^[58] Although HSCT carries risks such as graft rejection and graft-versus-host disease, advances in conditioning protocols and immunosuppressive strategies have contributed to reducing these complications.^[59] Allogeneic transplantation from unrelated donors is increasingly considered for patients without a suitable related donor.^[60] Studies indicate that, with rigorous donor selection, such transplants can be successful, though survival rates remain lower than those achieved with related donors.^[61] Efforts to improve the success of allogeneic HSCT include the use of haploidentical donors, which expands donor availability and has been associated with improved outcomes in recent protocols.^[62,63]

Conclusion

Contemporary advances in the treatment of beta-thalassemia are transforming the traditional therapeutic approach, shifting it toward a fundamentally new model that directly targets ineffective erythropoiesis, iron dysregulation, and β -globin synthesis. The emergence of novel therapeutic classes focusing on erythroid maturation, modulation of HbF production, correction of iron overload, and genome editing has enabled more effective and often durable correction of hemoglobin deficiency, while simultaneously mitigating many complications associated with chronic transfusion therapy. Despite these major breakthroughs, the need remains for rigorous safety monitoring, optimization of treatment protocols, and clearer definition of the role of combination strategies in the management of patients with beta-thalassemia.

Ethical statement

- Clinical trials: Given that this manuscript is a review of the latest therapies in beta-thalassemia, all cited evidence is derived from data, already published in the literature.
- The authors declared that no experiments on humans or human tissues were performed for the present study.
- The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.
- The authors declared that no experiments on animals were performed for the present study.

Conflict of interest

The authors have declared that no competing interests exist.

Use of AI

The graphical elements of the figures were created using AI tools and Excel, and the author prepared the textual content and final formatting.

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Author contributions

KS did the literature search, data extraction and critical evaluation of the evidence; developed the concept, structured the manuscript, and wrote the full text of the manuscript.

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