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Management of the Thalassemias

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During the last 30 years, in addition to the considerable progress made in control and prevention of thalassemias[3], there have also been major advances in their symptomatic management, at least in wealthier countries where appropriate facilities are available. Remarkable improvements in survival in the severe forms of thalassemia have followed the more judicious use of blood transfusion and, in particular, the ability to manage the iron accumulation resulting from transfusion with its severe and ultimately lethal effects on endocrine and cardiac function.

Because the management of severe and milder intermittent forms of β- and α-thalassemia have been described in detail recently (Weatherall and Clegg 2001; Higgs 2009; Olivieri and Weatherall 2009; Taher et al. 2011, 2012), after a short introduction to the general principles of management of these conditions, this article focuses on the control of iron overload in the different forms of thalassemia.

GENERAL PRINCIPLES OF THE MANAGEMENT OF THALASSEMIAS

Although the more severe thalassemias are an extremely heterogeneous group of disorders, their general management follows the same principles. At first presentation, it is absolutely essential to obtain an accurate diagnosis of the form of the disease, ideally including its molecular basis. It is also important to perform a detailed family study to assess the pattern of inheritance at the same time. Once this information is available, the family requires well-informed counseling about the likely future course of the illness and, equally important, about the relative risks of having further affected children.

It is not uncommon for babies to first present with thalassemia with particularly low hemoglobin levels associated with intercurrent infection. Although they may need to receive transfusions until they recover from the presenting illness, it is important not to establish them on regular transfusion without a reasonable period of observation. Unless this precaution is taken, babies with various forms of thalassemia of intermediate severity may be placed on lifelong unnecessary transfusion. The important features to observe before long-term transfusion is considered include the patterns of growth and growth velocity, activity compared with infants of the same age, the occurrence of progressive splenomegaly, and early evidence of any skeletal

[3] See Cao and Kan (2013).

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deformity. Although the hemoglobin level is also important, it should not be the only determinant of whether transfusion is required. In some forms of β-thalassemia intermedia, notably HbE β-thalassemia in particular, there is increasing evidence that patients may be able to adapt to relatively low hemoglobin levels and not require regular transfusion (Allen et al. 2010).

During later stages of development, these children—as well as continuing to be assessed regarding their growth, skeletal status, and spleen size—also need regular assessment of their hematologic findings together with their bone age, liver, endocrine and cardiac functions, as well as their iron status, which is considered in detail below.

Ideally, these patients should be managed in special centers with expertise in the management of thalassemia and with access to pediatricians in a variety of related specialties. Because so many of these patients now survive for much longer periods of time, it is also vital that these centers have staff with special knowledge of the manifestations of the thalassemias in adults, again with the appropriate specialist facilities in related fields.

Recent developments in more radical forms of treatment for the thalassemias—notably bone marrow transplantation, gene therapy, and stem cell therapy—have been reviewed elsewhere (Daley 2012; Lucarelli and Tisdale 2012; Nienhuis and Persons 2012).

IRON ACCUMULATION IN THALASSEMIA

Thalassemia patients who are not transfused may retain up to 75% of orally administered iron, accumulating between 3 and 9 mg of iron per day (Pippard et al. 1979). Because transfusions suppress erythroid expansion and reduce ineffective erythropoiesis, thereby reducing iron absorption (Pippard and Weatherall 1984), the goal of regular transfusions in thalassemia is to ameliorate these processes and correct anemia. The judicious application of a transfusion regimen in which pretransfusion hemoglobin concentrations do not exceed 9.5 g/dL achieves an optimal balance between accumulation of body iron and suppression of erythroid marrow activity (Cazzola et al. 1997). These regimens administer 100–200 mL RBCs/kg per year (Porter 2001). Transfusion requirements may be influenced by the severity of globin chain imbalance and by splenectomy, among other factors (Rebulla and Modell 1991), and daily accumulation of iron may therefore vary between 0.30 and 0.59 mg/kg (Cohen et al. 2008).

