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Guidelines for the Standard Monitoring of Patients with Thalassemia: Report of the Thalassemia Longitudinal Cohort

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Abstract

Chronic transfusion therapy has played a central role in extending life expectancy for patients with hemoglobinopathies such as thalassemia. However, this life saving therapy is associated with numerous complications that now comprise the bulk of management considerations for patients with thalassemia. This review reports on the experience of the Thalassemia Longitudinal Cohort and reviews available literature to establish guidelines for the management of patients with thalassemia.

Keywords

endocrinopathy; iron overload; thalassemia; transfusion; treatment

INTRODUCTION

Hemoglobinopathies, including sickle cell disease and thalassemia, are among the most common inherited disorders worldwide [1]. Thalassemia represents a group of disorders resulting from impaired hemoglobin synthesis and ineffective erythropoiesis. For patients with more severe forms of thalassemia, chronic lifelong blood transfusions are the mainstay of therapy. Untransfused children with severe thalassemia often do not survive beyond age 5 years. With transfusions and comprehensive care, birth cohorts followed from 1970 have shown life expectancy extending into the 4th decade of life and beyond [2]. Routine

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SUPPLEMENTAL DATA

Supplement I: TCRN Contributors and a List of Publications from the TCRN

transfusions have been life sustaining; however, complications of chronic blood exposure are now the predominant challenges in disease management.

METHODS

The Thalassemia Clinical Research Network (TCRN) was a multi-institutional, NIH-sponsored network established to evaluate clinical complications and treatment strategies for patients with thalassemia. Several studies have emerged from this network and have been fully described elsewhere (Table I). The Thalassemia Longitudinal Cohort Study (TLC), launched in 2007, was a longitudinal registry designed to measure the prevalence and incidence of complications of thalassemia. In the design of the TLC, a consensus among TCRN investigators for routine monitoring of clinically relevant measures was developed (Table II). This established a data set collected from over 400 North American and British patients [3]. In this paper, we describe the measures adopted by the TLC investigators and review available literature to provide guidelines for monitoring and management of patients with thalassemia. We describe guidelines for monitoring of iron overload and pain, as well as for transfusion and stem cell transplantation. We also briefly review important findings regarding quality of life. A full list of TCRN publications is included in Supplement A.

GUIDELINES AND DISCUSSION

Transfusions

Red blood cell (RBC) transfusions are the principal supportive intervention for patients with thalassemia major (TM), and are used intermittently in thalassemia intermedia. In patients with TM, transfusion therapy is often initiated before one year of age [4–6]. Complications directly related to transfusion include blood-borne infections, development of anti-RBC antibodies (both auto- and alloimmunization), and allergic, febrile or delayed hemolytic transfusion reactions.

Transfusion requirements—For chronically transfused patients, a complete blood count (CBC) should be obtained prior to each transfusion, with the goal to maintain a pre-transfusion hemoglobin level of 9-10 g/dL. Transfusions typically are administered every 3 to 4 weeks to achieve this target. Patients who are symptomatic on this schedule, or cannot tolerate the volume of transfusion (up to 20 ml/kg), may benefit from receiving transfusions at shorter intervals. The transfusion history, including volume of RBCs administered, should be recorded to allow for assessment of ongoing transfusional iron intake. It is recommended to obtain a RBC antigen profile prior to initiating transfusions, which aids in clinical evaluation should new RBC antibodies develop. Extended RBC antigen matching beyond ABO and RhD to include C, E and Kell is recommended in thalassemia because alloantibodies are most commonly directed towards these antigens [7–9]. Although this practice has effectively reduced alloimmunization rates in some populations [8], extended antigen matching was not associated with reduced alloimmunization rates in TCRN centers [5].

