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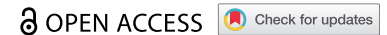


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REVIEW



Improving outcomes and quality of life for patients with transfusion-dependent β -thalassemia: recommendations for best clinical practice and the use of novel treatment strategies

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ABSTRACT

Introduction: β -thalassemia is one of the most common inherited monogenic diseases. Many patients are dependent on a lifetime of red blood cell (RBC) transfusions and iron chelation therapy. Although treatments have a significant impact on quality of life (QoL), life expectancy, and long-term health outcomes have improved in recent decades through safer RBC transfusion practices and better iron chelation strategies. Advances in the understanding of the pathology of β -thalassemia have led to the development of new treatment options that have the potential to reduce the RBC transfusion burden in patients with transfusion-dependent (TD) β -thalassemia and improve QoL.

Areas covered: This review provides an overview of currently available treatments for patients with TD β -thalassemia, highlighting QoL issues, and providing an update on current clinical experience plus important practical points for two new treatments available for TD β -thalassemia: betibeglogene autotemcel (beti-cel) gene therapy and the erythroid maturation agent luspatercept, an activin ligand trap.

Expert opinion: Approved therapies, including curative gene therapies and supportive treatments such as luspatercept, have the potential to reduce RBC transfusion burden, and improve clinical outcomes and QoL in patients with TD β -thalassemia. Cost of treatment is, however, likely to be a significant barrier for payors and patients.

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beti-cel; β -thalassemia; gene therapy; iron chelation therapy; luspatercept; management guidelines; quality of life; transfusion; transfusion-dependent

1. Introduction

β -thalassemia, an autosomal recessive disorder arising from single mutations that reduce the expression of β -globin, is one of the most common monogenic inherited diseases worldwide [1–3]. While β -thalassemia is prevalent in more than 60 countries across the world, most patients originate from Southeast Asia, the Middle East, and the Mediterranean [2,4,5]. β -thalassemia is characterized by the absence (β^0) or reduced synthesis (β^+) of the β -globin subunit of adult hemoglobin, causing an imbalance in the ratio of α -globin and β -globin chains, reducing hemoglobin production, and promoting ineffective erythropoiesis [6]. The premature destruction of red blood cell (RBC) precursors in the bone marrow and other extramedullary sites results in chronic anemia, reduced tissue oxygenation, and increased erythropoietin synthesis, which cause a wide range of clinical consequences, including bone changes, splenic enlargement, enlarged bone marrow, growth retardation, organ damage, vascular dysfunction, and jaundice [7–10].

Conventional treatments for patients with transfusion-dependent (TD) β -thalassemia are regular RBC transfusions plus iron chelation therapy (ICT) to correct anemia and reduce iron accumulation (Figure 1). Hematopoietic stem cell transplantation (HSCT), the only curative option, is only available

for a very limited subgroup of patients with a suitable matched donor (Figure 1) [8,11,12]. Patients with more clinically severe disease, known as TD β -thalassemia, often present with symptoms very early in life (before the age of 2 years), require lifelong disease management, and are dependent on regular RBC transfusions in order to prevent organ damage or early death [8,9]. Widespread adoption of safe RBC transfusion practices and improved ICT options have led to a longer life expectancy and improvements in the quality of life (QoL) for these patients; however, outcomes are still suboptimal for many [13,14]. TD β -thalassemia impairs the QoL of patients significantly compared with the general population [15,16]. Children and young adults are particularly affected as they lose important time in school with their peers due to regular hospital visits for treatments and appointments with numerous specialists [17]. Their frequent and invasive supportive treatments also cause long-term psychosocial effects.

Advances in the understanding of the pathogenesis of β -thalassemia have led to the development of several new treatment approaches and novel therapies that address the underlying cause of the disease. These can broadly be divided into three groups: those that aim to correct the imbalance in globin chain synthesis (i.e. gene therapy or gene editing), those that improve late-stage erythropoiesis

Article highlights

- The life expectancy and quality of life of patients with transfusion-dependent (TD) β -thalassemia have been improved by advances in the safety of red blood cell (RBC) transfusions and better iron chelation strategies, but lifelong transfusions and chelation therapy are still a huge social and economic burden for patients
- The first treatments addressing the underlying pathology of TD β -thalassemia have recently been approved: the gene therapy betibeglogene autotemcel (beti-cel) and luspatercept, an activin ligand trap that reduces ineffective erythropoiesis
- Gene therapy using globin lentiviral vectors has the potential to provide curative treatment for patients with TD β -thalassemia, offering the possibility of long-term transfusion independence previously only available following hematopoietic stem cell transplantation
- Luspatercept improves late-stage erythroid maturation and has been shown to significantly reduce RBC transfusion requirements in patients with TD β -thalassemia with a notable proportion of patients in clinical trials achieving RBC transfusion independence
- Practical guidance on the use of gene therapy and luspatercept in real-world clinical practice are provided as consensus expert recommendations on the use of these new treatments become available

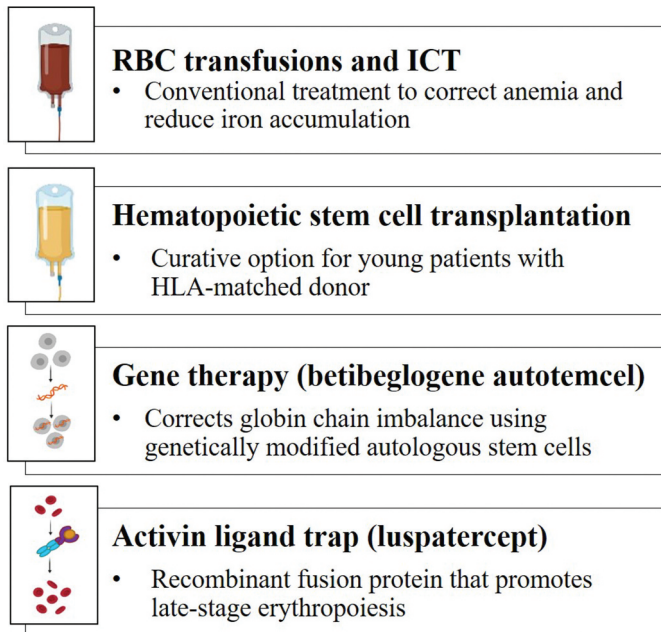


Figure 1. Currently approved treatments for transfusion-dependent β -thalassemia.

