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A comprehensive review of thalassemia disease, current treatment and managing endocrinopathies

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Abstract
Thalassemia Is a Blood Disorder. Thalassemia is the most common form of inherited anemia worldwide. The World Health Organization reports suggest that about 60000 infants are born with a major thalassemia every year.
The term "thalassemia" is derived from the Greek words "Thalassa" (sea) and "Haema" (blood) and refers to disorders associated with defective synthesis of alpha- or beta -globin subunits of hemoglobin (Hb) A (alpha-; beta), inherited as pathologic alleles of one or more of the globin genes located on chromosomes 11 (beta) and 16 (alpha).
The thalassemia's represent the most common monogenetic disorder worldwide. Because thalassemia heterozygosity confers some immunity against malaria, there is a particularly high incidence of thalassemia (2.5%-25%) in the Mediterranean basin, the Middle East, the tropical and subtropical regions of Africa, the Asian subcontinent, and Southeast Asia, where milder forms of the disease are most commonly seen. Cases of thalassemia also occur sporadically in virtually every ethnic group and geographic location.
As per Act 2016 Thalassemia Is blood Disability (Include In 21 Bench Mark Disabilty)

Keywords: bleeding disorder, epidemiology, genetic disorder, thalassemia is rare disease continuously changing blood in major thalassemia

Introduction

Despite important advances on curative approaches such as stem cell transplantation and promising results of gene therapy, blood transfusions and iron chelation still remain as cornerstones of disease management
The term "thalassemia" is derived from the Greek words "Thalassa" (sea) and "Haema" (blood) and refers to disorders associated with defective synthesis of alpha- or beta -globin subunits of hemoglobin (Hb) A (alpha-; beta), inherited as pathologic alleles of one or more of the globin genes located on chromosomes 11 (beta) and 16 (alpha).
More than 200 deletions or point mutations that impair transcription, processing, or translation of alpha- or beta globin mRNA have been identified. The clinical manifestations are diverse, ranging from absence of symptoms to profound fatal anemias in utero, or, if untreated, in early childhood.
Thalassemia is the most common form of inherited anemia worldwide which is characterized by the decreased or abolished production of either the alpha-like (alpha-thalassemia) or the beta-like (betathalassemia) globin chains that are produced to form hemoglobin tetramers (alpha2gamma2, HbF; alpha2- beta2, HbA; alpha2delta2, HbA2) during the fetal and postnatal life.
The thalassemia syndrome is classified according to which of the globin chains, alpha- or beta is affected. These 2 major groups, alpha- or beta thalassemia, are subclassified according to absent alpha c.- or beta c.) or reduced (alpha+ or beta+) globin chain synthesis. In addition, where delta-chains together with alpha-chains compose fetal hemoglobin (HbF) in the fetus and gamma chains in combination with alpha-chains compose hemoglobin A2 in adults, impaired synthesis of delta-globin or gamma-globin chains can occur.

Symptoms

- Extreme Anemia
- Shortness Of Breath
- Recurring Infection
- Fatigue
- Heart Problem
- Iron overrated

Causes of Thalassemia

- Thalassemia is caused by variant or missing genes that affect how the body makes hemoglobin.
- There are many Possible combination of variant genes that cause the various types of Thalassemia.
- A person who inherits a Thalassemia gene or genes from One parent and normal gens from the other parent is carrier

Types of Thalassemia

- Alpha Thalassemia
- Beta Thalassemia
- Delta-Beta- Thalassemia
- Thalassemia Intermedia
- Hemoglobin lepor

