Outlines of Beta-Thalassemia and Its Treatment Lines

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Abstract

Background: Thalassemia is a group of hereditary blood disorders characterized by a reduction or lack of synthesis of some globin chains. Mutations in the beta-globin gene can lead to beta-thalassemia. Anemia is caused by inefficient erythropoiesis, which occurs when there are either fewer beta-globin chains or none at all. The thalassemia syndromes are a heterogeneous group of single gene disorders due to defective biosynthesis of β- or α-globin chains which causes partial or total suppression of normal hemoglobin production. A deficiency in the alpha chain results in alpha thalassemia, while a deficiency in the β chain is associated with β thalassemia . Treatments for thalassemia major include managing iron chelation, hematopoietic stem cell transplantation, gene therapy, regular blood transfusions, and promotion of fetal hemoglobin production.

Keywords: beta-thalassemia, treatment lines

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1.Introduction:

In thalassemia, the aberrant production or decreased rate of forming normal α- or β-globin subunits of hemoglobin (Hb) A is the defining characteristic. The β-globin genes are located on chromosome 11, whereas the α-globin genes are on chromosome 16, according to Adly et al. (2015). Red blood cells include the protein hemoglobin, which is responsible for transporting oxygen from the alveoli to the tissues in the body. Normal individuals include three different types of hemoglobin, which are HbA, HbA2, and HbF. These types of hemoglobin contain α2; β2, α2; δ2, and α2; γ2 subunits, respectively (Thein, 2018).

Thalassemia is classified as β, α, δ γ, δβ, and γδβ based on the globin chain that is impacted. Two main types of thalassemia, α- and β-, are determined by four and two genes, respectively, according to Gibbs and Burdick (2009) and Sirachainan et al. (2016). More than a hundred changes to the same DNA sequence are required to make it. Globin chains that aren't coupled aren't stable. Because of their abrupt cellular death, they cause the premature elimination of red blood cell precursors and reduce the blood's capacity to hold mature RBCs. When hemoglobin decomposes, it releases iron and heme, which facilitate chemical processes that generate reactive oxygen species (ROS) or free radicals. According to Adly et al. (2015), hepatocytes and islets of Langerhans activities are impaired by these radicals and ROS.

According to Galanello and Origa (2010), beta-thalassemia is characterized by a decrease or complete lack of the β-globin chain's synthesis rate. In 1925, Cooley and Lee were the ones who initially defined thalassemia (Franco et al., 2014). Base substitutions on introns, exons, and promoter regions of β-globin genes cause β-thalassemia, whereas deletions of the α gene cause α-thalassemia (Stauder et al., 2018). According to Lei et al. (2019), microcytic and hypochromic anemia, along with various syndromic variants, can result from diminished (β+) or nonexistent (β0) globin chain formation, which further divides it into different categories.

2.1. Types of beta-thalassemia

2.1.1. Beta-thalassemia major

The most severe form of thalassemia, called Cooley's anemia, is when people have a more severe mutation in the β chain and are either homozygous (B+/B+, B0/B0) or compound heterozygous (B+/B0) for the gene (Galanello & Origa, 2010; Tari et al., 2018). In most cases, it takes anywhere from six months to two years. Severe anemia (heart failure, fatigue, and cachexia) is a symptom of serious thalassemia. Hb levels below 7 g/dl and Hb F levels below 90% are possible. Bone deformities, an enlarged spleen, and stunted growth were consequences of the bone marrow's expansion as a response to decrease in hemoglobin. Pulmonary hypertension, lithiasis, and ulceration of the leg are all symptoms of excessive hemolysis. Additionally, this disease is hindered by hypercoagulability. There are a number of complications that can arise from regular blood transfusions, including iron overload in various organs, diabetes, hypothyroidism, hypoparathyroidism, hypopituitarism, cirrhosis, cardiac arrhythmia, myopathy, and a 71% mortality rate for thalassemia major patients (Leiet al., 2019). Additional risks associated with HIV infection include osteoporosis, blockage in blood, and chronic hepatitis B and C. Moreover, according to Borgna-Pignatti et al. (2004), there is a significant likelihood of liver cancer in those who have liver infections.

2.1.2. Beta-thalassemia intermedia

Individuals with thalassemia intermediate, a type of heterogeneous genetic mutation, have a minor capacity to produce the β chain of hemoglobin (B+/B+, B+/B0). Both α and β mutations can occur at the same time in certain cases (Galanello & Origa, 2010). Between the ages of 2 and 6, it happens. A milder form of anemia is seen in thalassemia intermediate. Blood transfusions are unnecessary when hemoglobin levels range from 7 to 9 to 10 g/dl. (Birgens & Ljung, 2007), the patient can live with or with very little blood transfusions. Growth retardation, bone deformities, and infertility are among issues that can arise when bone marrow expands with age. Hemolysis, in contrast, increases tissue iron levels (Taher et al., 2011).

2.1.3. Beta-thalassemia minor

Thalassemia carrier trait, commonly known as B0/B or B+/B, happens when one β globin gene copy is normal and one copy is faulty (Galanello & Origa, 2010; Tarie et al., 2018). Physiological stress, pregnancy, and children are the most common triggers for thalassemia minor. Although there are no outward signs of the disease, irregularities in the shape of red blood cells might cause moderate anemia in rare cases (Romanello et al., 2018). Patients with β-thalassemia minor or who are carriers may have a hemoglobin level more than 10g/dl. If both mothers carry the thalassemia gene, the chances of the baby being born with the condition are 25% (Moi et al., 2004).

3. Hereditary Transmission And Mutations Of Beta-Thalassemia

Having beta-thalassemia at birth is a result of an autosomal recessive gene. When one or both parents have the mutation in the β globin chromosome, the offspring are considered obligate heterozygotes. At birth, each child born to parents who are heterozygous has a 25% chance of being a carrier but unaffected, a 25% chance of being an afflicted carrier, and a 50% chance of being an asymptomatic carrier (Canatan & Koç, 2004; Galanello & Origa, 2010).

According to Yatim et al. (2014), there are over 200 mutations in the β-globin gene on chromosome 11, most of which are point mutations, which contribute to the molecular heterogeneity of the beta form of thalassemia. Deletions are uncommon in β-thalassemia, which is characterized by a decrease or absence in the rate of β-globin chain formation. Al-Akhras et al. (2016) and Giardine et al. (2007) offer a list of mutations according to their prevalence by ethnicity and severity.

