

Gene Therapy

Clinical Guidelines

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Contents

Introduction	3
FDA-approvals.....	3
Indications.....	3
Beta thalassemia.....	3
Cerebral adrenoleukodystrophy.....	6
References	9

Gene Therapy

Introduction

The term “gene therapy” usually has been used to describe an ex vivo or in vivo therapy whereby RNA or DNA are introduced into target cells (ex vivo) or tissues (in vivo) by a delivery vector while “cellular therapy” is a broad term that encompasses both the infusion of a cellular product for the purpose of hematopoietic reconstitution and the infusion of a cellular product intended to have a direct immunologic impact (Sharma et al., 2022). There is a general consensus among the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the American Society of Gene and Cell Therapy (ASGCT) defining gene therapy as changes in gene expression, achieved by replacing or correcting a disease-causing gene, inactivating a target gene, or inserting a new or modified gene, using a vector or delivery system of genetic sequence or gene, genetically modified microorganisms, viruses, or cells (EMA, 2020; FDA, 2018; ASGCT, 2021). The rapid growth of cellular and gene therapies over the past few years has revealed the need for an accurate and uniform taxonomy. Work is ongoing across a number of industry stakeholders including clinicians, scientists, payers, and coders to standardize nomenclature regarding what constitutes a cellular therapy or a gene therapy (Sharma et al., 2022). In the United States, the FDA establishes the regulatory framework for clinical trials and approval of therapeutic agents such as gene and cellular therapy. Specifically, the FDA Center for Biologics Evaluation and Research regulates cellular therapy products and human gene therapy products as biologics, as well as some devices related to cellular and gene therapy (FDA, 2018).

FDA-approvals

Zynteglo® (betibeglogene autotemcel) is an autologous hematopoietic stem cell-based gene therapy that received FDA-approval August 17, 2022, for the treatment of adult and pediatric patients with β -thalassemia who require regular red blood cell (RBC) transfusions.

Skysona® (elivaldogene autotemcel) was approved by the FDA on 9/16/2022 as the first gene therapy to treat boys 4 – 17 years of age with early, active cerebral adrenoleukodystrophy (CALD). The indication is approved under accelerated approval. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Indications

Beta thalassemia

Thalassemias are a class of disorders caused by imbalance to the alpha (α) and beta (β) globin chains that make up the principal adult oxygen transporter hemoglobin A ($\alpha_2 \beta_2$). Beta thalassemias result from an excess of α chains due to a reduced production of β globin chains and in some instances, increased dosage of α globin genes (Mettananda et al., 2018). The beta thalassemia phenotype is determined by the degree of the imbalance and ranges from minimal effects in beta thalassemia trait to severe transfusion-dependent anemia. Complications are numerous and include growth failure, bone disease, cardiac abnormalities (pulmonary hypertension, heart failure, arrhythmias), predisposition to thrombosis, extramedullary hematopoiesis (splenomegaly, masses with compression), and a broad range of

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endocrinopathies (Ali et al., 2021). Traditionally, beta thalassemia has been more common in certain regions of the world such as the Mediterranean, Middle East, and Southeast Asia. However, the prevalence is increasing in other regions, including Northern Europe and North America, primarily due to migration. According to the National Organization for Rare Disorders (NORD), the incidence of symptomatic cases in the United States is estimated to be approximately 1 in 100,000 individuals in the general population; males and females are equally affected. In many states, infants are diagnosed with a hemoglobin disorder through newborn screening. Each state's newborn screening program and the specific disorders tested for is different. Most states do not routinely test for thalassemia (NORD, 2018).

Beta thalassemias have been classified as thalassemia major, thalassemia intermedia, and thalassemia minor (trait), but a more useful classification is one of transfusion-dependent thalassemia (TDT) of non-transfusion-dependent thalassemia (NTDT) (Khandros & Kwiatkowski, 2019). The decision to initiate regular transfusions includes objective laboratory data as well as clinical findings.