Mechanism of IE and hemolysis in thalassemia

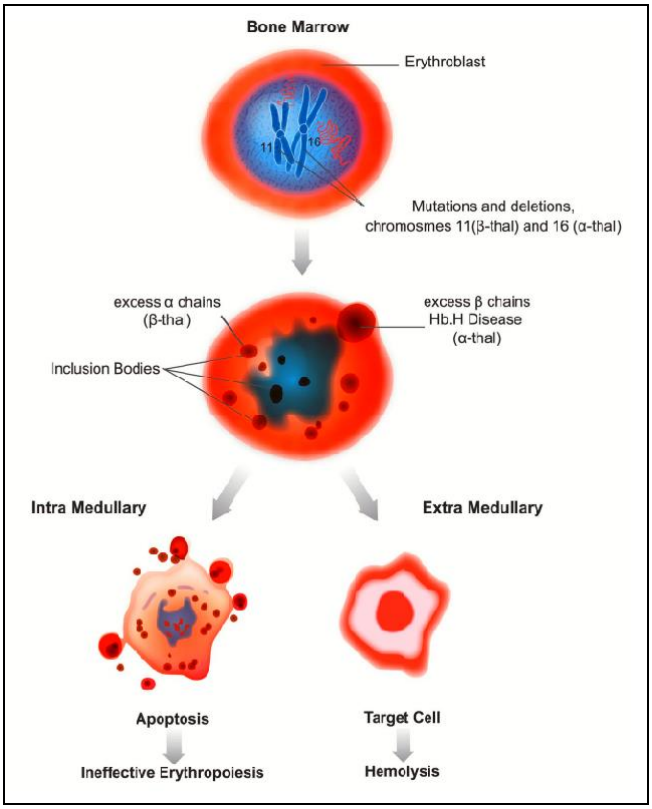

Fig 1

Pathology and Pathophysiology

Although clinical spectra vary depending on coinheritance of other genetic modifiers, the underlying pathology among the types of thalassemia is similar. This pathology is characterized by decreased Hb production and red blood cell (RBC) survival, resulting from the excess of unaffected globin chain, which form unstable homotetramers that precipitate as inclusion bodies. Alpha-Homotetramers in beta-thalassemia are more unstable than Beta-homotetramers in Alpha-thalassemia and therefore precipitate earlier in the RBC life span, causing marked RBC damage and severe hemolysis associated with ineffective erythropoiesis (IE) and extramedullary hemolysis.

Severe beta-thalassemia in which both beta-genes (one on each copy of chromosome 11) are affected (betat/betat) usually becomes manifest during the first year of life, when synthesis of fetal hemoglobin decline but switching to adult hemoglobin cannot be allowed, because of diminished synthesis of betaglobin chains to partner the alpha-globin chains.

The major determinant of the severity of beta-thalassemia is the extent of alpha-/non-alpha-globin chain imbalance, which is mainly determined by the molecular defects in the beta-genes, in which more than 200 point mutations and some deletions have been described, resulting in either reduction (betaz-thalassemia) or absence (beta0 - thalassemia) of beta-globin chain synthesis.

The insufficient synthesis of beta-globin chains is resulted with a relative excess of alpha-globin chains which precipitate in erythroid precursors and lead to oxidative damage of the cell membrane, thereby resulting in ineffective erythropoiesis and in mature red cells causing hemolysis. This primary pathology leads to severe anemia which causes tissue hypoxia stimulating erythropoietin synthesis, erythroid marrow expansion, and splenomegaly. Marrow expansion results in characteristic bone deformities and osteopenia and also leads to increased iron absorbtion from the gut which is ultimately resulted with iron overload. Recent progress in understanding regulation of iron homeostasis has contributed greatly in understanding how hypoxia and ineffective erythropoiesis mediate increased iron absorption in thalassemia.

Severe IE, chronic anemia, and hypoxia also cause increased gastrointestinal (GI) tract iron absorption. Without transfusion support, 85% of patients with severe homozygous or compound heterozygous -thalassemia will die by 5 years of age because of severe anemia.6 However, transfusions lead to progressive iron accumulation because of inadequate excretory pathways. When serum transferrin saturation exceeds 70%, free iron species, such as labile plasma iron, have been found in the plasma as well as labile iron pool in the rbcs. These iron species are mainly responsible for generating reactive oxygen species with eventual tissue damage, organ dysfunction, and death. There have been attempts to ameliorate oxidative stress in thalassemic blood cells using antioxidants, but so far they have not met with clinically significant success Iron chelation therapy has proven to be the only option to reduce morbidities and prolong survival into the fourth and fifth decades of life.

The Alpha-thalassemias

Molecular studies using nucleic acid hybridization techniques and endonuclease analysis have identified loss of Alpha-gene function related to gene deletion or nonrelational mutations causing hypofunctional genes and terminator codon mutations as responsible for the various Alpha-thalassemia syndromes.

Nearly 70 different nondeletional mutations exist that may be coinherited with deletional mutations or other genetic

modifiers that result in variable genotypic and/or phenotypic expression.

The diagnosis is suspected in the presence of microcytic hypochromic anemia not because of iron deficiency, with normal HbA2 levels in Hb electrophoresis identified. Silent carriers of Alpha-thalassemia and/or Alpha-thalassemia trait are in general clinically asymptomatic and may present with either normal blood count and morphology or with mild microcytic hypochromic anemia.

A differential diagnosis must be made to distinguish patients with iron deficiency anemia from those with Alpha-thalassemia trait. No specific treatment is recommended unless the patient is anemic. Folic acid (1-5 mg/day) can be given when the diet is deficient in folate and/or in the presence of infection, malabsorption, and where the patient is pregnant.

