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LUSPATERCEPT – AN INNOVATIVE APPROACH TO THE TREATMENT OF ANEMIA IN BETA-THALASSEMIA AND MYELODYSPLASTIC SYNDROMES

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ABSTRACT

Ineffective erythropoiesis (IE) is a hallmark of several hematologic disorders, including β-thalassemia and myelodysplastic syndromes (MDS), leading to chronic anemia and transfusion dependence. IE is often driven by disrupted late-stage erythroid maturation, mediated by overactivation of the Smad2/3 signaling pathway within the transforming growth factor-β (TGF-β) superfamily. This review summarizes current evidence on the mechanism of action and clinical efficacy of luspatercept, a novel activin receptor ligand trap that enhances erythroid maturation by inhibiting Smad2/3 signaling. A literature search was conducted using PubMed through February 2025, focusing on clinical trials and mechanistic studies of luspatercept in β-thalassemia and MDS. In β-thalassemia, luspatercept significantly reduced transfusion burden in phase I–III trials. The pivotal BELIEVE study demonstrated that ≥33% transfusion reduction was achieved in a significantly higher proportion of patients receiving luspatercept compared to placebo. In low-risk MDS (LR-MDS), phase II PACE-MDS and phase III COMMANDS trials showed that luspatercept induced erythroid response (HI-E) and transfusion independence (RBC-TI) in a substantial proportion of patients. COMMANDS further revealed that luspatercept outperformed epoetin alfa in achieving ≥12-week RBC-TI and ≥1.5 g/dL hemoglobin increase, regardless of SF3B1 mutation status or baseline erythropoietin levels. Luspatercept presents a promising treatment strategy for IE in β-thalassemia and LR-MDS. Its ability to promote erythropoiesis, reduce transfusion needs, and maintain a favorable safety profile supports its potential as a new standard of care. Ongoing research will help define its role across broader patient populations.

KEYWORDS

Luspatercept, Smad 2/3, TGF- β, β-thalassemia, MDS

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1. Introduction

Erythropoiesis is the process by which progenitor cells destined for the erythroid lineage develop and ultimately differentiate, leading to the formation of red blood cells (RBCs). Ineffective erythropoiesis (IE) refers to a disrupted maturation process of erythroid precursor cells, resulting in insufficient RBC production. Anemia resulting from IE is a common consequence of various conditions, ranging from nutritional deficiencies to malignancies. IE occurs both in cases of insufficient erythroblast production, such as in aplastic anemia, and in disorders associated with defective erythroid maturation (EMD), such as β-thalassemia or myelodysplastic syndromes (MDS). [1]

The TGF-β protein family includes a broad range of factors, such as activins, growth differentiation factors (GDFs), and bone morphogenetic proteins (BMPs), which play a crucial role in signaling within the hematopoietic stem cell niche in the bone marrow. Signal transduction in this family is mediated by seven different type I and five type II transmembrane receptors. Receptors such as ALK2, ALK4, ALK7, and activin receptor type IIA (ActRIIA) are typically responsible for mediating the effects of activins. ActRII receptors also play a role in the signaling of certain BMPs and GDFs. Upon activation, the Smad2/3 signaling pathway is triggered [2], which under physiological conditions inhibits erythroid differentiation by inducing apoptosis and cell cycle arrest in erythroblasts [3]. In patients with IE caused by defective erythroid maturation (EMD), excessive activation of the Smad2/3 pathway is observed, leading to impaired terminal erythroid maturation [4]. Luspatercept is a recombinant fusion protein composed of the human activin receptor type IIB (ActRIIB) fused to a fragment of the IgG protein [5]. Its mechanism of action involves inhibition of the Smad2/3 pathway through binding to selected TGF-β superfamily ligands, such as GDF-11 and activin B (Figure 1). This mechanism supports erythroid maturation by promoting the differentiation of erythroid precursors at late developmental stages (normoblasts) in the bone marrow [6].