3.1. Prevalence/incidence

Mediterranean countries, including those in Central Asia, the Middle East, Southern China, India, South America, and those along the north coast of Africa, have the highest prevalence of β-thalassemia (Weatherall, 2010). With an 18% carrier percentage of the population, the Maldives has the highest incidence of thalassemia in the world. According to Weatherall (2010), the estimated frequency of β-thalassemia ranges from 3% to 8% in China, 5% to 10% in Iran, 1% in Thailand, and up to 16% in Cyprus. The spread of β-thalassemia to previously thalassemia-free areas, such Northern Europe, is

due to human migration and marriages (Vichinsky, 2005). According to assessments, every year around 80-90 million people are born with β-thalassemia, and approximately 1.5 percent of the world's population carries the gene for the disease. Additionally, it has been predicted that 1 out of 10,000 people in the EU experience symptoms each year, and 1 out of 100,000 people globally do. The impact of β-thalassemia is comparable on boys and females (Hossain et al., 2017).

4. Pathophysiology

The result of insufficient (ß0) or decreased (ß+) amounts of β-globin chain synthesis is ineffective erythropoiesis, which in turn causes anemia. The process of ineffective erythropoiesis occurs when there are an excess of unpaired α-globin chains in the blood. These chains create chemicals that are imbalanced and insoluble, which then settle into erythroid precursors in the bone marrow. Unfortunately, this leads to premature destruction of the erythrocytes and injuries to the plasma membrane of RBCs. According to Shariati et al. (2016), this process is most common in both immature red blood cell precursors and mature red blood cells, and it leads to anemia due to poor erythropoiesis/hemolysis. Bone marrow enlargement can reach 25 to 30 times the normal rate and defects in bone structure can develop as a consequence of anemia-induced increased erythropoietin production. While the bone marrow does its best to prevent serious anemia by speeding up the generation of red blood cells (RBCs), this is not always enough. According to Sangkhae and Nemeth (2017), the release of heme from broken down red blood cells leads to an increase in the absorption of iron in the gastrointestinal tract. Inadequate regulation of hepcidin causes high iron absorption, which regulates iron intake from the duodenum. Overload of iron occurs as a result of increased erythropoiesis and continuous blood exchange. Hyperoxidation of iron causes membrane lipid peroxidation and impacts several organs, including the heart, by the production of harmful reactive oxygen species (Hobanet al., 2015). Hemichromes are typical inclusions that form when α-chain subunits oxidize, interacting with the membrane-bound proteins spectrin and ankyrin. The anomalies cause an increase in membrane phospholipids and cholesterol. According to Chakrabartie et al. (2013), the oxidized α chain interacts with proteins, making the membranes less stable and more stiff.

5. Complications

5.1. Iron overload

Because of blood exchange, individuals with more severe types of β-thalassemia major or intermediate store iron in the reticuloendothelial system. Iron overload manifests more slowly in cardiac tissues but also in a number of endocrine tissues, including hepatic parenchyma. Maintaining an optimal iron concentration is the key to human homeostasis (Ganz & Nemeth, 2011). Every day, the body loses 1 mg of iron through cell loss in the urinary tract, colon, dermis, and other endodermal tissues. In contrast, 1 ml of transfused blood contains 1 mg of iron, so a total of 200 mg of iron ends up in tissues.

Because their bodies are unable to excrete iron, patients with severe thalassemia who receive blood transfusions are at high risk of developing iron deposition (Camaschella & Nai, 2016). Ineffective erythropoiesis, caused by RBC overload during cellular death, prevents the hepatic system from managing hepcidin. Hepcidin is a 25-amino acid peptide hormone that normalizes iron flow into serum in a harmful way and prevents the body from absorbing iron from food. It also releases iron from Kupffer cells and discharges the buildup from hepatocytes (Ganz & Nemeth, 2011; Kim & Nemeth, 2015). In the liver's spleen and Kupffer cells, an iron exporter known as ferroportin is located. This protein has many passes across the cell membrane. A decrease in growth differentiation factor 15 (GDF15) and a suppression of hepcidin production were found in primary human hepatocytes of thalassemia patients (Sangkhae & Nemeth, 2017). Iron can be released from macrophages and absorbed more easily from the intestines when hepcidin manifestations are suppressed. Recent research has examined the normal and pathological control of hepcidin production (Finianos et al., 2018). A synthetic miniaturized hepcidin with an extended half-life was administered orally to mice and found to decrease iron absorption. It has also been suggested as a potential beneficial mediator for patients with severe β-thalassemia (Preza et al., 2011). Following its release from cells, iron is transported to the bone marrow and other soft tissues. Approximately 20–25 mg of iron can circulate in a 24-hour cycle bound to transferrin, and less than 1% of the body's total iron is always in circulation. According to Evans et al. (2008), iron that is not bound with transferrin, commonly known as non-transferrin-bound iron (NTBI), can likewise take on several forms in serum. Endocrinopathies, diabetes, infertility, and liver cirrhosis can all be caused by an excess of iron. Instead of using the transferrin receptors, non-transferrin-bound iron can enter tissues through multiple cellular channels, which have the ability to damage cells (Wang et al., 2012). According to Evans et al. (2008) and Fernandes et al. (2016), chelators can reduce the amount of iron that is not bound to transferrin in thalassemia patients. When it comes to decreasing NTBI, intravenous delivery of chelators is superior to subcutaneous administration. Desferrioxamine and other oral chelators mostly eliminated iron by eliminating the soluble plasma iron in serum, but deferiprone and deferasirox effectively admitted and reduced the intracellular labile iron segments (Jansová & Šimůnek, 2019). According to Brissot et al. (2012) and Hershko (2010), there are different ways to understand labile plasma iron (LPI), which is a part of the non-transferrin-bound iron pool. LPI activates metabolically by interacting with membrane components and impacts the plasma membrane by triggering the production of free radicals or reactive oxygen species. These radicals stimulate oxidative stress and cause lipid peroxidation, DNA oxidation, and protein oxidation.