Transfusions are recommended if the steady-state hemoglobin level is less than 7 g/dL. Poor growth, the development of frontal bossing or maxillary hyperplasia or other symptoms of anemia and ineffective erythropoiesis, even in the absence of severe anemia, should prompt initiation of transfusions. The goals of regular RBC transfusion therapy are relief of anemia symptoms (allowing for normal growth) as well as suppression of endogenous ineffective erythropoiesis. This generally is accomplished by administering transfusions every 3 to 5 weeks to maintain hemoglobin level greater than 9.5 g/dL before transfusion. As beta thalassemia is characterized by abnormal iron metabolism resulting in increased iron absorption, monitoring and management of iron overload is an essential part of treatment. Patients with TDT are at greater risk of rapid iron loading because of the high content of iron within transfused cells. Iron deposits in the liver, heart, and endocrine glands cause significant morbidity. Iron chelation therapy is administered with the goal of reducing the toxic effects of iron overload. Three iron chelators are approved for use in the United States: deferoxamine, deferasirox, and deferiprone.

Allogeneic hematopoietic stem cell transplantation (HSCT) from a human leukocyte antigen (HLA)-matched sibling donor (MSD), performed in childhood, has been the gold standard treatment for TDT for decades with probabilities of overall and thalassemia-free survival exceeding 90% and 85%, respectively. Unfortunately, siblings are available only for the minority of patients leaving fully matched unrelated donors (MUD) as the second option with similar results in terms of survival. (Oikonomopoulou & Goussetis, 2021; Strocchio & Locatelli, 2018).

Gene Therapy

Gene therapy is a novel and potentially curative treatment strategy for TDT patients that has been designed to correct the underlying α/β -globin chain ratio, thus improving the production of functional Hb, the erythropoiesis, and the chronic anemia. After isolating hematopoietic stem and progenitor cells (HSPCs), exogenous β -globin genes are incorporated into the host-cell genome using a self-activating vector. After full or partial myeloablative busulfan conditioning, these genetically modified autologous HSPCs are returned to the patient where they replicate and repopulate in the blood compartment and facilitate normal Hb synthesis. Lentiviral vectors have the ability to transfer complex genetic structures into quiescent hematopoietic stem cells. For gene therapy to be successful in beta thalassemia, certain conditions must be met: high-efficiency HSC engraftment and gene transfer, high expression of the β/γ -globin gene and appropriate expression, with minimal or no risk of insertional mutagenesis (Bou-Fakhredin et al., 2022).

Two nonrandomized, open-label, single dose phase I/II studies (HGB-204, NCT01745120 and HGB-205, NCT02151526) were initiated in 2013 and enrolled 22 patients (12 – 35 years of age) with transfusion-dependent beta thalassemia. Transfusion dependence was defined as the receipt of at least eight transfusions or at least 100 ml per kilogram of body weight of packed red cells per year in the 2 years before enrollment. Patients with advanced organ damage were not eligible. Mobilized autologous CD34+ cells were obtained and transduced ex vivo with LentiGlobin BB305 vector. The cells were reinfused after the patients had undergone myeloablative busulfan conditioning. At a median of 26 months (range, 15 – 42) after infusion of the gene-modified cells, all but 1 of the 13 patients who had a non- β^0/β^0 genotype had stopped receiving red-cell transfusions. Correction of biologic markers of dyserythropoiesis were achieved in evaluated patients with hemoglobin levels near normal ranges. In 9 patients with a β^0/β^0 genotype or two copies of the IVS1-110 mutation, the median annualized transfusion volume was decreased by 73%, and red-cell transfusions were discontinued in 3 patients. Treatment-related adverse events were typical of those associated with autologous HSCT. Grade 3 or higher adverse events occurring in two or more patients included, but were not limited to, stomatitis (n=12), febrile neutropenia (n=10), and veno-occlusive liver disease (n=2); the veno-occlusive liver disease was attributed to busulfan conditioning (Thompson et al., 2018).