ICT, iron chelation therapy; HLA, human leukocyte antigens; RBC, red blood cell.

(e.g. activin ligand traps, JAK2 inhibitors), and those that reduce iron accumulation (e.g. hepcidin-like molecules, transmembrane protease serine 6 inhibitors) [11,18]. This review will focus on the potential to improve QoL for patients with TD β -thalassemia by summarizing current management recommendations and focusing on clinical use of two novel treatments that have recently been approved (gene therapy and the activin ligand trap, luspatercept; Figure 1). These treatments have the potential to dramatically improve QoL outcomes for patients, necessitating guidance for physicians as we await their inclusion in treatment guidelines [8,19–21].

2. Current treatment strategies and their effect on QoL

2.1. Conventional treatment approach

The management of patients with TD β -thalassemia is complex. Regular monitoring and intervention are required to manage complications, including cardiovascular disease, liver disease, bone disease, endocrine disease, and growth abnormalities [8]. Infection risk is increased due to both the disease and treatment. Patients often require specialist care for psychological support and issues related to fertility and pregnancy.

Treatment options for TD β -thalassemia generally include supportive care (e.g. RBC transfusion, ICT) and potentially curative therapies (e.g. HSCT, gene therapy). Splenectomy can reduce transfusion requirements and the risk of iron overload [22]. Due to the risk of complications, splenectomy use has decreased in recent decades and is not generally recommended for patients with TD disease, provided that patients receive adequate RBC transfusions and ICT, as discussed below [8].

2.2. RBC transfusions and ICT

Patients who have TD β -thalassemia require lifelong treatment with regular RBC transfusions every 2–5 weeks to maintain pre-transfusion hemoglobin levels of 9–10.5 g/dL [8]. The current international recommendations for clinical practice to ensure safe blood transfusions for thalassemia patients are summarized in Table 1. Patients who are regularly transfused face a number of important and potentially serious complications, including increased risk of viral infection from contaminated blood [23,24] and alloimmunization [8,25]. It is therefore important to screen all donated blood for viral contamination and use Rh- and K-matched donor blood for all transfusions. In countries where TD β -thalassemia is endemic, the need for regular, safe blood supplies is a major healthcare burden [14,26–28]. Even in relatively wealthy nations, the demand for blood supplies is a significant burden for healthcare systems. In Greece, for example, it was reported that the 4506 patients with hemoglobinopathies in the Greek national registry between 1997 and 2010 utilized 18% of the country's total supply of RBCs [28]. Uncertainties in securing adequate blood supply on an individual basis cause significant psychological burden on patients. Therefore, treatment strategies that reduce RBC transfusion requirements would have benefits for national healthcare services as well as for individual patients. Moreover, the SARS-CoV-2 pandemic has led to global shortages in blood donation and supplies since the beginning of 2020 [29–33], leaving patients with β -thalassemia particularly vulnerable.

Despite improvements in screening for pathogens and efforts to minimize allogenic reactions, both remain as consequences of transfusion and have potential to increase treatment burden [14,34]. These treatment burdens, while not universal, clearly affect health-related quality of life (HRQoL) in RBC transfusion recipients. Numerous longitudinal studies from the international Thalassemia Clinical Research Network have demonstrated impaired HRQoL in patients with β -thalassemia compared with the general US population [34].

Table 1. Current international recommendations for safe blood transfusion of patients with transfusion-dependent β -thalassemia.

Thalassemia International Federation 2021 recommendations for transfusions

- Patients with confirmed β -thalassemia should receive RBC transfusions every 2–5 weeks to maintain a pre-transfusion level of hemoglobin in the range 9–10.5 g/dL (11–12 g/dL recommended for patients with cardiac complications)
- Ensure appropriately screened donor blood is available (voluntary, regular and non-remunerated donations preferred)
- Extended RBC antigen typing of patients to be carried out prior to first transfusion. Type for at least D, C, c, E, e, and K antigens
- Transfuse ABO, Rh-compatible blood at each transfusion, matched for ABO, C, c, E, e, and K antigens if possible
- A full cross-match and screening for new antibodies should be carried out before each transfusion (centers that meet regulatory requirements perform an electronic cross match)
- Leukoreduced packed RBCs should be used for transfusion; filtration before storage is highly recommended but blood bank pre-transfusion filtration is acceptable (bedside filtration is only acceptable if the other two filtration options are not available)
- Washed RBCs should be used for patients who have severe allergic reactions
- RBCs stored in CPD-A should be transfused within 1 week of collection; RBCs stored in additive solutions should be transfused within 2 weeks of collection
- Post-transfusion hemoglobin levels should be kept lower than 14–15 g/dL
- Records for each patient should be kept detailing annual transfusion requirement, red cell antibodies, and any transfusion reactions/allergic reactions

CPD-A, citrate-phosphate-dextrose-adenine; RBC, red blood cell [8].

The burden of RBC transfusion and related morbidity can be safely assumed to contribute to these impairments. HRQoL worsened with increasing transfusion frequency and in line with the average distance traveled each month to receive blood, with school functioning being the domain most impacted [35].

Patients receiving regular RBC transfusions must adhere to an adequate ICT regimen to prevent complications or death due to iron toxicity. Iron can accumulate at a rate of 0.3–0.6 mg/kg per day in transfused patients and cannot be excreted by the body [8]. The accumulated iron has a number of toxic effects that include damage to the heart and liver, growth retardation, endocrine dysfunction, and osteoporosis, all of which may contribute to decreased QoL [36].

While improved chelation regimens have reduced mortality due to cardiac failure, the leading cause of premature death in patients with TD β -thalassemia, patients continue to experience complications and stress from cardiac-related mortality [37]. In addition, long-term health issues that negatively affect patients' QoL, such as bone pain, osteoporosis, liver disease, liver cancer, and anxiety, have emerged [15,38–41]. While children receiving optimal transfusion and chelation have better QoL, over time this worsens due to the numerous complications related to iron overload and repeated transfusions [36].

