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Review Article

Pulmonary Complications in Anemia and Thalassemia: Recent Advances in Therapeutic Management

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Abstract

Anemia and thalassemia represent significant global health challenges that affect the lungs, particularly in regions with limited healthcare resources. This review examines recent advances in the therapeutic management of these conditions, with an emphasis on novel approaches reshaping treatment paradigms. Traditional management strategies, including transfusion protocols and iron chelation, have significantly improved outcomes but remain associated with substantial limitations. Recent years have witnessed remarkable progress in curative approaches, notably gene therapy utilizing viral vectors and CRISPR-Cas9 technology. Additionally, novel pharmacological agents targeting ineffective erythropoiesis and iron homeostasis offer promising non-curative alternatives. This review synthesizes current evidence regarding these emerging therapeutic modalities and discusses their comparative effectiveness, special population considerations, and future directions. While significant challenges remain in terms of accessibility and long-term outcomes, these innovations represent the most substantial therapeutic advances in decades and hold the potential to fundamentally transform the management landscape for patients with anemia and thalassemia worldwide.

Keywords: *Pulmonary Complications; Thalassemia; Anemia; Hemoglobinopathies; Respiratory Medicine; Iron Overload; Gene Therapy; Lung Disease; Therapeutic Management; Pulmonary Hypertension*

Introduction

Anemia encompasses a diverse spectrum of hematological disorders characterized by impaired hemoglobin production or red blood cell function, leading to reduced oxygen delivery to tissues and subsequent clinical manifestations [1]. While thalassemia's represent the most common inherited anemias globally, affecting millions across the Mediterranean basin, the Middle East, and Southeast Asia [2], acquired anemias including chronic kidney disease-associated anemia and anemia of chronic disease affect substantially larger patient populations worldwide. Thalassemia's are characterized by imbalanced globin chain synthesis, resulting in ineffective erythropoiesis, chronic hemolysis, and progressive end-organ damage due to iron overload [3]. In contrast, other forms of anemia, such as those associated with chronic kidney disease or heart failure, present distinct pathophysiological mechanisms and therapeutic challenges.

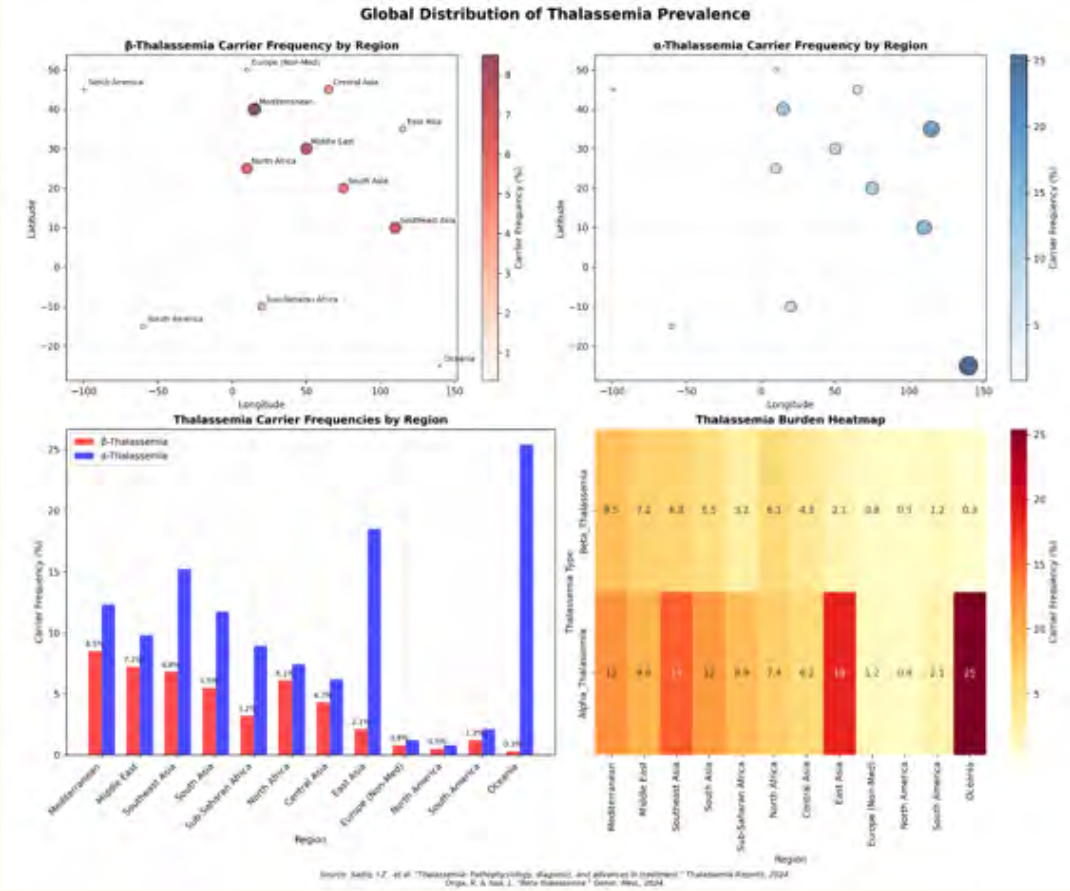

Figure 1

The clinical manifestations of thalassemia vary considerably depending on the specific genetic defect and the number of affected genes. β-thalassemia is caused by mutations in the β-globin gene, leading to reduced or absent β-globin chain synthesis, while α-thalassemia results from deletions or mutations in one or more of the four α-globin genes [13]. The severity spectrum ranges from asymptomatic carrier states to transfusion-dependent thalassemia major, which, if untreated, results in growth retardation, skeletal deformities, and early mortality [2].