Transfusion reactions—All patients with thalassemia should be monitored for allergic and febrile transfusion reactions, which typically occur during or immediately after

transfusion. Premedication with acetaminophen and diphenhydramine should be considered in patients with a history of febrile or urticarial reactions, respectively. Immune-mediated hemolytic transfusion reactions can be acute or delayed up to 14 days. During a reaction, laboratory evaluation may reveal a new RBC allo- or autoantibody, anemia, indirect hyperbilirubinemia, and/or hemoglobinuria. When present, anti-RBC antibodies can complicate cross-matching, reduce survival of transfused cells and delay safe provision of blood. There is limited published support for immunomodulation to treat allosensitization; however, corticosteroids, intravenous immunoglobulin (IVIG) and rituximab have been used in some studies to control autoimmune hemolysis or delayed hemolytic transfusion reactions [10]. The alloimmunization rate among transfused patients enrolled in TCRN studies was 16.6% [5]. The most common RBC antigens identified in alloimmunized patients were anti-E, -Kell, -C and -Kidd. Autoantibodies were detected in 4.9% of the population at enrollment. When pre-transfusion hemoglobin levels are significantly lower than predicted based on transfusion volume and interval in an asymptomatic patient, laboratory investigation for a transfusion reaction should be considered.

Transfusion-associated infections—Transfused patients with thalassemia should receive all routine age-appropriate immunizations and should have annual surveillance serologic testing for Hepatitis A, Hepatitis B, Hepatitis C, and HIV. Approximately 24% of TCRN patients were seropositive for Hepatitis C at the outset of the TLC [5]. As testing for Hepatitis C has become widely available, fewer young patients seroconvert. Once a patient has seroconverted for any of these pathogens, annual surveillance practices should follow disease-specific guidelines, such as annual liver ultrasound and alpha-fetoprotein monitoring for risk of hepatocellular carcinoma secondary to Hepatitis B or C.

Transfusion-Associated Iron Deposition: Cardiac and Liver Effects

Transfusional iron overload is implicated in over 90% of mortality in patients with thalassemia [11]. Iron deposits in and is toxic to endocrine organs, liver and heart tissue. In transfusion-dependent patients, iron overload can develop after 1-2 years of regular transfusions. In birth cohorts of patients with thalassemia prior to 1980, cardiac iron deposition was associated with death in the second or third decade of life [12–14]. In the last 20 years, advances in both monitoring and treatment for iron overload have led to significant reductions in liver iron concentration (LIC) and encouraging downward trends in the frequency of cardiac complications in transfusion-dependent patients [3, 12].

Serum ferritin and LIC have long been utilized for monitoring iron overload. Serum ferritin greater than 2000 ng/ml or LIC greater than 15 mg/g dry weight were associated with increased risk of complication and death in early observational studies [15]. Serum ferritin remains an important predictor of survival [16–18], but weakly correlates with degree of cardiac siderosis [19]. Though ferritin has limited utility in estimating daily iron stores, it is readily available and over time correlates well with changes in total body iron stores. Ferritin should be measured at least every 3 months.

Assessment of LIC may begin after 1-2 years of regular transfusions or when transfusion history suggests risk of iron overload. For very young children, the need for sedation during

LIC assessment is balanced with the information to be gained from the study. If transfusion volumes and chelation history are known and the ferritin is in an acceptable range, the initial LIC measurement may be deferred until age 5 years. The LIC is usually monitored annually, and this practice led to changes in chelation after 40% of MRI studies [20]. More frequent assessments (every 6 months) may be considered when the iron burden is high and intensive chelation is utilized. Conversely, if the LIC and ferritin are well controlled, monitoring the LIC every 18 to 24 months may be acceptable. Until recently, the gold standard for measuring LIC had been liver biopsy with quantification of liver iron by weight. The frequency of liver biopsy in the TCRN decreased significantly as R2- and T2*-based MRI sequences have improved [3]. Such MRI techniques have been validated to provide liver iron estimates that are equivalent to liver biopsy [16, 18]. Increased use of MRI has likely increased adherence to monitoring recommendations due to decreased morbidity of MRI compared to biopsy [3]. Iron deposition in the liver causes inflammation and fibrosis or cirrhosis, which predisposes to an increased risk of thrombosis and hepatocellular carcinoma, thereby contributing to approximately 10% of the morbidity in the TM population [11]. Hepatic transaminases and liver function tests should be assessed at least every 6 months and more frequently if taking medications with hepatoxicity.

