14. IRON OVERLOAD

Principles

- To prevent transfusional iron overload in SCD.
- To diagnose and monitor transfusional iron overload.
- To initiate the appropriate iron chelation therapy at the appropriate time.
- To monitor chelation therapy.

Recommendations

Prevention

- Red blood cell transfusions should only be administered when medically necessary.
- Avoid transfusion for uncomplicated acute painful episodes if: i) the patient's hemoglobin concentration is near their baseline level, ii) there is appropriate reticulocyte response, and iii) the patient has no symptoms of anemia.

Monitoring and Diagnosis

- Maintain an accurate record of volume of red blood cell transfusions.
- In chronically transfused patients, serum ferritin should be measured regularly (e.g., every 3 months).
- Liver iron should be assessed yearly in chronically transfused patients who are not undergoing chelation.

Chelation Therapy

Initiation

- Chelation should be started in each patient who has evidence of increased total body iron; individual patient factors must be considered in determining the best timing for initiation.
- Deferoxamine or deferasirox are appropriate first-line therapy.
- Deferasirox should be avoided in patients with renal insufficiency.
- Data are lacking regarding combination chelation therapy for patients with SCD.

Baseline investigations prior to starting chelation therapy include: Serum ferritin, transferrin saturation, creatinine and liver enzymes.

- Liver iron content and cardiac iron should be assessed by MRI
- Liver iron content may be assessed by liver biopsy if MRI is contraindicated or unavailable, or if there are additional indications for liver biopsy (e.g., assessment in co-existing chronic hepatitis infection).
- Ancillary testing of cardiac function may also be performed (e.g., echocardiogram).
- Baseline and regular auditory and ophthalmic testing should be performed in all patients.

Monitoring in Patients on Chelation Therapy

1. Deferoxamine (DFO)
   - Serum ferritin, creatinine, and liver enzymes should be measured regularly (e.g., every 3 months).
   - Maintain therapeutic index of <0.025 calculated quarterly:

$$\textbf{Therapeutic index} = \frac{\textbf{(Mean daily dose of DFO in mg/kg)}}{\textbf{(Serum ferritin in ug/L)}}$$

- Auditory and ophthalmic testing annually.
- Liver iron and cardiac iron should be assessed every 6 to 12 months, depending on iron overload severity.

2. Deferasirox (DFX)
   - Serum ferritin, creatinine, and liver enzymes should be measured regularly (e.g., every 3 months).
   - Patients on DFX should be monitored for proteinuria monthly.
   - Auditory and ophthalmic testing annually.
   - Liver iron and cardiac iron should be assessed every 6 to 12 months, depending on iron overload severity.

I. End-organ Effects of Iron Overload

In healthy individuals, 1 to 2 mg of iron is absorbed daily from dietary intake, and an equal amount is lost, mostly from the gastrointestinal tract. The majority of body iron is present in hemoglobin. Additional iron is stored in the liver, spleen and bone marrow as ferritin or hemosiderin. The body does not have a homeostatic mechanism for excreting excess iron; therefore, if levels in the body increase, as occurs with repeated blood transfusions, iron can be deposited in the organs, starting with the liver.

Patients with sickle cell disease (SCD) who receive recurrent red blood cell transfusions are susceptible to iron overload,[1] which can be associated with significant morbidity and mortality.[2] One unit of red blood cells contains approximately 200 mg of iron (1 mL of erythrocytes = 1 mg iron).[3]

Avoiding unnecessary transfusion can prevent iron overload. Patients presenting with acute SCD pain episodes generally do not require RBC transfusion; as long as their hemoglobin level is at baseline, there is appropriate reticulocyte response, and there are no symptoms of anemia (*see Part II, section 1 on Pain*). Nonetheless, patients with SCD may require transfusions for medical reasons, including primary or secondary stroke prevention, acute chest syndrome, or surgery. SCD patients will develop iron overload proportional to the volume of blood transfused.[4,5] Iron overload is often under-recognized and under-treated in previously transfused patients with SCD.[6]

II. Assessment of Iron Overload

i) *Serum Ferritin and Other Laboratory Tests*

Serum ferritin level is the most commonly used test to screen for iron overload. It is inexpensive and widely available. False positives can occur in the presence of inflammation, liver disease and vitamin C deficiency. In patients with SCD, ferritin is elevated during vaso-occlusive episodes and for several weeks thereafter.[7] Trends in serum ferritin are poor predictors of changes in liver iron concentration in patients with SCD.[8,9] Nevertheless, when SCD patients are clinically stable, serum ferritin may be used in conjunction with monitoring transfusion volumes[6] and evaluating liver and cardiac iron (see below) to track response in patients on chelation therapy. Elevated transferrin saturation (>50%) should only be present in states of true iron overload,and may therefore be used as an additional test to evaluate iron stores.

ii) *Evaluation of Hepatic Iron*

In the presence of increasing body iron stores, the liver is the first organ to become overloaded with iron. Liver magnetic resonance imaging (MRI) is a safe, non-invasive, and accurate method of assessing liver iron content (LIC).[12,13] Although MRI machines are accessible in many medium- and large-sized centres in Canada, they may not available in smaller communities. Furthermore, MRI protocols specific to this indication are required (e.g., R2 Ferriscan or R2*), and staff must be trained in their application.

