CHAPTER 25

Evaluation and treatment of secondary iron overload

Antonio Piga, Simona Roggero, Filomena Longo, Olivier Ernst, Christian Rose
1. Conditions associated with secondary iron overload

The term secondary iron overload defines a heterogeneous group of chronic conditions, genetic or acquired, where iron overload is not due to a primary defect of the iron regulation system. Table 1 contains a partial list of these conditions, most of which are characterised by anaemia.

<table>
<thead>
<tr>
<th>Table 1: A partial list of conditions potentially associated with secondary iron overload</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Hereditary disorders</strong></td>
</tr>
<tr>
<td>Thalassaemias</td>
</tr>
<tr>
<td>Glucose-6-phosphate dehydrogenase (G6PD) deficiency</td>
</tr>
<tr>
<td>Pyruvate kinase deficiency</td>
</tr>
<tr>
<td>Congenital dyserythropoietic anaemias</td>
</tr>
<tr>
<td>Severe haemolytic anaemias (Hereditary spherocytosis, etc.)</td>
</tr>
<tr>
<td>Sideroblastic anaemias</td>
</tr>
<tr>
<td>Porphyrias</td>
</tr>
<tr>
<td>Aplasia</td>
</tr>
<tr>
<td><strong>B. Acquired disorders</strong></td>
</tr>
<tr>
<td>Aplasia</td>
</tr>
<tr>
<td>Sideroblastic anaemia</td>
</tr>
<tr>
<td>Dyserythropoietic anaemias</td>
</tr>
<tr>
<td>Myelodysplastic syndromes</td>
</tr>
<tr>
<td>Liver diseases</td>
</tr>
<tr>
<td>Dietary iron overload</td>
</tr>
<tr>
<td>Inappropriate iron treatment (iron deficiency, dialysis patients, athletes, etc.)</td>
</tr>
<tr>
<td>Off-therapy leukaemias, bone marrow transplant recipients</td>
</tr>
<tr>
<td>Post-portacaval shunting</td>
</tr>
<tr>
<td>Dysmetabolic iron-overload syndrome</td>
</tr>
</tbody>
</table>

The source of iron may be parenteral, from transfusions or iron compounds, or from increased oral intake (diet, iron compounds, or enhanced iron absorption due to ineffective erythropoiesis or liver disease). The common pathophysiological mechanism is often the down-regulation of hepcidin expression (1). More than one factor may be present in the same patient. The coexistence of mutations involved in genetic haemochromatosis may or not aggravate a secondary iron overload (2). In the past the clinical relevance of iron overload and its treatment for the most severe of the above conditions was limited by the poor prognosis of the underlying disease, which overshadowed the long term risk of iron-related complications.
Today several factors facilitate a more comprehensive approach: advances in diagnostics, progress in the management of the underlying diseases, especially the improved long-term results obtained in thalassaemia, and the availability of new oral chelators. There is growing interest in a variety of conditions where iron overload may be less obvious. These include patients with low risk myelodysplastic syndromes (3, 4) and patients who have been treated for leukaemias (5) and lymphomas or have received stem cell transplantation (6).

2. Evaluation of iron overload
An accurate assessment of iron status is initially required, to evaluate its clinical relevance, the need for treatment, and the timing and monitoring of therapy. Different diagnostic tools may be useful in evaluating different aspects of iron overload (Table 2). The diagnostic methods may also be distinguished on the basis of being direct approaches (atomic absorption spectrometry and SQUID magnetic susceptometry) or indirect (all the others).

Table 2: Methods for iron overload assessment according to the type of evaluation

