How we manage iron overload in sickle cell patients

Thomas D. Coates1 and John C. Wood2

1Hematology Section, Children’s Centre for Cancer, Blood Diseases and Bone Marrow Transplantation, Keck School of Medicine, University of Southern California, and 2Division of Cardiology at the Children’s Hospital Los Angeles, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

Summary

Blood transfusion plays a prominent role in the management of patients with sickle cell disease (SCD), but causes significant iron overload. As transfusions are used to treat the severe complications of SCD, it remains difficult to distinguish whether organ damage is a consequence of iron overload or is due to the complications treated by transfusion. Better management has resulted in increased survival, but prolonged exposure to iron puts SCD patients at greater risk for iron-related complications that should be treated. The success of chelation therapy is dominated by patient adherence to prescribed treatment; thus, adjustment of drug regimens to increase adherence to treatment is critical. This review will discuss the current biology of iron homeostasis in patients with SCD and how this informs our clinical approach to treatment. We will present the clinical approach to treatment of iron overload at our centre using serial assessment of organ iron by magnetic resonance imaging.

Keywords: sickle cell disease, anaemia, chelator, iron overload, management.

Sickle cell disease (SCD) is an inherited chronic haemolytic anaemia that results from a single amino acid substitution in the β-globin chain, producing the abnormal haemoglobin-S (HbS). Unlike normal haemoglobin, HbS polymerizes at low oxygen tension, triggering the conversion of the normally flexible red blood cell (RBC) into a rigid, crescent or “sickled” shape RBC that obstructs blood flow in the microcirculation. This sickling process is continual; however, episodic exacerbations occur that result in severe vaso-occlusion and pain, pulmonary failure, and stroke. The median survival for SCD patients in the United States is about 42 years, with significant pre-morbid complications (Powars et al, 2005), although recent data suggest survival may be better in some western countries (Gardner et al, 2016). Currently, about 95% of children in the US and Europe survive until 18 years of age (Quinn et al, 2010), but have significant vascular complications by age 20 years as well as chronic organ failure leading to premature death in their fourth and fifth decade (Powars et al, 2005; Bernaudin et al, 2015). A high proportion of adults suffer from severe, chronic pain that significantly diminishes their quality of life (Smith et al, 2005, 2008). About 240 000 children born annually in Africa have SCD, and only 20% survive to their second birthday (Makani et al, 2011). All of the morbidity seen in SCD is due to vascular disease and tissue necrosis that occur as a consequence of the chronic haemolytic anaemia (Dettirich et al, 2015; Novelli & Gladwin, 2016).

Blood transfusion plays a prominent role in the management of patients with SCD, but causes significant iron overload (Ballas, 2001; Wood et al, 2005; Fung et al, 2007; Puliyl et al, 2014; Vitrano et al, 2016). Chronic transfusions are used to treat patients with severe complications of SCD. Despite the significant morbidity associated with iron overload (Ballas, 2001), it remains difficult to distinguish whether organ damage in SCD is a consequence of iron from transfusions used to treat SCD complications or due to the complications themselves. We know from experience with thalassaemia, where the causal relation of iron overload to mortality is clear (Modell et al, 1982, 2008; Berdoukas & Modell, 2008), that iron overload is toxic, and can be lethal. Nevertheless, we also know that the same degree of iron loading is less toxic in SCD than in thalassaemia (Vichinsky et al, 2005; Walter et al, 2006). Some investigators have even questioned whether treatment of iron overload in SCD is advisable (Lucania et al, 2011), although it is strongly recommended by the United States National Institutes of Health Guidelines based on evidence of moderate quality (Yawn et al, 2014), and iron may be responsible for up to 11% of deaths in SCD subjects (Perronne et al, 2002; Darbari et al, 2006). While rare, iron cardiomyopathy is detectable in about 2.5% of chronically transfused SCD patients (Meloni et al, 2014), and it is one iron toxicity that is separable from SCD damage, indicating that iron can cause serious health.
issues in some SCD patients. We suspect that the incidence of iron-related complications is actually higher than reported because the diagnosis is often not considered and the magnetic resonance imaging (MRI) methodology for tissue iron detection is not readily available. Iron toxicity is related to the duration and severity of iron overload and, over decades, can result in multiple problems, including malignant transformation. As survival is improving in adults with SCD, we feel that iron overload should ideally be treated with the goal of bringing iron levels to a normal range. This opinion is based largely on the general effect of iron on survival and the strong association with malignant transformation [reviewed in (Coates et al, 2016)].

This review will discuss the current biology of iron homeostasis in humans and how this new knowledge has informed our thinking and has modified our approach to clinical management in this population with transfusional iron overload. We will present the clinical practice at our centre, where we follow approximately 120 patients on chronic transfusion each year, from early childhood to 40 years of age. Our approach relies heavily on readily access to serial assessment of organ iron by MRI, established at our centre since 2003.

Transfusion in SCD

In general, transfusion is used to treat symptoms of anaemia or to stop or prevent complications of SCD-related vaso-occlusion. There is general agreement for using transfusion to prevent strokes in children, to treat severe acute chest syndrome, and as a preoperative precaution (de Montalembert et al, 2014; Noetzli et al, 2011, 2012). Liver iron concentration (LIC) is highly correlated ($r^2 = 0.98; P < 0.001$) with total body iron (Angelucci et al, 2000); however, there is a very poor correlation between LIC and pancreatic, pituitary or cardiac iron concentrations, indicating that besides total iron, other factors control iron trafficking in these organs. In response to intensive iron chelation, the LIC can be reduced by 50% in 1-5 months, whereas it takes about 13 months to remove half of the iron from the heart (Anderson et al, 2004). Pancreatic loading and unloading rates are intermediate. These significant differences in loading and unloading between various tissues (see Fig 1), derived from serial MRI measurements in iron-loaded humans, are consistent with very elegant biochemical studies of iron regulation over the past two decades [reviewed in (Coates, 2014)], and have a direct impact on the diagnosis, monitoring and treatment of SCD patients with iron overload, as summarized below.