Previously, liver biopsy was the gold standard in measuring hepatic iron, reported in “mg/g dry weight”. Liver biopsy provides a direct, quantitative assessment of LIC. Biopsy is associated with procedural risks[12], however, and, since liver iron deposition is not uniform, liver biopsy can be associated with sampling error.[13,14] Liver biopsy is still performed to assess for potential complications in selected patients, including liver fibrosis, cirrhosis, or hepatocellular carcinoma.[15] Decisions about the role of liver biopsy in SCD patients should be made together with a liver specialist.

iii) Evaluation of Cardiac Iron

In chronically transfused patients, cardiac iron loading typically occurs more slowly than liver iron loading and generally appears with increasing age. Nonetheless, cardiac iron deposition can occur even at low liver iron levels.[4] In comparison with patients with thalassemia, patients with SCD are less likely to have abnormal cardiac iron at the same levels of liver iron.[16,17] This may be due to an overall lower transfusion burden in patients with SCD compared with thalassemia major. Longer duration of chronic transfusion and poor adherence to prescribed chelation therapy are associated with a higher risk of cardiac iron overload.[18]

Cardiac MRI is used to assess myocardial iron.[19] Measurements — expressed as T2 or T2* — correlate with cardiac dysfunction: T2* <20 msec is associated with presence of cardiac iron and ventricular dysfunction. Conversely, T2* is >20 msec when no cardiac iron or ventricular dysfunction are present.[19]

As cardiac iron overload occurs more slowly than liver iron loading, the corollary is also true – cardiac iron is also removed more slowly.[19]

iv) Other Laboratory Tests

Non-transferrin-bound iron (NTBI) is present in the blood when transferrin is highly saturated and, therefore, measurement of NTBI is an intriguing method for quantifying iron overload. There is little standardization of NTBI testing, however. Until reproducible protocols are available, it is primarily used in scientific research.[20]

III. Treatment of Iron Overload

i) Dietary Iron

For patients with sickle cell anemia (SCA) with iron overload, dietary iron intake should be minimized, including iron-containing supplements, red meat, and other high-iron foods. In addition, increased vitamin C intake can increase iron absorption from the diet.

ii) Reviewing Transfusion Regimen

Erythrocytapheresis, also referred to as "red cell exchange", is a process by which the patient's red blood cells are removed via an apheresis machine and replaced by donor packed red blood cells. For patients requiring a program of chronic red blood cell transfusion, erythrocytapheresis can be used in place of simple transfusion. Small, nonrandomized studies of patients who have received exchange transfusion show that they have less iron overload than patients receiving simple transfusion,[7] and that existing iron overload can be improved or stabilized.[21-23]

Despite evident decrease in iron loading, apheresis also has drawbacks. Firstly, blood utilization is increased by approximately 50% compared with a simple transfusion program.[21] This results in increased exposure to the risk of alloimmunization and transfusion-related adverse effects. Furthermore, the blood banking and other associated costs of apheresis make it more expensive.[21] Secondly, although iron levels are better controlled on an apheresis program, the majority of patients still require chelation therapy.[21,23]

It has been argued that the increased costs of apheresis need to be weighed against the potential costs saved by preventing iron-related organ damage.[21] Erythrocytapheresis is an appealing concept to prevent iron overload or control existing iron overload in patients on a chronic transfusion program, but the apparent benefits do not clearly outweigh the potential harms. Further study would be informative.

Partial manual exchange is a less resource-intensive method of red cell exchange that appears to be an effective method of slowing the rate of iron loading in chronically transfused patients with SCD.[24] (*See more on Transfusion, Erythrocytapheresis and Partial manual exchange in Part I, Section 2*).

ii) Chelation Therapy

Chelation therapy is used to treat or prevent the accumulation of high levels of iron in the body. It works by binding excess iron and facilitating its excretion. Continuous blood levels are optimal to maximize chelation. The goal is to have a negative iron balance.

Clinical judgment is required when selecting the optimal time to begin chelation therapy. In one study of chelation in SCD,[25] serum ferritin ≥1000 g/L was required for study entry; Superconducting Quantum Interference Device testing (SQUID) was then performed to determine LIC. To be enrolled, patients had to have a liver iron concentration of ≥2 mg/g if receiving simple transfusions and ≥5mg/g if receiving exchange transfusions.