<table>
<thead>
<tr>
<th>A. Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Signs and symptoms</td>
</tr>
<tr>
<td>• Iron-related complications</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Serum markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Serum iron</td>
</tr>
<tr>
<td>• Serum transferrin</td>
</tr>
<tr>
<td>• Transferrin saturation</td>
</tr>
<tr>
<td>• Serum ferritin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C. Tissue iron concentration/Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Liver iron concentration (LIC) by:</td>
</tr>
<tr>
<td>- Liver biopsy</td>
</tr>
<tr>
<td>- SQUID magnetic susceptometry</td>
</tr>
<tr>
<td>- Quantitative MRI</td>
</tr>
<tr>
<td>• Cardiac MRI</td>
</tr>
<tr>
<td>• MRI of other tissues/organs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D. Iron toxicity markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Non transferrin bound iron (NTBI), labile plasma iron (LPI)</td>
</tr>
<tr>
<td>• Markers of oxidative damage</td>
</tr>
<tr>
<td>• Liver fibrosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>E. Iron balance calculations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Iron load with transfusions</td>
</tr>
<tr>
<td>• Iron removal by phlebotomy</td>
</tr>
<tr>
<td>• Iron excretion by chelators</td>
</tr>
</tbody>
</table>
2.1 Clinical features
The timing of appearance of signs or symptoms depends on the rate of iron overload. In severe conditions such as thalassaemia major, they may appear in childhood, with skin hyperpigmentation, growth impairment, delayed puberty, cardiac arrhythmias and the onset of overt organ dysfunction, including congestive heart failure or diabetes. Otherwise, as in genetic haemochromatosis, signs and symptoms may be very late and non-specific: weakness, fatigue, loss of libido, and/or arthralgia. If the iron burden progresses and is not treated, all the clinical features may become manifest, with heart disease, diabetes, hypothyroidism, hypoparathyroidism, hypogonadism, and cirrhosis. A clear association with the risk of developing hepatocellular carcinoma has been established, at least for thalassaemias (7). In acquired conditions requiring regular blood transfusions, in particular MDS patients, the impact of iron overload is less clearly established, but seems to be more prone in low-risk patients where non-leukaemia related complications are the main causes of death (4).

2.2 Serum markers
Serum ferritin is the most widely used and the least expensive parameter for assessing iron status. A positive correlation exists between serum ferritin concentration and iron stores (8), but independent conditions may falsely elevate ferritin levels (cancer, hepatitis, inflammation, haemolysis, vitamin C deficiency) (9). Furthermore, the accuracy diminishes at high ferritin values and the correlation may have different slopes in different haematological conditions such as thalassaemia intermedia where serum ferritin values notably underestimate iron overload (10). Therefore serial assessments are recommended.

Transferrin saturation (TS) is usually extremely high in regularly transfused patients and its level may suggest the site of iron accumulation (reticuloendothelial iron overload alone is associated with normal TS, whereas parenchymal iron overload leads to a high TS value).

2.3 Iron toxicity markers
A high transferrin saturation value and other markers may be useful in the assessment of iron toxicity. When serum transferrin is almost fully saturated (above 70%) a toxic fraction of plasma iron appears. This is called non-transferrin-bound (NTBI) or labile plasma iron (LPI), according to the method used to measure it (11, 12). NTBI promotes the formation of free hydroxyl radicals and the peroxidation of membrane lipids. It possibly represents the fraction of iron directly involved in iron-induced tissue toxicity and is related with the intracellular labile iron pool (LIP).
Preliminary results showed a positive correlation between the presence of serum NTBI in thalassaemic patients with transfusional iron overload and an increased risk of siderotic heart disease (13). However, these assessments are limited to a few laboratories and clinical correlations are still limited (13).

Iron toxicity may be assessed by looking at levels of lipid peroxidation products such as malondialdehyde, and physiological antioxidants such as vitamin E, A and C. The clinical significance of these changes and the benefits of antioxidant supplementation have not been fully explored by controlled studies.

### 2.4 Tissue iron concentration/distribution

The liver contains most of the body iron stores (70-80%) and is the main crossroads of iron trafficking (storage from intestinal absorption and from red-cell catabolism, chelation by iron chelating drugs, excretion through the bile). Where liver biopsy is performed, the histology may provide a semi-quantitative evaluation of iron load and its distribution, the degree of fibrosis or cirrhosis, and possible independent factors as viral hepatitis, alcohol and steatosis.

Liver iron concentration (LIC) determined chemically after a liver biopsy has been till recently the gold standard (14) and was largely used in prospective studies on iron chelators (15-17). LIC is well correlated with total body iron stores in thalassaemia and haemochromatosis (14, 18).

High LIC level predicts cardiac disease and early death in thalassaemia (19). Recent advances in non-invasive techniques for the assessment of LIC (20, 21) and liver fibrosis (22) have drastically reduced the indications for performing a liver biopsy in iron overload conditions.

A comparison of these techniques with tissue biopsy is summarised in Table 3.

