FerriScan®

MRI Measurement of Liver Iron Concentration

Evidence for the Effect of FerriScan® Measurements on Outcome for Patients at Risk of Iron Overload from Blood Transfusions

FerriScan® is a non-invasive magnetic resonance imaging (MRI) method for measuring the degree of body iron burden through quantification of liver iron concentration (LIC).

Published clinical evidence supports the argument that the use of FerriScan® improves health status of patients at risk of iron overload by reducing the risk of iron-induced cardiac failure through improved decision making in relation to iron chelator dosing. In addition to improving patient health outcomes, reducing rates of cardiac failure reduces health budget spending on treatment of cardiac failure.

This document provides a summary of the evidence supporting the case for FerriScan® to be reimbursed for patients at risk of iron overload as a result of chronic blood transfusion.

Each statement is presented with summaries of the published evidence to support it. The summaries are taken either from the abstracts or conclusions/summaries of published papers. While not providing an exhaustive list, the summaries highlight the key published evidence.

Summary of the Linked Evidence

- Link 1: Patients receiving regular blood transfusions are at risk of iron overload.
- Link 2: Unchelated patients receiving chronic blood transfusion therapy have poor survival and poor complication-free survival
- Link 3: The major cause of death in chronically transfused thalassaemia patients is heart failure
- Link 4: Well chelated patients receiving chronic blood transfusion therapy have better survival and complication-free survival
- Link 5: Iron chelation in sufficient doses acts to reduce body iron burden
- Link 6: Liver iron concentration is a good surrogate measure of total body iron burden
- Link 7: High liver iron concentration is associated with cardiac iron overload and poor cardiac disease free survival
- Link 8: There is a wide range of liver iron concentration in the population of patients receiving chronic transfusion therapy and iron chelation covering both LIC in the safe range (<7 mg Fe/g dw) and LIC in the high risk range (>15 mg Fe/g dw)
- Link 9: Identification of patients with high LIC is difficult without a direct measure of LIC with biopsy or MRI or biomagnetic liver susceptometry. Serum ferritin is not sufficient to identify all patients at risk of severe iron overload.
- Link 10: Identification of high LIC leads to clinical decisions to increase chelator dose and increased patient counselling to improve adherence to chelation therapy resulting in reduced body iron burden.

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Evidence Links Together with Summaries from Published Data

Link 1: Patients receiving regular blood transfusions are at risk of iron overload.

The Evidence

(Erlandson et al. 1964)

Evidence for accumulation of excessive amounts of iron by patients with homozygous thalassemia receiving multiple transfusions of blood has been found both in the clinical courses and also in histologic examinations and chemical analyses of tissues.

Death has occurred in 25 patients in our institution who had homozygous thalassemia and received multiple blood transfusions. In 16 cases the death was attributable to cardiac failure which developed after the onset of cardiac arythmias, defects of cardiac conduction and evidence of myocardial damage. Similar cardiac involvement was present in an additional 4 of these 21 patients even though not the immediate cause of death. This sequence of events has also been reported to occur in patients with primary or idiopathic hemochromatosis. Histologic findings in patients with thalassemia dying in this institution were indistinguishable from those of idiopathic hemochromatosis and have been previously detailed by Ellis et al. (Ellis et al. 1954). Findings in similar patients dying elsewhere have been discussed by Harold Fink (Fink 1964).

Link 2: Unchelated patients receiving chronic blood transfusion therapy have poor survival and poor complication-free survival

The Evidence

(Brittenham et al. 1994)

Background: To determine whether deferoxamine prevents the complications of transfusional iron overload in thalassemia major, we evaluated 59 patients (30 were female and 29 male; age range, 7 to 31 years) periodically for 4 to 10 years or until death.

Methods: At each follow-up visit, we performed a detailed clinical and laboratory evaluation and measured hepatic iron stores with a noninvasive magnetic device.

Results: The body iron burden as assessed by magnetic measurement of hepatic iron stores was closely correlated ($R = 0.89$, $P<0.001$) with the ratio of cumulative transfusional iron load to cumulative deferoxamine use (expressed in millimoles of iron per kilogram of body weight, in relation to grams of deferoxamine per kilogram, transformed into the natural logarithm). Each increase of one unit in the natural logarithm of the ratio (transfusional iron load to deferoxamine use) was associated with an increased risk of impaired glucose tolerance (relative risk, 19.3; 95 percent confidence interval, 4.8 to 77.4), diabetes mellitus (relative risk, 9.2; 95 percent confidence interval, 1.8 to 47.7), cardiac disease (relative risk, 9.9; 95 percent confidence interval, 1.9 to 51.2), and death (relative risk, 12.6; 95 percent confidence interval, 2.4 to 65.4). All nine deaths during the study occurred among the 23 patients who had begun chelation therapy later and used less deferoxamine in relation to their transfusional iron load ($P<0.001$)