Biological organisms have evolved to conserve iron, an essential metal for numerous biochemical processes in humans, and thus, humans have no mechanisms to excrete iron. Approximately 1–2 mg iron per day (0.05% of total body iron) is lost through desquamation of the gastro-intestinal tract lining and skin, and in smaller amounts, through blood loss (Green et al, 1968). Iron balance is maintained entirely through the regulation of dietary iron absorption, primarily in the duodenum, and the recycling of iron from RBC. About 25 mg of iron are reclaimed daily through the phagocytosis and degradation of senescent autologous or transfused RBC by macrophages. The reclaimed iron in the macrophage is in the ferrous state ($Fe^{2+}$), and is called labile cellular iron (LCI). LCI increases the levels of ferritin and is either utilised by the cell, taken up and buffered by ferritin, or exported to the plasma via ferroportin (FPN), the cellular iron exporter. Ferritin, while primarily intracellular, can leak into the plasma through damaged cell membranes. Thus, serum/plasma ferritin levels are a rough measure of iron loading. Ferritin also serves as a major intracellular buffer of toxic $Fe^{2+}$ by converting it to the ferric state ($Fe^{3+}$). Haemosiderin, which is made up of large aggregates of ferritin, is the primary species that is detected by MRI [reviewed in (Ganz, 2013; Coates, 2014; Frazer & Anderson, 2014)].

Normally, $Fe^{3+}$ is bound to transferrin in the circulation, and it enters cells by receptor-mediated endocytosis via the transferrin receptor, TIR1, also termed TFRC. TIR1 transcription decreases when $Fe^{2+}$/LCI increases, thereby preventing
cellular iron overload. However, when total body iron increases dramatically, as it is the case in multiply transfused patients, the transferrin-binding ability is rapidly exceeded, and circulating non-transferrin bound iron (NTBI) appears in the plasma. NTBI rises considerably when the transferrin saturation reaches around 60%, and a highly reactive Fe$^{+2}$ subspecies of NTBI called labile plasma iron (LPI) increases concomitantly. LPI can enter cells through ion transporters that are normally designed to carry divalent cations like zinc and calcium. For the most part, these ion transporters are not regulated by intracellular iron concentration; thus, iron loading proceeds, even when cytosolic iron levels are very high. The iron transport through these channels is organ-specific and may explain why the rate of loading observed by serial MRI is different (liver > pancreas > heart) (Murphy & Oudit, 2010; Coates, 2014; Khamseekaew et al., 2016). While most information regarding the physiology of cardiac iron loading is based on studies in animals, the recent demonstration that the calcium channel blocker amlodipine decreases cardiac iron loading in patients with thalassaemia suggests that this mechanism is also operative in humans (Fernandes et al., 2016).

The flow of iron from enterocytes and macrophages into the plasma is regulated by hepcidin, a 25 amino acid, defensin-like peptide that is made in the liver and binds to FPN, thereby causing FPN internalization and degradation (Nemeth, 2010). Hepcidin is elevated in iron overload and inflammatory states (Nemeth et al., 2003; Ganz, 2013). While inflammation increases hepcidin and blocks iron release into the plasma (Ganz & Nemeth, 2012), hypoxia, anaemia and erythropoiesis reduce hepcidin production, increasing the release of Fe$^{+2}$ into the plasma and iron absorption. Thus, the state of bone marrow activity has a significant impact on hepcidin production and on the levels of reactive LPI.

The toxicity from iron is due to NTBI/LPI and LCI, the Fe$^{+2}$ reactive forms of iron, and is mediated through production of reactive oxygen species (ROS), either through direct effects or through ROS signalling. Fe$^{+2}$ reacts with ROS, such as hydrogen peroxide (H$_2$O$_2$) to produce hydroxyl radical (HO•; Fenton reaction). HO• is a potent oxidant that can react rapidly with most molecules, including DNA, thereby permanently altering genetic material. In conditions of iron overload when NTBI and LPI/LCI levels are high, and during inflammation when high levels of ROS are produced, severe oxidant damage to tissues can occur [reviewed in (Koskenkorva-Frank et al., 2013)]. Clinical evidence also supports the idea that NTBI/LPI is the toxic form of iron. NTBI/LPI represents the pool of iron that is immediately accessible to chelators, and NTBI/LPI levels in the blood can be reduced to near zero within minutes to hours of starting chelation with deferoxamine (DFO) (Porter et al., 1996) (see below). When patients with severe myocardial iron loading and decreased left ventricular function were treated with continuous iron chelation therapy, normalization of ejection fraction occurred within 3 months of starting chelation, even though the cardiac iron levels detected by MRI remained remarkably elevated. Thus, chelating the NTBI/LPI was sufficient to improve cardiac function (Anderson et al., 2004), and having a chelator in the circulation can be protective, even before tissue levels of iron have been reduced.

Iron loading and toxicity in SCD

Generally, the toxicity of iron overload is substantially less in patients with SCD than in patients with thalassaemia. When populations of SCD and thalassaemia patients who had equal exposure to blood transfusion and equal LIC were compared, thalassaemia patients had a 3.5-fold greater risk of developing heart failure and hypogonadism after controlling for differences in transfusion duration (Vichinsky et al., 2005), consistent with the known lower levels of NTBI/LPI in SCD.
eliminated (Farmaki et al., 2010; Porter et al., 2016) and the role played by LPI in toxicity [reviewed in (Coates, 2014; Porter & Garbowski, 2014)]. Nonetheless, we have followed several SCD patients who had clear-cut, clinically symptomatic iron cardiomyopathy (Meloni et al., 2014). Interestingly, SCD patients with significant cardiac iron loading (T2* < 20 ms) have surprisingly low HbS concentration and reticulocyte counts in the 3–10% range (Meloni et al., 2014). Iron is toxic to the bone marrow, probably because iron and oxidants play a role in causing ineffective erythropoiesis (Gardenghi et al., 2007; Rivella, 2009; Breda & Rivella, 2014; Dussiot et al., 2014; Camaschella & Nai, 2016). Thus, we suspect that the surprisingly low HbS levels in these extremely overloaded SCD patients are due to iron-mediated marrow toxicity, resulting in an ineffective erythropoiesis phenotype that favours development of iron cardiomyopathy.