ICT is very effective in preventing iron overload if patients comply with and adhere to treatment, but these regimens can be very demanding of patient time, patient health, and health-care resources and result in reduced QoL [2,9,14,42]. Three

Table 2. Standard ICT regimens for transfusion-dependent β -thalassemia patients receiving regular blood transfusions.

First-line ICT	<ul style="list-style-type: none"> • Deferoxamine: 20–40 mg/kg/day over 8–24 hours subcutaneous continuous infusion via portable pump; 40–50 mg/kg/day given as an intravenous infusion over 8–12 hours (recommended); 500–1000 mg intramuscular • Deferasirox: 20–40 mg/kg/day administered once daily
Second-line treatment or when ICT with deferasirox or deferoxamine is inadequate	<ul style="list-style-type: none"> • Deferiprone: 75–100 mg/kg/day divided over 3 doses
Indications to intensify ICT	<ul style="list-style-type: none"> • Serum ferritin levels \geq 2500 ng/mL • Liver iron content $>$ 7 mg/g dry weight • Cardiac T2* MRI $<$ 20 ms
Indications to stop ICT	<ul style="list-style-type: none"> • Serum ferritin $<$ 300 ng/mL • Liver iron concentration $<$ 3 mg/g

ICT, iron chelation therapy; T2* MRI, T2*-weighted magnetic resonance imaging.

iron chelator drugs are currently available: deferoxamine, deferiprone, and deferasirox. Deferoxamine is administered by subcutaneous or intramuscular injection or intravenous infusion on a 5–7 days per week dosing schedule [43]. The two oral agents, deferiprone and deferasirox, are taken three times daily [44,45]. Suggested guidelines for ICT regimens are summarized in Table 2. Non-oral ICT can substantially affect HRQoL due to frequent, often daily, administration through a subcutaneous pump for at least 8–10 consecutive hours. This generally occurs during the night, with the potential to impair sleep, and is also associated with pain at the site of injection [46,47]. Oral ICT is preferred by patients, which leads to better adherence [48–50] and (possibly) QoL [14]. In a recent meta-analysis (2008–2016) that included 2961 patients with TD β -thalassemia, those receiving deferoxamine and combination therapy had poorer HRQoL status across all eight domains of the 36-item Short Form (SF-36) health survey than those receiving deferasirox [48]. In addition, a new film-coated formulation of deferasirox that can be taken with a meal, rather than on an empty stomach, has advantages in adherence, satisfaction/preference, and patient concerns compared to the dispersible formulation [51]. The dose of ICT must be adjusted for each patient and careful regular monitoring is required to manage the adverse effects, such as nausea, joint pain, kidney injury, and agranulocytosis, which may be associated with treatment and may compromise adherence [8,9,17,52,53]. Additionally, over time, comorbidity due to iron overload and transfusion complications is likely to lead to polypharmacy, which has been shown to be a major issue for patients who do not adhere to ICT [47]. Other concerns with ICT use reported by both adhering and non-adhering patients include the high cost and the lack of immediate results from ICT [47].

3. HSCT

Allogeneic transplantation with HLA-matched hematopoietic stem cells is the only curative treatment option for patients with TD β -thalassemia. This approach, however, is only suitable for young patients who have an HLA-matched donor,

usually a sibling [54]. Consensus statements currently recommend offering HSCT to patients younger than 14 years of age who have a suitable HLA-matched donor [55,56]. It is estimated that > 70% of patients do not have a suitable sibling HLA-matched donor, although non-sibling-related donors may also be available, particularly in populations where large families and consanguineous marriages are common [54,57,58]. Some evidence suggests that good outcomes can be achieved with unrelated donors, provided that donor and recipient are closely HLA-matched; in some cases, outcomes with unrelated donors were comparable to those achieved using matched sibling donors [8,57,59–62]. Other alternative HSCT strategies, such as HLA-antigen-mismatch donors [58], pretransplant immunosuppression [61], or double-unit unrelated cord blood transplantation [62], may further broaden the safety and/or applicability of HSCT. In addition, advances in preimplantation genetic diagnosis have enabled the selection of an HLA-matched embryo to produce a sibling donor, although the ethics of producing ‘savior siblings’ have been questioned [63,64].

Patients who undergo conventional HSCT before 14 years of age have a very low (< 10%) procedure-related mortality rate and the disease-free survival rate is at least 80% [55,56]. In a 30-year follow-up study (median follow up 11 years), Caocci and colleagues reported equivalent long-term survival in 258 HSCT-treated (including 161 [63.4%] patients < 16 years; 30-year overall survival rate $82.6 \pm 2.7\%$) and 258 conventionally treated patients ($85.3 \pm 2.7\%$); patients with unrelated donors experienced shorter survival compared with those who had a sibling donor [65]. Follow-up after HSCT should include careful monitoring for engraftment and possible relapse, infection, and graft-versus-host disease (GVHD), particularly in the first year after transplantation [8]. Thereafter, patients should be monitored for potential long-term complications, including iron overload, endocrine impairment, and issues related to growth and development [8]. Post-HSCT management of iron overload may require ICT or phlebotomy but should not be initiated until the graft is stable and immunosuppressive therapy has been discontinued. Issues related to endocrine dysfunction and infertility should be managed by a specialist.

After 20 years, improved HRQoL has been reported in patients who had HSCT compared with those who had conventional treatment [35,66]. The socioeconomic benefits to patients include less time off for medical appointments, improved education and job prospects, and better daily QoL. Studies have shown that HSCT improves HRQoL and is particularly valuable for young children as it offers the potential for lifelong freedom from RBC transfusions and ICT, allowing for increased continuity in education and social situations [66,67].

Even though the costs of HSCT and follow-up vary between countries [68], a successful transplant can be considered cost-effective compared with the costs of a lifetime of conventional treatment [9,56,69]. Disadvantages of HSCT include the intensive myeloablative and immunosuppressive conditioning that are required before the procedure, the risk of acute or chronic GVHD, negative effects on fertility, and the limited number of patients for whom the treatment is an option due to the lack of a suitable donor [8,9,39]. In a recent systematic review, studies reported both acute and chronic GVHD having

a negative effect on HRQoL scores [67]. Treatment of GVHD may also worsen QoL due to side effects including seizures and posterior leukoencephalopathy, although the replacement of cyclosporine by mycophenolate mofetil has led to a reduction in these complications [70,71].