Traditional management approaches, including regular blood transfusions and iron chelation therapy, have transformed thalassemia from a fatal pediatric disease to a manageable chronic condition [17]. However, these conventional strategies are associated with significant limitations, including transfusion-related complications, chelator-associated toxicities, and reduced quality of life due to burdensome treatment regimens [14]. Furthermore, access to these therapies remains limited in many high-prevalence regions, particularly affecting pediatric populations [7].

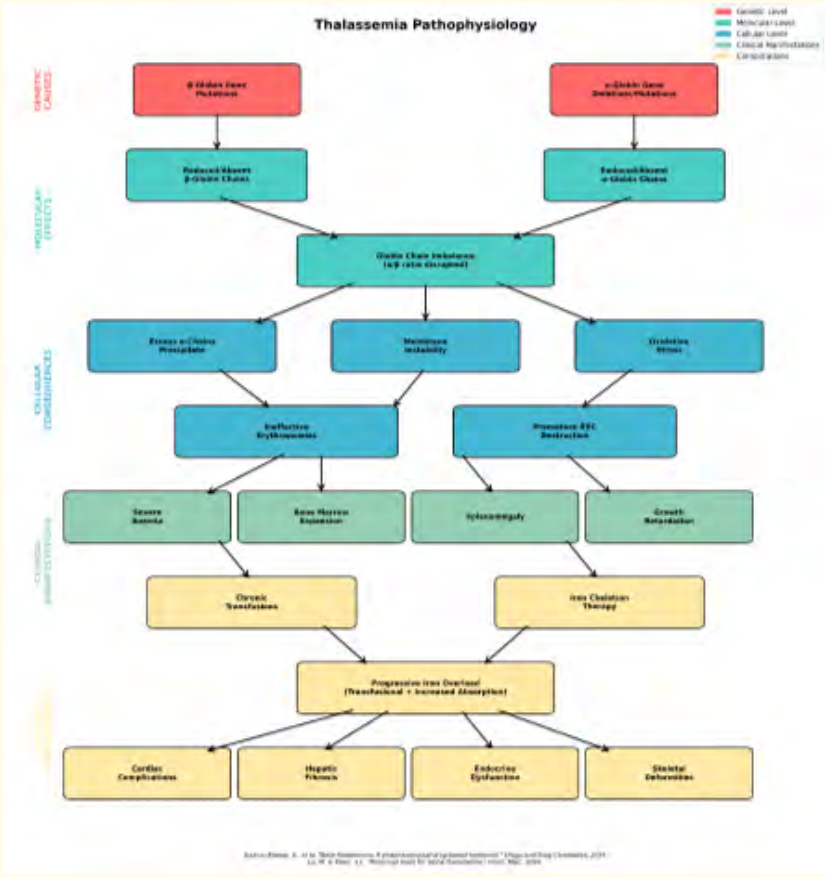

Figure 2

Recent years have witnessed unprecedented advances in therapeutic approaches for anemia and thalassemia. Gene therapy strategies using viral vectors or gene editing technologies have demonstrated curative potential [5,15], while novel pharmacological agents targeting ineffective erythropoiesis or iron metabolism offer promising non-curative alternatives [8,11]. This review synthesizes current evidence regarding these emerging therapeutic modalities and evaluates their potential to transform the management landscape for patients with anemia and thalassemia.

Traditional management approaches

Conventional management of transfusion-dependent thalassemia (TDT) has centered on two cornerstones: regular blood transfusions and iron chelation therapy [17]. Transfusion protocols aim to suppress ineffective erythropoiesis while providing adequate hemoglobin levels for normal growth and development. The decision to initiate lifelong transfusion therapy should be based on definitive diagnosis and clinical criteria such as failure to thrive or bone changes, rather than hemoglobin levels alone [20]. International guidelines recommend transfusions administered every two to five weeks to maintain pre-transfusion hemoglobin levels above 9 - 10.5 g/dL, promoting normal growth, allowing normal physical activities, and adequately suppressing bone marrow activity while minimizing transfusional iron accumulation [20]. This approach has significantly improved outcomes but carries inherent risks, including alloimmunization, transfusion reactions, and transfusion-transmitted infections [3].