The occurrence of iron cardiomyopathy clearly shows that iron toxicity arises in SCD. One of our SCD patients, a 24-year-old woman who was in clear clinical congestive heart failure (CHF) with a cardiac T2* < 10 ms and an ejection fraction of 45% by MRI, was asymptomatic 3 weeks after starting aggressive chelation with deferoxiprone, essentially proving her CHF was related to her high levels of cardiac iron. While we are aware of several other cases of cardiac iron in SCD and are convinced that iron overload is a serious contributor to morbidity in SCD in general, we have yet to find a published case series that clearly separates iron-related toxicity from SCD-related complications. The toxicity of iron depends on the tissue iron concentration, the duration of the exposure, and the adequacy of the individual anti-oxidant systems. In general, measurable changes in organ function due to iron exposure require years to develop, though the exact timing is not known.

Regardless, as survival in SCD is increasing (Gardner et al., 2016), the lifetime exposure to iron will increase and we can expect iron-related complications to become more frequent in these patients, as is the case in thalassaemia [reviewed in (Coates et al., 2016)].

Principles of iron overload management in SCD

While there are some differences in iron homeostasis between SCD and other transfusion-dependent anaemias, the approach to chelation therapy and monitoring of the overload is not different. The treatment goals for iron overload are to reduce plasma and cytosolic levels of reactive labile iron (Fe^{2+};NTBI/LPI) as quickly as possible, and to remove all excess iron from the body. In our opinion, regardless of the underlying disease process, the major goal of treatment should be to maintain these reactive forms of iron in the normal range throughout life. If this can be achieved, most of the complications of iron overload can be reduced or even eliminated (Farmaki et al., 2010; Kolnagou & Kontoghiorghes, 2010a,b; Kolnagou et al., 2010; Kontoghiorghes, 2010; Coates et al., 2016). However, achieving this goal without risking unacceptable treatment toxicity may not be possible, and some experts do not agree with trying to keep iron at near normal levels. Maintaining iron levels in the low range (LIC < 3 mg/g) should only be attempted at centres with the ability to monitor organ iron by MRI and expertise in chelation. These levels cannot be safely achieved using ferritin measures alone as a surrogate for organ iron loading.

Diagnosis and monitoring of patients with iron overload

The methods for clinical diagnosis and monitoring of iron overload are summarized in Table I. Ferritin levels and transferrin saturation are simple tests that have been used for many decades to diagnose and monitor iron overload. Intra-cellular ferritin levels increase in response to LCI, but are also significantly increased by interleukin 6 in response to inflammation. Thus, the blood levels of ferritin reflect the degree of cellular membrane leakage, the LCI and the degree of inflammation. A good correlation has been found between ferritin levels and total iron, but only in patient populations. The relation of ferritin to total iron in individual patients is poor and the trends in ferritin are opposite to the trends in total iron 23% of the time (Puliyel et al., 2014; Aubart et al., 2016). Figure 2 shows the scatter in ferritin at low LIC and demonstrates that attempting to achieve tight iron control (LIC < 3 mg/g) with ferritin alone would increase the risk of over-chelation. Ferritin cut-off levels have been published that reduce the risk of over-chelation when ferritin alone is used to estimate LIC (‘Taher et al., 2014). If MRI LIC measures are available, we use these values to adjust chelation, regardless of the ferritin. Because of its great variability, ferritin should be measured frequently and only the trends over many measurements should be used for any therapeutic decision-making. We routinely measure ferritin after each transfusion, usually every 3 weeks. Generally, we recommend acquiring LIC measurements annually, and sooner if ferritin trends are not consistent with the clinical circumstance (Table I). Critical treatment decisions based on ferritin alone should be made with great caution, especially at low LIC levels.

Transferrin saturation is the only common test that reflects the toxic NTBI/LPI pool. If the transferrin saturation is greater than 50%, NTBI/LPI levels are likely to be high, and if it is >70%, NTBI/LPI levels are significantly elevated (Sahlsstedt et al., 2001; Porter et al., 2016). Transferrin saturation has been used to screen for iron overload in epidemiology studies and can predict long-term complications of iron overload in large populations [reviewed in (Puliyel et al., 2015; Coates et al., 2016)]. However, transferrin saturation can change literally within minutes to hours, and should be assessed while the patient is fasting. It can go from 5% to 60% and back down to 5% within 60 min of a single oral iron dose, and it drops as quickly after a dose of iron chelator. As the half-life of NTBI/LPI inferred by transferrin saturation is very short, transferrin saturation and direct LPI
Table I. Monitoring iron overload.