School function was the most severely affected domain in an Indian study of HSCT versus conventional therapy [35], and there was no improvement in social domain scores in many of the studies in the systematic review by Badawy and colleagues [67]. Both issues potentially stem from the need for prolonged hospitalization and isolation to avoid infection [67]. In addition, impaired growth and increased likelihood of being overweight may add to existing stigma related to the disease [67,72].

4. Beti-cel gene therapy

Gene therapy is a novel and potentially curative treatment strategy for TD β -thalassemia that has been designed to correct the underlying globin chain imbalance, thus improving the production of functional hemoglobin, erythropoiesis, and chronic anemia. Significantly, gene therapy does not require a matched donor. The aim of gene therapy is to enable patients to achieve long-term transfusion independence [5,39,73]. Patients undergo autologous hematopoietic stem cell mobilization and harvesting, followed by intensive myeloablative conditioning and immunosuppression. The autologous stem cells obtained are then transduced outside the body with self-inactivating lentiviral vectors that insert a gene construct containing the globin gene and other genetic elements required for gene expression. The transduced stem cells are then reinfused into the patient where the modified cells replicate, repopulate the blood compartment, and facilitate normal hemoglobin synthesis (Figure 2). [73,74]

The first gene therapy, betibeglogene autotemcel (beti-cel; bluebird bio), is currently in clinical trials in the USA for patients with TD β -thalassemia aged ≤ 50 years for whom HSCT is appropriate but no HLA-matched donor is available. Beti-cel is a genetically modified autologous CD34+ cell enriched population that contains hematopoietic stem cells transduced with a lentiviral vector encoding the β^{A-T87Q} -globin gene [75]. Patients undergo mobilization and apheresis to collect CD34+ stem cells and a full myeloablative conditioning regimen with busulfan prior to beti-cel infusion.

Lentiviral vector-based gene therapy has been successful in several animal models of β -thalassemia and proof-of-principle studies in an adult patient with TD β -thalassemia [76–80]. In two non-randomized open-label phase 1/2 studies, mobilized autologous CD34+ cells were obtained from 22 patients with TD β -thalassemia and transduced with a lentiviral vector encoding adult hemoglobin A with a T87Q substitution. The transduced stem cells were then re-infused after the patients had undergone myeloablative conditioning with busulfan [81]. Both studies (NCT01745120, NCT02151526) reported increased levels of hemoglobin A and a sustained reduction in transfusion requirement. The adverse events reported were similar to those associated with autologous stem cell transplantation and no clonal dominance related to lentiviral vector

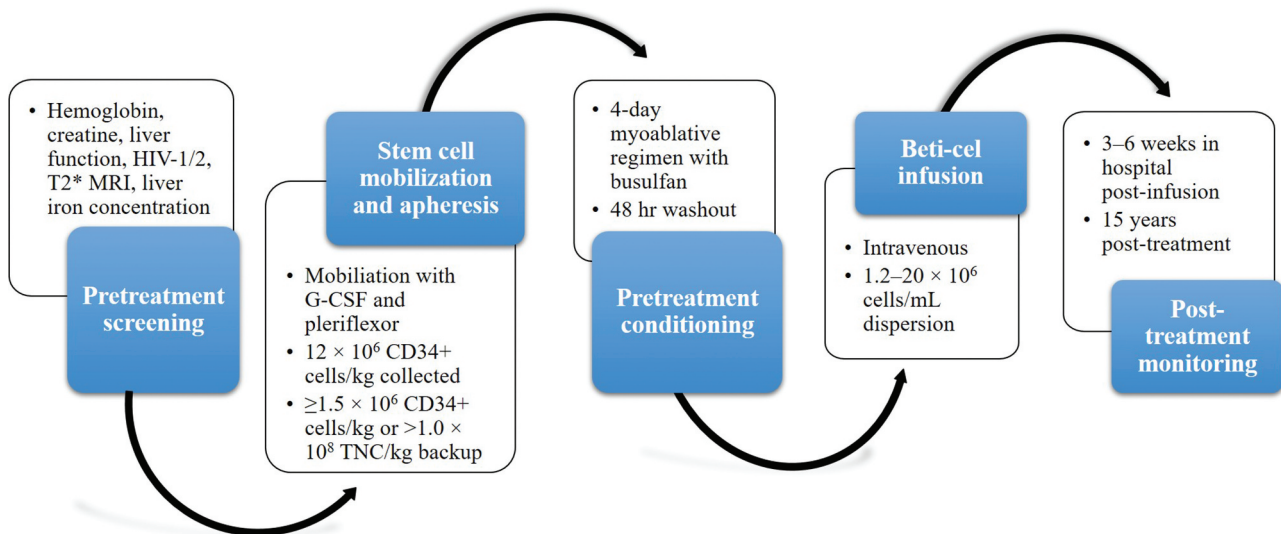


Figure 2. Gene therapy clinical process.

Beti-cel, betibeglogene autotemcel; G-CSF, granulocyte colony-stimulating factor; HIV, human immunodeficiency virus; T2* MRI, T2*-weighted magnetic resonance imaging; TNC, total nucleated cell count.

integration was observed [81]. At a median of 26 months after receiving gene therapy, all except 1 of 13 patients with non- $\beta^0\beta^0$ genotypes had achieved transfusion independence and biological markers indicated that ineffective erythropoiesis had been corrected [81]. Although the benefits of treatment were most pronounced in patients with less severe genotypes, 9 patients with $\beta^0\beta^0$ genotypes achieved a 73% reduction in median annual transfusion volume and 3 of these patients discontinued RBC transfusions [81].