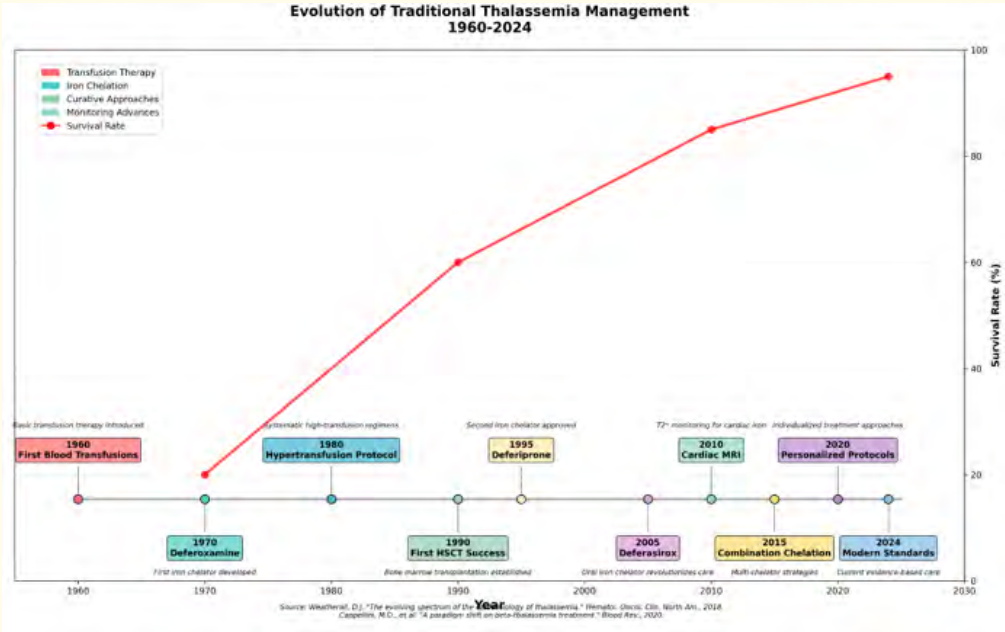

Figure 3

Iron overload represents an inevitable consequence of chronic transfusion therapy, as the human body lacks a mechanism to excrete excess iron [20]. Each unit of blood contains approximately 200-250 mg of iron, and patients receiving regular transfusions accumulate 0.3 - 0.5 mg/kg/day of iron from transfusions alone, compounded by increased intestinal iron absorption due to hepcidin suppression [8]. Without effective chelation, progressive iron accumulation leads to cardiomyopathy, endocrinopathies, hepatic fibrosis, growth retardation, and multiple endocrine abnormalities, with myocardial iron overload potentially inducing heart failure from cardiomyopathy as early as the second decade of life [17,20]. Three iron chelators are currently available: deferoxamine, deferiprone, and deferasirox. Each demonstrates distinct pharmacokinetic properties, organ-specific efficacy, and adverse effect profiles [14]. Real-world evidence highlights significant challenges with chelation therapy, including suboptimal adherence, inconsistent monitoring practices, and variable access across different healthcare settings [14].

Hematopoietic stem cell transplantation (HSCT) has represented the only established curative option for thalassemia for decades [4]. Advances in conditioning regimens have significantly improved outcomes, with overall and thalassemia-free survival exceeding 90% with optimized protocols [4]. Traditional myeloablative conditioning using busulfan-cyclophosphamide has gradually evolved to incorporate agents like fludarabine, treosulfan, and thiotepa, with protocols tailored according to patient characteristics, including age, Pesaro risk classification, and donor type [9]. Modern HSCT approaches have made significant strides in minimizing transplant-related mortality while maintaining engraftment and disease-free survival [9].

Despite these advances, traditional management approaches remain associated with significant limitations. Transfusion and chelation therapies represent lifelong commitments with substantial impacts on quality of life [14]. HSCT availability is constrained by donor limitations, with only 20 - 25% of patients having suitable sibling donors [9]. Furthermore, access to these therapies remains highly inequitable globally, with many patients in high-prevalence, resource-limited regions unable to access even basic transfusion support [7].

Gene therapy advances

Gene therapy has emerged as a transformative approach for hemoglobinopathies, with recent advances demonstrating unprecedented potential for long-term cure without the need for a compatible donor [5]. Current genetic strategies fall into three major categories: β-globin gene addition to restore function, genetic correction of causal mutations, and fetal hemoglobin (HbF) upregulation [5].

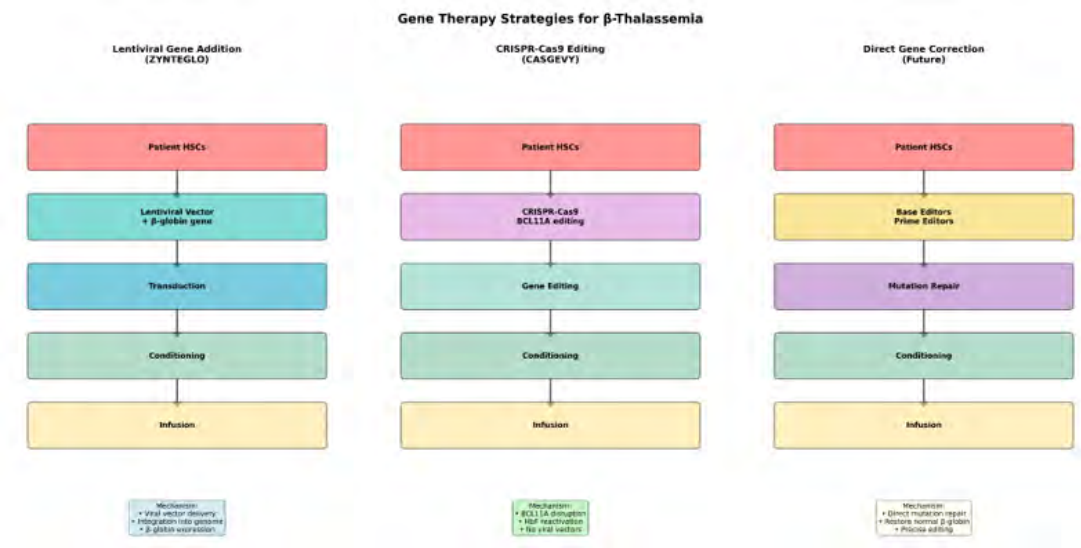

Figure 4

Lentiviral vector-mediated gene addition has yielded remarkable clinical success, culminating in regulatory approvals of the first gene therapies for β-thalassemia. Betibeglogene autotemcel (beti-cel, ZYNTEGLO) utilizes a self-inactivating lentiviral vector containing the β-globin gene with a T87Q mutation and regulatory elements from the β-globin locus control region [10]. Phase 3 clinical trials demonstrated that 89% of treated transfusion-dependent β-thalassemia patients achieved transfusion independence with near-normal hemoglobin levels [10]. This groundbreaking therapy received FDA approval in 2022, marking a milestone in thalassemia treatment [16].