Regular assessment of cardiac iron deposition is a critical component of long-term monitoring. Cardiac iron deposition causes arrhythmias, left ventricular dysfunction, and eventually heart failure. In patients with thalassemia, cardiac iron accumulation and subsequent unloading with chelation may lag behind that of the liver, making LIC an insufficient marker of cardiac siderosis [19, 21, 22]. Though heart failure is a late finding, functional assessment and anatomic measurements by echocardiogram have been used to stratify risk of cardiac siderosis [23]. The development of cardiac MRI, which provides a more direct assessment of cardiac iron, has led to important changes in monitoring and survival. As T2*-sequences have become more widely available, MRI has become the standard for monitoring cardiac iron loading. Cardiac T2* measurements are stratified according to risk of heart disease: >20 ms, normal; 10-20 ms, moderate or at-risk; <10 ms, severe or high-risk. In European cohorts, monitoring with T2* in the last decade has identified patients at high-risk for cardiac events, thereby guiding treatment intensification and resulting in fewer cardiac deaths [11, 12]. In a large prospective trial, 47% of patients with T2* <6 ms developed heart failure within one year of monitoring [24]. Annual T2* and echocardiogram can begin at age 10 years, given that younger children infrequently have abnormal studies [19]. Patients with high-risk T2* should have more frequent assessments (every 6 months) until measurement shifts into a lower risk category.

Transfusion-Associated Iron Deposition: Endocrine Effects

Endocrine complications of thalassemia are common and may be difficult to manage. A broad overview and guidelines are described below, but consultation with an Endocrinologist should be obtained as needed.

Hypogonadism—Hypogonadism occurs in 50-60% of patients with thalassemia major [2, 25]. Iron deposition in the pituitary results in deficient gonadotropin secretion (secondary hypogonadism), and is partially reversible by intense chelation therapy [26]. There is also

limited evidence of primary gonadal dysfunction, caused by transfusional hemosiderosis [27, 28]. Hypogonadism can present as delayed puberty in an adolescent, or as “pubertal arrest” in a teenager who exhibited spontaneous signs of sexual development but failed to reach sexual maturity. Development of secondary amenorrhea in adult females, or of decreased vigor and libido in males, are typical presentations in adults. Consequences of untreated hypogonadism include increased risk for osteoporosis and infertility. Infertility is a growing concern as life expectancy increases and quality of life improves with current therapies [29, 30].

Clinicians should be familiar with pubertal manifestations, their onset, and examination by Tanner staging to evaluate for hypogonadism. Lack of sexual development by age 13 years in girls or 14 in boys, primary amenorrhea by age 16, or secondary amenorrhea should all prompt further evaluation. Adolescents should undergo complete physical examination with Tanner staging every 6 months throughout puberty. Failure to complete puberty within 4 years after its onset may also indicate development of hypogonadism [27]. Annual monitoring of serum gonadotropins (LH and FSH), early morning testosterone (for males), and estradiol (for females) are biochemical markers that can be helpful in the evaluation of hypogonadism. Menstrual history and reproductive health should be reviewed annually. In adolescents, growth rate is a useful clinical parameter, as patients with either delayed puberty or hypogonadism grow at pre-pubertal rates and appear to decelerate compared to their peers.

Diabetes—Diabetes mellitus has been reported among 14% of transfused patients with thalassemia major in North America [25]. Limited data suggest that both low serum insulin, due to iron-induced beta cell toxicity, and insulin resistance are involved in its pathogenesis [31, 32]. Patients rarely present with frank ketosis; many manifest polyuria, polydipsia and weight loss, or are initially asymptomatic. In the TCRN, patients were screened with a fasting glucose annually beginning at age 10 years. Among patients who have additional risk factors, such as severe iron load, Hepatitis C, or HIV, a more sensitive screen, such as an oral glucose tolerance test, should also be considered. Hemoglobin A1C, which is used as an index of diabetes control in the general population, is unreliable in thalassemia because it is affected by hemolysis and regular transfusions.