ASSESSMENT OF IRON IN VIVO

Serum Ferritin Concentration

Concentrations of plasma or serum ferritin, commonly used to estimate body iron, derive from ferritin synthesis as well as its release from damaged cells. If serum ferritin concentration exceeds 4000 μg/L, suggested as an upper physiological limit of the rate of synthesis, higher concentrations are believed to be due to the release of ferritin from damaged cells (Prieto et al. 1975; Worwood et al. 1980). Interpretation of values may be complicated by a variety of conditions, all common in thalassemia, that alter concentrations independently of changes in body iron burden, including ascorbate deficiency, fever, acute infection, chronic inflammation, acute and chronic hepatic damage, hemolysis, and ineffective erythropoiesis (Olivieri and Brittenham 1997). The 95% prediction intervals for hepatic iron concentration, given the plasma ferritin, are too broad to make the determination of ferritin a reliable predictor of body iron stores (Brittenham et al. 1993). A retrospective analysis in deferoxamine-treated patients found that during a period of 15 years, maintenance of serum ferritins of 2500 μg/L was associated with estimates of improved cardiac-disease-free survival (Olivieri et al. 1994). These findings were confirmed in subsequent studies, with lower ferritin concentration reported to predict even longer survivals (Telfer et al. 2000; Borgna-Pignatti et al. 2004a; Davis et al. 2004). These findings should not be interpreted to suggest, in the day-to-day management of individual patients, that serum ferritin is an accurate assessment of body iron burden,

although in clinical practice serum ferritin continues to be measured, usually at 6-mo intervals. Documentation of changes may be useful to encourage patients and clinicians in compliance with treatment (Davis and Porter 2000) and, as described further below, regular measurements may also be useful in monitoring the risk of deferoxamine toxicity, especially in children (Porter and Davis 2002).

Liver Iron Concentration

The liver is the major repository of transfused iron. Hepatic parenchymal iron accumulation may rapidly progress to portal fibrosis in a significant percentage of patients, including children (Iancu and Neustein 1977). In thalassemia major, progressive liver disease itself is an important cause of death in young adults (Zurlo et al. 1989) and represents a risk factor for hepatocellular carcinoma (Borgna-Pignatti et al. 2004b).

The uncertainties with respect to serum ferritin concentration have led to recommendations for the application of quantitative measurements of body iron, especially in studies to evaluate the effectiveness of new chelating agents. Liver iron correlates closely with total body iron. In patients with transfusion-dependent thalassemia, the concentration of total body iron (in milligrams per kilogram of body weight) is equivalent to 10.6 times the hepatic iron concentration (in milligrams per gram of liver, dry weight [dw]). Using this equation, it is possible to reliably estimate total body iron stores that reach as high as 250 mg/kg of body weight, with a standard error of $<$7.9 (Angelucci et al. 2000). Elevated levels of liver iron are useful in predicting the risk of complications of iron loading in vivo (Brittenham 2011). Historically, assessment of liver iron was determined through biopsies of the liver but now generally relies largely on magnetic resonance imaging (MRI) exploiting the paramagnetic effects of tissue iron on surrounding tissues, which alters the relaxation time of molecules excited by application of a magnetic field (Porter and Shah 2010). One MRI method (R2; Ferriscan) that uses widely available equipment has been standardized and validated to be predictive over a clinically useful range of liver iron concentrations (St Pierre et al. 2005).

Assessment of Cardiac Iron

Even in transfused, nonchelated patients with thalassemia, cardiac disease related to iron overload does not usually develop during the second decade of life. As more extensively outlined below, this complication has become rare in patients in whom deferoxamine therapy is available and who are managed by attentive medical personnel.

Cardiovascular T2-star (T2*) magnetic resonance (CMR T2*) has been used to guide iron-chelating therapy (Anderson et al. 2001), but calibrated methods are not available for all patients (Brittenham 2011). Early, short-term cross-sectional studies involving CMR T2* (Anderson et al. 2002, 2006) suggested poor correlations between CMR T2* and liver iron (as well as serum ferritin) concentrations and proposed that CMR T2* measurements were superior to serial determinations of liver iron in the evaluation of responses to iron-chelating therapy. These conclusions have been challenged by the identification of a calibration error in T2* liver measurements conducted by the London investigators, leading in many studies to repeated underestimation of liver iron concentration (Pennell et al. 2006; Tanner et al. 2008). Even if iron within the heart is correctly imaged (Garbowski et al. 2008), simple cross-sectional associations between the two organs may have limited usefulness because of delays in loading and removal of cardiac iron, relative to these processes in the liver (Noetzli et al. 2008). The influences on CMR T2* of the rate of tissue iron loading, the age at the start of iron loading, the processes of iron absorption and ineffective erythropoiesis, and the particular iron-chelating therapy administered remain poorly understood. The clinical significance of measurements of CMR T2* was further questioned by a recent U.S. Food and Drug Administration inspection of a trial (Pennell et al. 2006) using this modality to evaluate the relative effectiveness of two iron-chelating therapies (Food and Drug Administration 2011).