<table>
<thead>
<tr>
<th>Ferritin µg/l</th>
<th>LIC (MRI) mg/g dw</th>
<th>Cardiac T2*</th>
<th>R2* m/s</th>
<th>Pancreatic R2* Hz</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal: 25–300</td>
<td>Normal: 8–1.5</td>
<td>Normal: &gt;30</td>
<td>&lt;33</td>
<td>Normal: &lt;40</td>
<td>R2 = 1000 × 1/T2</td>
</tr>
<tr>
<td>Low: 300–800</td>
<td>Low: 1.5–3.5</td>
<td>Low: 20–30</td>
<td>&gt;33</td>
<td>Moderate: 40–100</td>
<td>R2* = 1000 × 1/T2*</td>
</tr>
<tr>
<td>Moderate: 800–1700</td>
<td>Mild: 3.5–5.0</td>
<td>Moderate: 10–20</td>
<td>&gt;50</td>
<td>Severe: 100–300</td>
<td>Heart Fe mg/g tissue = 45 × (T2*)1.22</td>
</tr>
<tr>
<td>High: 1700–2500</td>
<td>Moderate: 5.0–0</td>
<td>Moderate-sever: 8–10</td>
<td>&gt;100–125</td>
<td>Very severe: &gt;300</td>
<td>Liver R2 and R2* are highly correlated with each other, but can diverge so use one or the other or the average of both.</td>
</tr>
<tr>
<td>Very high: &gt;2500</td>
<td>High: 10–20</td>
<td>Severe: 6–8</td>
<td>125–167</td>
<td></td>
<td>(a) Can be measured in same image plane as LIC</td>
</tr>
<tr>
<td></td>
<td>Very high: &gt;20</td>
<td>Very severe: &gt;6</td>
<td>&gt;167</td>
<td></td>
<td>(b) Chronically low reticulocytes and %HbS suggests Fe toxicity to marrow and switch to ineffective erythropoiesis.</td>
</tr>
<tr>
<td>First study</td>
<td>&gt;10 transfusions</td>
<td>Ferritin &gt; 500</td>
<td></td>
<td></td>
<td>(a) When LIC is done</td>
</tr>
<tr>
<td></td>
<td>Suspect iron loading</td>
<td>Suspect iron loading</td>
<td></td>
<td></td>
<td>(b) Usually part of the decision to initiate therapy</td>
</tr>
<tr>
<td>Start chelation</td>
<td>&gt;1000</td>
<td>&gt;3.5</td>
<td></td>
<td></td>
<td>(a) Depends on initial LIC, less often if LIC is moderate-high, every 6 months when first entering the mild to low LIC range. LIC is the main marker for over-chelation risk.</td>
</tr>
<tr>
<td>Monitoring frequency</td>
<td>With each transfusion, at least monthly</td>
<td>(a) 12–18 months.</td>
<td></td>
<td>(a) Annual or when “first study” criteria persist. Depends on last value. Much more often in mod or worse iron cardiac iron</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If ferritin trends don’t fit with clinical picture</td>
<td>(b) With each LIC measurement</td>
<td></td>
<td>(b) Low or higher cardiac iron levels ⇒ adjust dose to even out plasma chelator levels (e.g. BID DFX).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low – Nil every 6–8 months.</td>
<td></td>
<td></td>
<td>(b) Moderate or higher ⇒ adjust dose to even out plasma levels (e.g. BID DFX).</td>
<td></td>
</tr>
</tbody>
</table>

Consider chelation combination (see Table IV)  
(a) >1700 or no apparent response after 6–12 months on adequate monotherapy  
(b) High or greater LIC with apparent inadequate response.

Therapy changes (see Table IV)  
(a) >2000 single agent  
(b) <1000 reduce dose  
(c) <800 reduce dose, hold depending on transfusion burden

Add DFP if T2* < 10  
Arrhythmia or failure is an emergency. Follow AHA guidelines (Pennell et al, 2013).  
Not a major factor in starting combination therapy.  
(a) We would confirm by LIC and prefer not to use ferritin alone.  
(b) LIC is main determinant of all treatment dose decisions.  
(a) If only ferritin is available (Taher et al, 2015). Otherwise, base decision on LIC regardless of ferritin level.  
(b) If slower rate of iron reduction, adjust to eliminate valleys in plasma chelator levels even if LIC is low.

AHA, American Heart Association; BID, twice daily; DFP, Deferiprone; DFX, Deferasirox; LIC, liver iron concentration; MRI, magnetic resonance imaging.
measurements are of limited help for monitoring iron overload therapy (Porter et al, 2016; de Swart et al, 2016). The parameter we would like to have is the area under the curve of exposure to NTBI/LPI over time.

LIC accurately reflects total body iron loading (Angelucci et al, 2000), and is best measured by MRI imaging (Wood, 2015). LIC measurements can be accurately made on commercially available 1.5 Tesla MRI machines that are equipped with the proper software packages. However, significant errors in quantitation can occur if the radiology centre has not been properly trained to make these measurements. The MRI scanner measures relaxation times that are described as T2 and T2* (“t two star”) and expressed in milliseconds. T2/ T2* decreases in a non-linear fashion as iron increases. R2 and R2* are the reciprocals of T2 and T2*, respectively, and increase as iron increases. While R2 and R2* are highly correlated, they cannot be used interchangeably (Wood et al, 2015). Table I shows the relationships between these parameters as well as the conversion factors to iron concentration. A normal LIC is between 0.8 and 1.5 mg/g dry weight of liver. Quantitation by MRI becomes very unreliable at LIC > 35 mg/g. Details of MRI techniques have recently been reviewed (Wood, 2015). Many centres are now routinely using 3 Tesla (3T) MRI machines because of better image resolution. Iron measurements on 3T MRI machines require special calibration that is not routinely available, but is under development (Wood, 2015).

MRI has allowed us to study partitioning of iron into multiple organs, most importantly, the heart. Cardiac iron must be measured directly by MRI, as it cannot be predicted accurately based on LIC values. In thalassaemia, cardiac T2* of 8 ms or less predicts arrhythmia and heart failure (Kirk et al, 2009; Wood, 2011). While significant cardiac iron overload occurs only in about 2.5% of SCD patients, it is life threatening and requires a more intensive approach to chelation, using guidelines established in thalassaemia patients (Pennell et al, 2013). Certainly, cardiac T2* should be measured in any SCD patient who has had significant liver iron loading (LIC > 20 mg/g) over many years or a pancreatic R2* > 100 Hz (Table I).

Pituitary iron, pituitary volume, pancreatic iron and renal iron can also be measured by MRI, but they are not standard or routinely available. Our own studies have demonstrated the usefulness of these measures (Wood, 2011, 2014). In particular, pancreatic iron deserves more attention. Pancreas iron measures can be conveniently obtained with the MRI images taken for LIC quantitation. The detection of iron in the pancreas gives us some sense of the “area under the curve” exposure to toxic LPI, as the pancreas only loads when there has been persistent exposure to LPI. Pancreatic R2* reflects the “area under the curve” exposure to LPI, in the same way that HbA1c reflects glucose exposure in diabetes. Mild levels of pancreatic iron were seen in 38% of SCD patients in the TWiTCH (Transcranial doppler With Transfusions Changing to Hydroxyurea) trial, but no patient had pancreas R2* exceeding 100 Hz, the value associated with pancreatic damage and cardiac iron deposition (Wood et al, 2016). This observation paralleled our single centre results (Noetzli et al, 2011) and is consistent with the higher levels of hepcidin and lower levels of LPI in SCD patients (Koren et al, 2010; Porter et al, 2016). Interestingly, all SCD patients with cardiac iron had pancreatic R2* > 100 Hz, with some as high as 450 Hz (Meloni et al, 2014). In fact, we have never observed cardiac iron loading in the absence of pancreatic iron loading, though the converse certainly is not true (Noetzli et al, 2009). Thus, if pancreatic iron is not detectable, we believe it is not necessary to assess cardiac iron.