5.2. Hepatitis

Contagion connected to viruses is a significant risk for thalassemia patients. When people receive blood and blood transfusion products for an extended period of time, it might lead to pathological hepatitis. Although thalassemia patients and donors can benefit substantially from hepatitis B immunizations,

hepatitis C is particularly challenging to prevent in this population because no vaccine is currently available (Mousa et al., 2016; Soliman et al., 2014).

5.3. Osteoporosis

Almost all thalassemia patients will develop osteoporosis, a condition characterized by brittle bones and associated discomfort. Axial bone density increases more rapidly than fringe bone density as we mature. Osteoporosis in β-thalassemia patients can lead to endocrine deficits, bone marrow enlargement, iron toxicity, and the possible toxicity of chelators (Terpos & Voskaridou, 2010). Iron accumulation in hepatocytes up to 7 mg/g (dry weight) may be tolerable, but chronic iron overload and liver fibrosis caused by frequent transfusions without iron chelation raise the risk of liver cancer (Mancuso, 2010).

6. Diagnosis

Several laboratory tests can be used to detect and diagnose thalassemia. These include genetic testing (DNA analysis), complete blood counts (CBC), blood smears, prenatal testing (genetic testing of amniotic fluid), iron studies, and hemoglobin electrophoresis (Alqahtani et al., 2018). Mutations in the β- and α-globin chain genes can be detected with the use of a DNA analysis test. Although it is not commonly done, it can also assist detect if someone is a carrier of thalassemia. Mutations can vary in their symptoms; some do not manifest at all, some reduce β-globin chain formation in B-thalassemia, and yet others prohibit β-globin from being made at all (Sagar et al., 2015).

6.1. Hematologic diagnosis

The Hb concentration ranges from 7 to 10 g/dl, the mean corpuscular volume is between 50 and 80 fl, and the MCH is between 16 and 24 pg. These parameters classify thalassemia intermediates. A higher hemoglobin A2 level, along with lower MCH and MCV, classifies a person as a mute or silent carrier of thalassemia.

7. Prevention

Genetic counseling, prenatal diagnostics, and identifying carriers could potentially prevent beta-thalassemia (Origa & Comitini, 2019). A genetic counselor can help you understand the risks associated with being a carrier, both for yourself and your children. Prenatal diagnosis can be achieved by studying the fetal gene around four to five months of development or by sampling chorionic villi at eleven weeks of gestation. To identify mutations in the father, it may be helpful to examine fetal cells in maternal blood and fetal DNA in mother's serum (Mavrou et al., 2007). According to Khan et al. (2019), there are three cell types that are used as sources of fetal DNA: lymphocytes, trophoblasts, and nucleated erythrocytes (NRBCs). Preventing the birth of homozygotes can alleviate some of the thalassemia burden. A large number of Western and Mediterranean nations have managed to significantly change their homozygote populations throughout the past 20 years. According to Italia

et al. (2019), thalassemia control programs are also in place in several republics, including China, Lebanon, Iran, Canada, Egypt, Malaysia, and Pakistan.

8. Treatment

People with thalassemia characteristics do not require treatment. The fact that they can pass on defective genes to their children suggests that this might be an intentional form of genetic counseling (Mutar et al., 2019). Mild anemia is a lifelong symptom for those with β-thalassemia intermedia. Constant monitoring and blood transfusions may be necessary. According to Kumar et al. (2012), iron supplementation is not typically prescribed, although folic acid supplementation is frequently suggested. Hypersplenism, a complication of thalassemia, can lead to growth retardation, increasing anemia, and other mechanical abnormalities caused by splenomegaly. Although thalassemia intermediate can cause symptoms, the acute form of the disease requires splenectomy for therapy (Origa, 2014).

8.1. Splenectomy

Overactivity of the spleen happens as a result of severe hemolysis in thalassemia major and thalassemia intermedia. Regular blood transfusions can help avoid splenomegaly in young children. Nevertheless, hypersplenism can manifest in youngsters between the ages of 5 and 10. With a decrease in transfusion requirements, an improvement in Hb level, and a fall in iron accumulation, splenectomy protects patients against ill health and growth retardation (Pecorari et al., 2008). When the annual transfusion requirements exceed 200–220 ml RBCs/kg with 70% hematocrit and 250–275 ml RBCs/kg with 60% hematocrit, spleen removal is recommended. According to Ikeda et al. (2005), it is advised to get a meningococcal and pneumococcal vaccine before having the spleen surgically removed. Following the procedure, it is recommended to take penicillin for antimicrobial prophylaxis in order to reduce the risk of infections.

8.2. Iron chelation therapy

According to Sarker et al. (2014), when blood is regularly transmitted, the body accumulates 0.3-0.6 mg/kg of iron every day since each red blood cell carries 200 milligrams of iron. Deferasirox (DFX), deferiprone (DFP), and deferoxamine (DFO) are the three main types of iron chelators. According to Adewoyin and Oyewale (2015), iron removal is a crucial part of blood transfusion treatment. The DFO, which is derived from Streptomyces pilosus, has a molecular weight of 657 and a half-life of 8-10 minutes. As the iron chelator deferoxamine in plasma and bile, it penetrates the parenchymal cells of the liver and chelates the iron. According to Borgna-Pignatti et al. (2004), the amount of iron that is overloaded after a transfusion determines the length of the dose, which varies from patient to patient. Deferoxamine is recommended for transfusion-dependent thalassemia patients at a dosage of 30-40 mg/kg per week for the first week of treatment, then 40-50 mg/kg and thereafter 60 mg/kg for teenagers and adults, respectively. Between the ages of 2 and 4, chelation therapy begins following the transfer of 20 to 25 RBC units (Taher & Cappellini, 2018). A synthetic chemical called DFP became

famous in the 1980s in New York. The gastrointestinal tract absorbs deferiprone, and its half-life in plasma is 1.5-4 hours. Adal et al. (2019) suggested a daily dose of 75 mg/kg, given orally three times a day with meals; this dose might be increased to 100 mg/kg if needed. Deferiprone can chelate intracellular iron and penetrates cell membranes faster than deferoxamine. By removing iron from the heart, it improves cardiac function and protects against heart disorders caused by iron excess (Buaboonnam & Charuvanij, 2017). As a precaution against the possible risk of agranulocytosis, 1% of patients treated with DFP must have their total blood counts monitored regularly, once a week. A highly bioaccumulative chelator called Deferasirox DFX (Exjade) was approved for usage in 2005 for people who were transfusionally overloaded (Crichton et al., 2019). It is ingested orally. Deferasirox is advised to be taken orally once day and has a half-life of 12 to 18 hours. The recommended dosage is 20-30 mg/kg daily, however some people may find relief by increasing it to 40 mg/kg daily. It works in both adults and children (Rivière et al., 2012).