In summary, no robust data appear to effectively contradict the long-established association of liver iron concentration and the risk of development of complications in thalassemia. Body iron burdens corresponding to hepatic iron concentrations exceeding ~15–20 mg iron/g liver, dw have been shown to place patients at heightened risk of cardiac disease and early death (Brittenham et al. 1994; Telfer et al. 2000), liver dysfunction (Jensen et al. 2003), and acceleration of hepatic portal fibrosis (Angelucci et al. 2002). Lack of certainty exists with respect to optimal hepatic iron concentrations that minimize the risk that hepatic fibrosis will progress to cirrhosis and its ultimate complication, hepatocellular carcinoma (Borgna-Pignatti et al. 2004a,b; Ko et al. 2007).

It is also of clinical relevance that the development of cardiac disease may be predicted from a liver iron concentration obtained as much as 13 years previously (Telfer et al. 2000). This suggests that measurements of liver iron may provide an opportunity to optimize therapy, before organ dysfunction develops, that is more extended than reportedly provided by measurements of CMR T2* (Kirk et al. 2009).

Extrahepatic Iron

The most common clinical problem in transfused patients with thalassemia is hypogonadotropic hypogonadism (Porter and Shah 2010), related to selective iron deposition in pituitary gonadotropes (Bergeron and Kovacs 1978) as body iron burden increases (Musallam et al. 2011). Following early studies observing that anterior pituitary iron imaged by magnetic resonance (Fujisawa et al. 1988) could be correlated with biochemical markers of hypogonadism (Chatterjee et al. 1998), techniques to image the anterior pituitary have improved (Argyropoulou et al. 2003; Christoforidis et al. 2007; Au et al. 2008b; Noetzli et al. 2011b) but are not widely used in clinical practice. Diabetes mellitus, attributed to several processes including insulin resistance as well as chronic pancreatic iron overload, is also a frequently observed complication in patients in whom body iron burden is poorly controlled (Olivieri and Brittenham 1997). During the last decade, there has been progress in the MRI of pancreatic iron (Midiri et al. 1999; Au et al. 2008a,b; Noetzli et al. 2009, 2011a); correlation of pancreatic MRI parameters with tests of pancreatic function is still awaited.

Nontransferrin-Bound Iron

In thalassemia, after plasma iron exceeds the transport capacity of circulating transferrin, a fraction of iron known as nontransferrin-bound iron (NTBI) appears in plasma. NTBI comprises a heterogeneous assortment of iron complexes that are believed to be the major mediators of extrahepatic tissue damage in transfusional iron overload (Breuer et al. 2000). NTBI enters hepatocytes, cardiomyocytes, anterior pituitary cells, and pancreatic β cells, leading to the generation of reactive oxygen species. Damage to lipids, proteins, DNA, and subcellular organelles may result in cellular dysfunction, apoptosis, and necrosis (Brittenham 2011). In addition to removing excess iron from cells, chelating therapy agents may reduce NTBI, but in clinical practice measurements they are not generally used to assess the response to therapy (Jacobs et al. 2005).

Other Means of Assessing Iron Loading

Serum iron, transferrin, transferrin saturation, transferrin receptor concentration, and urinary iron excretion do not quantitatively reflect body iron stores. A study of the iron-chelating agent deferasirox based the initial dose on a calculated rate of transfusional iron loading and then adjusted the dose according to measurements of serum ferritin levels and safety markers over a 1-yr period (Cappellini et al. 2010). As noted, the long-term efficacy and safety of this strategy are uncertain (Brittenham 2011).

CHELATION IN CLINICAL PRACTICE

Iron-chelating therapy should be considered in all patients with thalassemia who require long-term red-cell transfusion. Chelators should be avoided in patients who are pregnant or breast-feeding. Ideally, therapy should be initiated

prophylactically, before clinically significant iron accumulation has occurred. Patients who have already undergone repeated transfusion without sufficient chelation can also be successfully treated, but they may require intensive regimens (Brittenham 2011).

Initiation of Iron-Chelating Therapy

A study in children with thalassemia major found that liver iron may exceed 7 mg/g dw between the 10th and 20th transfusion (Saxon et al. 1997). Before initiation (and any adjustment) of iron-chelating therapy, detailed documentation of the history of transfusion, previous iron-chelating therapy, if any, estimation of the rate of transfusional iron loading, and determination of the body iron load by measurement of the hepatic iron concentration should be undertaken. In clinical practice, body iron is also estimated regularly by serum ferritin concentration. The extent of any existing iron-induced hepatic, cardiac, or endocrine dysfunction should be established. In children and adolescents, height and weight velocity and percentiles and stage of sexual maturation should be documented. Pretherapy toxicity evaluations should be tailored to the chelating agent to be implemented, as detailed below.