Hypothyroidism, Hypoparathyroidism and Calcium Metabolism—The prevalence of hypothyroidism in thalassemia is approximately 8-10%, thus annual screening with free thyroxine (T_4) and TSH concentration is recommended [2, 25]. Hypoparathyroidism occurs in 2% of North American patients with thalassemia and is associated with severe iron overload [25, 33]. Independent of hypoparathyroidism, patients with TM also have high rates of hypercalciuria, (up to 50%) and nephrolithiasis (approximately 10%) [25, 33]. Although the etiology of hypercalciuria is unclear, it may be related to chelator use. In addition, the incidence appears to increase when 25-hydroxyvitamin D levels rise above 30ng/ml [25]. We recommend monitoring serum and urine calcium along with annual PTH and vitamin D.

Growth & Bone Disease

Growth failure occurs in 25-28% of patients, regardless of the thalassemia syndrome [25]. Contributing factors include chronic anemia or inadequate transfusion support, chelation toxicity, nutritional deficiencies, growth hormone deficiency, and other iron-associated endocrinopathies as outlined above [25]. Historically, thalassemia has been associated with marked osseous changes, including frontal bossing, maxillary hyperplasia, and limb deformities, which are attributed to bone marrow hyperplasia and cortical thinning due to massive ineffective erythropoiesis. The introduction of regular transfusions in the mid 1960's enabled patients to maintain a near-normal hemoglobin level resulting in improvement or prevention of bone deformities. However, since transfusion and chelation therapies were introduced, growth patterns in thalassemia have not significantly improved [34].

Many early reports and interventional studies conducted outside the United States have shown that nutritional inadequacy may contribute to growth failure in some patients [35, 36]. In a recent TCRN study, 12% of pediatric, non-chronically transfused patients were underweight for height [37]. Patients who were able to maintain sufficient lean mass and fat stores had greater overall height and more optimal growth patterns, after correction for age, gender, ethnicity and transfusion status [36]. A more recent TCRN cross-sectional analysis suggests that nearly one-third of patients with thalassemia consumed inadequate amounts of nutrients important for optimal growth and bone health, such as calcium, vitamin D and magnesium [38].

Approximately 60-75% of adult patients with thalassemia have reduced bone mass for age, defined as a bone mineral density Z-score <−2.0, regardless of transfusion status [34]. In the TCRN, the proportion of patients with low bone mineral density increased with age. Low bone mass is found in 8.7% of patients under 10 years of age, 44% in the 11-19 year-old group, and in 61% of patients over 20. Patients with thalassemia have many risk factors that adversely affect bone mass including: bone marrow hyperplasia, anemia, poor growth, endocrinopathies, decreased physical activity and low vitamin D levels [34].

Children and adolescents with thalassemia should have linear growth and weight measured regularly. Patients receiving chronic transfusion therapy should be assessed at least quarterly. Growth velocity should be calculated annually from birth until the end of the growing period (females: 18 years, males: 21 years). Sitting height should be measured every 6 months to assess for truncal shortening associated with chelator toxicity. Head circumference should also be measured every 6 months to assess for skull changes due to anemia and ineffective erythropoiesis. In non-transfused patients, the development of bony changes may be an indicator to initiate chronic transfusion therapy. All patients should have a bone density assessment by dual energy x-ray absorptiometry (DXA) performed annually beginning at age 10 years to evaluate for low bone mass. Treatment options for low bone density include optimization of vitamin D and zinc levels, encouragement of weight bearing activity, and possibly a trial of bisphosphonates [34, 38, 39].

Pain

Despite improvements in treatment, patients with thalassemia continue to report frequent pain. In the TCRN, several standardized tools were used to assess pain and its impact on quality of life and mental health, including the Child Health Questionnaire (CHQ PF-28), and the Medical Outcome Study Short Form-36 (SF-36) and Hospital Anxiety and Depression Scale (HADS). No consensus was reached on the best tool to use, but routine assessment of pain with a standardized tool is recommended as part of comprehensive care.

In the TLC, 69% of adolescents and adults reported having pain in the last 4 weeks, and 28% of the time the pain was of moderate intensity. Parents reported pain in 56% of children and that pain occurred fairly often in 11% [40]. Pain was localized to the back (24%), knees (15%), head/neck (10%), large bones (8%) and small bones/ribs (5%). The overall rate of pain is comparable to the 62% frequency [41] and 21% moderate intensity [42] reported in other thalassemia cohorts. Pain was found to increase with age, diverging most sharply from U.S. age-matched normal values at age 35 years. Pain is also associated with increased anxiety and depression and with a decrease in quality of life observed in patients with thalassemia as they age [40].