After intravenous infusion of the thawed LentiGlobin drug product, neutrophil engraftment occurred within a median of 18.5 days (range, 14.0 - 30.0) in HGB-204 and 16.5 days (range, 14.0 - 29.0) in HGB-205. Platelet engraftment occurred within a median of 39.5 days (range, 19.0 - 191.0) in HGB-204 and 23.0 days (range, 20.0 - 26.0) in HGB-205, during which time there were no bleeding complications resulting in serious adverse events (Thompson et al., 2018).

Locatelli et al. (2022) report on an interim analysis of an open-label, phase III study (HGB-207, NCT02906202 [Northstar-2]) using beti-cel that was manufactured with a refined process. In HGB-205 and HGB-206, 11 of 14 patients with beta thalassemia and a non- β^0/β^0 genotype had transfusion independence after infusion of beti-cel. In these patients, however, the weighted average hemoglobin levels after infusion, which ranged from 9.1 – 13.2 g/dL, were often lower than normal levels. The vector copy number and the percentage of lentiviral vector-positive cells in beti-cel were shown to be associated with hemoglobin levels; therefore the transduction process was refined to increase the vector copy number in beti-cel and, consequently, to increase the levels of gene therapy-derived adult hemoglobin (HbA) with a T87Q amino acid substitution (HbA^{T87Q}). The primary endpoint of this study was transfusion independence defined as a weighted average hemoglobin level of at least 9 g/dL starting 60 days after the last transfusion in patients who had not received red-cell transfusions for 12 months or longer.

A total of 23 patients were enrolled and received treatment, with a median follow-up of 29.5 months. Transfusion independence occurred in 20 of 22 patients who could be evaluated (91%), including 6 of 7 patients (86%) who were younger than 12 years of age. Transfusion independence was durable; the median duration was 20.4 months (range, 15.7 – 21.6). The two evaluable patients who did not have transfusion independence had 67.4% and 22.7% reductions in transfusion volume from 6 months to the last follow-up (at 48.2 and 27.2 months, respectively). The average hemoglobin level during transfusion independence was 11.7 g/dL (range, 9.5 – 12.8). Twelve months after infusion, the median level of gene therapy-derived HbA with a T87Q amino acid substitution (HbA^{T87Q}) was 8.7 g/dL (range, 5.2 – 10.6) in patients who achieved transfusion independence. Neutrophil engraftment occurred at a median of 23 days (range, 13 – 32) after beti-cel infusion. Neither primary nor secondary graft failure occurred. Platelet engraftment occurred at a median of 46 days (range, 20 – 94) after beti-cel infusion. A more rapid trend toward neutrophil and platelet recovery was noted in patients who had undergone splenectomy than in those with an intact spleen, even without splenomegaly or hypersplenism. Grade 3 or higher adverse events occurring in two or more patients included, but were not limited to, thrombocytopenia (n=22),

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neutropenia (n=18), anemia (n=14), and stomatitis (n=14). The median duration of hospitalization from conditioning through discharge was 45 days (range, 30 – 90). Additional follow-up will more fully characterize the long-term efficacy and safety of bet-cel (Locatelli et al., 2022).

Betibeglogene autotemcel (Zynteglo®) is considered medically necessary as a one-time single dose for the treatment of adult and pediatric patients with transfusion-dependent β -thalassemia.

- Transfusion dependence is defined as a minimum of eight transfusions or at least 100 ml per kilogram of body weight of packed red cells per year in the most recent two years
- Prior to mobilization, apheresis, and myeloablative conditioning are initiated, there must be confirmation that HSCT is appropriate for the patient.
- It is recommended that patients be maintained at a Hb \geq 11 g/dL for at least 30 days prior to mobilization and 30 days prior to myeloablative conditioning.
- Patients should be screened for hepatitis B virus (HBV), hepatitis C virus (HCV), human T-lymphotropic virus 1 & 2 (HTLV-1/HTLV-2), and human immunodeficiency virus 1 & 2 (HIV-1/HIV-2) prior to collection of cells for manufacturing.