The dose of an iron-chelating agent is determined by the presence or absence of cardiac iron overload, the rate of transfusional iron loading, and the body iron burden. In the absence of cardiac iron overload, the long-term objective is to maintain body iron at a level that permits safe storage while avoiding chelator toxicity. The greater the rate of transfusional iron loading, the greater the dose of an iron chelator that will be needed to control the accumulation of iron (as outlined in Table 1 [adapted from Brittenham 2011]).

Monitoring of Effectiveness

The toxic manifestations of iron depend not only on tissue concentrations but also the rate of accumulation, duration of exposure to increased iron, ascorbate status (which helps to determine the allocation of iron between macrophage and parenchymal cells), extent of internal redistribution of iron between macrophage and parenchymal sites, and noniron-related factors, such as alcohol and viral hepatitis (Olivieri and Brittenham 1997). If cardiac iron overload is present, eliminating excess iron from the heart becomes the primary therapeutic goal (see Table 1). Because chelators remove iron from the heart much more slowly than from the liver, prolonged, intensive iron-chelating therapy is usually needed. As a result, in chelated patients, the presence of cardiac iron cannot be predicted from the liver iron concentration. Iron-chelating therapy may have reduced the liver iron to an optimal range despite the persistence of severe cardiac iron overload. Nevertheless, cardiac iron loading can be prospectively predicted in the presence of sustained severe iron overload with elevated hepatic iron concentrations (Noetzli et al. 2008).

In the absence of cardiac iron overload, the primary therapeutic goal then becomes maintenance of the body iron burden at a level that permits safe storage while avoiding chelator toxicity from administering excessive amounts relative to the body iron. The best measure of the body iron load is the hepatic storage iron concentration, which reflects iron accumulations in both hepatocytes and reticuloendothelial macrophages (Kupffer cells). Therapy to maintain body iron at levels found in healthy, never-transfused individuals, corresponding to a hepatic iron of ~0.2–1.6 mg iron/g liver, dw (Brittenham et al. 1982) may increase the probability of dose-related chelator toxicity. At the opposite extreme, body iron burdens corresponding to hepatic iron concentrations exceeding ~15–20 mg iron/g liver, dw place patients at risk of serious complications of iron loading (Brittenham et al. 1994; Telfer et al. 2000; Angelucci et al. 2002; Jensen et al. 2003). In transfusion-dependent patients with thalassemia, hepatic iron concentrations of ~3–7 mg/g of liver, dw are generally regarded as optimal, seeming to minimize the risks both of adverse drug effects and complications from iron overload. The safety and long-term effectiveness of off-label regimens of therapy during which body storage iron is reportedly normalized (Farmaki et al.

Table 1. Usual doses of deferoxamine or deferasirox for transfusional iron overload (to minimize interference with growth and skeletal development)