While tissue-specific measures of iron correlate with organ function, it is still important to serially monitor organ function. It is very difficult to make specific recommendations for patients with SCD, as there is no clear association between iron overload and end organ failure. The liver is a primary target for iron toxicity in the third decade and beyond, and liver function needs to be monitored. We suggest an annual panel consisting of monitoring of thyroid function, glucose metabolism, morning cortisol, adrenocorticotropic hormone and sex hormones in severely iron-loaded SCD patients (LIC > 20 mg/g), and certainly if pancreatic, pituitary or cardiac iron has been detected. We do not recommend routine monitoring of echocardiograms or electrocardiograms to detect iron-related cardiac pathology.

Severely iron-loaded SCD patients had low levels of thiamine (38-5% of patients), ascorbate (56-7%), vitamin A (73-7%), selenium (67-5%) and pyridoxine (34-2%) (Claster et al, 2009), although we do not understand the mechanism behind these findings. We monitor these micronutrients annually in all severely iron-loaded patients and prescribe replacement therapy if the levels are low.

Fig 2. Ferritin levels in patients with sickle cell disease show very broad scatter. The liver iron concentration (LIC) levels at 3, 7 and 20 mg/g dry weight liver correspond to levels that have been related to ferritin in Table IV (Taher et al, 2015).
Treatment of iron overload

Obviously, reducing the amount of transfused blood can help decrease iron loading. Phlebotomy has been the mainstay for treatment of iron overload in settings where marrow function is normal, and can be considered in SCD patients who have adequate elevation of their haemoglobin on hydroxycarbamide/hydroxyurea (Aygun et al., 2015; Ware et al., 2016). In chronically transfused patients, red cell exchange (RCE) transfusion significantly reduces iron loading and maintains HbS levels in a therapeutic range (Danielson, 2002; Kim, 2014; Yawn et al., 2014). If the patients have adequate venous access, this approach can take less time than simple transfusion, may permit keeping HbS at a low level when used at 4–5 weeks intervals, and can leave a patient in neutral iron balance without the need for chelators. However, if the patient is already significantly iron overloaded, chelation will have to be added. Programmatic administrative costs, amount of blood required and venous access can be major barriers (Kim, 2014). Nonetheless, this approach should be considered in all SCD patients who require long-term chronic transfusion. Partial exchange transfusion approaches where a moderate amount of blood is drawn and replaced with saline at the time of simple periodic transfusion is favoured by some providers, but its benefits are not well documented (Savage et al., 2013; Fasano et al., 2016).

Iron chelation is the primary treatment for transfusional iron overload in patients with SCD. The agents and their toxicities are listed in Tables II and III. Treatment should start when patients have received 10 transfusions, have a serum ferritin >1000 μg/L, or LIC > 3 mg/g dry weight liver (Tables I and IV). We do not start chelation in children before 2 years of age and increase the dose over a period of 1 year to avoid toxicity. Currently, there are three licensed iron chelators available in the US and Europe. These agents along with their properties are listed in Table II. There are decades of experience with these agents, showing that they are effective at reducing iron in both SCD and thalassaemia patients (Maggio et al., 2011; Vichinsky et al., 2011c; Hoffbrand et al., 2012; Piga et al., 2013; Calvaruso et al., 2014; Aydinoğlu et al., 2015; Tsouana et al., 2015). There is substantial evidence that these agents improve the clinical outcome in thalassaemia (Modell et al., 2008). As it is extremely difficult, if not impossible, to separate the complications of iron overload from those of SCD, there are minimal and

Table II. Chelators.

<table>
<thead>
<tr>
<th></th>
<th>Deferoxamine (DFO)</th>
<th>Deferiprone (DFP)</th>
<th>Deferasirox (DFX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>560</td>
<td>139</td>
<td>373</td>
</tr>
<tr>
<td>First clinically available</td>
<td>1968</td>
<td>1999</td>
<td>2005</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Parenteral</td>
<td>Oral (tablet or solution)</td>
<td>Oral (Dispersible tablet (ExJade) Film-coated tablet (Jadenu) 8–16 h)</td>
</tr>
<tr>
<td>Plasma half-life</td>
<td>30 min</td>
<td>3 h</td>
<td>20–40 mg/kg per day (ExJade) 14–28 mg/kg per day (Jadenu)</td>
</tr>
<tr>
<td>Usual dose</td>
<td>40–50 mg/kg per day</td>
<td>75–100 mg/kg per day</td>
<td>Once daily; used BID to improve tolerance and perhaps efficacy, but no clear data on BID dosing yet.</td>
</tr>
<tr>
<td>Administration</td>
<td>Over 10–24 h</td>
<td>Every 8 h; TID</td>
<td>Effective over long periods of time</td>
</tr>
<tr>
<td>Route of excretion</td>
<td>Urine, faecal especially at higher dose</td>
<td>Urine</td>
<td>Faecal</td>
</tr>
<tr>
<td>Use in decreased renal function</td>
<td>Can be used, dialysable</td>
<td>Can be used, dialysable</td>
<td>Nephrotoxic. Should not be used unless totally dialysis dependent.</td>
</tr>
<tr>
<td>Removal of cardiac iron</td>
<td>Effective especially by continuous infusion</td>
<td>Most effective at removal of cardiac iron</td>
<td>Effective over long periods of time</td>
</tr>
<tr>
<td>Cardiac function</td>
<td>Effective by continuous infusion</td>
<td>Most effective for improving cardiac function, even at high levels of cardiac iron</td>
<td>Functional improvement has not been demonstrated.</td>
</tr>
<tr>
<td>Reduction in total Fe (LIC)</td>
<td>All three agents are effective as single agents at the high end of the dose ranges above. Higher doses required with higher transfusion burden.</td>
<td>Most effective for cardiomyopathy</td>
<td>Longest half life, can be given once a day</td>
</tr>
<tr>
<td>Advantage</td>
<td>Long experience, can be given intravenously</td>
<td>Most effective for cardiomyopathy</td>
<td>Longest half life, can be given once a day</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Local reactions, severe allergic reactions, retinal damage, hearing loss, osteoporosis, growth failure</td>
<td>Gastrointestinal, arthralgias, transient transaminitis, rare idiosyncratic agranulocytosis</td>
<td>Increase GFR in 30%, proteinuria, renal failure is rare, moderate gastrointestinal toxicity, rare gastrointestinal bleeding.</td>
</tr>
</tbody>
</table>

BID, twice daily; GFR, glomerular filtration rate; LIC, liver iron concentration; TID, three times daily.