The causes of pain remain unclear. The most commonly postulated sources include compression or pathologic fractures in association with osteopenia, osteoporosis, nerve root impingement by extramedullary hematopoietic masses, non-specific thoraco-lumbar throbbing related to intramedullary hematopoietic expansion, as well as localized injection site discomfort due to the use of subcutaneous chelation. Effective chronic transfusion may be helpful to diminish the stimulus for pain. Health care providers should assess for pain at every visit.

Treatments: Chelation Therapy and Bone Marrow Transplantation

Chelation therapy is critical to mitigate the toxic effects of transfusional iron overload. Monitoring of chelation therapy includes assessment of efficacy through monitoring of iron burden (see above) as well as evaluation for potential adverse effects related to chelation therapy. Currently, three chelators are licensed for use in the U.S.: deferoxamine, deferasirox, and deferiprone. These agents, studied alone and in combination, have exhibited varied benefit, efficacy, and adverse effect profiles (Table III), which have been recently reviewed [43]. The schedule of testing for adverse effects will vary based on the chelator(s) being used. Chelation history, compliance and adverse event monitoring should be assessed frequently.

Deferoxamine—Deferoxamine is administered as a continuous infusion. When given subcutaneously, local reactions including erythema and induration are common. Ophthalmological and audiologic toxicities are more common when the chelator dose is high relative to the total body iron burden and can be minimized by maintaining a ratio of deferoxamine dose (mg/kg of body weight) to the serum ferritin level below 0.025 [44, 45]. The risk of ocular toxicity may be higher in patients who have diabetes [46]. Annual ophthalmologic and audiologic evaluations are recommended in patients taking any chelator, though the risk of these toxicities with deferiprone is not clear. Growth retardation and

skeletal changes including rickets-like lesions and genu valgum may develop in growing children who use deferoxamine [47], and also are more common with “overchelation”. Deferoxamine may increase zinc excretion, leading to zinc deficiency. Zinc deficiency also may develop during treatment with deferiprone or deferasirox [48–50]. It is recommended to measure levels of this trace element annually and to supplement if low. Vitamin C levels are lower in patients with thalassemia than in controls, evidence of ongoing oxidative stress. Vitamin C levels should be measured annually in all patients. Administration of ascorbic acid with deferoxamine enhances iron excretion in patients with vitamin C deficiency [51]. However, because vitamin C can also increase the toxicity of iron, low dose vitamin C (100 mg) should be administered only on days when chelator is taken [52].

Deferasirox—Dose-related gastrointestinal side effects including nausea, vomiting, abdominal pain, and diarrhea are common with deferasirox, occurring in 15.8% of children younger than 16 years [53]. Patients should be queried regularly for such symptoms as they may lead to poor adherence. Elevations in serum creatinine to more than 33% above baseline and above the normal range occurred in 8.8% of patients with thalassemia in a long-term follow-up study [53]. Renal function should be monitored monthly with downward dose adjustments if the creatinine rises to the abnormal range. Monthly urinalysis to assess for proteinuria is also recommended. Elevated alanine aminotransferase (ALT) is another potential side effect; 1% of patients developed increases of 10 times baseline or higher, documented on 2 consecutive laboratory tests, in the 5-year follow-up study [53]. Rare episodes of fulminant hepatic failure have also been reported. Therefore, it is recommended to obtain liver function tests two weeks after drug initiation then two weeks later and monthly thereafter. Cytopenias have been reported rarely with the use of this drug, generally in patients with other comorbidities. It is prudent to monitor the CBC with differential at least every three months.

Deferiprone—Deferiprone is licensed as a second line agent for the treatment of transfusional iron overload in thalassemia. The most serious associated adverse event is agranulocytosis. In the largest study reported to date, agranulocytosis (ANC $< 500 \times 10^9$/L) occurred at a rate of 0.2 per 100 patient years and milder neutropenia (ANC 500-1500) at rate of 2.1 per 100 patient-years [54]. Neutropenia is reversible with discontinuation of the drug, but often recurs with reinstitution of therapy [54, 55]. Weekly blood counts are recommended to monitor for this side effect. A rise in serum ALT also may be seen with the use of deferiprone and appears to occur more commonly in patients with hepatitis C [49, 54] or high LIC [54]. This effect is often transient and may resolve even with continued drug administration at the same or reduced dose [54, 56]. Serum ALT should be monitored at least every three months in patients taking deferiprone.