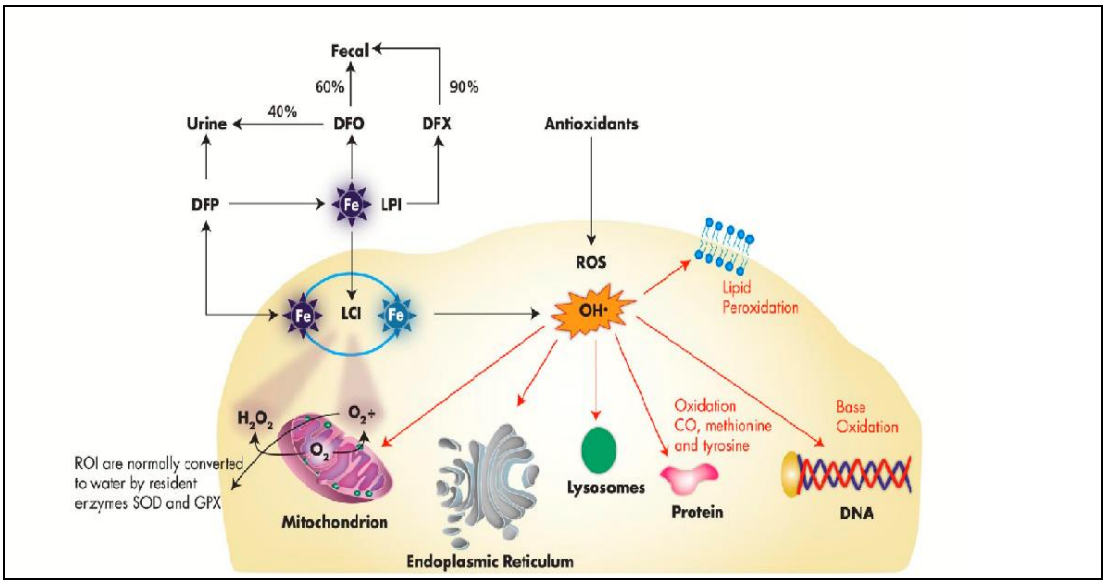

Fig 2

The Beta-thalassemia's minor

In making a diagnosis of Beta-thalassemia minor, one must rule out the existence of iron deficiency, which may alter the usually elevated HbA2 levels. High levels of HbF are also seen, depending on the underlying genetic mutation. A carrier's RBC is microcytic (mean corpuscular volume Less Than 79 fL) and hypochromic.

The clinical manifestations of Beta-thalassemia minor are usually mild, and patients with this condition generally have good quality of life. In the majority of carriers, the anemia is not clinically significant and does not require specific treatment, although carriers have occasionally been reported with splenomegaly, mild bone changes, leg ulcers, or cholelithiasis.

Couples and their close relatives should be evaluated for silent or atypical Alpha and Beta-mutations, and if they are detected, prenatal genetic counseling for diagnostic purposes should be provided.

Beta-thalassemia intermedia

Nearly 10% of Beta-thalassemia patients have Beta-thalassemia intermedia (TI). Genetically, this group may have homozygous Beta- thalassemia, homozygous or compound heterozygous Beta celsious thalassemia, and/or Beta+ thalassemia mutations. These may present with or without the concurrent inheritance of an Alpha-thalassemia gene deletion, mutation, or triplication, or of Lamda mutation.

Beta- thalassemia Major

Beta-thalassemia major (also called Cooley anemia, Mediterranean anemia, and von Jaksch anemia) denotes the homozygous or compound heterozygous forms of the disease, which are characterized by severe anemia (range, 1-7 g/dL of Hb), hemolysis, and massive IE.

Clinical manifestations appear in infancy and include severe anemia characterized by extreme pallor, jaundice, or failure to thrive, accompanied by poor feeding, irritability, decreased activity, and/or increased somnolence.

Epidemiology and Prevention

The World Health Organization report suggests that about 1.5% of the world's population might be carriers of thalassemia and that about 60 000 infants are born with a major thalassemia including homozygous betathalassemia, E/beta-thalassemia, homozygous alpha0 thalassemia and HbH disease every year.6 The extensive studies strongly indicated that the carrier status for either alpha- or beta-thalassemia offers protection against the Falciparum malaria, which explains high carrier frequency in areas where malaria has been endemic.

Long established screening programs for detecting carriers in the population with genetic counseling and the option of prenatal diagnosis at risk pregnancies have resulted in a marked reduction in the rate of affected birth in Mediterranean countries. Systematic carrier screening has recently been established in parts of Middle East and Asia countries.

Following identification of both disease-causing alleles, prenatal diagnosis can be performed by analysis of DNA extracted from fetal cells obtained by either amniocentesis or chorionic villus sampling (at 15–18 weeks and 10–12 weeks of gestation respectively). Preim plantation genetic diagnosis would also be an option for getting pregnant to an unaffected child. It is expected that the analysis of circulating fetal DNA in maternal blood will play an

increasingly important role in the future practice of prenatal diagnosis.

TI treatment strategy

The need to identify complications that can be managed with transfusion support in TI patients is now being recognized because of the frequency of age-related complications associated with chronic anemia because of increased GI tract iron absorption that occurs even in untransfused patients.

We think that, in TI patients whose ferritin levels are well above 500 g/dL, monitoring of iron excess using only serum ferritin is insufficientand we recommend annual assessments of liver iron concentration (LIC) by liver biopsy or by the more recently applied noninvasive T2* magnetic resonance imaging (MRI) beginning in late childhood or early adolescence Iron chelation therapy is warranted when LIC exceeds 5-7 mg/g dry weight and to prevent serious endocrine and cardiac complications similar to those seen in TM patients. Monitoring for splenomegaly and hypersplenism is mandatory as a possible indication of the need for splenectomy. Other common complications include postsplenectomy thrombocytosis, cholelithiasis, leg ulcers, hyperuricemia, and aplastic crisis secondary to folic acid deficiency, which is an uncommon complication.