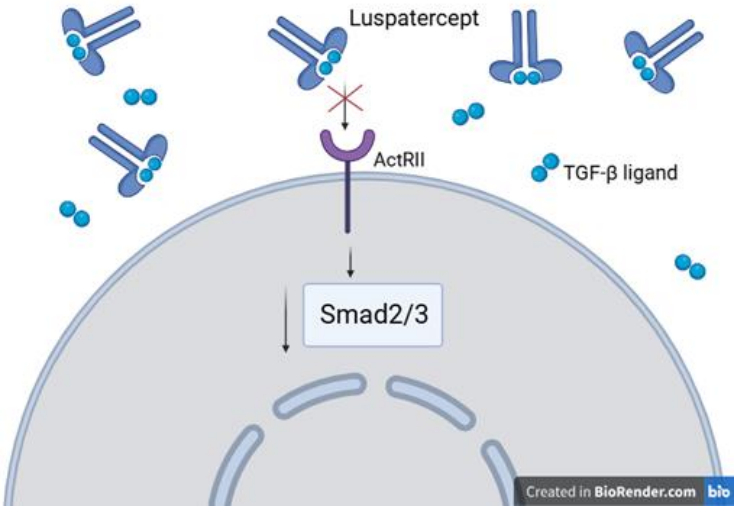

Fig. 1. *Simplified mechanism of action of luspatercept. Created with BioRender.com.*

2. Materials and Method

A literature review was conducted using the PubMed platform, covering articles published up to February 2025. Keywords used included "luspatercept," "Smad2/3," and "TGF-β ligand." The aim of this review was to gather up-to-date and reliable information regarding the mechanism of action of luspatercept and its efficacy in treating patients with ineffective erythropoiesis resulting from defective erythroid maturation.

Results

3. Luspatercept in the Treatment of Anemia in β-Thalassemia

3.1. General Information on β-Thalassemia

β-thalassemias are a group of genetic disorders associated with abnormal hemoglobin synthesis. They are most commonly found in Southern Europe, the eastern Mediterranean region, and Southeast Asia. However, due to migration, the prevalence of these disorders has increased in Northern Europe and the Americas [7].

Historically, three main clinical forms of β-thalassemia were distinguished: β-thalassemia major, β-thalassemia intermedia, and β-thalassemia minor. However, in the past decade, a simplified classification system has been introduced, which better reflects actual patient needs and holds greater clinical relevance. Patients with β-thalassemia are now classified based on their dependence on red blood cell transfusions—into two main groups: transfusion-dependent (TD) and non-transfusion-dependent (NTD) patients. This classification facilitates appropriate treatment selection, prognosis assessment, and disease monitoring [10].

Both forms result from absent or reduced production of the beta-globin chain, a component of hemoglobin. TD patients usually present with symptoms within the first two years of life and require regular blood transfusions for survival. In contrast, NTD patients have a more variable clinical course—symptoms may arise at different ages, and the anemia tends to be milder, often allowing the avoidance of regular transfusions during early childhood [8].

A hallmark of the pathophysiology of β-thalassemia is reduced β-globin chain synthesis, which disturbs the balance between α- and β-globin. Excess α-globin chains accumulate in erythroid cells, causing oxidative stress, increased apoptosis, and ineffective erythropoiesis. In response, the body activates compensatory mechanisms such as hematopoietic expansion, accompanied by impaired production of hepcidin—a key hormone regulating iron metabolism. Hepcidin deficiency leads to excessive iron absorption in the intestines and progressive iron accumulation in tissues and organs. Additionally, chronic hemolysis and the need for frequent blood transfusions exacerbate iron overload, which—alongside ineffective erythropoiesis—is one of the most serious clinical challenges in β-thalassemia. As a result, in addition to anemia, patients frequently suffer from organ damage caused by iron toxicity, necessitating appropriate monitoring and iron chelation therapy (ICT) [9].

3.2. Efficacy of Luspatercept in Treating Patients with β-Thalassemia – Phase I, II, and III Clinical Trials

In recent decades, significant progress has been made in the treatment of patients with transfusion-dependent (TD) β-thalassemia, leading to a notable increase in life expectancy. Improved symptom management and treatment of comorbidities—including regular red blood cell transfusions, iron chelation therapy (ICT), and comprehensive supportive care—have enabled more patients to reach adulthood in good health [11, 12].

