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Emerging Therapies

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Abstract

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 (GT) of patient specific hematopoietic stem cells (HSCs) 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.

Keywords

β-thalassemia; β-Globin; Gene transfer; Hemichromes; New Therapies; Trap Ligands

Introduction

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

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Conflict of Interest statement

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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 pharmacological treatments to target pathways that modulate erythropoiesis and iron homeostasis. Here, we review emerging therapies in clinical trials and pre-clinical stages of development.

Emerging Therapies in Clinical Trials

Sotatercept (ACE-011) and Luspatercept (ACE-536) are two 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 (ECDs) of Activin Receptor A Type 2A (ACVR2A) or 2B, these peptides act as ligand traps for TGFβ-like molecules [3,4]. Growth differentiation factor 11 (GDF11), a member of TGFβ 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 analog, RAP-536, to BT mice ameliorates intracellular accumulation of hemichromes (HCM), 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 hemoglobin 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 0.2–1.25 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 hemoglobin 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 units from baseline (NCT02604433). In the phase 2a study of sotatercept among adults with TD or NTD BT (NCT01571635, completed), data indicated increase in hemoglobin 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 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 FDA as a JAK2 inhibitor was ruxolitinib [14]. Studies on mice models of BT, show that the JAK2 inhibitor reduces ineffective erythropoiesis 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 pre-transfusional hemoglobin levels (by 0.5 g/L increase) and a trend towards reduced transfusion requirements (by 45 mL of hematocrit-adjusted red blood cell volume per 4 weeks) following 30 weeks of treatment. Mean spleen volume also decreased during ruxolitinib treatment. No major adverse effects were reported.

The only cure available for patients suffering from BT is a BMT with cells harboring a functional HBB gene, however finding a donor source is challenging. GT technology and autologous BMT provides an alternative with potential to reach more patients. The development of safe lentiviral vectors and discovery of the β-globin's LCR, has made GT a possibility for BT. The first clinical study (LG001) in a BT patient tested the HPV569 vector [17–20] harboring a critical amino acid modification (T87Q) that allowed researchers to successfully identify modified cells and accurately measure viral integration and chimerism [21]. The patient became transfusion independent one year after GT, exhibiting increased levels of several Hb variants including HbF with equal proportions of HbA containing the T87Q mutation. New vectors are currently in various stages of clinical trials (NCT02633943, NCT02453477, NCT03275051, NCT02453477, NCT01745120, NCT02151526, NCT03207009, NCT02906202, NCT01639690) (Table 1). Interim data from a phase1/2 study of autologous hematopoietic stem cells transduced ex vivo with a lentiviral vector among patients with TD BT (NCT01745120) suggest increased levels of HbA and reduced transfusion requirements [22]. New strategies for allogenic BMT and reduced intensity conditioning (RIC) are also in clinical trials (NCT00408447, NCT02038478, NCT02165007), which could eventually also aid the success of GT (Table 1).

Innovative Therapies in Pre-Clinical Stages

Patients with high levels of endogenous HbF do not exhibit the symptomology associated with BT. Chemical agents such as hydroxyurea are used to induce HbF in BT patients [23], however these agents are not effective in all patients [24,25]. Genome-wide associated studies [26] identified *BCL11a* as a regulator of HbF. Knock-down studies of *BCL11a* using RNAi [24,2728] proved it to be rheostat for silencing of the γ-globin gene. One novel approach to induce HbF by silencing *BCL11a* uses an erythroid specific promoter to drive a microRNA-adapted shRNAs (shRNAmiR) [29,30]. By using an erythroid specific HS2 and HS3 regions of the β-globin LCR alongside its promoter, the toxicity and engraftment impairments characteristic of Pol III/II driven shRNA and microRNAs are circumvented while simultaneously inducing HbF in erythroid cells [30].

Other strategies for *BCL11a* inhibition in preclinical stages employ gene editing (GE) strategies: zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENS) and clustered regularly interspaced palindromic repeats (CRISP) in association with Cas 9 (CRISP/Cas9). All GE strategies have successfully targeted *BCL11a* [31–34] decreasing protein expression of BCL11a and causing expression of γ-globin. Several studies using ZFNs, TALENS, and CRISP/Cas9 systems have also shown the potential of editing HBB in both patient derived CD34+ cells and induces pluripotent stem cells (iPSC) [35–38]. Although questions concerning off-target events remain, latest studies show GE as a strategy with clinical potential [34,39].