TM treatment strategies

Transfusion therapy

The decision to initiate a regular transfusion program in a child newly diagnosed with thalassemia must take into account both laboratory and clinical findings. An overlap of genotype and phenotype expression make the clinical assessment the most important step in distinguishing TM from TI. If the child is growing poorly and has developed facial or other bone abnormalities, and/or when Hb levels are Less Than 7 g/dL, regular transfusions will be beneficial

Before the first transfusion, patients' RBCs are typed for Rh and ABO antigens. At the same time, cytomegalovirus status should be obtained. Cytomegalovirus-negative blood products are recommended for potential candidates for curative stem cell transplantation (SCT). Parents and first-degree relatives should not be blood donors for these candidates. Hepatitis B vaccination is given before transfusion therapy, as is hepatitis A vaccine when age appropriate.

Transfusions of washed, leukocyte-depleted RBCs are recommended for all the patients to reduce the incidence of febrile and urticarial reactions as well as infectious cytomegalovirus contamination. If they are not available, frozen thawed RBCs should be administered

A clinical record of all transfusion events should be monitored annually to identify hypersplenism. A record of weight, the amount of blood transfused at each visit, and the pretransfusion Hb level is needed to calculate the annual transfusion requirement.

Managing TM complications

Cardiac complications

Cardiac failure and serious arrhythmias are the major causes of life-threatening morbidity and mortality in iron-overload patients. Before the availability of chelation therapy, cardiac disease was inevitable during the second decade and still occurs in older patients or those who are poorly compliant with chelation therapy. Therefore, cardiac function is monitored annually beginning at 7 or 8 years of age by electrocardiogram, echocardiogram, 24-hour Holter monitor, and recently by cardiac T2* MRI, which can detect preclinical cardiac iron accumulation.

Pericarditis

Thalassemia patients are susceptible to benign pericarditis, possibly caused by viral and mycoplasmal organisms, bacterial or fungal infections, or associated with the engraftment syndrome in posttransplantation thalassemic patients. Pericarditis is best managed with bed rest and aspirin. Steroids may be helpful with engraftment syndrome and iron chelation with hemosiderosis. When a significantly large pericardial effusion is present, the patient should be hospitalized and observed. Pericardiocentesis and diuretics are recommended to prevent cardiac tamponade. Surgical intervention may be necessary if significant pericardial effusions recur.

Managing Endocrinopathies

Growth and development

Normal growth and development can be achieved in the first decade by maintaining near-normal pretransfusion Hb levels of 9-10 g/dL. However, iron-induced damage to the hypothalamic pituitary axis can cause delayed pubertal growth and sexual development despite timely initiation of iron chelation in early childhood. Therefore, annual endocrine evaluations are recommended, including measures of pancreatic, thyroid, parathyroid, gonadal function, and bone health with nutritional counseling.

Tanner staging should be performed every 6 months in the prepubescent child. Annual bone age films are performed to assess skeletal maturation. We begin annual monitoring between 8 and10 years of age for luteinizing hormone, follicular stimulating hormone, insulin-like growth factor, and insulin-like growth factor binding protein-3. Tests measuring these factors are required to make early diagnoses of growth hormone deficiency, which can be managed successfully with hormone replacement before the completion of puberty. If pubertal changes have not developed by 13 years of age in females, or 16 years of age in males, the use of gonadotropin releasing hormone and gonadal steroids may be necessary. Starting at 8-10 years of age, annual glucose tolerance testing for the early detection of insulin resistance is recommended to identify prediabetic or diabetic states caused by pancreatic destruction, which might benefit from metformin administration or indicate the need for insulin therapy.

Bone disease

Although RBC transfusions suppress IE, making skeletal abnormalities less common today than in the past, bone health in thalassemia patients must be monitored to identify age-related low bone mass. Nearly 90% of TM patients, including 30% of those younger than 12 years, have low bone mass Z-score (Greater than 2.0). For this reason, beginning in childhood, yearly studies that include bone mineral density as well as studies of calcium, vitamin D3 metabolism, and thyroid and parathyroid function should be performed.

Low bone mass is associated with a high prevalence of fractures in TM (17%) and TI (12%) patients, and the frequency increases with age, hypogonadism, and increased bone turnover.

It seems that early administration of iron chelation is effective in preventing endocrine complications. According to the Thalassemia Clinical Research Network, 96% of chelated thalassemia patients with a median age of 20 years were free of hypoparathyroidism, 91% had no thyroid disease, and 90% were free of diabetes. Overall, 62% were free of any endocrinopathy. However, this is not always the case because some patients may develop endocrine complications despite chelation.

