

## **Indications for Successful Iron Overload Treatment and Monitoring: Hereditary Haemochromatosis**

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Hereditary haemochromatosis (HC) results from mutations in one of several genes. The most common form of HC, Type 1, or HFE-HC, accounts for 90% of cases and is an autosomal recessive disorder associated with homozygosity for the C282Y mutation in the HFE gene. It occurs most often in people of Northern European descent. The three non-HFE forms of HC include Type 2A/Type 2B, or juvenile HC, which results from mutations in haemojuvelin and hepcidin genes, respectively; Type 3, or transferrin receptor 2 (TfR2) HC, which is due to transferrin receptor 2 mutations, and Type 4 HC, or ferroportin disease, which results from mutations in ferroportin. Hepcidin deficiency is a pivotal pathogenic factor in Types 1, 2, and 3. The therapy of choice for these forms of HC is phlebotomy, or venesection. Phlebotomy should be initiated for grade 2 HC, ie, when serum ferritin levels exceed 300 µg/L in men and 200 µg/L in women. It is administered weekly during the induction phase until serum ferritin is <50 µg/L, then continued every 1 to 4 months as lifetime maintenance therapy.

Phlebotomy reduces iron overload by inducing the release of iron from hepatocytes, resulting in improvement of overall health and reductions in hyperpigmentation and hypertransaminasaemia. It may not, however, diminish the symptoms of arthralgia or minimize insulin dependence. In addition, if cirrhosis is already present, phlebotomy does not prevent the risk of hepatocellular carcinoma. Phlebotomy may increase intestinal iron absorption by enhancing hepcidin deficiency, as well as contributing to plasma transferrin saturation and the appearance of labile plasma iron—a toxic form of circulating iron. The use of phlebotomy is limited if venipuncture is not technically possible, or when anaemia is present. In these cases, iron chelation offers an important option.

Until recently, the use of iron chelation has been limited. The first available chelator, desferrioxamine, requires administration through subcutaneous infusion, and thus interferes with patients' normal lifestyles. Although the oral chelating agent, deferiprone, is also available, it is not advisable in these diseases given a rare but unpredictable risk of agranulocytosis. The newest agent, deferasirox, currently tested in an international safety

trial, shows promise as an alternative when phlebotomy is contraindicated/cannot be used or in association with phlebotomy for the treatment of massive iron overload. In general, the respective roles of phlebotomy and iron chelation depend on the pathophysiologic mechanism underlying the iron overload. Management of Types 2 and 3 HC is similar to that of Type 1. In cases of massive iron damage, phlebotomy may be combined with oral iron chelation to accelerate reduction of excess iron. In contrast, the presence of anaemia may preclude the use of phlebotomy in Type 4 HC and in hereditary aceruloplasminaemia. Therefore, in these conditions, oral chelation may be the therapy of choice. This webcast presents an overview of the principles, indications, and limitations of phlebotomy and iron chelation, and discusses possible future therapies that might correct the hepcidin deficiency underlying Types 1, 2, and 3 HC.

### **Suggested Readings**

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9. Montosi G, Donovan A, Totaro A. Autosomal-dominant hemochromatosis is associated with a mutation in the ferroportin (SLC11A3) gene. *J Clin Invest.* 2001;108:619-623.