Cerebral adrenoleukodystrophy

Adrenoleukodystrophy (ALD) is an X-linked disorder caused by pathogenic variants within the *ABCD1* gene, which encodes for a peroxisomal membrane protein responsible for transportation of very long-chain fatty acids (VLCFA) into the peroxisome, where they are subsequently degraded via β -oxidation. The incidence of ALD is 1 in 14,000 to 17,000 births (Gupta et al., 2022). The severity of the disease is much more prominent in males, although the majority of affected women show symptoms in adulthood related to spinal cord involvement (Huffnagel et al., 2019). In males, there are three primary presentations associated with ALD; adrenal insufficiency (AI), cerebral inflammatory demyelination, termed cerebral ALD, and axonal myeloneuropathy. There is no known association between genotype and phenotype, and therefore while multiple persons may have the same *ABCD1* pathogenic variant, there is no identified means of determining which males with ALD will develop which clinical features of the disorder. By adulthood, approximately 40% of the patients develop cerebral ALD, a severe, neuroinflammatory condition that is generally progressive and fatal without intervention (Gupta et al., 2022). As elevations in VLCFA were recognized to be present at birth, the potential to use newborn screening for ALD was appreciated (Moser et al., 2016). More than half of the states in the United States currently screen for ALD and many more have started efforts to incorporate ALD into their current newborn screening protocol (ALD Alliance, 2022).

Cerebral ALD is an inflammatory, demyelinating, progressive leukodystrophy with a mean age of clinical onset of 7.1 years. It is observed in approximately 40% of males with ALD through age 20, although it is also observed in adults with ALD as well. Although the rate of deterioration can be variable, rapid progression is common, with total disability developing by 6 months to 2 years and death within 5 to 10 years of diagnosis (Zhu et al., 2020). Early signs of developing cerebral disease may include impaired ability to sustain attention and focus, declining performance in school, or behavioral concerns such as hyperactivity, irritability, or aggression. The development of neurocognitive and behavioral symptoms is associated with both the extent and the location of the demyelinating lesion. The diagnosis of cerebral ALD is established by MRI. As a demyelinating disease, progressive T1/T2 changes are observed in the white matter. The presence of contrast enhancement is often observed and is thought to be an indication of blood-brain barrier disruption due to active neuroinflammation. Untreated, 85-90% of boys with

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symptomatic cerebral disease die or progress to a vegetative state within several years (Gupta, 2022). An MRI-based severity score (Loes score) uses a 0 -34 point system related to the location and extent of involvement and the presence of atrophy to evaluate the extent of involvement and define progression. The Loes score correlates with clinical findings, as patients with symptomatic disease are likely to have a score of 10 or higher (Moser & Fatemi, 2018). Clinical outcomes have commonly been scored using the ALD-specific neurologic function scale (NFS), that assesses the severity of neurologic dysfunction by assigning scores to 15 different disabilities. Lower scores indicate fewer symptoms, and higher scores indicate a more significant disability. The NFS score can be used to guide the recommendation for hematopoietic stem cell transplantation (HSCT), but there is no score that absolutely determines the decision for HSCT (Zhu et al., 2020).

Allogeneic HSCT can arrest the progression of the neurologic disease when performed in the early stages of cerebral ALD, however the precise mechanism by which that occurs is not clear. The survival advantage of transplantation compared to no transplant in patients with early stage cerebral ALD was demonstrated in a retrospective analysis by Mahmood et al. in 2007. The projected 5-year survival in the transplanted population was 95% in comparison to 54% in the non-transplanted group. While there are no universally accepted standard criteria for HSCT in boys with cerebral ALD, the general criteria are a genetically and/or clinically confirmed diagnosis of ALD and the presence of cerebral disease that is not advanced, based on neurological symptoms and evidence of cerebral disease on brain MRI with the presence of gadolinium contrast enhancement around a consistent lesion. HSCT is not effective in patients with advanced cerebral ALD. There are drawbacks to allogeneic HSCT. In addition to the lack of efficacy in advanced disease, transplantation does not reverse neurologic findings present at the time of transplant and does not stabilize cerebral disease for 3 to 24 months after stem cell infusion. Symptoms can progress during this time. Treatment failure is usually due to transplant-related complications or rapid disease progression during the engraftment of donor cells (Eichler et al., 2017). Transplant is ineffective for the adrenal manifestations of disease and is not felt to impact the development of adult onset adrenomyeloneuropathy (Zhu et al., 2020).