A deeper understanding of the pathophysiological mechanisms of β-thalassemia has laid the foundation for the development of innovative therapeutic strategies. One of the most promising approaches is the use of erythropoiesis-modifying agents such as luspatercept, which not only enhances erythropoiesis efficiency but also reduces transfusion requirements and alleviates symptoms of ineffective erythropoiesis [13].

A promising phase I clinical trial involved 32 healthy volunteers randomized in a 3:1 ratio to receive subcutaneous doses of luspatercept (0.0625–0.25 mg/kg) or placebo every two weeks. Luspatercept was well tolerated, and a dose-dependent increase in hemoglobin levels and red blood cell count was observed after just one dose [14].

Next, an open-label, non-randomized, uncontrolled phase II study aimed to determine the optimal therapeutic dose. The study included 31 NTD patients and 32 TD patients with β-thalassemia, who received subcutaneous luspatercept every three weeks at doses ranging from 0.2 to 1.25 mg/kg [15]. In the NTD group, the primary endpoint—an increase in hemoglobin of ≥1.5 g/dL within 14 days—was achieved by 58% of patients receiving higher doses (0.6–1.25 mg/kg). In the TD group, 81% of patients receiving higher doses experienced a ≥20% reduction in transfusion burden (TB) over 12 weeks compared to baseline (Table 2).

Groundbreaking results came from the pivotal phase III BELIEVE trial, which enrolled 336 adult patients with TD β-thalassemia and a transfusion-free interval >35 days within the 24 weeks prior to randomization. Patients were randomized in a 2:1 ratio to receive luspatercept (1–1.25 mg/kg) or placebo every three weeks for at least 48 weeks [16]. Standard supportive care, including red blood cell transfusions to maintain baseline hemoglobin levels and ICT according to previous guidelines, was continued in both groups.

Table 1. Summary of the drug Luspatercept.

Phase of the clinical trial	III
Indication	Indicated for the treatment of transfusion-dependent anemia in adult patients with thalassemia or myelodysplastic syndromes (MDS).
Mechanism of action	As a result, Smad2/3 signaling is attenuated, leading to an increased number and improved quality of mature erythrocytes.
Route of administration	Podskórnie

The results clearly demonstrated the superiority of luspatercept over placebo. A significantly greater proportion of patients in the luspatercept group achieved the primary endpoint—a ≥33% reduction in transfusion burden during weeks 13–24 compared to baseline. Furthermore, analysis of secondary endpoints showed that a ≥33% reduction in transfusion burden during weeks 37–48 and in any 12- or 24-week period was more frequently achieved in the luspatercept group. Moreover, a markedly higher proportion of patients treated with luspatercept achieved a ≥50% reduction in transfusion burden compared to the placebo group across all evaluated time periods [16] (Tables 1 and 2).

Table 2. Summary of key efficacy results from Phase II and III clinical trials

Outcome	Interval	Patients, n (%) Luspatercep	Placebo	OR (95% CI)	P value
Phase II		N = 63	-		-
NTD		n = 31			
Hb increase ≥ 1,5 g/dl for ≥ 2 weeks (in the absence of RBC transfusi	Any 12-week interval	18 (58)	-	(39,1 - 75,5)	-
Hb increase ≥ 1 g/dl for ≥ 12 weeks (in the absence of RBC transfusic	Any 12-week interval	22 (71)	-	(52,0 - 85,8)	-
Hb increase ≥ 1,5 g/dl for ≥ 12 weeks (in the absence of RBC transfu	Any 12-week interval	14 (45)	-	(27,3 - 64,0)	-
Decrease in LIC ≥ 2 mg/g dry weight c	Any 12-week interval	5 (33)	-	(11,8 - 61,6)	-
TD		n = 32			
≥ 20% transfusion burden reduction a,b	Any 12-week interval	26 (81)	-	(63,6 - 92,8)	-
≥ 33% transfusion burden reduction a	Any 12-week interval	23 (72)	-	(53,3 - 86,3)	-
≥ 50% transfusion burden reduction a	Any 12-week interval	20 (63)	-	(43,7 - 78,9)	-
Phase III BELIEVE (TD only)		N = 224	N = 112		
≥ 33% transfusion burden reduction a,b	Week 13-24	48 (21,4)	5 (4,5)	5,79 (2,24 -14,97)	<0,001
≥ 33% transfusion burden reduction a	Week 37-48	44 (19,6)	4 (3,6)	6,44 (2,27 - 18,26)	<0,001
≥ 33% transfusion burden reduction a	Any 12-week interval	158 (70,5)	33 (29,5)	5,69 (3,46 - 9,35)	-
≥ 33% transfusion burden reduction a	Any 12-week interval	92 (41,1)	3 (2,7)	25,02 (7,76 - 80,71)	-
≥ 50% transfusion burden reduction a	Week 13-24	17 (7,6)	2 (1,8)	4,55 (1,03 - 20,11)	0,03
≥ 50% transfusion burden reduction a	Week 37-48	23 (10,3)	1 (0,9)	11,92 (1,65 -86,29)	0,002
≥ 50% transfusion burden reduction a	Any 12-week interval	90 (40,2)	7 (6,3)	9,95 (4,44 - 22,33)	-
≥ 50% transfusion burden reduction a	Any 24-week interval	37 (16,5)	1 (0,9)	20,37 (2,86 - 144,94	-

