# Emerging Therapies

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**KEYWORDS**

• β-Thalassemia • β-Globin • Gene transfer • Hemichromes • New therapies • Trap ligands

**KEY POINTS**

- At present, the only definitive cure for β-thalassemia is a bone marrow transplant (BMT); however, HLA–blood-matched donors are scarcely available.
- Current therapies undergoing clinical investigation with most potential for therapeutic benefit are the β-globin gene transfer of patient-specific hematopoietic stem cells followed by autologous BMT.
- Other emerging therapies deliver exogenous regulators of several key modulators of erythropoiesis or iron homeostasis.
- This review focuses on current approaches for the treatment of hemoglobinopathies caused by disruptions of β-globin.

## INTRODUCTION

Hemoglobinopathies arise from genetic mutations in HBA1, HBA2, and HBB that compromise the structure-function of the α-globin and β-globin chains of hemoglobin (Hb). Collectively, mutations in the β-globin gene are referred to as β-thalassemia (BT).[1] Mutations in the HBB are remarkably heterogeneous at the molecular level with more than 300 variations identified (http://globin.cse.psu.edu/). Despite the diversity of mutations, most cause disruption in the α-globulin, β-globin balance, resulting

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in long-term ineffective erythropoiesis (IE) and extramedullary hematopoiesis of the spleen and liver. IE leads to various degrees of chronic hemolytic anemia and transfusion dependence as well as upregulation of iron absorption. Strategies to treat BT are based on gene therapy strategies as well as pharmacologic treatments to target pathways that modulate erythropoiesis and iron homeostasis. Here, the authors review emerging therapies in clinical trials and preclinical stages of development.

## EMERGING THERAPIES IN CLINICAL TRIALS

Sotatercept (ACE-011) and luspatercept (ACE-536) are 2 compounds that showed success in clinical trials (**Table 1**). Sotatercept was originally developed to treat bone-loss disorders, but clinical studies unexpectedly revealed increased hematocrit and Hb levels in treated patients.[2] Structurally designed to compete with the extracellular domains of Activin Receptor A Type 2A (ACVR2A) or 2B, these peptides act as ligand traps for transforming growth factor-β (TGF-β)–like molecules.[3,4] Growth differentiation factor 11 (GDF11), a member of TGF-β superfamily, is the identified ligand target for luspatercept. Treatment with luspatercept is thought to remove GDF11 from circulation and cause subsequent increases of Hb levels.[5] GDF11 is well established as a ligand capable of activating the SMAD2/3 pathway through ACVR2A or 2B.[6] Administration of the luspatercept mouse analogue, RAP-536, to BT mice ameliorates intracellular accumulation of hemichromes (HCMs), oxidative stress, and splenomegaly, while also inducing late-stage erythroid progenitor differentiation.[7] In phase 1 studies of healthy volunteers, luspatercept and sotatercept showed a dose-dependent and sustainable increase in Hb level and were well tolerated.[8,9] Luspatercept subsequently entered a phase 2, open-label, dose-ranging study in adults with BT (NCT01749540, completed) including an ongoing 2-year extension (NCT02268409). Patients received luspatercept at doses of 0.2 to 1.25 mg/kg administered subcutaneously every 3 weeks. Available data indicate that luspatercept was generally well tolerated and had a favorable safety profile. Luspatercept reduced transfusion requirements and liver iron concentration among patients with transfusion-dependent (TD) BT and increased Hb levels, reduced liver iron concentration, and improved patient-reported outcomes among those with non-transfusion-dependent (NTD) BT.[10,11] A double-blind, randomized, placebo-controlled phase 3 study (BELIEVE) has begun to evaluate the efficacy and safety of luspatercept among adults with TD BT. Demonstration of efficacy will require at least a 33% improvement in the number of transfused red blood cell (RBC) units from baseline (NCT02604433). In the phase 2a study of sotatercept among adults with TD or NTD BT (NCT01571635, completed), data indicated an increase in Hb levels, a reduced transfusion burden, and a favorable safety profile,[12] but no phase 3 studies are publicly announced.

The JAK2 pathway has been long thought of as a potential link between erythropoiesis and iron metabolism.[13] Negating effects of erythropoietin (EPO) overstimulation in BT by inhibiting the JAK2/STAT3 pathway has been an attractive area of therapy exploration. One of the first agents to be approved by the US Food and Drug Administration as a JAK2 inhibitor was ruxolitinib.[14] Studies on mice models of BT show that the JAK2 inhibitor reduces IE and splenomegaly.[13,15] A single-arm, phase 2 study (NCT02049450, completed) to evaluate the efficacy and safety of ruxolitinib administered orally at a starting dose of 10 mg twice daily among adults (n = 30) with TD BT and splenomegaly has been completed.[16] Ruxolitinib was associated with a slight increase in pretransfusional Hb levels (by 0.5 g/L increase) and a trend toward 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. No major adverse effects were reported.