The most important differences between these agents relate to the route of administration, the half-life and the toxicities. DFO (Desferal) was the first effective chelator. Because it is not orally absorbed and it has a very short half-life (30 min), it has to be administered by continuous subcutaneous or intravenous infusion (Table II). While DFO is effective, the parenteral route of administration limits its acceptability to patients. Deferiprone (Ferriprox, DFP) is the first oral iron chelator and has a half-life of six to eight hours. Deferasirox (ExJade, JadeNu; DFX) is an oral agent with a 14-h half-life, allowing once-daily dosing and prolonged circulating chelator levels. While all three chelators can lower cardiac iron, DFP appears to be the most effective

### Table III. Chelator toxicity.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Incidence</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desferal (DFO)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>Common</td>
<td>Make sure a small subcutaneous needle is used that is perpendicular to the skin and goes all the way through the dermis. Intra-dermal injection is a major cause of local reaction. Rotate the injection sites. Lower the DFO concentration. A small amount of hydrocortisone can be put into the DFO, but should be avoided.</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>Rare</td>
<td>This is a rare serious reaction. If the patient has systemic allergic symptoms from DFO, we would discontinue the drug. Desensitization can be done. However, given the adherence issues with DFO, patients stop the DFO and then restart several days later and can have a serious reaction. We do not recommend desensitization.</td>
</tr>
<tr>
<td>Infection</td>
<td>Rare</td>
<td>Increased risk of infection with ferophilic organisms like Yersina Enterocolitica, V. Vulcanificus and Mucorales</td>
</tr>
<tr>
<td>Retinal/Auditory</td>
<td>Rare</td>
<td>Change in colour perception or visual impairment should prompt immediate stopping of DFO. May restart when symptoms resolve. DFP and DFX essentially do not have these complications (isolated cases) and are alternatives.</td>
</tr>
<tr>
<td>Deferiprone (DFP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>33% at first</td>
<td>Symptoms are usually mild and transient. Starting at a lower dose (40 mg/mg per day) and increasing over a period of weeks to months can help. Liquid formulation may be better tolerated. DFP is well tolerated and gastrointestinal symptoms usually resolve after month or two.</td>
</tr>
<tr>
<td>Transaminitis</td>
<td>7%</td>
<td>Transaminases can be 2–4 times normal levels from severe iron overload. There may be transient increase in the first few months of DFP treatment. If there is significant increase, hold the drug and restart at lower dose after return to baseline levels to see if elevations are truly due to DFP. Evidence of cholestasis suggests other pathology.</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>8%</td>
<td>Hold medication until recovery and re-challenge. Make sure patients know to stop DFP and seek medical attention for any fever/mouth sores.</td>
</tr>
<tr>
<td>(ANC &lt;1.5 × 10^9/l)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agranulocytosis</td>
<td>1.5%</td>
<td>Most cases occur during first year on DFP. Make sure patients know to stop DFP if any significant fever or mouth sores and seek immediate medical attention and notify the emergency personal they are on a drug that causes agranulocytosis. They should be treated with parenteral antibiotics if febrile. GCSF may be helpful.</td>
</tr>
<tr>
<td>(ANC &lt;0.5 × 10^9/l)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthropathy</td>
<td>3–9–40%</td>
<td>More likely at high LIC. Stop DFP and restart at lower dose. Treat with antiinflammatory agents.</td>
</tr>
<tr>
<td>Deferasirox (DFX)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>15%</td>
<td>Major toxicity of DFX. Starting at lower dose increasing slowing can help with nausea. LactAid can help some with lactose intolerance. Splitting the dose twice a day can also help. Some patients find taking the dose at night is helpful. The new formulation Jadenu, is much better tolerated and does not contain lactose. Significant gastrointestinal bleeding is rare but has occurred and the risk may be higher at low LIC levels. Patients should be warned to stop the drug and seek attention for several abdominal pain.</td>
</tr>
<tr>
<td>Renal</td>
<td>36%</td>
<td>33% will have a 30% increase in creatinine. Increase above the upper limit of normal is very rare, though we have seen renal failure and severe hypertension when the renal complication was unrecognised. The urine protein/creatinine ratio must be followed carefully although this can be difficult in SCD because of SCD-related renal disease. Hold DFX and re-challenge at a 10 mg/kg lower dose per the specific recommendations in the DFX package insert. We monitor renal function and urine protein/creatinine at each transfusion visit.</td>
</tr>
<tr>
<td>Transaminitis</td>
<td>&lt;5%</td>
<td>Monitor liver function every 3 months. Liver toxicity is rare with DFX. Comments for DFP apply.</td>
</tr>
</tbody>
</table>

The above toxicities are not exhaustive, see references.

ANC, absolute neutrophil count; GCSF, granulocyte colony-stimulating factor; LIC, liver iron concentration, SCD, sickle cell disease.
in protecting and restoring cardiac function (Pennell et al., 2013; Berdoukas et al., 2015).

The primary goal of chelation is to clear the circulating reactive forms of iron and to protect tissue from iron toxicity. Clinically, this translates into keeping the NTBI/LPI levels in the normal range, essentially zero, at all times. NTBI/LPI constitutes the so-called “chelatable pool” and, as can be seen in Fig 3, NTBI/LPI levels drop to zero coincident with the onset of DFO infusion and increase again very quickly when the DFO infusion is stopped. All three chelators have the ability to rapidly drop plasma levels of NTBI/LPI. This pharmacology drives our clinical approach to chelation. As LPI is the reactive sub-species of NTBI that enters the heart and the endocrine and other tissues in an unregulated fashion, and can be quickly reduced by chelation, the ideal chelator would be the one with significant levels in the circulation at all times in order to bind reactive iron and block entry into tissue.