<table>
<thead>
<tr>
<th>Biopsy (AAS)</th>
<th>SQUID Susceptometry</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Direct method</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Sampling error</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Histology</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Availability</td>
<td>Yes</td>
<td>Poor</td>
</tr>
<tr>
<td>Validation (Liver)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Heart assessment</td>
<td>Not useful</td>
<td>No</td>
</tr>
</tbody>
</table>

**Table 3: Characteristics of method for assessment of iron overload**

AAS: atomic absorption spectrometry
2.5 SQUID magnetic susceptometry

Superconducting quantum interference device (SQUID) susceptometry is potentially the most accurate non-invasive method for quantitative estimation of the LIC (19). The peculiar paramagnetic response of iron in ferritin and haemosiderin in a constant magnetic field is detected by a very sensitive SQUID. The system has been validated with chemically measured LIC, demonstrating direct linearity up to 12 mg/g dry weight (23). It has been applied to the evaluation of the long-term efficacy of iron chelators (24, 25-27) and the relationship between serum ferritin and LIC (28, 29). Availability is however poor, with only four systems working in the world. Current research on room temperature susceptometers may make these precise instruments less expensive and more widely available.

2.6 Magnetic resonance imaging (MRI)

The iron concentration is indirectly assessed by the effect of ferritin and haemosiderin iron in shortening proton relaxation times and in decreasing the signal intensity and getting the tissue darker (30). If specific methods in strict conditions are applied, MRI may have low variability (31), good transferability (32, 33), inter-scan reproducibility (34, 35) and the ability to assess iron loading in various organs. MRI assessment of liver iron load is largely validated, and was found to be well correlated with chemically measured LIC values in many studies (20, 31, 36-38). However, methods remain numerous and not standardised, mainly because several technical parameters are able to influence the level of precision: magnetic field strength, imaging sequences (time echo (TE), repetition time), type of proton relaxation time studied (T2 or R2, 1/T2, T2*, signal intensity ratio liver/muscle), mathematical method used to analyse the relaxation curve) (37).

The pros and cons of the commonly used methods are summarised in Table 4.

<table>
<thead>
<tr>
<th>Technique</th>
<th>References</th>
<th>Advantages</th>
<th>Drawbacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gradient-recalled-echo imaging. Liver/muscle intensity ratio</td>
<td>Gandon Y Rose C</td>
<td>Routine MR scanners Free methods for signal analysis*</td>
<td>Less accurate</td>
</tr>
<tr>
<td>R2 (1/T2) relaxometry</td>
<td>St Pierre</td>
<td>Accuracy</td>
<td>Requires phantoms and each scan requires a centralised data analysis</td>
</tr>
<tr>
<td>R2* (1/T2*) relaxometry</td>
<td>Anderson LJ Virtanen JM</td>
<td>Transferability between different scanners</td>
<td></td>
</tr>
</tbody>
</table>

2.6.1 Cardiac MRI
As the primary cause of death in severe iron overload and low risk MDS is heart failure, an affordable cardiac assessment is extremely useful for clinical management. In the past many limitations have led to difficulties achieving this aim: the uneven distribution of iron in the heart (39), its relatively low concentration (10 times lower than in the liver), blood flow and motion artifacts and the limited possibility of validating MRI measurements against tissue samples. Nevertheless cardiac MRI (myocardial T2*) is today able to accurately assess the magnitude of cardiac iron overload (40). A retrospective study on thalassaemic patients on deferoxamine (DFO) treatment found a significant correlation between myocardial T2* and left ventricular function (21). Many patients with a T2* below 20 ms had ventricular dysfunction (40). Cardiac T2* did not correlate with serum ferritin value and LIC (21). This is true only in patients on long term chelation, but led to the important finding that both iron loading and iron clearance follow different patterns in the liver and the heart (41). Up to now data on cardiac iron in conditions other than thalassaemia, such as MDS, are limited and conflicting (42-44). As cardiac iron loading appears late in thalassaemic patients on regular transfusion and chelation (45), an MRI assessment is not needed before 6-8 years of age, when it requires anaesthesia.

2.6.2 Iron load in other tissues
Appropriate MRI acquisition techniques allow an estimation of iron in target tissues (pancreas, thyroid, pituitary, hypothalamus (46, 47)) and may be of help in preventing the other clinical complications of iron overload.