The clinical efficacy and safety of beti-cel in patients with non- $\beta^0\beta^0$ and $\beta^0\beta^0$ genotypes have been demonstrated in the HGB-212 and HGB-207 phase 3 studies (NCT02906202, NCT03207009) [82]. After a median 24.3-month follow-up, 30 of 34 (88.2%) patients treated in phase 3 were transfusion independent [83]. Of 7 evaluable $\beta^0\beta^0$ patients, 6 (85.7%) achieved transfusion independence (defined as Hb \geq 9 g/dL without packed RBC transfusions for \geq 12 months) for $>$ 20.6 months [83]. The safety profile of beti-cel treatment was similar to that seen following myeloablative conditioning with busulfan [83]. Following initial positive results, the phase 3 studies were expanded to include pediatric patients; interim results in the 28 pediatric and adolescents enrolled in these studies up to March 2021 show that pediatric patients achieve transfusion independence at comparable rates (91%) to adults with a similar safety profile [84,84].

In an ongoing 13-year follow-up study (LT-303) involving 32 patients from the phase 1/2 and phase 3 studies, transfusion independence was achieved by 14 of 22 patients from the phase 1/2 studies (64%; 12 in the parent study, 2 in LT-303) and 9 of 10 (90%) treated in the phase 3 Northstar-3 study [81,84]. In addition, patients in the phase 3 study continue to experience improved erythropoiesis, reduced iron burden, and cessation of ICT (median follow-up 14.4 months) [85]. Thus, while most patients treated with beti-cel achieved long-term transfusion independence, it is important to note that some patients may still require intermittent transfusions, albeit at a lower rate than before treatment.

An analysis of data from 110 patients followed up for up to 5 years in 6 studies of beti-cel in TD β -thalassemia, sickle cell disease, and cerebral adrenoleukodystrophy found that gene therapy carried no risk of graft rejection or GVHD, and no clinically relevant clonal dominance or lentiviral vector-mediated replication competent lentivirus were observed [86]. A temporary hold of clinical trials of beti-cel in β -thalassemia, due to investigations into the development of acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) in 2 patients with sickle cell disease in a related clinical trial, has been lifted; the MDS diagnosis has been revised to TD anemia and the AML case was reported to be unlikely related to treatment [87]. While provisional approval by the European Medicines Agency (EMA) was given in 2019, bluebird bio has recently announced they will no longer be focusing on gaining further market access for beti-cel in Europe due to payor challenges [88]. Another gene therapy involving intrabone administration of hematopoietic stem cells transduced with the lentiviral vector GLOBE is also undergoing clinical development and has shown promising early results in a phase 1/2 clinical trial (NCT02453477) [89].

4.1. Beti-cel gene therapy: benefits and challenges

Gene therapy has important potential to expand the number of patients who can receive potentially curative treatment for TD β -thalassemia as it avoids the need for an HLA-matched donor, there is no risk of GVHD, and long-term immunosuppression is not required. The potential risks associated with lentiviral gene therapy include viral toxicity and the activation of oncogenes causing tumor development and transmission in the germ line. None of these issues have been observed in clinical trials of beti-cel in patients with TD β -thalassemia, but long-term data are needed and will be provided by the long-term follow-up study LT-303 [82,83,86]. Additionally, the toxicity of the myeloablative conditioning regimen and difficulties in adequate hematopoietic stem cell mobilization and

harvesting can be compromised by the suppressive effect of long-term transfusions and ICT on the bone marrow [18].

The impact of gene therapy on patient QoL remains to be fully determined and should be further evaluated in future clinical trials of beti-cel. However, data from the phase 3 Hgb-207 (Northstar-2) and Hgb-212 (Northstar-3) studies showed that patients under 18 years of age who achieved transfusion independence had an improved EuroQoL 5 dimensions (Youth) (EQ-5D-Y) score (67 [range 50–96] versus 92.5 [85–95]) after 12 months [67,90]. In addition, HSCT has been shown to have a positive impact on both physical and emotional aspects of HRQoL in patients with TD β -thalassemia and, given GVHD was the most common cause of impaired HRQoL in these patients, a similar or greater benefit would be expected from gene therapy [67].

Gene therapies have an extremely high initial cost, which will be challenging for health authorities and payors and may not be affordable in developing countries [91]. The hematopoietic stem cell mobilization/apheresis protocol and the myeloablative conditioning regimen are very resource intensive and the requirement of individualized treatment prevents any economies of scale in production. As has been previously described for HSCT, gene therapy could theoretically be cost-effective if it allows patients to achieve transfusion independence and avoid the high monthly costs associated with long-term transfusions, ICT, and related healthcare expenses; however, the cost of gene therapy is considerably higher than that of HSCT. A recent health economic analysis of beti-cel therapy versus standard of care for TD β -thalassemia in France showed that beti-cel was cost-effective with an incremental cost-effectiveness ratio of EUR 49 per quality-adjusted life-year (QALY), rising to EUR 427/QALY when indirect costs such as unemployment and loss of productivity were included [92].

4.2. Beti-cel gene therapy: clinical practice points

Beti-cel gene therapy can only be administered in an experienced treatment center by a multidisciplinary team experienced in delivering HSCT and treating patients with TD β -thalassemia. Beti-cel is prepared on an individual patient basis; it is for autologous use only and should be administered once as an intravenous infusion following full myeloablative conditioning.

Eligible patients ≥ 12 years of age must have hemoglobin levels ≥ 11 g/dL for 30 days prior to mobilization and during myeloablation; creatinine clearance ≤ 70 mL/min/1.73 m²; normal liver function tests; negative serology HIV-1/2; and cardiac T2*-weighted magnetic resonance imaging (T2* MRI) ≥ 10

msec. If MRI liver iron concentration is ≥ 15 mg/g, liver biopsy should be performed to confirm absence of fibrosis, cirrhosis, or active hepatitis. Negative serum pregnancy tests must be provided before mobilization and conditioning, and before beti-cel infusion. Beti-cel is not recommended for women who are breastfeeding. Ova and semen cryopreservation are recommended before treatment. Anti-retroviral medications and/or hydroxyurea should be stopped ≥ 1 month prior to and until ≥ 7 days after conditioning and ICT must be stopped ≥ 7 days before conditioning. It is recommended that patients receive prophylaxis to prevent veno-occlusive disease and prophylaxis against seizures should also be considered.