Hypercoagulable state

Because improvements in the medical management of patients with TM and TI have resulted in significant prolongation of life, previously undescribed complications are now being seen. These include the existence of a hypercoagulable state, particularly in splenectomized patients with TI who do not receive regular transfusions.

Splenectomy

The severe hemolysis in TM and TI results in progressive overactivity of the spleen, which eventually aggravates the severity of the anemia and consequently increases transfusion requirements. After the initiation of a regular transfusion program from an early age, splenomegaly may be averted, but hypersplenism may nonetheless develop, usually in children between 5 and 10 years of age.

The susceptibility to overwhelming infections after splenectomy can be reduced by immunization with pneumococcal and meningococcal vaccines before splenectomy and antimicrobial prophylaxis with penicillin after splenectomy. Fever over 38°C (101°F) developing in splenectomized patients with no focus of infection requires immediate intravenous broad-spectrum antibiotics. TI patients or those who have had previous thrombotic events should be carefully monitored for postsplenectomy thrombocytosis requiring thrombophilia prophylaxis or platelet deaggregating agents.48 However, before recommending splenectomy, one should bear in mind that, in a recent evaluation of 584 patients with TI, significantly higher rates of complications were documented in splenectomized patients.

Iron chelation therapy

In cases of ongoing transfusion therapy, with each RBC unit containing -200 mg of iron, cumulative iron burden is an inevitable consequence. In TI and TM patients, the rate of transfusional and GI tract iron accumulation is generally 0.3-0.6 mg/kg per day. Increased GI tract iron absorption can result from severe anemia and IE, which down-regulate the synthesis of hepcidin, a protein that controls iron absorption from the GI tract and increases release of recycled iron from macrophages.

A proper monitoring of chelation has of importance for measuring response rate to a chelation regimen and providing dose adjustments to enhance chelation efficacy but avoid toxicity. Chelation therapy should be maintained at liver iron concentration (LIC) of about 3.2–7 mg iron/g dry weight (d.w.) (normal ranges 0.6–1.2 mg iron/g d.w.)

Iron gained by regular blood transfusions is required to be removed by iron chelation therapy for preventing iron toxicity in TM. The primary objective of iron chelation is to maintain body iron at safe levels at all times, but once iron is accumulated, the objective of iron chelation is to reduce tissue iron to the safe levels

To date, there are 3 major classes of iron chelators

1. Hexadentate (deferoxamine [DFO], Desferal), in which 1 atom of iron is bound to 1 DFO molecule.
2. Bidentate (deferiprone, L1 [DFP]), in which 1 atom of iron is bound to 3 DFP molecules
3. Tridentate (deferasirox [DFX], Exjade), in which 1 atom of iron is bound to 2 DFX molecules.

DFO, a naturally occurring sideraphore derived from Streptomyces pilosus with a high molecular weight of 657 and a very short half-life of 8-10 minutes, requires intravenous or subcutaneous parenteral administration. DFO enters hepatic parenchymal cells, chelates iron, and appears in the serum and bile as the iron chelator feroxamine. It also chelates iron released after catabolism of senescent RBCs and is excreted in the urine. The proportions and the long-term patient survival of DFO-chelated iron vary from patient to patient and are related to the degree of iron loading, chelator dose, frequency or duration, and IE activity. Maintaining normal ascorbic acid levels optimizes DFO iron excretion. Continuous slow subcutaneous infusions of DFO with a lightweight portable battery-operated pump enables longer exposure to circulating labile plasma iron

DFP (L1) is a synthetic compound originally identified in the 1980s in London, hence the designation L1. It is absorbed by the GI tract and has a plasma half-life of 1.5-4 hours. The recommended daily dose is 75 mg/kg per day, which can be increased to 100 mg/kg per day, given orally in 3 divided doses with meals. DFP penetrates cell membranes more rapidly than DFO, expediting the chelation of toxic intracellular iron species. Initial clinical efficacy studies were encouraging, indicating that DFP is capable of rapidly removing intracellular iron, and more recent reports suggest its efficacy in removing iron from the heart, improving cardiac function, and preventing iron-induced cardiac disease.

DFX (Exjade), approved in 2005 for use in transfusional overload patients, is an orally ingested, highly bioavailable chelator that is absorbed in the GI tract. Because of its dose-dependent half-life of 12-18 hours, it can be taken once a day. Daily use of a single oral dose of 20-30 mg/kg per day results in dose-dependent decreases in LIC with similar trends in serum ferritin comparable with those achieved by subcutaneous 8-hour administration of 40-60 mg/kg per day DFO. The efficacy of DFX dosing is related to transfusional iron intake. Some patients may benefit by escalating the dose up to 40 mg/kg per day. Moreover, in a group of 114 patients who had cardiac IO, levels of cardiac iron measured by T2* MRI were decreased after 1 year of DFX.

Properties, effectiveness, and unwanted effects of iron chelators

Three chelators are currently available for the purpose of preventing and removing iron overload. DFO is administered prolonged (8–12 hours) subcutaneous infusion at least 5 days a week. Adequate doses of DFO are 20–40 mg/kg/day in children and 30–60 mg/kg/day in adults.