CRISPR-Cas9 gene editing has emerged as another revolutionary approach, offering potential advantages over viral vector-based methods [15]. Current CRISPR strategies primarily focus on reactivating fetal hemoglobin production by disrupting regulatory elements like BCL11A [8]. Exagamglogene autotemcel (exa-cel, CASGEVY), which employs this approach, has demonstrated robust clinical efficacy with 95% of treated patients achieving transfusion independence in clinical trials [15]. This therapy received FDA approval in late 2023, representing the first CRISPR-based therapy to reach clinical practice [5].

While these advances represent remarkable achievements, significant challenges remain. Current gene therapy approaches require sophisticated infrastructure for *ex vivo* cell manipulation, myeloablative conditioning, and specialized care during engraftment [16]. The prohibitive cost of these therapies (exceeding $2.8 million per treatment) represents a substantial barrier to global access [16]. Ongoing research aims to address these limitations through the development of *in vivo* gene editing approaches that could potentially simplify manufacturing and treatment processes while minimizing risks associated with *ex vivo* procedures [5].

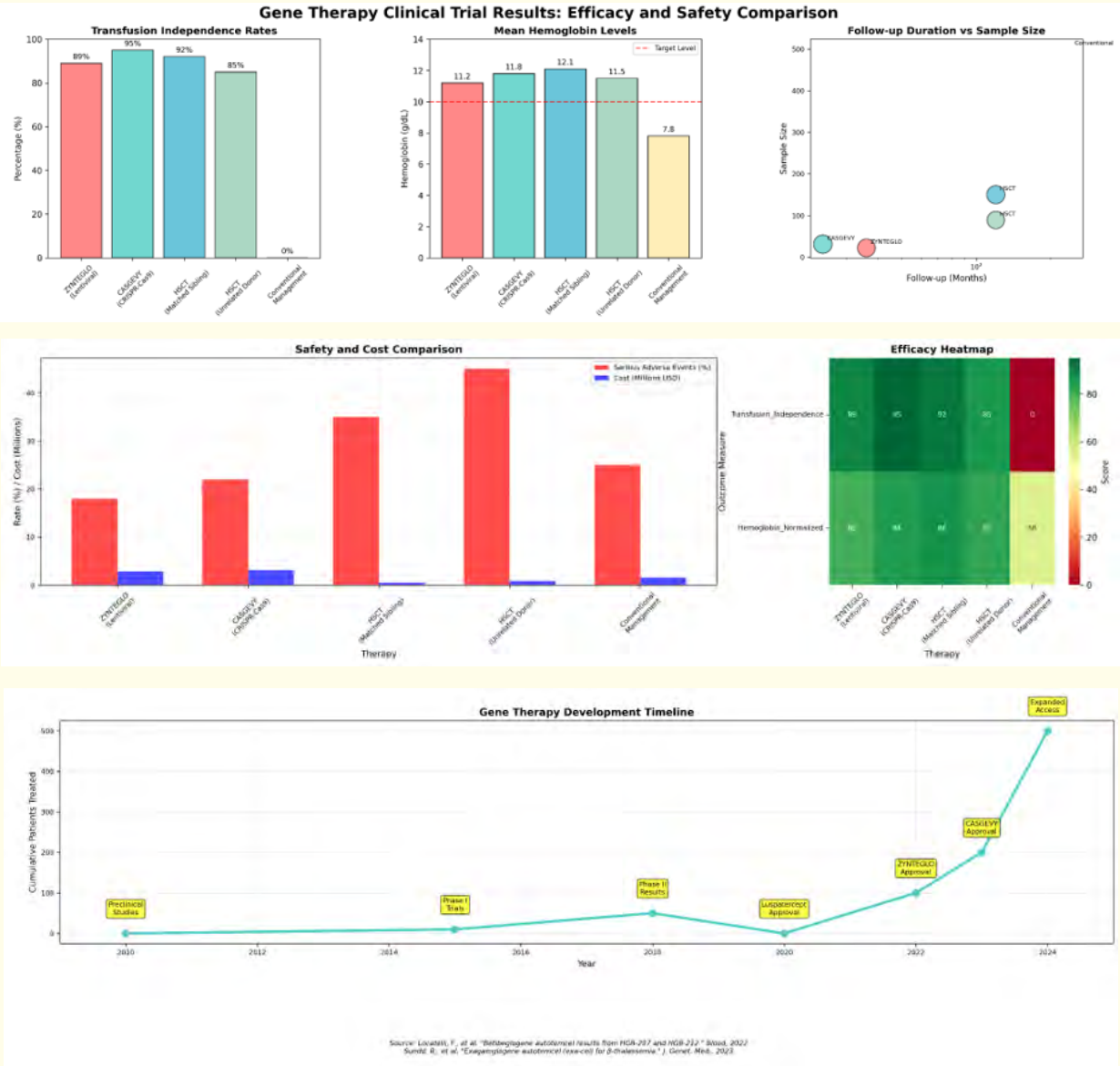

Figure 5

Novel pharmacological agents

Recent years have witnessed significant advances in non-curative pharmacological approaches for anemia and thalassemia, with novel agents targeting specific pathophysiological mechanisms. Transforming growth factor β (TGF-β) superfamily inhibitors have emerged as particularly promising therapeutic modalities [11,18].