8.3. Transplantation of bone marrow

Patients with thalassemia still have the option of undergoing bone marrow transplantation as their primary definitive treatment (Majolino et al., 2017). The 1980s saw the completion of the most successful bone marrow transplants. A 3% mortality rate and an 87% thalassemia-free survival rate were observed in the young patients. One drawback of bone marrow transplantation (BMT) is the need for a donor whose leukocyte antigen is compatible with the patient's (Sabloff et al., 2011). In the youngest patients, the greatest outcomes include a rejection rate of 23%, a mortality rate of 7%, and a thalassemia-free survival rate of 70%. The availability of bone marrow transplantation as a treatment for thalassemia is still an issue for some individuals in India (Jeengar et al., 2017).

Effective chelating therapy, control of excessive iron problems, and consistent transfusion of packed red cells are the current options for treatment of β-thalassemia in low socio-economic nations (Grubovic et al., 2017).

8.4. Blood transfusion

The purpose of transfusion rehabilitation in β-thalassemia major is to treat anemia caused by endogenous erythropoiesis and to keep the plasma hemoglobin level stable (Cihanet al., 2017). Once a thalassemia diagnosis has been confirmed, blood transfusion therapy should be initiated in the event of severe anemia. Growth retardation, increased splenomegaly, facial abnormalities, and bone enlargement are some of the symptoms that should be monitored in persons with Hb > 7 g/dl. Due to the development of various red cell antibodies and the difficulty in finding eligible blood donors, regular blood transmission would not occur until after the second or third year. There have been several proposed transfusion treatments over the years, but the most widely accepted aim is to have a pre-transfusion hemoglobin level of approximately 9 to 10 g/dl and a post-transfusion level of 13 to 14 g/dl. According to Swakat et al. (2019), this prevents organ dysfunction, growth retardation, and bone deformities, which could result in a normal quality of life and increased activity levels. Several factors, including the patient's weight, hematocrit and hemoglobin levels, and other medical

conditions, determine how often blood transfusions are necessary (Taher & Cappellini, 2018). The recommended daily transfer of red blood cells (RBCs) for blood transfusion therapy is 15 to 20 ml/kg in order to prevent an excessive increase in blood volume. Because these numbers can allow for the monitoring of iron intake and the demand of red blood cells (RBCs), they are useful for evaluating the efficacy of transfusion therapy (Galanello & Origa, 2010).

8.5. Gene therapy

The stem cells of patients are used in gene therapy to permanently cure β-thalassemia major. Patients' peripheral blood, bone marrow, or umbilical cord blood are used to get hematopoietic stem and progenitor cells (HSPCs). After that, a therapy can be administered to the cells or tissues, causing DNA changes in the design. A normal β or γ gene is introduced into a host cell's genome by a lentiviral vector. According to Breda et al. (2010), humans are also intentionally transferring the hemoglobin genome into pluripotent hematopoietic cells. Reinserted into patients, the cells containing the appropriate genes flourish in the bone marrow. To circumvent the need for high-variation proficiency in future gene therapies, induced pluripotent stem cells (iPSCs) could be utilized.The process involves transforming fibroblasts, which are somatic cells, into a pluripotent state by exhibiting various characteristics including Sox2, Klf4, Oct3/4, and C-Myc (Yang et al., 2016). To achieve the desired gene modification, induced pluripotent stem cells must be used. Induced pluripotent stem cells differentiate into hematopoietic stem cells and progenitor cells after they reach an appropriate developmental stage. The next step is to reinfuse the patient with these HSPCs cells. While HSPCs created from iPSC are not yet practical for HSCT due to the cells' limitations in multiplying in the bone marrow, this technique will still control many of the extents in directly harvesting HSPCs from the patient.

8.6. Transplantation of hematopoietic stem cells

According to Angelucci et al. (2014), stem cell transplantation could be a potential treatment for thalassemia major. The treatment of thalassemia and other diseases makes use of this system. This treatment for thalassemia involves transferring hematopoietic stem cells harvested from healthy people's bone marrow. This treatment was effective for about 80% of transplant recipients (Bernardo et al., 2012). According to Cario (2018), the most serious and dangerous issue with bone marrow transplants is graft versus host disease (GVHD), which can cause the patients to die.

8.7. Induction of fetal hemoglobin production

Red blood cells have a longer lifespan in people who have long-term symptoms of thalassemia induced fetal hemoglobin. Medications like hydroxyl urea are used to stimulate the formation of fetal hemoglobin. It is possible that hydroxyurea can treat thalassemia and sickle cell disease. According to Tari et al. (2018) and Wilber et al. (2011), hydroxyurea improves hematological and quantitative indicators in thalassemia intermedia patients and increases the production of γ-globin. Hydroxyurea inhibits ribonucleotide reductase and is a harmful chemical during the cell cycle's synthesis phase

(Finotti et al., 2015). The GATA-2 fetal hemoglobin gene is regulated and its expression is increased in relation to apoptosis and the cell cycle. Additionally, the GATA-1 gene is suppressed. In addition to increasing erythropoietin levels, it can stimulate the proliferation of progenitor cells (Pace et al., 2015).

9. Conclusions

The process of beta-thalassemia is brought about by changes in the β-globin gene, leading to a decrease or elimination of the normal β-globin chain production rate. Severe anemia is caused by oxidative stress and the early death of red blood cells (RBCs) due to an excess of mismatched α-globin chains and a lack of β-globin chains. Iron excess is worsened by blood transfusion therapy, which cures anemia. Prenatal testing, genetic counseling, carrier discovery, and premarital screening can all help prevent this condition. For people with thalassemia, the sole definitive treatment option is gene therapy in conjunction with bone marrow transplantation.