Targeting iron regulation by direct action on the main iron transporter, transferrin has had promising results. Studies on BT mice treated with exogenous apo-transferrin resulted in a net decrease of iron uptake by RBC precursors through TfR1 and subsequent reduction of HMCs [40]. As HMCs were reduced, the lifespan of RBCs and total amount of Hb in circulation increased. Additionally, haplo-insufficienct TfR1 mice also resulted in improved erythropoiesis with results closely mirroring findings of exogenous apo-transferrin treatment [41]. Increasing circulating hepcidin and manipulating the hepcidin pathway by targeting its regulators may provide patients with more effective options for iron overload management. Preclinical studies of administration of exogenous sources of hepcidin, such as minihepcidins and other hepcidin agonists, and well as inhibiting negative regulators of *Hamp (*TMPRSS6) expression show to successfully prevent iron overload, improve anemia and ameliorate ineffective erythropoiesis in mice models of BT [42–46]

Novel tools for drug development and therapy discover

Novel therapeutics are not possible without innovation at the bench side. New animal models, *in vitro* systems with potential to more closely mimic *in vivo* conditions and tools for gathering *in vivo* data in mice models are necessary for the advancement of BT therapies. A Thal-Biobank has been established with goals to supply researchers with the samples of the same cells for studies aimed at solving the plethora of biological and biomedical issues involved in using patient cell cultures [47]. Erythroid pre-cursors collected from 72 BT patients, were expanded, cryopreserved, characterized with respects their individual Hb profile and tested for abilities to produce HbF by hydroxyurea. Furthermore, several laboratories characterized samples from the same donors, showing that data were reproducible using protocols developed by the Thal-bank.

In the last decade immortalizing human progenitor cells has become possible. Two cell lines in particular stand out, Human Immortalized Erythroid Progenitor Cell Lines (HUDEPs) [48] and the newly established Mui009 [49]. HUDEPs were generated form human umbilical cord blood and immortalized with conditional (doxycycline-inducible) expression of Human Papilloma Virus (HPV)-derived E6/E7 proteins. The cells can be expanded infinitely and characterization shows them to be arrested at the pro-erythroblast stage. The line has several clones available, each with its own unique gene expression fingerprint of erythroid specific markers. These cells can be differentiated into enucleated RBCs, providing a useful tool to study erythropoiesis. The Mui0009 cell lines were generated from 32-year-old male with homozygous β-globin deletion and heterozygous α-thalassemia. Peripheral blood mononuclear cells were enriched for CD34+ cells and reprogrammed into iPSC cells. Resultant cells exhibited embryonic stem cell characteristics, including the capability of differentiating into the endodermal, ectodermal and mesodermal germinal layers. However, work is still needed to determine if the cells are suitable for studies requiring RBC differentiation.

Measuring potential therapeutics for inhibition of iron overload has been limited by the inability to measure iron loading on live animal models. The use of magnetic resonance imaging (MRI) offers a clinically relevant assessment tool to measure the presence of iron loading in humans, and recently has been optimized for the use on small animal models [50].

Tissue resonance relaxation rates, spleen volumetric and cardiac function are now quantifiable in live BT mouse models during treatment course.

Discussion

Despite the success of GT in the last decade, improvements of both the transduction efficiency of lentiviruses and HSC expression of the β-globin transgene are needed. Patients treated with GT display a spectrum of phenotypic heterogeneity in endogenous and GT-delivered β-globin variants. Although some patients treated reach therapeutic HbA thresholds, a majority are left TD [17,21,51]. The potential of GE and reactivation of HbF production awaits future data from human studies.

Therapeutic strategies aiming to modulate iron metabolism are also showing promise in reducing IE, ROS and ameliorating anemia. Exogenous administration of apo-transferrin ascertains to be a therapeutic with much potential. The safety profile and Hb increasing abilities in clinical trials has been previously reported in treating hypotransferrinemia [52]. RNAi technology has been used in innovative ways to target modulators of both erythropoiesis. Activating HbF by using RNAi is pushing the bounds of discovery by creating new molecules capable of intervening at the level of transcriptional regulation.