Luspatercept, a recombinant fusion protein that acts as a ligand trap for TGF-β superfamily members, enhances late-stage erythropoiesis by binding to select endogenous TGF-β superfamily ligands, thereby reducing SMAD2/3 signaling [18]. The phase 3 BELIEVE trial evaluated

luspatercept in adults with transfusion-dependent β-thalassemia, demonstrating that 21.4% of luspatercept-treated patients achieved a ≥33% reduction in transfusion burden during weeks 13-24 compared to only 4.5% in the placebo group ($p<0.001$) [18]. Notably, 70.5% of treated patients achieved this reduction threshold during any 12-week interval, indicating substantial clinical benefit [18]. The drug received FDA approval in 2020 for transfusion-dependent β-thalassemia.

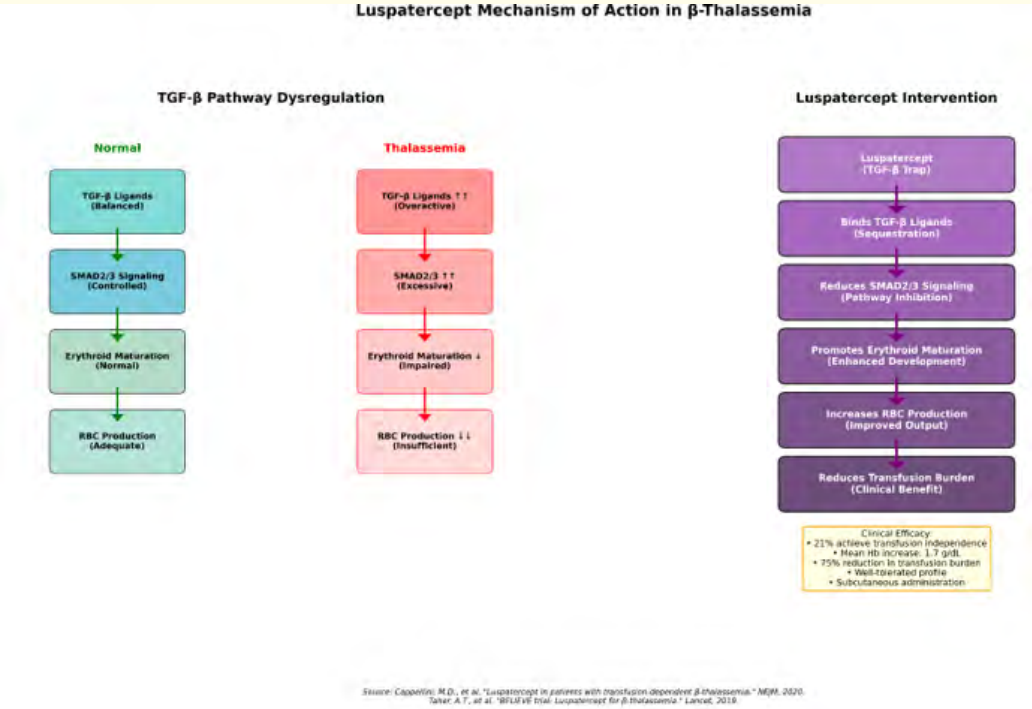

Figure 6

Similarly, promising results were observed in non-transfusion-dependent thalassemia patients in the phase 2 BEYOND trial, where luspatercept treatment resulted in hemoglobin increases of ≥1.0 g/dL in 77.1% of patients versus 0% with placebo [12]. The hemoglobin response was durable, with 70.8% of luspatercept-treated patients maintaining a ≥1.0 g/dL increase during any 12 consecutive weeks from weeks 13-48 [12]. These findings suggest that luspatercept offers significant benefits across the thalassemia severity spectrum.

Another promising pharmacological approach involves modulation of the hepcidin-ferroportin axis to address iron overload and ineffective erythropoiesis [8]. Hepcidin, the principal regulator of systemic iron homeostasis, is pathologically suppressed in thalassemia due to expanded erythropoiesis and increased erythroferrone production [8]. Preclinical studies have demonstrated that hepcidin modulation through various approaches-including synthetic hepcidin mimetics, TMPRSS6 inhibitors, and ferroportin inhibitors-can reduce iron overload while unexpectedly improving anemia by decreasing the formation of toxic α-globin aggregates and extending red cell lifespan [11]. Clinical development of these agents is ongoing, with two phase 2 trials evaluating TMPRSS6 inhibitors in non-transfusion-dependent thalassemia patients [8].