2.7 Iron balance calculations

2.7.1 Iron load with transfusions
Knowing that each gram of haemoglobin contains 3.4 mg of iron, the precise amount of transfusional iron can be easily and accurately estimated. Depending on data given by the blood bank (weight, volume, haematocrit or total haemoglobin), simple calculations may be applied (Table 3). Transfusion-dependent conditions such as aplasias or severe thalassaemias have a blood consumption of 100-200 mL/kg/year of red blood cells, corresponding to 0.32-0.64 mg/kg/day. Differences among patients may be significant (varying from 0.15 to 0.80 mg/kg/day), depending on the underlying condition, transfusional scheme, spleen status and the presence of red cell immunisation. In transfusion dependent patients the accurate recording of transfused iron must be part of high quality monitoring and is relevant for efficient iron chelation (48).
2.7.2 Quantitative phlebotomy
The amount of iron removed by repeated phlebotomies gives a retrospective, accurate, direct measure of the total body iron stores. This is important in patients with genetic haemochromatosis, as survival and morbidity are related to the peak iron load. The same approach is applicable to patients with transfusion-dependent anaemias, such as when a successful bone marrow transplantation is followed by phlebotomy (5, 49). In thalassaemia patients a close correlation has been demonstrated between the iron removed and the liver iron concentration at the start of phlebotomies (14). This means that it is possible to estimate the total iron stores from a single liver iron concentration measurement, applying a simple formula (Table 5).

Table 5: Iron balance calculations

<table>
<thead>
<tr>
<th>A. Transfused iron (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Weight (grams) x haematocrit (ratio) x 1.16</td>
</tr>
<tr>
<td>• Volume (mL) x 1.056 x haematocrit (ratio) x 1.16</td>
</tr>
<tr>
<td>• Haemoglobin (total grams) x 3.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Iron removed by phlebotomy (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Patient’s Hb (g%) x blood removed (mL) x 0.034</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C. Total body iron stores (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Liver iron concentration (mg/kg dry weight x 10.6)</td>
</tr>
</tbody>
</table>

2.7.3 Iron excretion by chelators
Iron excretion induced by chelators is the sum of urinary and faecal fractions. For deferoxamine urinary iron excretion (UIE) represents around 50% of total excretion (50), for deferiprone 80-98% (51) and for deferasirox less than 5% (52). The evaluation of faecal iron excretion is laborious and limited to iron balance trials. The 24 hour UIE after deferoxamine or deferiprone may be useful in clinical practice in monitoring the iron chelation efficacy (53). UIE depends only in part on drug dose and degree of iron overload. For deferoxamine, the administration route and delivery time, the degree of erythropoietic expansion, the ascorbate status and liver disease influence the response, with important individual variations in the fraction of faecal iron excretion. For deferiprone, the glucuronidation efficiency appears to depend almost only on UGT1A6, especially in the liver. Genetic variations and differences in the expression of splice variants represent a potential source of variation in deferiprone metabolism (54).
3. Treatment of iron overload

3.1 Phlebotomy
Phlebotomy is the reference treatment for iron overload in genetic haemochromatosis. It may be applied also to patients after successful bone marrow transplantation for thalassaemia and other conditions, as indicated previously (49, 55).

3.2 Iron chelation therapy
The aims of iron chelation are the prevention of iron-related complications, the maintenance of safe tissue iron levels and the reversal of iron-related complications (56). More than 30 years of research have led to important advances in iron chelation (Figure 1).

Figure 1: Overview of iron chelation

DF0: deferoxamine. Hatched lines in deferasirox and deferiprone represent development period.

3.2.1 Deferoxamine
A single excellent drug, deferoxamine (DF0) has been available for many years. DF0 displays a strong and specific affinity for iron with a theoretically capability of binding 8.5 mg ferric iron every 100 mg of DF0. The subcutaneous slow infusion has been the standard iron chelation choice since the end of the seventies. In thalassaemia major the regular use of DF0 resulted in an impressive improvement in life expectancy and a reduction in the prevalence and severity of iron-related clinical
complications. With experience and skill it is possible to limit side effects and
optimise compliance in most patients (57).

The standard prescription is a slow subcutaneous infusion over 8-12 hours of a 10%
DFO solution by an infusion pump at a standard dose of 20-40 mg/kg for children,
and up to 50-60 mg/kg for adults. Alternatives in treatment modalities, such as s.c.
bolus injection or i.v. continuous infusion enable DFO to be used in a wide range
of conditions and special needs. Symptomatic heart disease can be reversed by high
dose intravenous treatment.