See ref [15,16]. From baseline. Primary endpoint. Includes patients with baseline LIC ≥3 mg/g dry weight who were treated for ≥ 4 months; n = 15

CI, confidence; Hb, hemoglobin; LIC, liver iron concentration; NTD, non-transfusion dependent; OR, odds ratio; TD, transfusion dependent.

These results provide a solid basis for recognizing luspatercept as a breakthrough therapeutic option for the treatment of β-thalassemia, particularly in transfusion-dependent patients, for whom reduced transfusion frequency may significantly improve quality of life and reduce the risk of iron overload-related complications.

4. Luspatercept in the Treatment of Anemia in MDS

4.1. Myelodysplastic Syndromes (MDS) – General Information

Myelodysplastic syndromes (MDS) are a heterogeneous group of acquired, clonal hematopoietic disorders that develop due to somatic mutations in bone marrow stem cells [17]. These pathological clones infiltrate the bone marrow, disrupting normal hematopoiesis. Hallmark features of MDS include peripheral blood cytopenias and dysplastic changes in bone marrow and blood cells. The clinical course of the disease is highly variable, ranging from mild, often asymptomatic blood cell deficiencies to aggressive forms with rapid deterioration and a high risk of transformation into acute myeloid leukemia (AML). Due to this clinical variability, MDS treatment must be individually tailored. Key factors in therapeutic decision-making include patient age, overall condition, comorbidities, and risk assessment based on current prognostic scoring systems [18].

In patients with lower-risk MDS (LR-MDS), who are expected to have a longer survival, the main goal of therapy is to improve hematologic parameters, particularly the treatment of anemia. In contrast, treatment for high-risk MDS (HR-MDS) focuses on prolonging overall survival (OS) and reducing the risk of progression to AML. This group may receive hypomethylating agents, intensive chemotherapy, or allogeneic hematopoietic stem cell transplantation (allo-HSCT) [19]. Advances in supportive care and the introduction of new therapies in recent years have improved both the quality and duration of life for patients with MDS.

4.2. Luspatercept in MDS – Results of Clinical Trials

Luspatercept represents a novel class of agents that modulate late-stage erythroid maturation in the bone marrow. Under normal conditions, this process is regulated by signaling pathways dependent on transforming growth factor beta (TGF-β). In patients with MDS, elevated levels of TGF-β receptor ligands, including growth differentiation factor 11 (GDF11), are observed. Overactivation of this pathway results in increased SMAD2 and SMAD3 signaling, which impairs erythroid maturation by promoting apoptosis and cell cycle arrest. The therapeutic action of luspatercept involves blocking TGF-β ligands (such as GDF11), thereby reducing excessive SMAD2/3 activity and supporting proper erythroid differentiation and maturation.

Luspatercept is a fusion protein composed of a modified extracellular domain of the human activin receptor type IIB (ActRIIB) linked to the Fc fragment of human immunoglobulin G1 [20,21].