	No cardiac iron overload (T_2^*, ≥20 msec); daily transfusional iron intake			Cardiac iron overload (T_2^*, <20 msec)	
Hepatic iron concentration	<0.3 mg/kg of body weight	0.3–0.5 mg/kg of body weight	>0.5 mg/kg of body weight	Mild to moderate T_2^*, 10 to <20 msec	Severe T_2^*, <10 msec
≥15 mg/g, dw	Deferoxamin: 40–50 mg/kg/d, 8–10 h/d, 6 or 7 d/wk, by subcutaneous infusion; deferasirox: infusion, deferasirox: oral dose of 30–40 mg/kg daily	Deferoxamine: 40–50 mg/kg/d, 8–10 h/d, 6 or 7 d/wk by subcutaneous infusion; deferasirox: oral dose of 30–40 mg/kg daily	Deferoxamine: 40–50 mg/kg/d, 8–10 h/d, 6 or 7 d/wk by subcutaneous infusion; deferasirox: oral dose of 30–40 mg/kg daily	Deferoxamine: 50 mg/kg/d by continuous intravenous infusion; deferasirox: oral dose of 40 mg/kg daily, but uncertain efficacy in reducing cardiac iron	Deferoxamine: 50 mg/kg/day by continuous intravenous infusion, deferasirox: oral dose of 40 mg/kg daily, but uncertain efficacy in reducing cardiac iron
7 to 15 mg/g, dw	Deferoxamine: 30–40 mg/kg/d, 8–10 h/d, 5 d/wk by subcutaneous infusion; deferasirox: oral dose of 20–30 mg/kg daily	Deferoxamine: 40–50 mg/kg/d, 8–10 h/d, 6 or 7 d/wk by subcutaneous infusion; deferasirox: oral dose of 30–40 mg/kg daily	Deferoxamine 40–50 mg/kg/d, 8–10 h/d, 6 or 7 d/wk by subcutaneous infusion; deferasirox: oral dose of 30–40 mg/kg daily	Deferoxamine: 40–50 mg/kg/d, 8–10 h/d, 6 or 7 d/wk by subcutaneous infusion; deferasirox: oral dose of 30–40 mg/kg daily	Deferoxamine: 40–50 mg/kg/d by continuous infusion; deferasirox: oral dose of 30–40 mg/kg daily
3 to <7 mg/g, dw	Deferoxamine: 30–40 mg/kg/d, 8–10 h/d, 5 d/wk, by subcutaneous infusion; deferasirox: oral dose of 20–30 mg/kg	Deferoxamine: 30–40 mg/kg/d, 8–10 h/d, 5 d/wk, by subcutaneous infusion; deferasirox: oral dose of 20–30 mg/kg daily	Deferoxamine: 30–40 mg/kg/d, 8–10 h/d, 5 d/wk by subcutaneous infusion: deferasirox: oral dose of 20–30 mg/kg	Deferoxamine: 40–50 mg/kg/d, 8–10 h/d, 6 or 7 d/wk, by subcutaneous infusion; deferasirox: oral dose of 30–40 mg/kg daily	Deferoxamine: 40–50 mg/kg/d by continuous infusion; deferasirox: oral dose of 30–40 mg/kg daily
<3 mg/g, dw	Deferoxamine: suspend therapy; deferasirox: suspend therapy	Deferoxamine: suspend therapy; deferasirox: suspend therapy	Deferoxamine: suspend therapy; deferasirox: suspend therapy	Deferoxamine: adjust intravenous or subcutaneous dose according to therapeutic index 32; deferasirox: adjust oral dose, monitoring renal and hepatic function and blood count	Deferoxamine: adjust intravenous or subcutaneous dose according to therapeutic index 32; deferasirox adjust oral dose, monitoring renal and hepatic function and blood count

The dose of deferoxamine in young children should not exceed 25–30 mg/kg of body weight. The dose should be adjusted according to the therapeutic index (Pennell et al. 2006). The bioavailability may affect the response. T_2^*, Cardiac transverse relaxation time on magnetic resonance imaging; dw, dry weight.

2010) await confirmation. Patients with higher body iron burdens exceeding 7 up to ~15 mg iron/g liver, dw are at an increased risk of hepatic fibrosis, diabetes mellitus, and other complications and need more intensive iron-chelation therapy (Angelucci et al. 2000). Patients with still higher body iron burdens, recognized as having a greatly increased risk of early death, are candidates for special programs of management (Brittenham 2011).

In principle, the ineffectiveness of any drug may be related to dose prescribed, adherence to treatment, blood transfusion rate, variability in absorption, metabolism of the drug, or a combination of these and other factors. Administration of a chelator will be needed as long as transfusion is continued and will be lifelong in most patients; effectiveness needs to be sustained over time. But how is effectiveness defined?

Robust criteria to evaluate the effectiveness of iron-chelating therapy are derived from published results of prospective studies of patients with iron overload (Cartwright et al. 1979; Brittenham et al. 1982, 1994; Olivieri et al. 1995) and are based on the ability of the chelator to reduce and maintain body iron at levels associated with favorable clinical outcomes. These criteria should be applied to the clinical evaluation of patients, including in clinical trials of new agents. In brief, a chelating agent is judged to be effective if it reduces or maintains body iron, assessed by hepatic iron concentration, to concentrations associated with prolonged survival free of the complications of iron overload (hepatic iron 3.2–7.0 mg/g liver, dw). A chelating agent is judged to be ineffective if the body iron increases to or is maintained at levels associated with increased risk of the complications of iron overload (hepatic iron 7.1–14.9 mg/g liver, dw), including those of cardiac disease and premature death (hepatic iron $\geq$ 15.0 mg/g liver, dw).