Conclusions: **The early use of deferoxamine in an amount proportional to the transfusional iron load reduces the body iron burden and helps protect against diabetes mellitus, cardiac disease, and early death in patients with thalassemia major.**

(Borgna-Pignatti et al. 2004)

Background and Objectives: Seven Italian centers reported data on survival, causes of death and appearance of complications in patients with thalassemia major. The interactions between gender, birth cohort, complications, and ferritin on survival and complications were analyzed.

Design and Methods: Survival after the first decade was studied for 977 patients born since 1960 whereas survival since birth and complication appearance was studied for the 720 patients born after 1970. Better survival was demonstrated for patients born in more recent years ($p<0.00005$) and for females ($p=0.0003$); 68% of the patients are alive at the age of 35 years. In the entire population 67% of the deaths were due to heart disease.

Results: There was a significant association between birth cohort and complication-free survival ($p<0.0005$). The prevalence of complications was: heart failure 6.8%, arrhythmia 5.7%, hypogonadism 54.7%, hypothyroidism 10.8%, diabetes 6.4%, HIV infection 1.7%, and thrombosis 1.1%. Lower ferritin levels were associated with a lower probability of heart failure (hazard ratio =3.35, $p<0.005$) and with prolonged survival (hazard ratio = 2.45, $p<0.005$), using a cut-off as low as 1,000 ng/mL.

Interpretation and Conclusions: **Survival and complication-free survival of patients with thalassemia major continue to improve, especially for female patients born shortly before or after the availability of iron chelation.**

Link 3: The major cause of death in chronically transfused thalassaemia patients is heart failure

The Evidence

(Borgna-Pignatti et al. 2004)

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Link 4: Well chelated patients receiving chronic blood transfusion therapy have better survival and complication-free survival

The Evidence

(Brittenham et al. 1994)

See evidence for Link 2 above

(Borgna-Pignatti et al. 2004)

See evidence for Link 3 above

Link 5: Iron chelation in sufficient doses acts to reduce body iron burden

The Evidence

(Cappellini et al. 2006)

Deferasirox (ICL670) is a once-daily oral iron chelator developed for the treatment of chronic iron overload from blood transfusions. A comparative phase 3 trial was conducted to demonstrate the efficacy of deferasirox in regularly transfused pa- tients with β-thalassemia aged 2 years or older. Patients were randomized and received treatment with deferasirox (n = 296) or deferoxamine (n = 290), with dosing of each according to baseline liver iron concentration (LIC). The primary end-point was maintenance or reduction of LIC; secondary endpoints included safety and tolerability, change in serum ferritin level, and net body iron balance. **In both arms, patients with LIC values of 7 mg Fe/g dry weight (dw) or higher had significant and similar dose-dependent reductions in LIC and serum ferritin, and effects on net body iron balance.** However, the primary endpoint was not met in the overall population, possibly due to the fact that proportionally lower doses of deferasirox relative to deferoxamine were administered to patients with LIC values less than 7 mg Fe/g dw.

Link 6: Liver iron concentration is a good surrogate measure of total body iron burden

The Evidence

(Angelucci et al. 2000)

Background and Methods: We tested the usefulness of measuring the hepatic iron concentration to evaluate total body iron stores in patients who had been cured of thalassemia major by bone marrow transplantation and who were undergoing phlebotomy treatment to remove excess iron.

Results: We began treatment with phlebotomy a mean (±SD) of 4.3±2.7 years after transplantation in 48 patients without hepatic cirrhosis. In the group of 25 patients with liver-biopsy samples that were at least 1.0 mg in dry weight, there was a significant correlation between the decrease in the hepatic iron concentration and total body iron stores ($r=0.98$, $P<0.001$). Assuming that the hepatic iron concentration is reduced to zero with complete removal of body iron stores during phlebotomy, the amount of total body iron stores (in milligrams per kilogram of body weight) is equivalent to 10.6 times the hepatic iron concentration (in milligrams per gram of liver, dry weight). With the use of this equation, we could reliably estimate total body iron stores as high as 250 mg per kilogram of body weight, with a standard error of less than 7.9.