Gene Therapy

Gene therapy with autologous CD34+ hematopoietic stem cells transduced with a lentiviral vector that contained ABCD1 complementary DNA (cDNA) has shown promising outcomes with patients demonstrating functional expression of ALD protein and disease stabilization. The FDA granted accelerated approval of Skysona based on 24-month Major Functional Disability (MFD)-free survival. Skysona does not prevent the development of or treat adrenal insufficiency due to adrenoleukodystrophy. Skysona carries a black box warning for hematologic malignancy. Several patients have been diagnosed between 14 months and 7.5 years after Skysona administration with hematologic malignancy, including several life-threatening cases of myelodysplastic syndrome. The cancers appear to be the result of the lentiviral vector, Lenti-D, integration in proto-oncogenes. The warning contains specific recommendations for life-long monitoring for malignancy (FDA, 2022).

The safety and efficacy of Skysona was assessed in two 24-month, open-label, single-arm studies in patients with early, active CALD as defined by Loes score between 0.5 and 9 and gadolinium enhancement (GdE+) on MRI, and a NFS of ≤ 1 . The patients enrolled and treated with Skysona (study 1, n = 32; study 2, n = 35) all had elevated VLCFA levels and confirmed mutations in the ABCD1 gene. Grade 3 or higher infections occurred in 21% of patients (12% bacterial, 3% viral, and 6% unspecified). The most common Grade 3 or higher infections were vascular device infections (7% of patients) diagnosed as late as 6 months after treatment and bacteremias (6% of patients) diagnosed as late as 8 months after treatment. Febrile neutropenia developed within 2 weeks after Skysona infusion in 72% of

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patients. Grade 3 or higher cytopenias on or after 60 days following treatment occurred in 47% of patients and included low platelet count (14%), low neutrophil count (22%), low lymphocyte count (27%), and low hemoglobin (2%). Grade 3 cytopenias persisted beyond Day 100 in 15% of patients and included low platelet count (7%), low neutrophil count (9%), and low lymphocyte count (6%). Serious adverse reactions of pancytopenia occurred in two patients who required support with blood and platelet transfusions as well as growth factors (FDA, 2022).

A post-hoc enrichment analysis in symptomatic patients compared time from onset of symptoms (NFS \geq 1) to time to first MFD or death in Skysona treated and natural history patients. The MFDs are defined as: loss of communication, cortical blindness, tube feeding, total incontinence, wheelchair dependence, or complete loss of voluntary movement. To be included in the analysis, patients had to have symptoms at baseline (NFS = 1) or be asymptomatic (NFS = 0) at baseline and have developed symptoms (NFS \geq 1) during the course of follow-up in the study. Additionally, they had to have at least 24 months of follow-up after NFS \geq 1 or have had an event (MFD or death). Slower progression to MFD or death from time of symptom onset (first NFS \geq 1) was seen for early, active CALD patients treated with Skysona compared to a similar natural history of disease. There were insufficient data beyond 24 months for the symptomatic Skysona subpopulation to assess long-term MFD-free survival as compared to the natural history of disease. There was insufficient duration of follow up to assess efficacy in Skysona treated patients who remained asymptomatic. There were insufficient data to compare relative efficacy of Skysona to allogeneic HSCT (FDA, 2022).

Elivaldogene autotemcel (SKYSONA®) is considered medically necessary as a one-time single dose to slow the progression of neurologic dysfunction in patients with early, active cerebral adrenoleukodystrophy meeting all of the following:

- Male, aged 4 – 17 years of age
- Asymptomatic or mildly symptomatic with neurologic function score \leq 1
- Gadolinium enhancement on brain MRI
- Loes scores of 0.5 - 9

Because of the risk of hematologic malignancy, consultation with hematology experts is highly recommended prior to Skysona treatment to inform benefit-risk treatment decision and to ensure adequate post-treatment monitoring.

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Review and Approval History	
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