Recent data show that a significant proportion of patients on long-term s.c. DFO
still have evidence of cardiac iron load despite low serum ferritin levels (58). A DFO-
starch polymer combination, 40SD02 regained attention and is now in phase II
development. With a single i.v. infusion it is possible to obtain a significant iron
excretion lasting up to several days, with limited side effects (59, 60).

3.2.2 Oral iron chelators

During the past few years the body of advances on iron chelation research has been
impressive, leading to the development of new oral chelators (61). Deferiprone (DFP)
(Apotex, Toronto, ON, Canada) also known as L1, CP20, Ferriprox and Kelfer, is a
1,2 dimethyl-3hydroxypyrid-4-one, was initially synthesised in 1982, but its
development did not follow a systematic design. DFP is a bidentate molecule that
forms 1:3 iron chelator complexes, absorbed with a mean half-life of 160 and 91
minutes in two different studies (62, 63). More than 90% of free drug is eliminated
from plasma within 3-6 hours of ingestion and excreted in urine. The drug is
inactivated by glucuronidation (64). From pharmacokinetic and metabolic studies
it was shown that 75 mg/kg/day of DFP on 7 days/week overall produces a similar
level of iron excretion to DFO 40 mg/kg given subcutaneously on 5 days/week (64).
Because of the short half-life, the recommended dosage is 75 mg/kg/day divided
in three doses. Several aspects of its safety and efficacy led to serious discussions
and controversies (64). The safety profile requires close monitoring. Nowadays many
independent studies indicate an overall efficacy similar to DFO (26, 65, 66). A
systematic review based on the Cochrane database (67) showed no consistent
difference in reduction of iron overload between DFO and DFP treatment. Due to
its membrane crossing ability, DFP has been shown to shuttle tissue iron into
circulation; studies in iron-loaded rat heart cells and in gerbils had shown its efficacy
in removing iron from myocardial cells at concentrations that can be achieved at
a therapeutic dosage (68). A retrospective study compared 54 thalassaemia major
patients treated with DFP with 75 treated with DFO for an average of 6 years. Survival
and heart disease rates were significantly better in the DFP group (69). A further
study on a larger series confirmed this type of difference between the two drugs (70). A randomised controlled on 61 thalassaemia major patients over 1 year of treatment of DFO or DFP, showed changes in myocardial T2* and LVEF significantly greater for DFP than DFO (71). Several studies suggest that doses up to 100 mg/kg/day may be safely utilised where indicated (64).

Deferasirox (ICL670, Exjade\textsuperscript{TM}) (DFX), a tridentate-bis-hydroxypheny-triazole chelator has been recently approved for treating transfusional iron overload. The drug is highly lipophilic and 99% protein-bound. Two molecules of DFX are required to bind one Fe\textsuperscript{3+}, forming a stable 1:2 iron-chelator complex (72). Due to its long half-life (8-16 hours), it can be taken once a day, 30 minutes before a meal, as the type of food, caloric and fat content influence DFX availability (73). Rapidly absorbed, DFX can efficiently and selectively mobilise iron from hepatocytes and cardiomyocytes, and can promote iron excretion. The DFX-iron complex is excreted in the faeces and not redistributed (71, 74). No significant differences in the pharmacokinetic, safety and efficacy profile of DFX were observed in paediatric and adolescent patients compared with adults (75). The results of pivotal data from a large-scale, randomised Phase III trial in transfusion-dependent beta-thalassaemia patients, showed that iron balance is achieved at 20 mg/kg/day, and significantly reduction in iron burden was observed at 30 mg/kg/day (76). The response to DFX depends both on dose transfusional iron intake (48). In other conditions including sickle cell disease and Diamond-Blackfan anaemia (DBA) efficacy results are similar to those observed in thalassaemia (77, 78).

Recent data on patients with beta-thalassaemia demonstrate that daily trough levels of DFX suppress LPI for 24 hours (79). In regularly transfused MDS patients, DFX is also efficient in reducing LIC (78). In this condition there is a higher rate of adverse events and more frequent discontinuation of therapy (80). Indications are only based on an expert consensus (81), additional data are required for a better definition of patients with the best risk-benefit ratio (82). In a recent study on MDS patients DFX may reduce transfusion requirement (83). The hypothesis that there is a direct effect of DFX on the neoplastic clone is under investigation (84). At high doses DFX shows a positive effect on heart iron (85-87). A systematic review on DFX analyses also its economic aspects (88).