Stem Cell Transplantation—The sole, currently available curative option for thalassemia is stem cell transplantation. An essential part of the anticipatory guidance at diagnosis of thalassemia, or with assumption of care by each new medical provider, is an assessment of donor availability and understanding of the attitude of the patient and family toward transplantation. Obtaining genotyping to confirm the diagnosis and HLA typing for transplant evaluation for all patients who require chronic transfusion is strongly

recommended. For pediatric patients, annual comprehensive follow up should include assessment of the availability of a related donor as well as a recommendation to bank cord blood and obtain HLA typing on all subsequently born full siblings. In general, the source of transplanted stem cells can be matched sibling bone marrow, matched unrelated donor marrow, or cord blood, though the overall survival and thalassemia-free survival (i.e. graft rejection), and incidence of acute or chronic graft versus host disease differ with each type of donor. Recent reviews suggest that sibling donor transplants in pediatric patients have an overall survival rate of 93%, with thalassemia free survival of over 80% [57, 58]. Related cord blood transplants have been similarly successful with lower rates of graft-versus-host disease [59]. With the introduction of high-resolution HLA typing, survival following transplantation using matched unrelated donors has improved, with overall survival rates of 96% in low-risk patients, and 65% survival amongst higher risk patients [60]. Unrelated cord blood transplants have not been as successful, with 77% survival and 65% thalassemia-free survival reported [57]. Stem cell transplants using alternative stem cell sources should generally be performed at centers with extensive transplant experience in the setting of a clinical trial.

Genetic Counseling

Genetic counseling is an important component to comprehensive care of a patient with thalassemia. Early discussions with affected families and couples who are carriers regarding the inheritance pattern of the disease and the likelihood of affecting future children can facilitate family planning [61]. Prenatal testing is available in many countries and has been used for pre-implantation diagnosis as well as identifying unaffected, HLA-matched siblings for cord blood banking. Several countries have successfully used population-based screening and pre-marital counseling to control the birth rate of patients with thalassemia, thereby reducing the social and economic impact of the disease [61–63]. Health care providers at all levels should be trained to provide counseling, to assure broad availability of support for families with thalassemia [61, 63].

Quality of Life

Chronic transfusions and chelation therapy reduce morbidity and improve survival of patients with thalassemia. Nonetheless, living with thalassemia may profoundly affect an individual's quality of life (QOL). Chronic hyper-transfusion requires missing school or work for one day every 3-4 weeks; daily parenteral chelation therapy is neither uncomplicated nor conducive to normal work, school or family life. Adverse effects of transfusions and chelation therapy also may impact quality of life. The TCRN reported QOL data collected on 102 children using parental proxy report, the CHQ PF-28. Parental report of their children's physical health was lower than US norms, with only slight decrements in psychological health. The report determined that having a child with thalassemia affects the family, limiting family activities, and negatively impacting parental time and emotion. Despite these stressors, parents reported better family cohesion. Familial, social, and psychosocial support are critical factors in improving QOL.

North American and United Kingdom patients with thalassemia had statistically significantly worse health-related QOL (HR-QOL) on physical functioning, role-physical,

general health, social functioning, and role-emotional summary scales than equivalent general US populations. Women, older patients, and those with more disease or chelation related side effects had lower HR-QOL [64]. The differences mostly related to lower general health and physical rather than emotional domains. Similar findings were present in two prior studies in the U.S. [65] and U.K. [66] Interestingly two Italian studies showed contrasting results [41, 67]. Although mental health domains of HR-QOL assessments are less affected than physical, of 276 TLC patients who completed the SF36 at baseline and the HADS, 33% indicated experiencing symptoms of anxiety and 11% had symptoms of depression. Mental health and quality of life should be assessed regularly using standardized tools.