In the phase II PACE-MDS clinical trial, treatment with luspatercept resulted in an erythroid response (HI-E) in 63% of patients with lower-risk MDS (LR-MDS), while 38% achieved red blood cell transfusion independence (RBC-TI) for at least 8 weeks. The best results were seen in patients with ring sideroblasts (MDS-RS). A higher HI-E rate was observed in patients with an SF3B1 mutation (77% vs. 40%) and those with ≥15% ring sideroblasts in the bone marrow (69% vs. 43%) [38].

Subgroup analysis also demonstrated a correlation between treatment efficacy and baseline erythropoietin (EPO) levels: the HI-E rate was 76% for EPO <200 IU/L, 58% for 200–500 IU/L, and 43% for >500 IU/L. Notably, patients previously treated with erythropoietin and/or lenalidomide achieved similar therapeutic responses as treatment-naïve individuals. Luspatercept was well tolerated—only three grade ≥3 adverse events were recorded during the study [22].

The promising results of the PACE-MDS trial formed the basis for the international, randomized, open-label, phase III COMMANDS study (NCT03682536). This trial compared the efficacy and safety of luspatercept versus epoetin alfa in previously untreated, transfusion-dependent LR-MDS patients who had not received erythropoiesis-stimulating agents (ESAs). A total of 301 patients were enrolled—149 received luspatercept and 152 received epoetin alfa. All patients had very low, low, or intermediate risk according to IPSS-R and were dependent on RBC transfusions [24].

The primary endpoint was the proportion of patients achieving RBC-TI for ≥12 weeks with a concurrent ≥1.5 g/dL increase in hemoglobin (Hb) within the first 24 weeks of treatment. This endpoint was met by significantly more patients in the luspatercept group (58.5%) compared to the epoetin alfa group (31.2%; $p < 0.0001$). Luspatercept also showed superiority in secondary endpoints: RBC-TI for ≥24 weeks and Hb increase of ≥1.5 g/dL within 24 weeks was achieved in 47.6% vs. 29.2% of patients ($p = 0.0002$), and a sustained Hb increase of ≥1.5 g/dL for ≥8 weeks was achieved in 74.1% vs. 51.3% ($p < 0.0001$) [24].

Hematologic improvement–erythroid (HI-E), a key efficacy marker, was observed in 58.5% of patients receiving luspatercept, significantly higher than in the epoetin alfa group (31.2%; $p = 0.0001$). Efficacy was independent of SF3B1 mutation status and baseline transfusion burden. Importantly, the therapeutic effect persisted over time, and responses were seen even in patients with high baseline endogenous EPO levels, making luspatercept a valuable alternative in cases of anticipated ESA resistance [24].

Luspatercept also demonstrated a favorable safety profile comparable to epoetin alfa. Most adverse events were mild to moderate (grade 1–2). Severe adverse events (SAEs) and grade 3–4 events occurred at similar rates in both groups. The rate of treatment discontinuation due to adverse events was 8% in both the study and control arms [24].

The COMMANDS trial results indicate that luspatercept provides significantly greater clinical efficacy than epoetin alfa in the treatment of transfusion-dependent anemia in LR-MDS patients, while maintaining a comparable safety profile. These findings support the adoption of luspatercept as a new standard of care in this patient population, particularly for those expected to be resistant to ESAs.

5. Discussion

Luspatercept is a promising agent for the treatment of ineffective erythropoiesis (IE), particularly in disorders of erythroid maturation such as β-thalassemia and myelodysplastic syndromes (MDS). Its mechanism involves inhibition of the TGF-β signaling pathway, which—when overactivated—disrupts red blood cell maturation. By modulating this pathway, luspatercept enhances erythropoiesis, supporting the production of healthy erythrocytes, reducing transfusion needs, and improving patients' quality of life.

Clinical trials have demonstrated its efficacy in both β-thalassemia and MDS. In β-thalassemia—especially among transfusion-dependent patients—luspatercept significantly reduced transfusion burden, with phase I, II, and the pivotal phase III BELIEVE study confirming its superiority over placebo. In MDS, luspatercept showed encouraging results in improving blood parameters and achieving transfusion independence, particularly in patients with ring sideroblasts. It was well tolerated and provided notable clinical benefits.

Further studies are essential—especially regarding its efficacy in different patient subgroups—to fully confirm its role in the treatment of ineffective erythropoiesis and related hematological disorders.

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