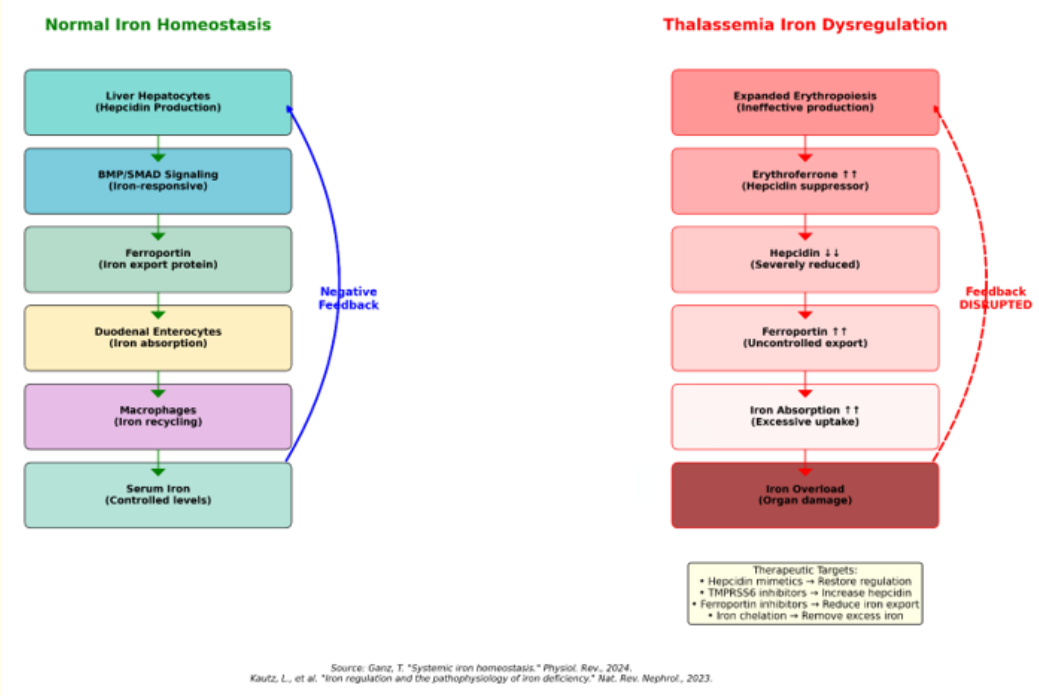

Figure 7

Pyruvate kinase activators represent another innovative therapeutic class with potential applications in thalassemia [19]. These agents, including mitapivat and etavopivat, enhance glycolytic pathway function in red blood cells, improving ATP production and cellular energetics [19]. Preliminary clinical data indicate that these agents can enhance α/β-globin chain balance, reduce ineffective erythropoiesis, and improve hemoglobin levels in both transfusion-dependent and non-transfusion-dependent thalassemia patients [19]. Phase 3 trials are currently evaluating these agents in various thalassemia populations.

Beyond thalassemia-specific therapeutic approaches, significant advances have emerged in treating other forms of anemia. Hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) represent a paradigm shift in managing chronic kidney disease-associated anemia, offering an alternative to traditional erythropoiesis-stimulating agents [21]. These oral agents work by stabilizing hypoxia-inducible factors, leading to increased endogenous erythropoietin production and improved iron utilization [21]. While distinct from thalassemia pathophysiology, HIF-PHI development has provided insights into erythropoietic regulation that may inform future thalassemia therapies.

Intravenous iron formulations have revolutionized the treatment of iron deficiency anemia across multiple clinical contexts. Recent randomized controlled trials demonstrate that intravenous ferric carboxymaltose significantly outperforms oral iron supplementation, achieving median hemoglobin increases of 3.65 g/dL versus 1.10 g/dL over three months, with superior iron store normalization rates (84.6% vs. 21%) [23]. These formulations minimize gastrointestinal intolerance associated with oral preparations while providing rapid iron repletion, particularly valuable in patients with inflammatory conditions or malabsorption. The clinical success of novel IV iron preparations demonstrates therapeutic advances that complement existing approaches for managing iron-related anemias.

The understanding of hepcidin regulation in inflammatory anemia has advanced substantially, revealing new therapeutic targets for anemia of chronic disease. Inflammation-induced hepcidin excess restricts iron availability through ferroportin degradation, creating

functional iron deficiency despite adequate iron stores [26]. This mechanism affects approximately 30% of chronic disease anemias through IL-6/SMAD signaling pathways [26]. Emerging therapeutics targeting hepcidin, including mini-hepcidin agonists for iron overload conditions and hepcidin antagonists for inflammatory anemia, show promising early clinical results with hemoglobin improvements in rheumatoid arthritis patients [26]. These advances in understanding iron-hepcidin interactions offer potential synergies with existing HIF-PHI approaches for managing multifactorial anemias.

Innovations in supportive care

Advances in supportive care have paralleled therapeutic innovations, contributing significantly to improved outcomes in thalassemia management. Modern transfusion medicine has evolved substantially, with extended phenotype matching and leukoreduction becoming standard practices to minimize alloimmunization risk [17]. Novel approaches to iron assessment, including liver and cardiac MRI, have enabled more precise monitoring of organ-specific iron burden and tailoring of chelation regimens [17].

Iron chelation strategies have been refined through improved understanding of the differential efficacy of available agents for specific organs. Combination therapy utilizing multiple chelators with complementary properties has demonstrated superior efficacy in patients with severe iron overload [14]. Real-world evidence has highlighted the importance of personalized approaches to chelation, considering factors such as iron burden distribution, age, comorbidities, and quality of life impacts [14].

Management of thalassemia-associated comorbidities has also advanced significantly. Endocrine complications, including growth failure, hypogonadism, and diabetes mellitus, require systematic monitoring and prompt intervention [17]. Cardiovascular complications, particularly iron-induced cardiomyopathy, remain the primary cause of mortality in inadequately treated patients, underscoring the importance of cardiac MRI monitoring and aggressive chelation in patients with cardiac iron loading [17].