Stem cell mobilization is performed approximately 2 months prior to beti-cel infusion using granulocyte-macrophage-colony stimulating factor and pleriflexor followed by apheresis to collect a minimum of 12×10^6 CD34+ cells/kg. Repeat cycles of mobilization and apheresis may be required to collect sufficient cells. A back-up collection of $\geq 1.5 \times 10^6$ CD34+ cells/kg or $> 1.0 \times 10^8$ TNC/kg (bone marrow harvest) is required. Pretreatment conditioning should only begin once the complete beti-cel doses have been received on site. Six days before beti-cel infusion, a full 4-day pretreatment myoablative conditioning regimen with busulfan is required, followed by a 48-hour 'washout' period. Beti-cel is administered intravenously in a hospital setting. Prior to initiating infusion, reconfirm that the identity of the patient matches the name on the infusion bag(s). Beti-cel ($1.2\text{--}20 \times 10^6$ cells/mL dispersion) should be infused within 4 hours of thawing and each infusion bag must be infused within 30 minutes. Patients should remain in the hospital for 3–6 weeks for monitoring.

Standard procedures for patient monitoring and management following HSCT must be followed after administration of beti-cel, including for thrombocytopenia and bleeding. Patients must be tested annually for leukemia or lymphoma for 15 years post treatment. The long-term effects of gene therapy on iron already accumulated in the liver and heart are not clear and patients may therefore need to continue or restart ICT following the procedure. Guidelines are needed for ICT post-gene therapy; current recommendations based on consensus opinion are shown in Table 3 [93].

It is important to provide adequate patient/parent/carrier counseling and education regarding the risks and complexity of this treatment prior to initiating gene therapy. It is particularly important that patients and their families understand the short-term risks associated with the intensive conditioning regimen that is required and the possible need to continue ICT after gene therapy. Patient enrollment in the product registry for 15 years following treatment should also be discussed.

Table 3. Recommendations for post-gene therapy ICT.

		Cardiac iron by T2* MRI	
		> 20 milliseconds	20–10 milliseconds
Liver iron concentration	< 8 mg/g	No ICT required	ICT is recommended
	8–15 mg/g	Consider ICT if serum ferritin levels > 2000 ug/L at day 90 OR if patient is positive for hepatitis B/C pre-gene therapy	ICT is recommended
	> 15 mg/g	ICT recommended	ICT is recommended

Each patient's pretreatment cardiac and liver iron assessments (based on cardiac and liver MRI and/or liver biopsy) determine the need for ICT post-gene therapy. ICT, iron chelation therapy; ms, milliseconds; T2* MRI, T2*-weighted magnetic resonance imaging.

5. Luspatercept

Luspatercept (Bristol Myers Squibb) is a novel recombinant fusion protein that binds transforming growth factor beta (TGF- β) superfamily ligands to inhibit aberrant Smad2/Smad3 signaling and promote late-stage erythropoiesis [94,95] (Figure 3). Luspatercept was approved for the treatment of anemia in adult patients with TD β -thalassemia by the US FDA in November 2019 and by the EMA in June 2020 [96,97]. In healthy volunteers, luspatercept treatment increased hemoglobin levels and was safe and well tolerated at effective dose levels [98]. A multicenter, open-label, randomized dose-finding phase 2 study (NCT01749540, NCT02268409) demonstrated that luspatercept at 0.2–1.25 mg/kg subcutaneously (s.c.) every 3 weeks for at least 5 cycles, was effective and well tolerated in 64 adults with TD or non-TD β -thalassemia [98]. A reduction in RBC transfusion burden of $\geq 20\%$ over a 12-week period was achieved by 26 of 32 TD patients (81%) in the study; the most common Grade 1 or 2 adverse events included bone pain, headache, and myalgia [99].

These findings led to the initiation of the pivotal randomized, double-blind, placebo-controlled, multicenter BELIEVE phase 3 study (NCT02604433) that confirmed the efficacy and safety of luspatercept at 1.0–1.25 mg/kg s.c. every 21 days for at least 48 weeks, in adults with TD β -thalassemia [100]. The proportion of patients in the BELIEVE study who achieved $\geq 33\%$ in RBC transfusion burden during Weeks 13–24, with a reduction of ≥ 2 RBC units (primary endpoint) was significantly greater with luspatercept compared with placebo (21.5% versus 4.5%, respectively; $P < 0.001$). During any 12-week period, a significantly greater proportion of patients receiving luspatercept achieved $\geq 33\%$ or $\geq 50\%$ reduction in

RBC transfusion burden compared with placebo [100]. Subgroup analysis of the BELIEVE study has shown that clinically meaningful reductions in transfusion burden were seen across all genotypes, though response rates were lower in patients with the most severe ($\beta^0\beta^0$) disease [101]. Luspatercept was well tolerated; adverse events that were more common with luspatercept than placebo were transient bone pain, arthralgia, dizziness, hypertension, and hyperuricemia [100]. Thrombotic adverse events were reported in 8 patients (4%) treated with luspatercept, mostly in splenectomized patients with known thrombotic risk factors.

Recent follow-up analyses from the BELIEVE study have confirmed that the benefit of luspatercept on transfusion burden is sustained over time. Patients who continued luspatercept treatment experienced sustained reductions in RBC units transfused and transfusion visits for at least 2 years in a longitudinal analysis of the open-label phase of the study [102,103]. As of 1 July 2019, the median duration of treatment for patients in the luspatercept and placebo groups was 119.1 weeks and 74.7 weeks, respectively. In patients treated with luspatercept, reductions in transfusion burden (≥ 2 RBC units) from baseline of $\geq 33\%$ and $\geq 50\%$ during any 48-week period were achieved by 27.7% and 12.5% of patients, respectively, compared with 1.8% and 0.9% of patients in the placebo group, respectively [103]. In patients initially randomized to the placebo arm who crossed over to luspatercept treatment during the open-label phase, 18.5% achieved $\geq 33\%$ reduction in RBC and 9.8% achieved reductions of transfusion burden of $\geq 50\%$ during Weeks 13–24 after crossover [103]. In addition, compared with placebo, luspatercept treatment was associated with a significant reduction in serum iron levels, liver iron concentration, and myocardial iron levels during the