Criteria that refer to "percentage changes" or "improving trends" from baseline hepatic iron may be fundamentally misleading in the interpretation of the effectiveness of an iron-chelating agent and may give rise to risks to individual patients. This is illustrated by contrasting the use of two criteria of effectiveness in two patients. Consider first a patient whose initial hepatic iron is 4 mg/g liver, dw and, after treatment with an iron-chelating agent, is shown to have hepatic iron of 6 mg/g liver, dw. Although the hepatic iron has increased by 30%, application of the criteria based on the reduction or maintenance of body iron at levels associated with favorable clinical outcomes would judge the chelator to be *effective*; the body iron has been maintained within optimal range. In contrast, the application of the criteria using "percentage changes" or "improving trends" would describe this therapy as *ineffective*. Next, consider another patient in whom initial hepatic iron was 40 mg/g liver, dw and, following iron-chelating treatment, has a hepatic iron of 36 mg/g liver, dw. Although hepatic iron has decreased by 10%, application of accepted criteria would judge the chelator to be *ineffective*, because body iron persists at a level associated with an increased risk of cardiac disease and premature death, but application of the criteria judging "percentage changes" or "improving trends" would describe this therapy as *effective*. Finally, the reporting of "mean changes" in tissue or serum parameters of iron loading, in the absence of provision of individual patient responses, does not adequately inform the clinician or patient about the expectation for effectiveness for a given agent. As above, changes or lack of changes in ferritin values, although potentially useful in retrospective evaluation of body iron, may be misleading and should not be used to define effectiveness in individual patients.

AGENTS USED FOR IRON CHELATION

Deferoxamine

Chemistry, Pharmacology, and Administration in Practice

Deferoxamine is a hexadentate chelator that binds iron at a 1:1 molar ratio, rendering it virtually inactive metabolically. The drug is poorly absorbed orally (Callender and Weatherall 1980) and rapidly metabolized in plasma (Summers et al. 1979), conferring a requirement for prolonged parenteral infusions during which plasma concentrations reach a plateau at 12 h.

Deferoxamine is administered subcutaneously or intravenously, usually using a portable pump, for 8–10 h/d, 5–7 d/wk (Propper et al. 1977; Pippard et al. 1978). Subcutaneous administration is preferred except in patients with severe cardiac iron deposition for whom continuous intravenous deferoxamine therapy is recommended (Davis and Porter 2000). Oral ascorbic acid at the equivalent of 2–3 mg/kg/d (Pippard et al. 1982) is usually prescribed at the beginning of an infusion.

Clinical Benefits

The evaluation of deferoxamine therapy antedates the common use of randomized, controlled trials (Brittenham 2011). For four decades following a randomized trial in which chronic intramuscular administration was shown to slow iron accumulation and arrest hepatic fibrosis in transfused patients (Barry et al. 1974), numerous observational studies provided evidence for deferoxamine-associated improvements in long-term survival related to improvements in cardiac disease. Cardiac disease even in transfused, nonchelated patients with thalassemia does not usually develop during the second decade of life, and if treatment with deferoxamine is available and supervised, it has become rare. Two trials of >10-yr duration confirmed unequivocally that long-term use of deferoxamine in thalassemia major is associated with long-term survival, free of the cardiac complications of iron overload (Brittenham et al. 1994; Olivieri et al. 1994). In one trial, patients with most serum ferritin concentrations <2500 μg/L had an estimated cardiac-disease-free survival of 91% after 15 years, whereas cardiac-disease-free survival in those in whom most ferritins had exceeded 2500 μg/L was <20% (Olivieri et al. 1994). The other trial classified patients as having received ineffective or effective chelation therapy using a threshold of body storage iron corresponding to a liver iron of ~15 mg iron/g liver, dw; the probability of survival to at least 25 yr was only 32% among patients above this threshold, whereas no deaths occurred among patients below the threshold (Brittenham et al. 1994). A subsequent report involving more than 250 patients reported that those who administered deferoxamine at least 4.7 times/wk enjoyed 95% survival at age 30 (Gabutti and Piga 1996). In the largest reported cohort in Italy, where deferoxamine was introduced in 1975, the prevalence of heart failure in patients aged ≥15 yr decreased from 5% in patients born between 1970 and 1974 to 2% in those born between 1980 and 1984 (Borgna-Pignatti et al. 1998). A follow-up report identified one death from cardiac disease in the 1980–1984 birth cohort and no such deaths in subsequent birth cohorts (Borgna-Pignatti et al. 2004a). These findings show that accumulation of iron in heart is not inevitable, provided that body storage iron is controlled (Porter 2007). These North American and Italian data are paralleled in expert programs in the United Kingdom (Porter and Davis 2002), although poorer results are reported in centers in that country where erratic compliance and other impediments to effective treatment are likely less well managed (Modell et al. 2000). It would therefore appear that cardiac disease develops almost exclusively in thalassemia patients in whom effective treatment is unavailable, who begin deferoxamine after irreversible damage has occurred and/or who are not expertly supervised during long-term treatment.