Summary

Over nearly a decade of monitoring, the experience of the TLC highlights both the challenges inherent in caring for patients with thalassemia and the promise of emerging interventions. In the course of a generation, hemoglobinopathies have gone from universally fatal to curable. As we continue to increase the likelihood of cure for many patients, the guide outlined above will help clinicians to anticipate and manage complications that have a significant impact on patients with thalassemia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table I

Summary of Referenced Thalassemia Clinical Research Network Studies

TCRN STUDY	PARTICIPANTS	STUDY PURPOSE	REFERENCE (See Appendix A for full citation)
Thalassemia Cross-Sectional Registry	Enrolled patients at TCRN sites, 2000-06	A registry to characterize demographic and clinical features of patients with thalassemia	Cunningham, 2004 [1]
TCRN Pain Study	All TCRN participants	A comprehensive assessment of pain in thalassemia	Haines, 2013 [4]
Low Bone Mass Cross-sectional Observational Study (LBMCOS)	TCRN participants over age 6 years	A cross-sectional study of the prevalence of low bone mass, fractures, and bone pain in patients with thalassemia	Vogiatzi, 2009 [18]
Thalassemia Longitudinal Cohort (TLC)	Enrolled patients at TCRN sites, 2007-09	A longitudinal registry to measure the prevalence and incidence of complications of thalassemia	Kwiatkowski, 2012 [7]

Table II

Schedule of Measurements including Laboratory details

TEST	AGES	FREQUENCY (if normal)
Genotype	All	Once
Transplant Evaluation / HLA typing	All	Once
CBC with differential, LFTs, Chem	All	Q 6 months, monthly if transfused
Hepatitis, HIV	All	Annual
αFP/liver ultrasound	Hepatitis B/C	Annual
Transfusion/Chelation history	All	Monthly
LIC	All	Annual
Echocardiogram & Cardiac MRI T2*	≥ 10 years	Annual
Ferritin	All	Q 3 months
FSH, LH, testosterone, estradiol	≥ 10 years	Annual
Menstrual history	≥ 8 years	Annual
Reproductive health	≥ 14 years	Annual
Tanner Stage	10 - 20 years	Q 6 months
Anthropometrics (height, truncal height, weight, head circumference, growth velocity)	All	Annual, Q 3-6 months during puberty and chronic transfusion
TSH or fT4, PTH, Vitamin D (1,25 and 25-OH)	≥ 6 years	Annual
Bone Mineral Density	≥ 10 years	Annual
Fasting ascorbate	All	Annual
Fasting glucose	≥ 10 years	Annual
Chelation History and Toxicity Monitoring	All	Annual

Abbreviations: CBC: complete blood count; FSH: follicle-stimulating hormone; HLA: human leukocyte antigen; LFT: liver function tests; LH: luteinizing hormone; HIV: human immunodeficiency virus; PTH: parathyroid hormone; TSH: thyroid stimulating hormone; fT4: free thyroxine

Table III

Chelators, Chelator Toxicities and Monitoring

CHELATOR AND ROUTE OF ADMINISTRATION	TOXICITIES	MONITORING RECOMMENDATIONS
Deferoxamine	Reduced visual acuity	Annual Eye exam
	Impaired color vision	Annual Hearing exam
Subcutaneous or parenteral infusion	Abnormal visual evoked potentials	Annual zinc level
	Night blindness	
	Lens opacities	
	High frequency sensorineural hearing loss	
	Tinnitus	
	Growth retardation	
	Genu valgum	
	Zinc deficiency	
Deferasirox	Gastrointestinal toxicity: nausea, vomiting, diarrhea, abdominal pain	LFTs every 2 weeks, at one month, then monthly
Oral		Renal function and urinalysis monthly
	Increased creatinine	
	Proteinuria	CBC with differential every 3 months
	Increased ALT	
		Consider annual eye exam
		Consider annual hearing exam
Deferiprone	Neutropenia / Agranulocytosis	CBC with differential weekly*
		Consider annual eye exam
Oral		Consider annual hearing exam

* In the US, deferiprone is subject to a Risk Evaluation and Management system (REMS) and limited distribution; both patients and prescribers must sign to the effect that they understand the importance of monitoring weekly CBCs.