Oral chelator DFP is a widely used regimen of 75 mg/kg/day at three divided doses up to 100 mg/kg, specifically for patients with TM when DFO is inadequate, intolerable, or unacceptable. There are still limited data available on the use of DFP in children between 6 and 10 years of age, and no data on DFP use in children under 6

years. Probably because of the rapid inactivation by glucuronidation within the liver, DFP shows less impressive effect on liver iron.17 However, the addition of subcutaneous standard dose of DFO (40–50 mg/kg) only twice weekly to daily DFP (75 mg/kg/day) resulted in higher negative iron balance, compared with either drug alone without increasing toxicity.

Comparison of the 3 leading iron-chelating drugs in the management of thalassemia

Compound	DFO	DFP	DFX
Molecular weight, Da	657	139	373
Chelating properties	Hexadentate	Bidentate	Tridentate
Recommended dose	30-60 mg/kg	75-100 mg/kg	20-40 mg/kg per day
Delivery	Subcutaneous or intravenous 8-12 h, 5-7 d/wk	Oral 3 times daily	Oral once daily
Half-life	8-10 min	1.5-4 h	12-18 h
Excretion	40%-60% fecal	90% urinary	90% fecal
Adverse effects	Ocular, auditory toxicity, growth retardation, local reactions, allergy	Gastrointestinal upset, arthralgia, neutropenia, agranulocytosis	Gastrointestinal upset, rash, ocular, auditory toxicity, reversible increases in creatinine, hepatitis

Fig 3

Toxic Effects of Iron Chelators

Designing an ideal iron chelator is a difficult challenge because of the iron paradox: iron is an essential element for many important metabolic functions (oxygen transportation and utilization, DNA synthesis, electron transport and many other biological processes), but it becomes toxic when accumulated. A chelator should remove only excess iron. Thus, in addition to possible direct toxic effects, iron chelators may alter iron homeostasis (absorption, distribution and utilization), interfere with iron-dependent enzymes (ribonucleotide reductase, lipooxygenase) or remove other metals such as zinc or calcium from essential metabolic pools. Characteristics of the compound such as molecular weight, lipophilicity/hydrophilicity balance, affinity and selectivity for Fe3+, pharmacokinetics, distribution and metabolism play a role in determining the boundary between safety and toxicity.

Important properties for an ideal iron chelator.

- High and specific affinity for Fe3+
- High chelating efficiency
- Slow rate of metabolism
- Tissue and cell penetration
- No iron redistribution
- Relatively non-toxic
- Achievement of negative iron balance
- Low cost
- Oral availability

Development of Iron Chelators

Development of an iron chelator requires several distinct and rigorous procedures, the first being the definition of the chemical properties of the ligand and of the ligand-iron complex. The second step consists of cellular studies using red blood cells, reticulocytes, cell lines and primary cell cultures (hepatocytes, myocardial and reticuloendothelial cells). Subsequently, animal models, both non-iron overloaded and iron-overloaded, are critical to evaluate the safety and efficacy of iron chelators. Unfortunately, the predictive power of the animal models is low because of the frequent differences between iron-overloaded animals and humans, and because of differences between species in iron metabolism. Efficacy in animals may not translate into comparable efficacy at tolerable doses in man. Both acute and long-term toxicity studies in different species of animals are essential for planning clinical trials.

To obtain the registration of a new compound, Phase I, II and III clinical trials, performed according to stringent requirements established by regulatory agencies, are necessary to define the safety and pharmacokinetic and pharmacodynamic characteristics of the chelator in humans, to find the therapeutic dose range and to evaluate the tolerability and the efficacy in comparison with the reference drug. Although the process of product development is very rigorous, the intrinsic limitations of clinical trials (e.g., efficacy-oriented, highly selected population, short duration, limited sample size, risk factors and exclusion criteria) make it difficult to detect all safety concerns during this phase. Post-marketing pharmacovigilance is defined as the ongoing process of evaluating and improving the safety of drugs. Once a product is marketed, there is generally a large increase in the number of patients exposed, including those with comorbid conditions and those being treated with concomitant medical products. Therefore, pharmacovigilance is critical to establish and regularly review the risk/benefit ratio of iron chelators.

Chemical structure of iron chelators under development

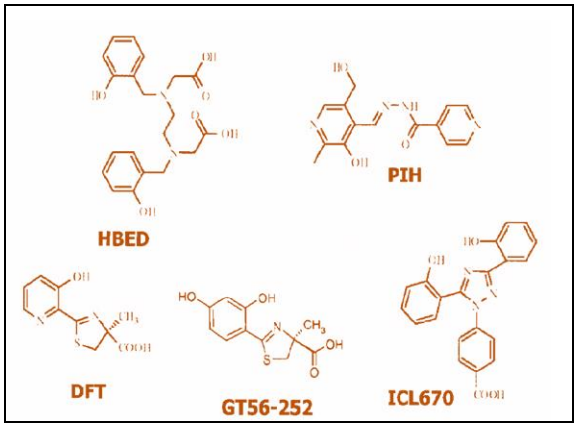

Fig 4

Combined Chelation Therapy

New chelators, particularly those that are orally available, are expected to have a major impact on the management of patients with thalassemia. A choice of more than one chelator would permit a flexible approach to chelation therapy and would probably improve compliance with treatment and overall quality of life. As an example, two

chelators might be administered simultaneously or sequentially. Combined chelation offers several potential advantages. Chelators with distinct chemical properties may have different ironcarrying capacities and accessibility to different iron pools.