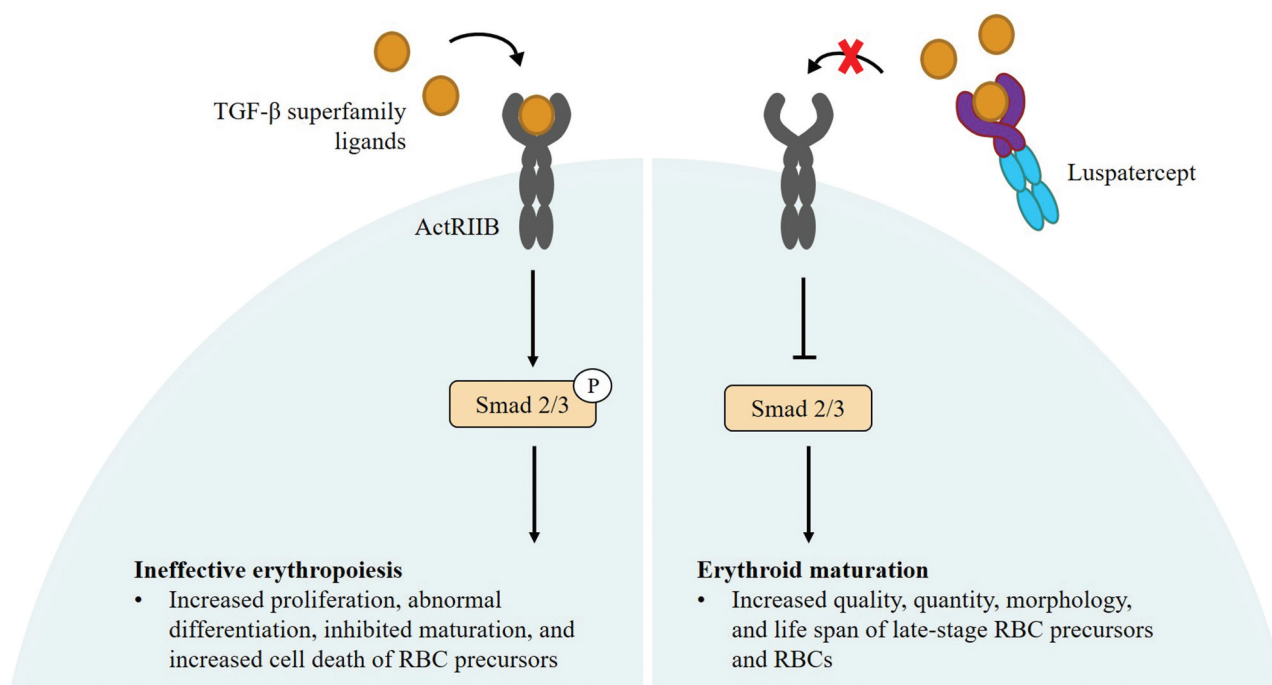


Figure 3. Schematic representation of the mechanism of action of luspatercept.

In the absence of luspatercept treatment (*left panel*), TGF- β superfamily ligands bind the ActRIIB and drive ineffective erythropoiesis. Luspatercept competes with the extracellular domain of the activin receptor to act as a ligand trap for TGF- β (*right panel*), reducing Smad 2/3 signaling, improving erythrocyte maturation, and reducing ineffective erythropoiesis. ActRIIB, activin b receptor type 2; RBC, red blood cell; TGF- β , transforming growth factor beta.

first 96 weeks of treatment [104]. Longer term use of luspatercept was associated with an increasing number of patients with serum ferritin levels < 1000 µg/L and trends toward a reduction in overall use of ICT and decreasing daily doses of deferasirox [105].

5.1. Luspatercept: benefits and challenges

Compared with gene therapy and HSCT, drugs that correct ineffective erythropoiesis, such as luspatercept, are less expensive and may therefore be more accessible to patients. Health economic studies will be needed to demonstrate the long-term cost-effectiveness of this new treatment. The long-term impact of luspatercept on transfusion burden (e.g. volume of RBC units transfused, frequency of transfusion visits) and comorbidities in the real-world setting is not yet known. Observational studies of clinical practice patterns should provide valuable insights on these important issues. Preliminary evidence from the BELIEVE study indicates that luspatercept provides a sustained reduction in serum ferritin levels, however, changes to cardiac and hepatic iron overload take time. Thus, patients will require close follow-up (e.g. T2* MRI). The anticipated benefits of luspatercept in reducing transfusion burden would be expected to translate into positive benefits on patients' physical and mental well-being. Preliminary data from the BELIEVE trial suggest luspatercept maintains HRQoL and improves physical functioning (as measured by the generic SF-36 health survey Physical Functioning and Physical Component Summary [PCS] questionnaire) compared with placebo [106]. Patients who achieved clinical benefit with luspatercept treatment were also more likely to experience meaningful improvement in Physical Functioning and PCS compared with placebo. Long-term QoL outcomes studies are needed to confirm this effect. In addition, the long-acting nature of luspatercept in conjunction with the associated reductions in transfusion burden and ICT use could potentially ameliorate some of the QoL burden of conventional therapy over time, by improving adherence and reducing transfusion-related complications.

5.2. Luspatercept: clinical practice points

Luspatercept should be administered s.c. once every 21 days [107]. The recommended starting dose is 1.0 mg/kg (maximum injected volume per site 1.2 mL) injected into the upper arm, thigh, or abdomen. A treatment response to luspatercept is defined as a reduction in RBC transfusion burden of at least one third (33%) after two consecutive doses. If no treatment response is seen at the starting dose, the dose should be increased to 1.25 mg/kg (maximum dose). If a patient loses their treatment response after initially responding to the starting dose, the dose of luspatercept can be increased to 1.25 mg/kg.