References:

[1] Adel, N. , Mantawy, E. M. , El-Sherbiny, D. A. , & El-Demerdash, E. (2019). Iron chelation by deferasirox confers protection against concanavalin A-induced liver fibrosis: A mechanistic approach. Toxicology and Applied Pharmacology, 382, 114–148. 10.1016/j.taap.2019.114748 [PubMed] [CrossRef] [Google Scholar]

[2] Adewoyin, A. S. , & Oyewale, O. A. (2015). Complications of allogeneic blood transfusion: Current approach to diagnosis and management. International Blood Research & Reviews, 4, 135–151. 10.9734/IBRR/2015/17874 [CrossRef] [Google Scholar]

[3] Adly, A. A. M. , El-Sherif, N. H. , Ismail, E. A. R. , El-Zaher, Y. A. , Farouk, A. , El-Refaey, A. M. , & Wahba, M. S. (2015). Vascular dysfunction in patients with young β-thalassemia: Relation to cardiovascular complications and subclinical atherosclerosis. Clinical and Applied Thrombosis/Hemostasis, 21(8), 733–744. 10.1177/1076029614541515 [PubMed] [CrossRef] [Google Scholar]

[4] Al-akhras, A. , Badr, M. , El-safy, U. , Kohne, E. , Hassan, T. , Abdelrahman, H. , Mourad, M. , Brintrup, J. , & Zakaria, M. (2016). Impact of genotype on endocrinal complications in β-thalassemia patients. Biomedical Reports, 4(6), 728–736. 10.3892/br.2016.646 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[5] Alqahtani, R. S. , Bedaiwi, A. A. , Alburkani, A. M. , AlFahed, M. M. , Alhoraibi, R. A. , & Tarawah, A. M. (2018). Knowledge and response of the community to premarital screening program (Sickle Cell Anemia\Thalassemia); AlMadinah, Saudi Arabia. Journal of Applied Hematology, 9(2), 59. 10.4103/joah.joah_1_18 [CrossRef] [Google Scholar]

[6] Angelucci, E. , Matthes-Martin, S. , Baronciani, D. , Bernaudin, F. , Bonanomi, S. , Cappellini, M. D. , Dalle, J.-H. , Di Bartolomeo, P. , de Heredia, C. D. , Dickerhoff, R. , Giardini, C. , Gluckman, E. , Hussein, A. A. , Kamani, N. , Minkov, M. , Locatelli, F. , Rocha, V. , Sedlacek, P. , Smiers, F. , … Peters, C. (2014). Hematopoietic stem cell transplantation in thalassemia major and sickle cell disease: Indications and management recommendations from an international expert panel. Haematologica, 99(5), 811–820. 10.3324/haematol.2013.099747 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[7] Bernardo, M. E. , Piras, E. , Vacca, A. , Giorgiani, G. , Zecca, M. , Bertaina, A. , Pagliara, D. , Contoli, B. , Pinto, R. M. , Caocci, G. , Mastronuzzi, A. , La Nasa, G. , & Locatelli, F. (2012). Allogeneic hematopoietic stem cell transplantation in thalassemia major: Results of a reduced-toxicity conditioning regimen based on the use of treosulfan. Blood, 120(2), 473–476. 10.1182/blood-2012-04-423822 [PubMed] [CrossRef] [Google Scholar]

[8] Birgens, H. , & Ljung, R. (2007). The thalassaemia syndromes. Scandinavian Journal of Clinical and Laboratory Investigation, 67(1), 11–26. 10.1080/00365510601046417 [PubMed] [CrossRef] [Google Scholar]

[9] Borgna-Pignatti, C. A. T. E. R. I. N. A. , Rugolotto, S. I. M. O. N. E. , De Stefano, P. , Zhao, H. U. A. Q. I. N. G. , Cappellini, M. D. , Del Vecchio, G. C. , & Piga, A. (2004). Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. Haematologica, 89(10), 1187–1193. [PubMed] [Google Scholar]

[10] Breda, L. , Kleinert, D. A. , Casu, C. , Casula, L. , Cartegni, L. , Fibach, E. , Mancini, I. , Giardina, P. J. , Gambari, R. , & Rivella, S. (2010). A preclinical approach for gene therapy of β-thalassemia. Annals of the New York Academy of Sciences, 1202, 134. 10.1111/j.1749-6632.2010.05594.x [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[11] Brissot, P. , Ropert, M. , Le Lan, C. , & Loréal, O. (2012). Non-transferrin bound iron: A key role in iron overload and iron toxicity. Biochimica Et BiophysicaActa (BBA)-General Subjects, 1820(3), 403–410. 10.1016/j.bbagen.2011.07.014 [PubMed] [CrossRef] [Google Scholar]

[12] Buaboonnam, J. , & Charuvanij, S. (2017). Severe deferiprone-induced arthropathy in young adolescent successfully treated with intraarticular triamcinolone acetonide injection: A case report. Journal of the Medical Association of Thailand, 100(7), 815. [Google Scholar]

[13] Camaschella, C. , & Nai, A. (2016). Ineffective erythropoiesis and regulation of iron status in iron loading anaemias. British Journal of Haematology, 172(4), 512–523. 10.1111/bjh.13820 [PubMed] [CrossRef] [Google Scholar]

[14] Canatan, D. , & Koç, N. (2004). The effect of transfusion on pulmonary function tests in patients with thalassemia. Turkish Journal of Haematolgy, 21(3), 137–139. [PubMed] [Google Scholar]

[15] Cario, H. (2018). Hemoglobinopathies: Genetically diverse, clinically complex, and globally relevant. European Medical Oncology, 11(3), 235–240. 10.1007/s12254-018-0402-4 [CrossRef] [Google Scholar]

[16] Chakrabarti, A. , Bhattacharya, D. , Deb, S. , & Chakraborty, M. (2013). Differential thermal stability and oxidative vulnerability of the hemoglobin variants, HbA2 and HbE. PLoS One, 8(11), 81–820. 10.1371/journal.pone.0081820 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[17] Cihan, M. K. , Belen, B. , Bolat, F. , Bülbül, Ö. G. , Korgalı, E. Ü. , & Koçak, Ü. (2017). The impact of transfusion and chelation on oxidative stress in immigrant Syrian children with β-thalassemia. Indian Journal of Hematology and Blood Transfusion, 33(4), 552–558. 10.1007/s12288-017-0791-2 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[18] Crichton, R. R. , Ward, R. J. , & Hider, R. C. (2019). The efficacy of iron chelators for removing iron from specific brain regions and the pituitary—ironing out the brain. Pharmaceuticals, 12(3), 138. 10.3390/ph12030138 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[19] Evans, R. W. , Rafique, R. , Zarea, A. , Rapisarda, C. , Cammack, R. , Evans, P. J. , Porter, J. B. , & Hider, R. C. (2008). Nature of non-transferrin-bound iron: Studies on iron citrate complexes and thalassemic sera. JBIC Journal of Biological Inorganic Chemistry, 13(1), 57–74. 10.1007/s00775-007-0297-8 [PubMed] [CrossRef] [Google Scholar]

