

Iron Chelator Basics

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The goals of iron chelation therapy in the management of chronic iron overload disease are to prevent iron stores from reaching levels at which tissue damage occurs and to remove excess iron already present, thereby reversing tissue/organ dysfunction. In order to prevent iron stores from accumulating, the amount of iron transfused must be balanced by the amount of iron chelated. Effective protection against iron toxicity requires detoxification of both extracellular iron stores (non-transferrin-bound or labile plasma iron) and intracellular iron stores (labile iron pool). To meet these goals, an ideal iron chelator should have a high and specific affinity for Fe^{3+} , be a highly efficient chelator, provide 24-hour coverage and good tissue penetration, have a clear drug-dose efficacy and toxicity relationship, and result in elimination—not redistribution—of chelated iron. Oral availability and suitability for monotherapy, two important factors in patient compliance, are especially desirable.

Three iron chelators are currently available: desferrioxamine (DFO), deferiprone (DFP), and desferosirox (DFS). DFO is administered SC or IV 8 to 12 hours, 5 days per week, a regimen that many patients find unacceptable. DFP and DFS are both given orally: DFP three times daily and DFS once daily. DFO and DFS are approved in Europe and North America for the treatment of chronic iron overload due to transfusion-dependent anaemias, whereas DFP is approved only in Europe and only for the treatment of thalassaemia major.

The importance of preventing/removing toxic iron is particularly evident in the case of cardiac iron. Several studies have shown a clear risk of cardiac dysfunction, as measured by decreased left ventricular ejection fraction, associated with decreased cardiac T2*, a marker of increased cardiac iron levels. Fortunately, this risk can be reversed with effective chelation. Patients treated with 6 months of DFS experienced significant decreases in both liver iron concentrations ($P = .0027$) and cardiac iron ($P = .0136$). DFP,

and especially the combination of DFP + DFO, also resulted in significant increases in mean cardiac T2*, indicating a reduction in cardiac iron stores. DFP was more effective in reducing cardiac iron than DFO; however, DFO, and especially DFO + DFP, resulted in greater reductions in hepatic iron than DFP. Thus, the superiority of DFO + DFP over either DFP or DFO separately seems to be a result of the combination of the different cardiac and hepatic benefits of the two agents. Other investigations have shown significant reductions in malondialdehyde, a marker of oxidant stress, following treatment with either DFS or DFO. DFS, but not DFO, also resulted in reduced levels of C-reactive protein, a marker of inflammation.

Data are now available on the long-term use of DFS in more than 650 adult and paediatric patients with thalassaemia, sickle cell disease, myelodysplastic syndrome, and other rare anaemias. In addition to demonstrating continued safety and tolerability with a median of 3.4 years of treatment, the data illustrated the benefit of doses of 30 mg/kg/day in achieving negative iron balance. Escalation of DFS doses to >30 mg/kg/day is also being explored and, in early trials, doses of 30 mg/kg/day to 40 mg/kg/day have resulted in significant decreases in serum ferritin levels compared with levels prior to drug escalation. Surprisingly, DFS >30 mg/kg/day was associated with reduced adverse events as well.

In summary, in order to ensure that patients receive the appropriate dose of iron chelation therapy, the transfusional iron intake as well as the patient's iron burden should be taken into account. DFS at a dose of 30 mg/kg/day is efficacious and safe, with higher doses now being studied. In general, serum ferritin levels decreased at DFS doses of 30 mg/kg/day and could then be maintained at doses of 20 mg/kg/day to 25 mg/kg/day. Finally, treating to a target serum ferritin level of 500 µg/L is a realistic goal.

Suggested Readings

Anderson LJ, Holden S, Davis B, et al. Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload. *Eur Heart J*. 2001;22:2171-2179.

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Porter JB. Concepts and goals in the management of transfusional iron overload. *Am J Hematol.* 2007;82:1136-1139.

Walter PB, Macklin EA, Porter J, et al. Inflammation and oxidant-stress in beta-thalassemia patients treated with iron chelators deferasirox (ICL670) or deferoxamine: an ancillary study of the Novartis C1CL670A0107 trial. *Haematologica.* 2008;93:817-825.