Table 6 shows the properties of available iron chelators.

### 3.2.3 Side effects of iron chelation

Most of the side effects of iron chelation are caused by the iron subtraction from iron-dependent physiological pathways. Age, high doses of chelator and low level of iron overload are the main risk factors, whereas certain side effects are
characteristic of each drug. For detecting early iron chelation toxicity and minimising its consequences, a close monitoring schedule should be individually tailored. This may include: auxological assessment (weight, body fat, standing and sitting height, pubertal stages, radiological assessment of bone age and the main metaphyses), bone densitometry, liver function tests, ophthalmological examination, audiometry, plasma zinc, rheumatological assessment are recommended. For DFO specific attention must be paid to early signs of infection for diagnosis and treatment of iron related complications as Yersinia enterocolitica septicaemia. For DFP weekly check of absolute neutrophil count is required. For DFX regular renal function monitoring is recommended. Table 7 shows a comparison of side effects of available iron chelators.

### 3.2.4 New approaches to treatment

The availability of more than one drug stimulated the search for benefits from combination therapy. Some *in vitro* data suggested the potential of an additive and even synergistic effect (89). These effects have been demonstrated *in vivo*. In a randomised trial in thalassaemia patients, the results of combined treatment were superior to DFO alone in removing myocardial iron and improving cardiac and endothelial function (90). Other studies confirmed these findings (91, 92). Many independent papers on the reversal of heart failure by combination therapy are available, even if most are single case or small series reports (93). A single uncontrolled study suggests that combination therapy may reverse endocrinological complications such as glucose intolerance in thalassaemia patients (94). The term “combination” is presently used for a wide range of treatment schemes that need to be distinguished, including the daily taking of both drugs at full doses.

<table>
<thead>
<tr>
<th>Property</th>
<th>Deferoxamine</th>
<th>Deferiprone</th>
<th>ICL670</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chelator: iron binding</td>
<td>1:1</td>
<td>3:1</td>
<td>2:1</td>
</tr>
<tr>
<td>Usual dosage</td>
<td>25-40 mg/kg/d</td>
<td>75 mg/kg/d</td>
<td>20-30 mg/kg/d</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Subcutaneous, intravenous</td>
<td>Oral, 3 times daily</td>
<td>Oral, once daily</td>
</tr>
<tr>
<td>Half-life</td>
<td>20-30 minutes</td>
<td>3-4 hours</td>
<td>12-16 hours</td>
</tr>
<tr>
<td>Excretion</td>
<td>Urinary, faecal</td>
<td>Urinary</td>
<td>Faecal</td>
</tr>
<tr>
<td>Effect in lowering liver iron</td>
<td>+++</td>
<td>From – to +++</td>
<td>+++</td>
</tr>
<tr>
<td>Effect in lowering heart iron</td>
<td>&gt;40 mg/kg and i.v. use</td>
<td>75-100 mg/kg</td>
<td>30-40 mg/kg</td>
</tr>
<tr>
<td>Difficulty in compliance</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>
and simultaneously, or alternating the two drugs during the week. The following is a suggested approach to a common terminology (95):

- **Monotherapy**: a single chelator is prescribed and taken for more than three months.
- **Alternate therapy**: in any single day only a single chelator is taken; the two chelators are alternated on a weekly, monthly or quarterly basis (e.g., DFP five days a week and DFO two days a week)
- **Combination therapy**: prescription of more than one chelator, to be taken on the same day for a significant part of the treatment period. Treatment may be:
  - **Sequential**: in a single day two chelators are taken in sequence; no substantial overlapping of the two drugs in the plasma (e.g., DFP three times a day and DFO night time).
  - **Simultaneous or concomitant**: in a single day two chelators are taken at the same time with substantial overlapping of the two drugs in the plasma.

Combination treatment may be considered every time there is a need to look for an additive or synergistic effect such as for reversing heart disease (90, 96). At the onset of clinical heart disease, it is important to minimise cardiotoxicity, suppressing NTBI by continuous treatment. Intensive DFO chelation with continuous intravenous infusion has been demonstrated to be effective. Subcutaneous 24 hours a day DFO infusions may be an alternative when i.v. treatment is not feasible. The addition of a second chelator may be considered to increase efficacy.