Quality of life considerations have gained increasing recognition as essential components of comprehensive thalassemia care. Psychosocial support, transition programs from pediatric to adult care, and attention to educational and vocational needs are now considered integral aspects of optimal management [7]. These supportive care innovations, while less dramatic than gene therapy or novel pharmacological approaches, remain crucial for maximizing outcomes with both traditional and emerging therapeutic modalities.

Special population considerations

Management approaches for thalassemia require modification for special populations, including pediatric patients, pregnant women, and individuals with distinct genetic backgrounds. Pediatric thalassemia management has evolved to emphasize early intervention while minimizing treatment-related toxicities [7]. Current pediatric guidelines recommend initiating transfusions based on clinical indicators such as failure to thrive or bone changes rather than solely on hemoglobin thresholds [7,20]. Challenges in pediatric iron overload management include determining optimal timing for initiating chelation and MRI monitoring, with deferasirox remaining the most widely used chelator in children due to its oral administration route [7].

Pregnancy in thalassemia patients presents unique challenges, with outcomes varying by disease severity [6]. A systematic review and meta-analysis examining pregnancy outcomes revealed that women with β-thalassemia intermedia face higher thrombosis risk (3.7%) compared to those with β-thalassemia major (0.92%), while heart failure risks appear similar between groups [6]. Transfusion requirements increase substantially during pregnancy in β-thalassemia major (from 102 to 139 ml/kg/year), and 70% of β-thalassemia intermedia pregnancies require blood transfusions [6]. Serum ferritin increases significantly during pregnancy, highlighting the importance of close monitoring and prompt postpartum resumption of chelation therapy [6].

Regional and ethnic differences in treatment response represent another important consideration. The global distribution of thalassemia encompasses diverse populations with distinct genetic backgrounds, potentially influencing treatment outcomes [2]. While

gene therapy approaches have demonstrated efficacy across different ethnic groups, pharmacological responses may vary based on underlying genetic modifiers [16]. These differential responses underscore the importance of inclusive clinical trial populations and personalized therapeutic approaches.

Anemia management becomes particularly complex in patients with comorbid conditions, requiring integrated therapeutic approaches. In patients with chronic kidney disease, anemia significantly impacts cardiovascular outcomes and quality of life, necessitating coordinated management strategies that consider both renal function and erythropoietic needs [21]. Similarly, anemia in heart failure patients has been associated with increased mortality and adverse cardiovascular events, highlighting the critical importance of anemia correction in this population [22].

Erythropoiesis-stimulating agents have evolved significantly, with newer alternatives demonstrating superior efficacy compared to traditional formulations. Recent phase 3 clinical trials comparing luspatercept with epoetin alfa in erythropoiesis-stimulating agent-naive patients revealed substantial improvements in transfusion independence rates (58.5% vs. 31.2%) with comparable safety profiles [24]. These findings represent a paradigm shift in ESA therapy, particularly for patients with myelodysplastic syndromes and other conditions associated with ESA resistance, offering enhanced therapeutic options without increased cardiovascular risks historically associated with high-dose traditional ESAs.

Cancer-associated anemia presents unique therapeutic challenges requiring specialized management approaches. Systematic reviews and meta-analyses of randomized controlled trials demonstrate that intravenous iron supplementation significantly reduces red blood cell transfusion requirements in chemotherapy-induced anemia (risk ratio 0.72; number needed to treat 20) while improving hematopoietic response rates without increased adverse events [25]. These approaches offer quality-of-life benefits through reduced fatigue and enhanced management strategies in oncology settings, complementing existing erythropoiesis-stimulating agent protocols. The integration of IV iron therapy in cancer care exemplifies evidence-based advances in managing complex anemia presentations.

These comorbid anemia presentations share pathophysiological similarities with thalassemia, including iron dysregulation and inflammatory processes, suggesting potential for therapeutic cross-learning between these distinct patient populations.

Comparative effectiveness of treatment strategies

As the therapeutic landscape for thalassemia expands, comparative assessment of different approaches becomes increasingly important for clinical decision-making. Gene therapy and HSCT represent potentially curative interventions with distinct risk-benefit profiles [9,16]. Traditional HSCT offers proven long-term efficacy with lower upfront costs but requires a compatible donor and carries risks of graft-versus-host disease (GVHD) and transplant-related mortality [9]. Gene therapy eliminates donor requirements and GVHD risk but involves substantial costs and limited long-term follow-up data [16].

Comparative effectiveness considerations differ substantially between high-resource and resource-limited settings. In regions with sophisticated healthcare infrastructure, gene therapy may eventually replace HSCT as the preferred curative approach for patients lacking matched sibling donors [16]. In contrast, resource-limited settings face significant barriers to implementing these advanced therapies, emphasizing the continued importance of optimizing conventional management and developing cost-effective alternatives [7].