[20] Fernandes, J. L. , Loggetto, S. R. , Veríssimo, M. P. A. , Fertrin, K. Y. , Baldanzi, G. R. , Fioravante, L. A. B. , Tan, D. M. , Higa, T. , Mashima, D. A. , Piga, A. , Coelho, O. R. , Costa, F. F. , & Saad, S. T. (2016). A randomized trial of amlodipine in addition to standard chelation therapy in patients with thalassemia major. Blood, 128(12), 1555–1561. 10.1182/blood-2016-06-721183 [PubMed] [CrossRef] [Google Scholar]

[21] Finianos, A. , Matar, C. F. , & Taher, A. (2018). Hepatocellular carcinoma in β-thalassemia patients: Review of the literature with molecular insight into liver carcinogenesis. International Journal of Molecular Sciences, 19(12), 4070. 10.3390/ijms19124070 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[22] Finotti, A. , Breda, L. , Lederer, C. W. , Bianchi, N. , Zuccato, C. , Kleanthous, M. , & Gambari, R. (2015). Recent trends in the gene therapy of β-thalassemia. Journal of Blood Medicine, 6, 69. [PMC free article] [PubMed] [Google Scholar]

[23] Franco, S. S. , De Falco, L. , Ghaffari, S. , Brugnara, C. , Sinclair, D. A. , Matte', A. , Iolascon, A. , Mohandas, N. , Bertoldi, M. , An, X. , Siciliano, A. , Rimmele, P. , Cappellini, M. D. , Michan, S. , Zoratti, E. , Anne, J. , & De Franceschi, L. (2014). Resveratrol accelerates erythroid maturation by activation of FoxO3 and ameliorates anemia in beta-thalassemic mice. Haematologica, 99(2), 267–275. 10.3324/haematol.2013.090076 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[24] Galanello, R. , & Origa, R. (2010). Beta-thalassemia. Orphanet Journal of Rare Diseases, 5(1), 11. 10.1186/1750-1172-5-11 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[25] Ganz, T. , & Nemeth, E. (2011). Hepcidin and disorders of iron metabolism. Annual Review of Medicine, 62, 347–360. 10.1146/annurev-med-050109-142444 [PubMed] [CrossRef] [Google Scholar]

[26] Giardine, B. , van Baal, S. , Kaimakis, P. , Riemer, C. , Miller, W. , Samara, M. , & Hardison, R. C. (2007). HbVar database of human hemoglobin variants and thalassemia mutations. Human Mutation, 28(2), 206. [PubMed] [Google Scholar]

[27] Gibbs, G. , & Burdick, C. O. (2009). Separating thalassemia trait and iron deficiency by even simpler inspection. American Journal of Clinical Pathology, 132(4), 643–644. 10.1309/AJCPORRCP16WILSB [PubMed] [CrossRef] [Google Scholar]

[28] Grubovic, R. M. , Georgievski, B. , Cevreska, L. , Genadieva-Stavric, S. , & Grubovic, M. R. (2017). Analysis of factors that influence hematopoietic recovery in autologous transplanted patients with hematopoietic stem cells from peripheral blood. Open Access Macedonian Journal of Medical Sciences, 5(3), 324. 10.3889/oamjms.2017.039 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[29] Hershko, C. (2010). Pathogenesis and management of iron toxicity in thalassemia. Annals of the New York Academy of Sciences, 1202(1), 1–9. 10.1111/j.1749-6632.2010.05544.x [PubMed] [CrossRef] [Google Scholar]

[30] Hoban, M. D. , Mendel, M. C. , Romero, Z. , Kaufman, M. L. , Joglekar, A. V. , Ho, M. , & Urbinati, F. (2015). Correction of the sickle-cell disease Mutation in human hematopoietic stem/Progenitor cells. Molecular Therapy, 125(17), 2597–2604. [PMC free article] [PubMed] [Google Scholar]

[31] Hossain, M. S. , Raheem, E. , Sultana, T. A. , Ferdous, S. , Nahar, N. , Islam, S. , Arifuzzaman, M. , Razzaque, M. A. , Alam, R. , Aziz, S. , Khatun, H. , Rahim, A. , & Morshed, M. (2017). Thalassemias in South Asia: Clinical lessons learnt from Bangladesh. Orphanet Journal of Rare Diseases, 12(1), 93. 10.1186/s13023-017-0643-z [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[32] Ikeda, M. , Sekimoto, M. , Takiguchi, S. , Kubota, M. , Ikenaga, M. , Yamamoto, H. , Fujiwara, Y. , Ohue, M. , Yasuda, T. , Imamura, H. , Tatsuta, M. , Yano, M. , Furukawa, H. , & Monden, M. (2005). High incidence of thrombosis of the portal venous system after laparoscopic splenectomy: A prospective study with contrast-enhanced CT scan. Annals of Surgery, 241(2), 208. 10.1097/01.sla.0000151794.28392.a6 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[33] Italia, K. , Chandrakala, S. , Nadkarni, A. , Ghosh, K. , & Colah, R. B. (2019). The genetic determinants for long-term response to hydroxyurea therapy in indian β-thalassemia patients. Clinical Research in Hematology, 2(1), 1–8. [Google Scholar]

[34] Jansová, H. , & Šimůnek, T. (2019). Cardioprotective potential of iron chelators and prochelators. Current Medicinal Chemistry, 26(2), 288–301. 10.2174/0929867324666170920155439 [PubMed] [CrossRef] [Google Scholar]

[35] Jeengar, R. K. , Upadhyaya, A. , Agarwal, N. , & Mehta, A. (2017). Red cell alloimmunization in repeatedly transfused children with beta thalassemia major. International Journal of Contemporary Pediatr, 4(3), 775–779. 10.18203/2349-3291.ijcp20171486 [CrossRef] [Google Scholar]