### Table 7: Comparison of iron chelators side effects

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Deferoxamine</th>
<th>Deferiprone</th>
<th>ICL670</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local side effects</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>G.I. symptoms</td>
<td>Rare</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Skin rashes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Growth arrest</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bone changes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Yes ?</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Liver enzymes changes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Yersinia infection</td>
<td>Yes</td>
<td>?</td>
<td>No</td>
</tr>
<tr>
<td>Arthropathy</td>
<td>Rare</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Retinal toxicity</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Lens opacity</td>
<td>Rare</td>
<td>No</td>
<td>Rare</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Renal changes</td>
<td>High doses</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Weight gain</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Agranulocytosis</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Rare</td>
<td>Yes</td>
<td>Rare</td>
</tr>
</tbody>
</table>
of DFP greatly enhances the efficacy and reduces the time needed to normalise tissue iron levels. Individually tailored combination may maintain efficacy and tolerability in patients with dose-related side effects to DF0 or DFP. Finally, different types of combination may be considered in the near future, looking at the different characteristics of the available chelators. Unpublished data on combined DF0/DFX seem to be promising.

4. Conclusions
The evaluation and monitoring of iron overload require an integrated use of several indices: clinical signs, genetic markers, iron toxicity markers, quantification of iron overload, evaluation of iron-related complications, indices of chelation therapy efficacy. None of them alone is sufficiently informative to guide the doctor in making the necessary clinical decisions. Iron overload conditions can today be diagnosed early and accurately, thanks to the recent progress in molecular medicine. Advances in biochemical and instrumental diagnostics allow an accurate quantification of iron overload and iron-related toxicity. The new treatment options greatly enhance the efficacy of iron chelation for preventing and treating the iron overload complications, even in conditions once considered irreversible.

References
9. Lee D, Jacobs DJ. Serum markers of stored body iron are not appropriate markers of health


44. Jensen PD, Jensen FT, Christensen T et al. Evaluation of myocardial iron by magnetic
resonance imaging during iron chelation therapy with deferrioxamine: Indication of close relation between myocardial iron content and chelatable iron pool. Blood 2003; 101: 4632-4639.


60. Harmatz P, Grady R, Dragsten P et al. Phase Ib clinical trial of starch-conjugated
601

CHAPTER 25  Secondary iron overload


77. Vichinsky E, Onyekwere O, Porter J et al. A randomised comparison of deferasirox versus


82. Cazzola M, Della Porta MG, Malcovati L. Clinical Relevance of Anemia and Transfusion Iron Overload in Myelodysplastic Syndromes. Hematology 2008; 166-175.


84. Messa E, Cilloni D, Messa F et al. Deferasirox treatment improved the hemoglobin level and decreased transfusion requirements in four patients with the myelodysplastic syndrome and primary myelofibrosis. Acta Haematol 2008; 120: 70-74.


87. Pennell D, Porter JB, Cappellini MD et al. Efficacy and Safety of Deferasirox (Exjade(R)) in Reducing Cardiac Iron in Patients with (beta)-Thalassemia Major: Results from the Cardiac Substudy of the EPIC Trial. ASH Annual Meeting Abstracts 2008; 112: 3873.


91. Maggio A, Vitrano A, Capra M et al. Long-term sequential deferiprone-deferoxamine versus


Multiple Choice Questionnaire

To find the correct answer, go to [http://www.esh.org/iron-handbook2009answers.htm](http://www.esh.org/iron-handbook2009answers.htm)

1. The appearance of NTBI or labile plasma iron (LPI) occurs when transferrin saturation level is about:
   a) 30% .................................................................
   b) 70% .................................................................
   c) 50% .................................................................
   d) 99% .................................................................

2. Ferritin levels can be influenced by all these conditions except one:
   a) Liver disease ..................................................
   b) Vitamin C deficiency ........................................
   c) Inflammation .................................................
   d) Hyperglycaemia ............................................

3. Which is the most accurate MRI technique for measuring cardiac iron?
   a) Signal Intensity Ratio (SIR) ............................... 
   b) R2 .................................................................
   c) T2* ..............................................................
4. **Which iron chelator has the longest half-life:**
   a) Deferoxamine
   b) Deferiprone
   c) Deferasirox
   d) Deferitrin

5. **In the management of iron chelation all the following are important except one:**
   a) Cardiac iron
   b) Transfusional iron input
   c) Liver iron concentration
   d) Serum iron