Sotatercept and luspatercept are front runners as emerging therapies for BT management. Although they were designed to target different TGFβ ligands, results of clinical studies show similar outcomes. The unknown role of the TGFβ ligands family on erythropoiesis and their potential contributions of BT treatment make the initial serendipitous sotatercept and luspatercept findings especially exciting. As very little is known about the role the activin pathways play on normal hematopoietic function and current mechanisms suggested do not completely explain the effects of sotatercept and luspatercept [5,7,8,53]. Further characterization of the TGFβ ligands will undoubtedly lead to new insights into both fundamental hematological mechanisms and therapies.

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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 (GT) of patient specific hematopoietic stem cells (HSCs) 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.

Table 1

Emerging therapies in clinical trials for treatment of β-Thalassemia.

Strategy	Phase	NCT Number	Study Title	Interventions	Status
Trap-ligand targeting TGFβ-ligands	Phase 2	NCT01571635	Study to Determine the Safety and Tolerability of Sotatercept (ACE-011) in Adults With Beta(β)-Thalassemia.	Sotatercept	Active, not recruiting
	Phase 2	NCT02268409	ACE-536 Extension Study - Beta Thalassemia	Luspatercept	Active, not recruiting
	Phase 3	NCT02604433	An Efficacy and Safety Study of Luspatercept (ACE-536) Versus Placebo in Adults Who Require Regular Red Blood Cell Transfusions Due to Beta (β) Thalassemia	Luspatercept	Active, not recruiting
HbF induction	Early Phase 1	NCT02981329	Fetal Hemoglobin Induction Treatment Metformin	Metformin	Recruiting
RIC	Phase 2	NCT00408447	Stem Cell Transplant in Sickle Cell Disease and Thalassemia	Busulfan, Fludarabine, Alemtuzumab	Recruiting
	Phase 2	NCT02038478	Allograft for Sickle Cell Disease and Thalassemia	Donor Stem Cell Transplantation	Recruiting
	Phase 1	NCT02165007	Haploidentical Hematopoietic Stem Cell Transplantation for Children With Sickle Cell Disease and Thalassemia Using CD34+ Positive Selected Grafts	Peripheral blood stem cell graft that are CD34+ selected	Recruiting
JAK2 inhibition	Phase 2	NCT02049450	Study of Efficacy and Safety of INC424 in Regularly Transfused Patients With Thalassemia.	Ruxolitinib	Completed
GT	Early Phase 1	NCT02633943	Longterm Follow-up of Subjects With Hemoglobinopathies Treated With Ex Vivo Gene Therapy	Safety and efficacy assessments	Enrolling by invitation
	Phase 2	NCT03275051	Long-term Safety and Efficacy Follow-up of Subject Treated With GSK2696277 for Transfusion Dependent Beta-thalassemia in San Raffaele Telethon Institute of Gene Therapy-Beta Thalassemia (TIGET-BTHAL) Study	Safety and efficacy assessments	Not yet recruiting
	Phase 1/Phase 2	NCT02453477	Gene Therapy for Transfusion Dependent Beta-thalassemia	GLOBE	Recruiting
	Phase 1	NCT01639690	β-Thalassemia Major With Autologous CD34+ Hematopoietic Progenitor Cells Transduced With TNS9.3.55 a Lentiviral Vector Encoding the Normal Human β-Globin Gene	TNS9.3.55	Active, not recruiting

Strategy	Phase	NCT Number	Study Title	Interventions	Status
	Phase 1/Phase 2	NCT02453477	Gene Therapy for Transfusion Dependent Beta-thalassemia	LentiGlobin BB305	Recruiting
	Phase 1/Phase 2	NCT01745120	A Study Evaluating the Safety and Efficacy of the LentiGlobin® BB305 Drug Product in Beta-Thalassemia Major Subjects		Active, not recruiting
	Phase 1/Phase 2	NCT02151526	A Study Evaluating the Efficacy and Safety of the LentiGlobin BB305 Drug Product in Beta-Thalassemia Major and Sickle Cell Disease		Active, not recruiting
	Phase 3	NCT03207009	A Study Evaluating the Efficacy and Safety of the LentiGlobin® BB305 Drug Product in Subjects With Transfusion-Dependent β-Thalassemia, Who Have a β0/β0 Genotype		Recruiting
	Phase 3	NCT02906202	A Study Evaluating the Efficacy and Safety of the LentiGlobin® BB305 Drug Product in Subjects With Transfusion-Dependent β-Thalassemia		Recruiting