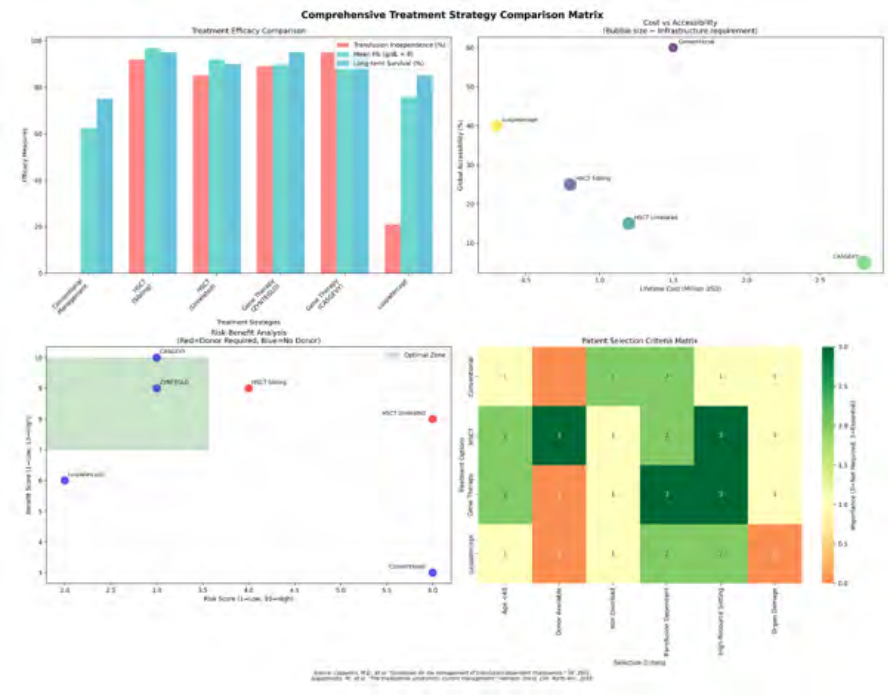

Figure 8

Novel pharmacological agents offer important non-curative options that may delay or prevent complications while potentially reducing transfusion requirements [18,19]. These approaches may be particularly valuable for patients ineligible for or without access to curative interventions [19]. The comparative effectiveness of these agents relative to each other and traditional management approaches remains an active area of investigation, with ongoing trials directly comparing different therapeutic strategies.

Cost-effectiveness represents a critical consideration in comparative assessment. The high costs of gene therapy (approximately $2.8 million per treatment) must be weighed against lifetime costs of conventional management (estimated at $1-3 million in high-resource settings) [16]. However, these economic analyses are highly context-dependent, with substantially different considerations in resource-limited settings where even basic transfusion and chelation support may be inconsistently available [7].

Future directions and emerging technologies

The therapeutic landscape for anemia and thalassemia continues to evolve rapidly, with several promising approaches on the horizon. *In vivo* gene editing represents a particularly exciting frontier, potentially eliminating the need for *ex vivo* cell manipulation and myeloablative conditioning [5]. Preclinical research is exploring various delivery systems for *in vivo* CRISPR-Cas9 administration, including lipid nanoparticles and adeno-associated viral vectors [15]. If successful, these approaches could substantially reduce the complexity and cost of gene therapy, potentially democratizing access to curative treatments.

Next-generation pharmacological agents targeting novel pathways involved in erythropoiesis and iron metabolism are in various stages of development [8,19]. These include refined hepcidin mimetics with improved pharmacokinetic properties, novel erythroferrone inhibitors addressing the upstream mediator of hepcidin suppression, and enhanced pyruvate kinase activators with greater specificity for

erythroid tissues [8,19]. Combination approaches utilizing these agents with complementary mechanisms of action may offer synergistic benefits.

Significant research gaps persist across the therapeutic spectrum. Long-term outcomes of gene therapy, including durability of effect and late complications, remain incompletely characterized given the recent implementation of these approaches [16]. The optimal timing of intervention, particularly whether early treatment before organ damage occurs, would improve outcomes and requires further investigation for both gene therapy and novel pharmacological agents [7]. Additionally, expanded research in special populations, including children and pregnant women, is needed to ensure safety and efficacy across diverse patient groups.

Implementation challenges represent substantial barriers to translating therapeutic advances into global health impact. The complex infrastructure requirements and prohibitive costs of advanced therapies like gene editing create significant access disparities, potentially exacerbating global health inequities [16]. Addressing these challenges will require coordinated efforts involving manufacturers, healthcare systems, policymakers, and international organizations to develop sustainable models for delivering these innovative treatments to patients worldwide.

Conclusion

Recent advances in the therapeutic management of anemia and thalassemia represent the most substantial progress in decades, offering unprecedented potential for disease modification and cure. Gene therapy approaches using viral vectors and CRISPR-Cas9 technology have demonstrated remarkable efficacy in clinical trials, resulting in regulatory approvals and providing curative options for patients without suitable transplant donors. Novel pharmacological agents targeting ineffective erythropoiesis and iron homeostasis offer promising non-curative alternatives that may reduce transfusion requirements and disease complications.

Despite these advances, significant challenges remain in translating these innovations into a global health impact. The complex infrastructure requirements and prohibitive costs of advanced therapies create substantial access disparities, potentially exacerbating healthcare inequities. Future research priorities should include developing simplified treatment approaches, identifying optimal patient selection criteria, and establishing sustainable models for delivering these therapies in diverse healthcare contexts.

The therapeutic landscape for anemia and thalassemia continues to evolve rapidly, with several promising approaches on the horizon. *In vivo* gene editing and next-generation pharmacological agents targeting novel pathways offer exciting possibilities for further improving outcomes while reducing treatment burden. As these innovations continue to develop, maintaining a patient-centered approach that considers individual preferences, quality of life impacts, and contextual factors remains essential for optimizing care across the diverse global population affected by these disorders.

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