The most common complication of iron loading in thalassemia, hypogonadism, is also prevented by effective use of deferoxamine (Bronspiegel-Weintrob et al. 1990), although secondary amenorrhea in women, and secondary hypogonadism in men, may develop after age 21, even in those who have attained normal puberty (Gamberini et al. 2008).

Tolerability and Toxicity of Deferoxamine

Discomfort at the site of infusion may be mitigated with topical anesthetic or glucocorticoid creams (Brittenham 2011). Dose-related deferoxamine toxicities including visual changes, auditory toxicity, attenuation of linear growth, and skeletal dysplasia (Olivieri et al. 1986; Rodda et al. 1995; Chan et al. 2002; De Sanctis et al. 2006) may be minimized by maintaining doses of no more than 25–30 mg/kg in young

children (Olivieri et al. 1992; Olivieri and Brittenham 1997). In both children and adults, as the hepatic iron concentration approaches optimal levels (see below), dose reduction is recommended; a useful recommendation is that the daily dose (mg/kg) divided by the serum ferritin (mg/L) should not exceed 0.025 (Porter and Huehns 1989; Porter et al. 1989). Allergy to deferoxamine is rare and most patients may be desensitized successfully (Porter 2001), with patients thereafter able to take deferoxamine. Monitoring of toxicity in patients who receive deferoxamine includes annual assessments of auditory function and vision and, in children, careful observations of linear growth including height velocity.

Deferasirox

Chemistry, Pharmacology, and Administration in Practice

The synthetic chelator deferasirox is a bis-hydroxyphenyl-triazole that, in contrast to deferoxamine, is well absorbed from the gastrointestinal tract and cleared from the circulation slowly with a plasma half-life of 11–19 h, supporting once-daily oral dosing (Galanello et al. 2003; Nisbet-Brown et al. 2003; Waldmeier et al. 2010). Because of low water solubility of the free ligand, deferasirox is administered as a suspension in water or fruit juice (Novartis Pharmaceuticals 2010). Hepatocytes readily take up deferasirox, which chelates hepatocellular iron. Deferasirox–iron complexes are excreted in the bile (Waldmeier et al. 2010).

The short-term effectiveness of deferasirox has been compared with deferoxamine in trials sponsored by Novartis (Cappellini et al. 2006; Piga et al. 2006; Vichinsky et al. 2007; Porter et al. 2008; Cappellini et al. 2010). In the largest trial in which 586 children with thalassemia were randomly assigned to either agent, with dosing according to the baseline hepatic iron concentration (Cappellini et al. 2006), the primary end point was the percentage of patients with either a maintained or reduced hepatic iron concentration at 1 yr. This end point was reached in 52.9% of patients assigned to deferasirox and in 66.4% of patients assigned to deferoxamine. This result, which did not meet a prespecified noninferiority target, was attributed to the relative underdosing of deferasirox (Brittenham 2011). No trial has established the long-term effectiveness of deferasirox in preventing organ toxicity or improving survival.

Tolerability and Unwanted Effects of Deferasirox

In the registration trial of deferasirox (Cappellini et al. 2006), gastrointestinal disturbances occurred in ~15% of patients, rash in 11%, and increases in serum creatinine levels in 38%. Similar rates have been observed in subsequent trials (Piga et al. 2006; Vichinsky et al. 2007; Porter et al. 2008). In 2010, on the basis of postmarketing studies, the Food and Drug Administration required a change in the prescribing information for deferasirox, stating that the drug could cause potentially fatal renal and hepatic impairment or failure as well as gastrointestinal hemorrhage. These adverse effects were reported to occur more frequently in older patients and in patients with high-risk myelodysplastic syndromes, thrombocytopenia, or underlying renal or hepatic impairment. In patients who receive deferasirox, serum creatinine, serum aminotransferases, and bilirubin levels should be assessed monthly (Novartis Pharmaceuticals 2010).

Deferiprone

In both the European Union and the United States, the approved use of the synthetic oral iron-chelating agent deferiprone is restricted to patients with transfusional iron overload owing to thalassemia syndromes when current chelation therapy is inadequate. Deferiprone is not approved for use in Canada. Because this agent is not recommended for primary iron-chelating therapy, it is considered here only briefly.