No studies to date have established specific thresholds for initiation of chelation in patients with SCD, or the effectiveness of chelation treatments specific to patients with SCD.[26] Consideration should be given to: serum ferritin level; liver iron concentration (by biopsy or MRI); and cardiac iron.

Although there are differences in the pathophysiology and natural history of iron overload in patients with SCD and thalassemia, in the absence of strong evidence to guide chelation therapy in SCD, clinicians may wish to use guidelines for chelation therapy in thalassemia major as a reference.[27,28]

Presently in Canada, three chelators are licensed for use:

1) Deferoxamine (DFO) has been in use for many years, and is widely available. Because of its high molecular weight, it has poor gastrointestinal absorption and is thus administered parenterally (intravenously or subcutaneously). DFO works by mobilizing iron in parenchymal cells and macrophages, and increasing iron excretion in the urine and feces. Clinical trials of DFO in chronically transfused patients with thalassemia major have shown high effectiveness in controlling body iron burden.[29] One small, randomized controlled trial (RCT) in patients with SCD showed a reduction in serum ferritin and improved hepatic function in all patients, with an apparent dose-response relationship.[30]

DFO removes iron more rapidly from the liver than from the heart,[32] making it a suboptimal choice for patients with documented cardiac iron accumulation. Patients may find it inconvenient because of the need for overnight subcutaneous infusions most nights of the week. Although DFO has long been the standard of care for transfusional iron overload in SCA, adherence is often suboptimal.[32] Adverse effects may include: reactions at infusion sites; abnormalities in vision or hearing; skeletal and growth abnormalities; zinc deficiency or Yersinia infection.[3] Several of these potential side effects have the potential to overlap with complications of sickle cell disease.[29] Typically, DFO is administered by subcutaneous infusion into the upper arm or abdomen over 8 to 12 hours. The daily dose of 20 to 60 mg/kg in infused 5 to 7 days of the week using a portable pump.[33] Dose adjustments are made to maintain a therapeutic (Porter) index under 0.025.

In severely iron-overloaded patients with thalassemia, DFO has been given by continuous, 24-hour intravenous infusion with good improvement in serum ferritin, arrhythmias, and ventricular dysfunction.[34]

2) Deferasirox (DFX) is an oral iron chelator licensed in Canada in 2006. It has been studied in one Phase III randomized clinical trial (RCT) in which it was compared with DFO in patients aged 2 years and older with thalassemia major.[35] Dosing of both drugs was based on baseline liver iron concentration (LIC) as measured by liver biopsy. The researchers found that patients with LIC ≥7 mg iron/g dry weight had "significant and similar dose-dependent reductions in LIC and serum ferritin". Noninferiority was not shown in the group of patients with lower LIC, however, possibly because of disproportionately low dosing of DFX relative to DFO.

One Phase II RCT comparing DFX and DFO in 195 patients with SCD who were aged 2 years or older found similar dose-dependent LIC reductions in both groups, with doses of DFX of 30 mg/kg and DFO of ≥50 mg/kg showing absolute change in ferritin.[25] Discontinuation rates were equivalent for DFX (11.4%) and DFO (11.1%). In a substudy of this trial, however, patient satisfaction was higher for those on DFX.[36] In a five-year follow-up study of patients on DFX,[37] ferritin levels were significantly reduced, and there were few drug-related adverse events.

Cochrane reviews demonstrated similar efficacy between DFX and DFO.[38]

Adverse effects of deferasirox noted in clinical trials include: rash, gastrointestinal (GI) symptoms (nausea, diarrhea), mild elevation of transaminases, hearing impairment, and nonprogressive elevation of serum creatinine. More recently, cases of acute kidney injury have been reported, particularly in patients with pre-existing renal impairment. In addition, there have been reports of hepatic failure and gastrointestinal hemorrhage (www.drugs.com/pro/exjade.html).

DFX is taken orally once daily at a starting dose of 20 mg/kg/day.[35] It may be increased in increments of 5 to 10 mg/kg/day every 3 to 6 months, based on trends in ferritin level.[39] Based on data from a subgroup of 264 patients with beta-thalassemia, SCD, and myelodysplastic syndromes pooled from four clinical trials, doses over 30 mg/kg/day appear to be effective and safe.[40]

3) Deferiprone is an oral iron chelator that has been available in Europe and other countries for many years, but was first licenced in Canada in 2015. Data from randomized clinical trials in thalassemia patients[41-43] suggest that deferiprone is as effective as DFO at decreasing iron load. In a randomized trial comparing deferiprone with DFO, patients with SCD also had similar reductions in body iron burden.[44] Studies showed more effective chelation of cardiac iron by deferiprone compared with DFO.[31]

Adverse effects can include: agranulocytosis, arthalgias, zinc deficiency; mild GI symptoms, and mild aminotransferase elevations.[3] Deferiprone may be obtained in Canada through an industry special-access program. It is not specifically approved by Health Canada for treatment of iron overload in SCD patients.

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