[36] Khan, M. A. , Khan, M. A. , Seedat, A. M. , Khan, M. , Khuwaja, S. F. , Kumar, R. , Usama, S. M. , & Fareed, S. (2019). Sensorineural hearing loss and its relationship with duration of chelation among major β-Thalassemia Patients. Cureus,11(8). 10.7759/cureus.5465 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[37] Kim, A. , & Nemeth, E. (2015). New insights into iron regulation and erythropoiesis. Current Opinion in Hematology, 22(3), 199. 10.1097/MOH.0000000000000132 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[38] Kumar, R. , Sharma, D. C. , & Kishor, P. (2012). Hb E/β-Thalassemia: The second most common cause of transfusion-dependent thalassemia in the Gwalior-Chambal region of central India. Hemoglobin, 36(5), 485–490. 10.3109/03630269.2012.699489 [PubMed] [CrossRef] [Google Scholar]

[39] Lei, M. , Sun, L. , Luo, X. S. , Yang, X. , Yu, F. , Chen, X. , & Wang, Z. (2019). Distinguishing iron deficiency anemia from thalassemia by the red blood cell lifespan with a simple CO breath test: A pilot study. Journal of Breath Research, 2, 4–6. 10.1088/1752-7163/aafe4f [PubMed] [CrossRef] [Google Scholar]

[40] Majolino, I. , Othman, D. , Rovelli, A. , Hassan, D. , Rasool, L. , Vacca, M. , & Ali, K. (2017). The start-up of the first hematopoietic stem cell transplantation center in the Iraqi Kurdistan: A capacity-building cooperative project by the Hiwa Cancer Hospital, Sulaymaniyah, and the Italian Agency for Development Cooperation: An innovative approach. Mediterranean Journal of Hematology and Infectious Diseases, 9(1), 45–54. 10.4084/mjhid.2017.031 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[41] Mancuso, A. (2010). Hepatocellular carcinoma in thalassemia: A critical review. World Journal of Hepatology, 2(5), 171. 10.4254/wjh.v2.i5.171 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[42] Mavrou, A. , Kouvidi, E. , Antsaklis, A. , Souka, A. , Kitsiou Tzeli, S. , & Kolialexi, A. (2007). Identification of nucleated red blood cells in maternal circulation: A second step in screening for fetal aneuploidies and

pregnancy complications. Prenatal Diagnosis, 27(2), 150–153. 10.1002/pd.1640 [PubMed] [CrossRef] [Google Scholar]

[43] Moi, P. , Faà, V. , Marini, M. G. , Asunis, I. , Ibba, G. , Cao, A. , & Rosatelli, M. C. (2004). A novel silent β-thalassemia mutation in the distal CACCC box affects the binding and responsiveness to EKLF. British Journal of Haematology, 126(6), 881–884. 10.1111/j.1365-2141.2004.05146.x [PubMed] [CrossRef] [Google Scholar]

[44] Mousa, S. M. O. , Afifi, M. F. , Saedii, A. A. , & El-Setohy, A. A. (2016). Ischemia modified albumin in children with transfusion-dependent β-thalassemia: A new marker for an old problem. The Egyptian Journal of Haematology, 41(2), 45. 10.4103/1110-1067.186397 [CrossRef] [Google Scholar]

[45] Mutar, M. T. , Majid, M. , Jaleel, A. , Saad, A. , Abdulmortafea, A. , & Talib, H. (2019). Awareness among parents of beta thalassemia major and intermedia patients in three centers in Baghdad and Al-Nasiriyah, Iraq in 2017. International Journal of Medical Sciences, 7(1), 6–10. 10.5195/ijms.2019.315 [CrossRef] [Google Scholar]

[46] Origa, R. (2014). Combination therapies in iron chelation. Thalassemia Reports, 4(3), 452. [Google Scholar]

[47] Origa, R. , & Comitini, F. (2019). Pregnancy in thalassemia. Mediterranean Journal of Hematology and Infectious Diseases, 11(1), 120. 10.4084/mjhid.2019.019 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[48] Pace, B. S. , Liu, L. , Li, B. , & Makala, L. H. (2015). Cell signaling pathways involved in drug-mediated fetal hemoglobin induction: Strategies to treat sickle cell disease. Experimental Biology and Medicine, 240(8), 1050–1064. 10.1177/1535370215596859 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[49] Pecorari, L. , Savelli, A. , Cuna, C. D. , Fracchia, S. , & Borgna-Pignatti, C. (2008). The role of splenectomy in thalassemia major. An update. Acta Pediatrics Mediterranea, 24, 57–60. [Google Scholar]

[50] Preza, G. C. , Ruchala, P. , Pinon, R. , Ramos, E. , Qiao, B. O. , Peralta, M. A. , Sharma, S. , Waring, A. , Ganz, T. , & Nemeth, E. (2011). Minihepcidins are rationally designed small peptides that mimic hepcidin activity in mice and may be useful for the treatment of iron overload. The Journal of Clinical Investigation, 121(12), 4880–4888. 10.1172/JCI57693 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[51] Rivière, I. , Dunbar, C. E. , & Sadelain, M. (2012). Hematopoietic stem cell engineering at a crossroads. Journal of Ameican Society and Hematology, 119(5), 1107–1116. 10.1182/blood-2011-09-349993 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[52] Romanello, K. S. , Teixeira, K. K. L. , Silva, J. P. M. O. , Nagamatsu, S. T. , Bezerra, M. A. C. , Domingos, I. F. , Martins, D. A. P. , Araujo, A. S. , Lanaro, C. , Breyer, C. A. , Ferreira, R. A. , Franco-Penteado, C. , Costa, F. F. , Malavazi, I. , Netto, L. E. S. , de Oliveira, M. A. , & Cunha, A. F. (2018). Global analysis of erythroid cells redox status reveals the involvement of Prdx1 and Prdx2 in the severity of beta thalassemia. PLoS One, 13(12), 208–316. 10.1371/journal.pone.0208316 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[53] Sabloff, M. , Chandy, M. , Wang, Z. , Logan, B. R. , Ghavamzadeh, A. , Li, C. K. , & Hale, G. A. (2011). HLA-matched sibling bone marrow transplantation for β-thalassemia major. Blood, 117(5), 1745–1750. 10.1182/blood-2010-09-306829 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[54] Sagar, C. S. , Kumar, R. , Sharma, D. C. , & Kishor, P. (2015). Alpha hemoglobin stabilizing protein: Its causal relationship with the severity of beta thalassemia. Blood Cells, Molecules, and Diseases, 55(2), 104–107. 10.1016/j.bcmd.2015.05.005 [PubMed] [CrossRef] [Google Scholar]