Chemistry, Pharmacology, and Administration in Practice

Deferiprone is a 3-hydroxypyridin-4-1 bidentate chelator that binds to iron in a 3:1 ratio

(Porter and Shah 2010). The drug has a plasma half-life of 1.5 h (Olivieri et al. 1990) and is usually given three times daily.

Clinical Benefits

In the United States, approval was based on a reduction in serum ferritin levels; sustained reduction in liver iron concentration during deferiprone treatment has not been shown. The FDA prescribing information states that there "are no controlled trials demonstrating a direct treatment benefit, such as improvement in disease-related symptoms, functioning, or increased survival" (Food and Drug Administration 2011).

Tolerability and Unwanted Effects

Common adverse effects include nausea, diarrhea, and arthropathy, including arthritis associated with clinically significant disability. The most serious adverse effects are agranulocytosis and neutropenia, increases in liver enzymes (Cohen et al. 2003), and progression of hepatic fibrosis associated with an increase in iron overload or hepatitis C. Weekly monitoring of the neutrophil count is recommended. Neurologic abnormalities have been reported during administration of higher-than-recommended doses (Beau-Salinas et al. 2009). In patients who receive deferiprone, weekly assessment of complete blood counts and monthly assessments of serum aminotransferases should be performed (European Medicines Agency 2009).

Approach to Therapy

An informed decision with respect to the choice of an iron chelator is best made with the patient or guardian. Despite the lack of data on long-term effectiveness, most patients now opt for deferasirox because of the ease of administration (Brittenham 2011). Patients, particularly those with severe iron overload with cardiac involvement, who are informed about the efficacy of deferoxamine in the reversal of iron-induced heart disease (Davis and Porter 2000) and improving long-term survival, may indicate a preference for the proven therapy. Deferasirox may be substituted for deferoxamine when cardiac function is improved, or it could also be a choice in patients who are unable to tolerate infusions of deferoxamine (Brittenham 2011).

Combination Therapy

The long-term effectiveness of a variety of binary combinations of chelating agents presently administered in off-label uses remains uncertain due to the absence of unequivocal evidence of the superiority of any specific combination over treatment with a single agent (Roberts et al. 2007; Brittenham 2011).

Monitoring

The control of iron-chelating therapy is best implemented by periodic measurements of hepatic iron and of cardiac function. Serum ferritin concentrations are usually measured twice a year. On an annual basis, hepatic, cardiac, and endocrine function should be evaluated and, in children and adolescents, growth and sexual maturation formally assessed. Monitoring of toxicity will depend on the potential adverse effects of the specific agent to be used as above.

Financial Costs of Iron-Chelating Therapy

In North America (Vichinsky et al. 2005) and Europe (Modell et al. 2001), the combined number of patients with transfusion-dependent thalassemia is $<$10,000. Globally, at least 100,000 patients with thalassemia require transfusions (Weatherall 2010). As previously discussed (Brittenham 2011), the annual per-patient costs of care for complications of iron overload are estimated to be \$15,000–\$20,000.

What is less well calculated, particularly in emerging countries, are costs associated with inadequate chelating therapy that may be collected from publications that report the costs in richer countries of failure of compliance with therapy (Delea et al. 2007). Full therapeutic doses of effective iron-chelating agents are affordable in only a minority of patients in countries worldwide, and regimens of treatment in

these countries include the wider application of less effective drugs and combinations of drugs, or homeopathic doses of deferoxamine or deferasirox. As expected, heart and liver disease and endocrine dysfunction are, ultimately, not prevented by these regimens. The complications of iron overload that can be expected to develop result in increased costs in medical care, which, like chelating therapy itself, are generally borne primarily by the family of the individual in these countries. Unassisted by patient organizations that focus most efforts in North America and Europe, this situation is now being addressed through efforts by smaller charities.

CONCLUSIONS

Clearly, there have been major improvements in the symptomatic management of severe thalassemias, at least in the wealthier countries of the world. Although, as discussed by Weatherall (2010), owing to increasing international collaboration, at least some progress is also being made in the developing countries, but the situation is still far from satisfactory. As these countries go through the epidemiological transition resulting from improvements in public health, nutrition, and medical care, the number of babies who would previously have died before presenting for treatment with thalassemia is likely to decrease; hence, it is almost certain that overall, the number of patients with this condition will increase in the future. It may be some time before more radical forms of treatment such as gene therapy become available and, even then, they are likely to be very expensive. Hence, despite the increased development of public education, counseling, and prenatal diagnosis, it is likely that the symptomatic approach to the management of thalassemias, as outlined in this brief article, will remain of considerable importance for the foreseeable future.

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