The other goal of chelation is to eliminate excess stored iron. This is driven primarily by the degree of total body iron loading reflected by LIC and ferritin. As the toxicity of iron is related to the total amount of iron and the duration of exposure, the objective of treatment is to lower tissue iron levels as quickly as possible and in a practical and tolerable manner for the patient. The presence of organ failure is a primary determinant of treatment intensity and urgency. Organ failure due to iron is less common in SCD than it is in thalassaemia; nonetheless, it definitely occurs in SCD (Meloni et al., 2014), supporting our recommendation of a low ferritin/LIC cut-off (Taher et al., 2015). Delay starting chelation in children until 2 years of age and increase the dose over a year to maximum tolerated.

Table IV. Chelator dosing.

<table>
<thead>
<tr>
<th>Iron load</th>
<th>Ferritin (µg/l)</th>
<th>LIC (mg/g dw)</th>
<th>DFO mg/mg per day over 10 h</th>
<th>DFP mg/kg per day Q 8 h/TID</th>
<th>DFX (a) mg/mg per day QD or BID</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferritin &lt; 300</td>
<td>30–40</td>
<td>75–100</td>
<td>20–30</td>
<td>Keep at low end of dose range if no LIC measure available. (d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LIC ≤ 3</td>
<td>[hold]</td>
<td>[hold]</td>
<td>[hold]</td>
<td>[hold] =&gt; if low iron input; on occasional transfusion or on red cell exchange.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferritin &lt; 800</td>
<td>30–40 (b)</td>
<td>75–100 (b)</td>
<td>20–30 (b)</td>
<td>If LIC near 3, stay in mid dose range. If near 7, consider increase in dose. If LIC is dropping, consider lowering dose as LIC approaches 3 mg/g.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LIC &lt; 7</td>
<td>[hold]</td>
<td>[hold]</td>
<td>[hold]</td>
<td>[hold] Increase based on tolerance. Most patients in negative balance at upper end of dose scale. If LIC dropping, may change to single agent or reduce dose as LIC approaches 7.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferritin &gt; 1700</td>
<td>40–50</td>
<td>75–100</td>
<td>20–40</td>
<td>(c) Increase based on tolerance. Consider splitting DFX dose BID or combination therapy.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LIC &gt; 15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferritin &gt; 2500</td>
<td>40–50</td>
<td>75–100</td>
<td>20–40</td>
<td>Get cardiac T2* especially if reticulocyte count &lt;15% and % HbS &lt;15%. (c) Increase based on tolerance. Consider splitting DFX dose BID or combination therapy.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LIC &gt; 20</td>
<td>Combination therapy containing DFP moved to 100 mg/kg as fast as tolerated. Cardiac T2* every 4–6 months. Critical to have circulating chelator 24 h a day 7 days a week. Follow AHA consensus statement (Pennell et al., 2013). Consult physician with experience managing severe iron cardiomyopathy.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferritin &gt; 2500</td>
<td>40–50</td>
<td>75–100</td>
<td>20–40</td>
<td>LIC clears first during intense chelation leaving heart loaded. (d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LIC &gt; 20</td>
<td>Toxicity is related to LIC. Monitor toxicity carefully. Need to continue chelation to clear heart. DFP at 100 as a single agent is probably safest in this circumstance.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2* &lt; 10 ms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LIC &lt; 5</td>
<td>40–50</td>
<td>75–100</td>
<td>20–40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2* &lt; 10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Superscripted letters in parentheses (a) refer to comments in the far-right column of the table on the same line.

AHA, American Heart Association; BID, twice daily; DFO, deferoxamine; DFP, Deferiprone; DFX, Deferasirox; LIC, liver iron concentration.

(a) Exjade dosing; for Jadenu multiply by 0.75.
(b) If LIC measurement not available consider holding if ferritin decreasing.
(c) Increase dose incrementally to high end of dose range every 2–3 months based on toxicity/tolerance.
(d) Risk of over chelation is highest at low ferritin/LIC. However, if regular transfusions are occurring, chelation should not be stopped. If ferritin/LIC is dropping in this low iron load range, reduce chelator dose. If ferritin is climbing but low, check the LIC before increasing the dose.
(e) Cut-off-LIC: x% ↑ y% ↑ means based on ferritin, there is x% chance the LIC is lower than the cut-off, and y% chance it is higher than the cut-off (Taher et al., 2015). Delay starting chelation in children until 2 years of age and increase the dose over a year to maximum tolerated.
recommending chelation 7 days a week as the ideal, though not always achievable, goal.

Though rare, iron cardiomyopathy is a life-threatening issue in SCD. Based on data from thalassaemia, if the cardiac T2* is 8 ms or less, there is a high risk of arrhythmia and heart failure and aggressive chelation is indicated. Excellent guidelines have been published for the management of iron cardiomyopathy (Pennell et al, 2013). It is important to stress that even severe cardiomyopathy due to iron is reversible, usually with full recovery if the patient can survive the first several days of severe symptoms, and if exposure to the chelator is maintained without interruption.

Iron overload treatment only works if patients adhere to therapy

All three chelators are very effective at controlling iron individually or in combination. Overwhelmingly, the dominant reason for failure of chelation therapy is failure of the patient to take the prescribed medicine (Origa et al, 2013). While there are data showing different absorption rates for some chelators (Chirnomas et al, 2009), the effect of poor adherence to recommended therapy is the dominant cause of treatment failure. SCD and transfusional iron overload are chronic, lifelong disorders, and thus patients are subject to all of the psychosocial and quality-of-life issues related to chronic disease. Patient adherence to treatment rather than chelator pharmacology is the primary driver of our approach to iron chelation. The main goal is to arrive at an effective plan that the patient agrees to follow, even if the regimen is not ideal based on pharmacology.