Formal balance studies and clinical trials with DFO and DFP have shown that two chelators may have additive or synergistic effects, resulting in an increased efficacy. To explain these effects, it has been proposed that a bidentate or tridentate ligand, with access to a variety of tissues, acts as a "shuttle" to mobilize iron from tissue compartments to the bloodstream, where the chelator may exchange iron with a larger hexandentate "sink." The "shuttle effect" has been directly demonstrated by following the fate of chelated iron in patients with thalassemia treated with DFO and DFP. While monotherapy with DFP resulted in temporary accumulation of chelated iron in the plasma, the addition of DFO produced a transfer of DFP-chelated iron to DFO and an increase in total chelated iron. Mourad *et al* reported that giving DFP every day and DFO 2 days a week produced iron excretion comparable to that achieved with DFO administered 5 days a week. This regimen of chelation is more tolerable and may be attractive for patients who are unable to comply with regular daily use of DFO. Since some of the toxic effects of the chelators are dose-dependent, combination therapy might make it possible to lower the dose of one or both drugs, reducing toxicity but maintaining effective chelation.

Giving two drugs sequentially, e.g., DFP during the day and DFO at night, might also reduce the level of NTBI. To date, no unexpected side effects have been consistently observed in patients receiving combination therapy with DFO and DFP.

Potential advantages of combined chelation therapy

- Access to different iron pools
- Prevention of nontransferrin bound iron (NTBI) accumulation
- Increased efficacy
- Decreased toxicity
- Better compliance
- Improved quality of life

Current status of iron chelators.

Table 1

Chelator	Current Status
Deferiprone	Approved in over 50 countries
ICL670	Phase III studies in progress
GT56-252	Phase I study completed
40SD02	Phase I study completed
HBED	Phase I study planned
PIH	Preclinical studies
Desferrithiocin	Preclinical studies

Abbreviations: HBED: hydroxybenzyl-ethylenediamine-diacetic acid, PIH: pyridoxal isonicotinoyl hydrazone.

Thrombosis And Fertility In Adult Patients With Thalassemia

In a recent review, Eldor and Rachmilewitz summarize data from many series and present compelling clinical evidence for increased risk of thrombosis in patients with not only β-thalassemia intermedia, but also β-thalassemia major, α-thalassemia syndromes and hemoglobin E/β-thalassemia (E/β-thal).9 These data are compiled in below Table. The difficulty in ascertaining clinical risk and determining preventive and treatment care is that many of these patients are not fully characterized in that their transfusion regimens are not known. Additionally, although in one series the incidence of deep venous thrombosis and pulmonary embolism was inversely correlated with hemoglobin levels, the details are lacking.

A retrospective review by Cappellini *et al* of 83 patients with thalassemia intermedia and 65 patients with thalassemia major demonstrated a prevalence of venous thromboembolic events (VTE) of 29% and 2%, respectively. Twenty-three of the 24 patients with thalassemia intermedia and VTE had been splenectomized. The author recommends short-term antithrombotic therapy both perioperatively and when patients are exposed to thrombotic risk factors.We recommend this approach and additionally recommend low-dose daily aspirin for all of our splenectomized patients with thalassemia and also for our splenectomized patients with thalassemia major who have platelet counts in excess of 600,000/μL.

Evidence of hypercoagulable pathology in patients with thalassemia syndromes.

Diagnosis	No. of Patients	Thromboembolic Diagnosis	%	Comments
β-TM	138	Stroke	0.02	Not regularly transfused
		TIA	20	Not regularly transfused
β-TM	735	Stroke	0.02	Not regularly transfused
β-TI	41	Asymptomatic cerebral ischemia	37	By MRI, Incidence correlated positively w/age and negatively w/hgb
β-TM	685	DVT or PE	3.95	
β-TI	52	DVT or PE	9.61	
β-TM	1146	DVT or PE	1.1	
β-TM	421	DVT or PE	3.3	Median age 28 y, 15% congenital or acquired risk factors
β-TI	74	DVT or PE	16.2	Median age 28 y, 15% congenital or acquired risk factors
β-TI	83	DVT, PE or portal vein thrombosis	29	11% of total with recurrent VTE, 99% splenectomized
β-TM	33	Pulm HTN	85	Age range 2–24 y, suspected microthrombi
β-TM+/-E	16	Pulm HTN	94	Age range 5–14 y, suspected microthrombi
β-TM	35	Pulm HTN	75	
β-TM/E	43	Pulm arteriolar organized thrombi	19	Autopsy findings, 17 splenectomized
β-TM	2	Pulm arteriolar platelet microthrombi	2	Autopsy findings

(This table summarized data from the Eldor and Rachmilewitz review article in Blood 2002.9 Data included are from multicenter studies, retrospective autopsy reviews and observational studies. Not all studies looked for evidence of all findings, nor did all report on the presence or absence of the spleen in patients.)