[55] Sangkhae, V. , & Nemeth, E. (2017). Regulation of the iron homeostatic hormone hepcidin. Advance Nutrition, 8(1), 126–136. 10.3945/an.116.013961 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[56] Sarker, N. R. , Ghosh, A. K. , Saha, S. K. , & Shahriar, A. (2014). Recent advances in the management of Thalassaemia: A Review Update. Journal of ShaheedSuhrawardy Medical College, 6(1), 31–37. 10.3329/jssmc.v6i1.31490 [CrossRef] [Google Scholar]

[57] Shariati, L. , Modaress, M. , Khanahmad, H. , Hejazi, Z. , Tabatabaiefar, M. A. , Salehi, M. , & Modarressi, M. H. (2016). Comparison of different methods for erythroid differentiation in the K562 cell line. Biotechnology Letters, 38(8), 1243–1250. 10.1007/s10529-016-2101-8 [PubMed] [CrossRef] [Google Scholar]

[58] Shawkat, A. J. , Jwaid, A. H. , & Awad, G. M. (2019). Evaluating health-related quality of life (HRQoL) in Iraqi adult and pediatric patients with beta-thalassemia major using two different iron chelation therapies. Iraqi Journal of Pharmaceutical Sciences, 28(1), 44–52. 10.31351/vol28iss1pp44-52 [CrossRef] [Google Scholar]

[59] Sirachainan, N. , Chuansumrit, A. , Kadegasem, P. , Sasanakul, W. , Wongwerawattanakoon, P. , & Mahaklan, L. (2016). Normal hemostatic parameters in children and young adults with α-thalassemia diseases. Thrombosis Research, 146, 35–42. 10.1016/j.thromres.2016.08.024 [PubMed] [CrossRef] [Google Scholar]

[60] Soliman, A. , Yassin, M. , Al Yafei, F. , Al-Naimi, L. , Almarri, N. , Sabt, A. , & De Sanctis, V. (2014). Longitudinal study on liver functions in patients with thalassemia major before and after deferasirox (DFX) therapy. Mediterranean Journal of Hematology and Infectious Diseases, 6(1), 322–330. 10.4084/mjhid.2014.025 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[61] Stauder, R. , Valent, P. , & Theurl, I. (2018). Anemia at older age: Etiologies, clinical implications, and management. Blood Journal of American Society and Hematology, 131(5), 505–514. 10.1182/blood-2017-07-746446 [PubMed] [CrossRef] [Google Scholar]

[62] Taher, A. T. , & Cappellini, M. D. (2018). How I manage medical complications of β-thalassemia in adults. Journal of American Society and Hematology, 32(17), 1781–1791. 10.1182/blood-2018-06-818187 [PubMed] [CrossRef] [Google Scholar]

[63] Taher, A. T. , Musallam, K. M. , Cappellini, M. D. , & Weatherall, D. J. (2011). Optimal management of β thalassaemiaintermedia. British Journal of Haematology, 152(5), 512–523. 10.1111/j.1365-2141.2010.08486.x [PubMed] [CrossRef] [Google Scholar]

[64] Tari, K. , ValizadehArdalan, P. , Abbaszadehdibavar, M. , Atashi, A. , Jalili, A. , & Gheidishahran, M. (2018). Thalassemia an update: Molecular basis, clinical features and treatment. International Journal of Biomedicine and Public Health, 1(1), 48–58. 10.22631/ijbmph.2018.56102 [CrossRef] [Google Scholar]

[65] Terpos, E. , & Voskaridou, E. (2010). Treatment options for thalassemia patients with osteoporosis. Annals of the New York Academy of Sciences, 1202(1), 237–243. 10.1111/j.1749-6632.2010.05542.x [PubMed] [CrossRef] [Google Scholar]

[66] Thein, S. L. (2018). Molecular basis of β thalassemia and potential therapeutic targets. Blood Cells Molecular Diseases, 70, 54–65. 10.1016/j.bcmd.2017.06.001 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[67] Vichinsky, E. P. (2005). Changing patterns of thalassemia worldwide. Annals of the New York Academy of Sciences, 1054(1), 18–24. [PubMed] [Google Scholar]

[68] Wang, C. Y. , Jenkitkasemwong, S. , Duarte, S. , Sparkman, B. K. , Shawki, A. , Mackenzie, B. , & Knutson, M. D. (2012). ZIP8 is an iron and zinc transporter whose cell-surface expression is up-regulated by cellular iron

loading. Journal of Biological Chemistry, 287(41), 34032–34043. 10.1074/jbc.M112.367284 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[69] Weatherall, D. J. (2010). The inherited diseases of hemoglobin are an emerging global health burden. Blood, 115(22), 4331–4336. [PMC free article] [PubMed] [Google Scholar]

[70] Wilber, A. , Hargrove, P. W. , Kim, Y.-S. , Riberdy, J. M. , Sankaran, V. G. , Papanikolaou, E. , Georgomanoli, M. , Anagnou, N. P. , Orkin, S. H. , Nienhuis, A. W. , & Persons, D. A. (2011). Therapeutic levels of fetal hemoglobin in erythroid progeny of β-thalassemic CD34+ cells after lentiviral vector-mediated gene transfer. Blood, 117(10), 2817–2826. 10.1182/blood-2010-08-300723 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[71] Yang, J. , Li, S. , He, X. B. , Cheng, C. , & Le, W. (2016). Induced pluripotent stem cells in Alzheimer's disease: Applications for disease modeling and cell-replacement therapy. Molecular Neurodegeneration, 11(1), 39. 10.1186/s13024-016-0106-3 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[72] Yatim, N. , Rahim, M. , Menon, K. , Al-Hassan, F. , Ahmad, R. , Manocha, A. , Saleem, M. , & Yahaya, B. (2014). Molecular characterization of α-and β-thalassaemia among Malay patients. International Journal of Molecular Sciences, 15(5), 8835–8845. 10.3390/ijms15058835 [PMC free article] [PubMed] [CrossRef] [Google Scholar]