In general, we use DFX first because of its long half-life and once daily administration. General dosing approaches are summarized in Table IV. Dividing the daily dose into two doses can help with gastrointestinal symptoms, may maintain higher blood levels over a longer time (Lu et al, 2015) and help to consistently reduce LPI. For patients with very high LIC (>15–20 mg/g), we will often use DFX in combination with DFP. Currently, none of these agents are licensed for use in combination. However, combinations of these agents have been increasingly used and additional toxicities have not been identified (Galanello & Origa, 2010; Kolnagou & Kontogiorghes, 2010b; Kolnagou et al, 2010; Lai et al, 2010; Maggio et al, 2011; Voskaridou et al, 2011; Cassinerio et al, 2012; Grady et al, 2013; Aydinok et al, 2015; Totadri et al, 2013; Gomber et al, 2016).

While we start chelation with the published dosing guidelines, the regimens are individually tailored for each patient to respect their life style and to minimise toxicity. As long as there is significant iron loading (LIC > 7 mg/g), we increase the chelator dose to near maximum over 6–12 months based on patient tolerance and toxicity. We generally do not reduce the dose until the LIC comes into the moderate range, even if LIC or ferritin starts dropping (Table IV). Chelator efficacy depends on transfusion load (Cohen et al, 2008) and specific chelator dosing regimens have been recommended based on transfusion rate, ferritin or LIC (Hoffbrand et al, 2012; Porter et al, 2013). These approaches are solidly based on retrospective response data, but these differences in dosing seem outweighed by unpredictability due to therapy adherence, thus we do not use such detailed dosing approaches. We base dosing on tolerance of the medication by the patients, LIC response and whether the patient is being regularly transfused or on RCE as noted in general guidelines in Table IV. If the patient is not on regular transfusion or is on exchange transfusions, there is increased risk of over-chelation at the low end of the iron loading range. Likewise, if the patient is on regular simple transfusions, the chelation should not be totally stopped, except intermittently for toxicity.

While we measure serum ferritin with each transfusion, we caution our patients not to become fixated on ferritin levels. A monotonic decrease in ferritin can be encouraging to the patients and a monotonic increase over time may indicate problems. However, we use MRI as the basis for treatment decisions. Especially at low iron levels, there can be very a big discordance between the ferritin trends and change in the LIC (Puliyel et al, 2014). In general, we monitor LIC by MRI annually, and more often if the ferritin changes do not seem to accurately reflect the clinical situation (Table I).

Maintaining a very supportive and positive collaboration with the patient is a very critical part of the chelation success, in our opinion. The patient is unlikely to adhere to a treatment plan if the patient does not sense that the team thinks chelation is important. Thus, an experienced multidisciplinary team is critical.
During treatment, we monitor blood pressure, creatinine, creatinine clearance, neutrophil and platelet counts, and urine protein/creatinine at every transfusion visit. We also monitor liver functions and electrolytes at least every 3 months. Audiogram and eye examinations are done annually, although the utility of these tests for iron complications in patients who are not on DFO is questionable. Even though DFX safety has been well established in large studies, we remain concerned about kidney function in SCD patients who are at risk for renal disease independently of chelation. Proteinuria, which can result from SCD itself, is problematic when patients are on DFX, a nephrotoxic agent. We make sure that all patients know that they need to report any severe abdominal pain that may suggest bleeding, and to stop DFX immediately and to contact the centre. They are also instructed to stop DFP immediately and go to the emergency room for a blood test if they have any fever. The major toxicities and their management are noted in Table III.

We recognise that many providers do not have access to MRI and must manage chelation based on ferritin levels alone. Excellent guidelines have been published for chelator management using ferritin based on results in thalassaemia (Taher et al, 2015). While we feel that normalization of iron (LIC 0–8–1.5 mg/g) is an ideal goal, we would not advocate trying to achieve an LIC less than 3–5 mg/g in the absence of easy access to accurate MRI measures and to a team with significant experience with chelation therapy, especially in a patient who is not adherent to therapy and may not understand the possible complications.

**Summary thoughts**

SCD is associated with effective erythropoiesis and an inflammatory phenotype that results in higher levels of hepatocidin and generally lower levels of reactive LPI. Thus, end organ toxicity in patients with SCD and severe iron overload seem to be significantly less than that seen in thalassaemia patients. However, severe complications of iron overload can occur in SCD. As severe complications of SCD are treated by transfusion, a correlation between organ damage and iron load is guaranteed. Nonetheless, we have seen a number of cases of significant iron-related organ damage in patients in their third and fourth decades. Therefore, we suspect that iron-related organ damage in SCD is under recognised, partly because the damage is often attributed to SCD itself and because of the lack of familiarity with iron overload by some providers.

While there are some differences in the biology of iron overload between SCD and thalassaemia or marrow failure, the pharmacological treatment is essentially the same. The incidence of severe iron cardiomyopathy is much lower in SCD, but the treatment is identical to that in thalassaemia.

We recommend treating iron overload in patients with SCD with the ideal intent of normalising plasma and tissue iron levels. As SCD subjects live longer, they will probably encounter complications of long-term iron exposure, and keeping their iron load as low as can be achieved safely would seem prudent. The success of chelation therapy is dominated by patient adherence to prescribed treatment; thus, adjustment of treatment regimens to increase the likelihood of adherence to treatment is fundamental.

**Acknowledgements**

This work was supported by funding from the NIH to J. C. Wood (1R01DK097115-01A1). TDC wrote the manuscript, JCW edited sections related to monitoring with MRI. The authors recognize the critical contributions of Susan Carson RN who manages the patients. The general approach described here is the result of many discussions regarding patients by TDC, SC and JCW over many years. The authors wish to thank Dr. Martine Torres for reviewing of the manuscript.

**Conflict of Interest**

Dr Coates is a consultant for Novartis, ApoPharma, Ionis Pharma, Celgene, Agios, and Prolong. Dr Wood is a consultant for ApoPharma, Ionis, Celgene, Vifor, WorldCare Clinical, BiomedInformatics, and AMAG.

**References**


Dallas, S.K. (2001) Iron overload is a determinant of morbidity and mortality in adult patients...
with sickle cell disease. Seminars in Hematology, 38, 30–36.