Prior to each dose of luspatercept, it is essential to assess the patient's hemoglobin level. If a transfusion is needed before starting treatment, the pre-transfusion hemoglobin level should be used to assess the starting dose of luspatercept [106]. During treatment, hemoglobin levels should be assessed regularly. If a patient's hemoglobin level increases >

2 g/dL within 3 weeks of a dose of luspatercept in the absence of a transfusion, the next dose of luspatercept should be reduced by 1 step (e.g. a 1.0 mg/kg to 0.8 mg/kg or 1.25 mg/kg to 1.0 mg/kg). If a patient's hemoglobin levels increase to > 11.5 g/dL with no transfusions in the previous 3 weeks, the next luspatercept dose should be delayed until their hemoglobin level is < 11.0 g/dL and a single-step dose reduction in luspatercept dose should be considered as described above. If a patient experiences a loss of response to luspatercept, the dose can be increased to 1.25 mg/dL after excluding potential causes such as a bleeding episode. If no treatment response is seen after 3 doses (e.g. 9 weeks) at the maximum dose level (1.25 mg/kg), treatment should be discontinued. No dose adjustments are required for patients with mild to moderate hepatic or renal impairment.

Adverse events, such as transient bone pain, arthralgia, dizziness, hypertension, and hyperuricemia, are usually transient and should be managed with prophylaxis. Patients, especially those with risk factors and previous splenectomy, should be actively monitored for thrombosis [108]. If patients develop persistent, high-grade (Grade 3 or above) adverse events related to treatment, the next dose of luspatercept should be delayed until the toxicity has resolved or significantly improved; treatment should be restarted at the previous dose (or a lower dose should be considered). Treatment should be discontinued if a patient experiences a Grade 3–4 hypersensitivity reaction.

6. Conclusions and challenges

HSCT continues to play a valuable role in the treatment of TD β-thalassemia, and improved techniques, such as the use of matched unrelated donors, are improving the safety and applicability of this approach. Emerging clinical evidence suggests that the newly available treatment options, gene therapy and luspatercept, are likely to further improve long-term clinical outcomes, reduce transfusion burden, improve long-term health, maintain HRQoL, and increase life expectancy for patients with TD β-thalassemia. Significant challenges remain with newly approved treatments, including barriers to treatment for patients and payors (e.g. the cost and cost-effectiveness of treatment, availability, and accessibility of treatment), the risks associated with gene therapy (i.e. intensive conditioning regimen, stem cell procurement), the impact of new treatments on future need for ICT and long-term QoL, and provision of appropriate patient education and counseling.

7. Expert opinion

Undoubtedly the long-term survival and QoL have significantly improved over the past decades for patients with TD β-thalassemia. The increased availability of safe, screened Rh- and K-matched blood, and oral ICT drugs have transformed and lengthened lives for many patients. However, the majority of patients with β-thalassemia live in resource-constrained areas of the world; for these patients, access to adequate transfusions and appropriate ICT as well as the life-long burden of this disease remains challenging. Even in patients

achieving effective control with these therapies, comorbidities increase over time and lead to reductions in life expectancy and QoL. As a potentially curative treatment, HSCT plays an important role for selected patients. New techniques improving the safety and efficacy of matched family and unrelated donors will continue to expand the candidates for HSCT. Despite these advances, however, not all patients will be eligible for HSCT. For these reasons, new treatment approaches that can reduce the long-term need for RBC transfusions and/or the dose/frequency of ICT are being developed.

Among the emerging new treatment options, gene therapy has the potential to increase the number of patients who can receive curative treatment that can offer lifelong independence from RBC transfusions without the need for a matched sibling donor. For some countries, such as those with limited availability of donated blood, the wider availability of a treatment that reduces the need for RBC transfusions will be important. However, the fact that gene therapy is a very expensive and specialized treatment limits its use in many areas of the world. Health economic studies are needed to demonstrate the cost/benefit of gene therapy over a patient's life. In addition, the long-term safety of gene therapy will need to be carefully monitored for the potential, though currently unsubstantiated, activation of oncogenes.

The approval of luspatercept has led to the availability of a new treatment for patients with TD β -thalassemia and may provide long-term sustained reductions in transfusion requirements and the need for ICT. These benefits should translate into improved long-term outcomes for patients and associated improvements in QoL. Long-term data from studies such as the phase 3 BELIEVE trial, which has a 5-year follow-up, are now emerging and will provide valuable insights in this respect, but initial signs are that luspatercept can provide sustained reductions in both transfusion burden and the frequency of transfusions.

The cost of treatment directly impacts access to new therapies and is a key consideration in the management of patients with TD β -thalassemia that will greatly impact the use of these treatments in the management of this disease. It is clear that there will be a need for updated treatment recommendations from national thalassemia societies/healthcare agencies to guide the integration of the novel therapies into standard care pathways and to inform physicians, payors, and patients on what to expect from, and how to prepare for, gene therapy and luspatercept treatment in clinical practice. Accordingly, the Thalassemia International Federation has recently updated its guidance on the use of gene therapy and luspatercept [8]. Several other novel treatments for TD β -thalassemia in clinical development aim to improve iron metabolism and reduce iron accumulation and erythropoiesis (e.g. gene editing, hepcidin-like molecules, TMPRSS6 inhibitors, ferroportin inhibitors), extend RBC survival (e.g. allosteric activators of pyruvate kinase, inhibitors of phosphodiesterase-9), or develop alternative sources of RBCs that may overcome infection risk or be compatible for patients with alloimmunization (e.g. *in vitro* RBC cultures, erythropoietic stem cells derivatives, induced pluripotent stem cells, genetically modified somatic cells). Several of these novel agents are expected to be approved within the next 5 years and collectively these new treatments

will improve long-term outcomes for patients with β -thalassemia.

List of Abbreviations

AML: acute myeloid leukemia
 CPD-A: citrate-phosphate-dextrose-adenine
 EMA: European Medicines Agency
 G-CSF: granulocyte colony-stimulating factor
 GVHD: graft-versus-host disease
 HIV: human immunodeficiency virus
 HRQoL: health-related quality of life
 HSCT: hematopoietic stem cell transplant
 ICT: iron chelation therapy
 MDS: myelodysplastic syndromes
 MRI: magnetic resonance imaging
 PCS: Physical Component Summary
 QALY: quality-adjusted life-year
 QoL: quality of life
 RBC: red blood cell
 s.c.: subcutaneously
 SF-36: 36-item Short Form
 TD: transfusion-dependent
 TGF- β : transforming growth factor beta
 TNC: total nucleated cell count

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