Fig 5

Abbreviations
HTN: hypertension
TM: thalassemia
TIA: transient ischemic attack;
E: hemoglobin E,
MRI: magnetic resonance imaging;
DVT: deep venous thromboembolism,
TI: thalassemia intermedia;
Pulm: pulmonary
PE: pulmonary embolism;
Y: year;

Stem Cell Transplantation (SCT) and Gene Therapy
Despite therapeutic progress on survival and quality of life in TM, SCT remained as the only curative method available today. Although more than 90% of patients who receive HLA-identical related donor SCT are surviving and 80–90% of them are being disease-free, there are still uncertainties how the curative but potentially lethal SCT can be applied for adult and patients with advanced disease or having matched unrelated donor. The major limitation of SCT is the lack of an HLA-identical sibling donor for the majority (70–75%) of affected patients. Gene therapy may overcome the problem of donor availability and provide ultimate cure for all patients with thalassemia.
Intensive clinical and molecular studies on the management of thalassemia and development of targeted therapies (such as reactivation of HbF production, gene therapy, and cell therapy) show promising results for beta-thalassemia patients. However, struggle for establishing widespread health services covering screening, counseling and prenatal diagnosis is still required to control this increasing global health burden

Conclusions
During the last 25 years, investigators have made great strides in developing new iron chelators for the treatment of iron overload in thalassemia. Many candidate drugs have been screened, but only a few have had the physicochemical and biological properties suitable for potential clinical application. Some of these are now under intensive investigation Patients may ultimately benefit from having a choice between several chelators, including orally active drugs. New strategies of chelation, such as combination therapy and organ-targeted chelation, may soon have a considerable impact on the therapeutic outcome and quality of life of patients with thalassemia.

References

1. Cooley TB, Lee OP. Series of cases of splenomegaly in children with anemia and peculiar bone changes. Trans Amer Pediatr Soc,1925:37:29.
2. Borgna-Pignatti C, Rugolotto S, De Stefano P, *et al*. Survival and disease complications in thalassemia major [abstract]. Cooley's Anemia-Seventh Symposium,1998:850:227.
3. Esposito BP, Breuer W, Sirankapracha P, Pootrakul P, Hershko C, Cabantchik ZI. Labile plasma iron in ion overload: redox activity and susceptibility to chelation. Blood,2003:102:2670-2677.
4. Giardina P, Forget B. Thalassemia syndromes. In: Hoffman R, Benz E, Shattil S, *et al*, eds. Hematology: Basic Principles and Practice (5th ed). Philadelphia, PA: Churchill Livingstone, 2008, 535-563.
5. Weatherall DJ. Genetic variation and susceptibility to infection: the red cell and malaria. Br J Haematol,2008:141(3):276-286.
6. Kalpravidh RW, Siritanaratkul N, Insain P, *et al*. Improvement in oxidative stress and antioxidant parameters in beta-thalassemia/Hb E patients treated with curcuminoids. Clin Biochem,2010:43(4):424-429.
7. Aessopos A, Farmakis D, Deftereos S, *et al*. Thalassemia heart disease: a comparative evaluation of thalassemia major and thalassemia intermedia. Chest,2005:127(5):1523-1530
8. Atichartakarn V, Chuncharunee S, Chandanamattha P, *et al*. Correction of hypercoagulability and amelioration of pulmonary arterial hypertension by chronic blood transfusion in an asplenic hemoglobin E/beta-thalassemia patient. Blood,2004:103(7):2844-2846.
9. Grady RW, Berdoukas V, Rachmilewitz EA, *et al*. Iron chelation therapy: metabolic aspects of combining deferiprone and deferoxamine [abstract]. 11th International Conference on Oral Chelation in the Treatment of Thalassaemia Major and Other Disease (Catania), 2001, 74-78
10. Liu PP, Henkelman M, Joshi J, *et al*. Quantification of cardiac and tissue iron by nuclear magnetic resonance relaxometry in a novel murine thalassaemia–cardiac iron overload model. Can J Cardiol,1996:12:155-164.
11. Cunningham MJ, Macklin EA, Neufeld EJ, Cohen AR, The Thalassemia Clinical Research Network. Complications of beta-thalassemia major in North America. Blood,2004:104:34-39.
12. Aydinok Y, Ulger Z, Nart D, Terzi A, Cetiner N, Ellis G, *et al*. A randomized controlled 1-year study of daily deferiprone plus twice weekly desferrioxamine compared with daily deferiprone monotherapy in patients with thalassemia major. Haematologica,2007:92:1599-606.