Innovative Research in Applied, Biological, and Chemical Sciences

ISSN: 3005-8449

INNOVATIVE RESEARCH JOURNALS

Letter to Editor

IRABCS, vol. 3, issue 1, pp. 80-81, 2025

Received: June 5, 2025
Revised: June 18, 2025
Accepted: June 23, 2025
https://doi.org/10.62497/irabcs.150

Luspatercept (REBLOZYL): A Game-Changer in Reducing Transfusion Burden for β-Thalassemia Patients

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How to cite: Advani A, Mughal SA. Luspatercept (REBLOZYL): A Game-Changer in Reducing Transfusion Burden for β-Thalassemia Patients. IRABCS; 3(1):80-81. DOI: https://doi.org/10.62497/irabcs.150 Available from: https://irjpl.org/irabcs/article/view/150

Introduction

β-thalassemia remains one of the most challenging inherited blood disorders, particularly in its transfusion-dependent form (TDT). Caused by mutations in the β-globin gene, it leads to ineffective erythropoiesis, chronic anemia, and a lifelong dependency on blood transfusions. While advances in iron chelation therapy have improved outcomes, many patients continue to face complications including iron overload, reduced quality of life, and early mortality. In this evolving therapeutic landscape, Luspatercept has emerged as a novel agent with the potential to transform management strategies [1–3].

Patients with TDT typically present in early childhood and require lifelong red blood cell (RBC) transfusions to maintain hemoglobin levels and prevent growth failure, organ damage, and cardiac complications. However, the cumulative burden of transfusion-related risks—including iron overload, alloimmunization, and infections—places immense physical, emotional, and financial stress on patients and caregivers. There remains a critical need for therapeutic agents that can reduce transfusion burden while preserving quality of life [3,4].

Luspatercept is a first-in-class erythroid maturation agent. It is a recombinant fusion protein comprising a modified extracellular domain of the human activin receptor type IIB (ActRIIB) linked to the Fc domain of human IgG1. It selectively binds ligands of the TGF-β superfamily, thereby inhibiting Smad2/3 signaling and promoting late-stage erythroid differentiation. Unlike erythropoietin, which primarily stimulates early erythroid precursors, Luspatercept enhances terminal maturation—offering a complementary pathway to address ineffective erythropoiesis in β-thalassemia [1,5]. Luspatercept has been approved by the FDA and EMA as the treatment of anemia in adults with β-thalassemia who require regular RBC transfusions [6].

Clinical Evidence: Trials and Outcomes

Phase I and II Trials

A Phase I trial in healthy volunteers demonstrated the safety and dose-dependent increases in hemoglobin following Luspatercept administration (NCT01432717) [7]. In a Phase II study involving transfusion-dependent and non-dependent β-thalassemia patients, Luspatercept showed reductions in transfusion requirements and improvements in hemoglobin levels [8].

The BELIEVE Trial

The BELIEVE trial (NCT02604433), a multicenter, randomized, double-blind, placebo-controlled Phase III study, enrolled 336 adults with TDT. Patients received Luspatercept or placebo every 3 weeks for ≥48 weeks. The trial showed that 21.4% of patients in the Luspatercept group achieved a ≥33% reduction in transfusion burden during weeks 13–24, compared with 4.5% in the placebo group ($p<0.001$) [2]. Reductions were sustained over longer durations, with improved hemoglobin levels and overall transfusion efficiency.

Quality of Life Data

A sub-analysis of the BELIEVE trial found that decreased transfusion burden correlated with improvements in energy, physical functioning, and social activities, suggesting a positive impact on health-related quality of life (HRQoL) [6].

Despite being a breakthrough in the reduction of transfusion burden, Luspatercept has a diverse side-effects profile, with the most commonly reported ones being bone pain, arthralgia, dizziness, hypertension, hyperuricemia and thrombi embolic events (TEEs). The believe trials show Patients with significant transfusion needs, as well as those with allo- or autoantibodies or hypersplenism, are generally not expected to benefit from luspatercept. Nevertheless, it may be beneficial to consider administering luspatercept to splenectomized patients experiencing a high transfusion burden, provided

they do not possess allo- or autoantibodies. Extramedullary hematopoiesis serves as a compensatory mechanism. Research indicates that EMH masses were observed in 3.2% of patients with B-thalassemia who were treated with luspatercept [5]. Case studies have reported the cases of spinal cord compression and cauda equina syndrome secondary to EMH. Luspatercept should not be administered to patients being treated for pre-existing EMH masse [9][10]. The existing data regarding its use in pregnant women is inadequate to assess the risks associated with significant birth defects or miscarriages. Nevertheless, animal reproduction studies suggest the potential for embryo-fetal toxicity [11].

Luspatercept ameliorates anemia and reduce transfusion burden by inhibiting binding to endogenous ActRIIB, thereby blocking Smad2/3 signaling and promoting late-stage erythroid maturation independently of erythropoietin. This therapeutic targeting provides a promising approach for the treatment of others with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) [11].

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