Conclusions: **The hepatic iron concentration is a reliable indicator of total body iron stores in patients with thalassemia major. In patients with transfusion-related iron overload, repeated determinations of the hepatic iron concentration can provide a quantitative means of measuring the long-term iron balance.**

Link 7: High liver iron concentration is associated with cardiac iron overload and poor cardiac disease free survival

The Evidence

(Noetzli et al. 2008)

High hepatic iron concentration (HIC) is associated with cardiac iron overload. However, simultaneous measurements of heart and liver iron often demonstrate no significant linear association. We postulated that slower rates of cardiac iron accumulation and clearance could reconcile these differences. To test this hypothesis, we examined the longitudinal evolution of cardiac and liver iron in 38 thalassemia major patients, using previously validated magnetic resonance imaging (MRI) techniques. On cross-sectional evaluation, cardiac iron was uncorrelated with liver iron, similar to previous studies. However, relative changes in heart and liver iron were compared with one another using a metric representing the temporal delay between them. Cardiac iron significantly lagged liver iron changes in almost half of the patients, implying a functional but delayed association. The degree of time lag correlated with initial HIC ($r = 0.47$, $P < .003$) and initial cardiac R2* ($r = 0.57$, $P < .001$), but not with patient age. **Thus, longitudinal analysis confirms a lag in the loading and unloading of cardiac iron with respect to liver iron, and partially explains the weak cross-sectional association between these parameters.** These data reconcile several prior studies and provide both mechanical and clinical insight into cardiac iron accumulation.

(Telfer et al. 2000)

Clinical complications of transfusional iron overload are still common in patients with thalassaemia major (TM) and it is not clear how best to monitor body iron stores during long-term follow-up to anticipate tissue damage. In this study, we have reviewed a group of 32 patients who underwent liver biopsy between 1984 and 1986. We developed a method of assessing the trend in serum ferritin (TSF) during long-term monitoring and compared this with mean serum ferritin (MSF) and initial liver iron (LI) concentration to determine whether, individually or in combination, they were accurate in predicting clinical outcome. LI levels were low (< 7 mg/g), medium (7 - 15 mg/g) and high (> 15 mg/g dry weight) in 15, 7 and 10 patients respectively. MSF was low (< 1500 mg/L), medium (1500 – 2500 mg/L) and high (> 2500 mg/L) in 10, 14 and 8 patients. TSF was low, medium and high risk in 9, 9 and 11 out of 29 evaluable patients. During a median follow-up of 13.6 years (range 2.3 - 14.8 years) after biopsy, nine patients died and an additional three patients developed heart failure. Hypothyroidism developed in five, hypoparathyroidism in four, and diabetes mellitus in seven patients. Cirrhosis developed in four of 10 evaluable patients. **The clinical end-point of death or cardiac failure was significantly associated with increasing iron load using all three means of assessment. [Note that only a single measurement of liver iron was made at the start of the observation period while MSF and TSF were monitored throughout the observation period of 2.3 to 14.8 years indicating the relative power of the liver iron measurement to predict outcome]**

Link 8: There is a wide range of liver iron concentration in the population of patients receiving chronic transfusion therapy and iron chelation covering both LIC in the safe range (<7 mg Fe/g dw) and LIC in the high risk range (>15 mg Fe/g dw)

The Evidence

(Cappellini et al. 2006)

The distribution of liver iron concentrations in 586 regularly transfused thalassaemia major patients from multiple centres across the globe was found to have a mean of 13.7 SD 9.7 mg Fe/g dw and median of 11.1 mg Fe/g dw with a range from 2.1 to 55.1 mg Fe/g dw.

Link 9: Identification of patients with high LIC is difficult without a direct measure of LIC with biopsy or MRI or biomagnetic liver susceptometry. Serum ferritin is not sufficient to identify all patients at risk of severe iron overload.

The Evidence

(Brittenham et al. 1993)

To examine the relationship between hepatic iron stores and plasma ferritin concentration in individuals treated with red cell transfusion and iron chelation therapy, 37 patients with sickle cell anemia and 74 patients with thalassemia major were studied. In each patient, hepatic iron stores were measured by an independently validated noninvasive magnetic method, and plasma ferritin was determined by immunoassay. The correlation between hepatic iron and plasma ferritin was significant both in patients with sickle cell anemia ($R = 0.75$, $P<0.0001$) and in those with thalassemia major ($R = 0.76$, $P <0.0001$). Regression analysis showed no significant difference between the two groups in the linear relationships between hepatic iron stores and plasma ferritin. Considering all 111 transfused patients as a group, the coefficient of correlation between hepatic iron stores and plasma ferritin was highly significant ($R = 0.76$, $P < 0.0001$). Regression analysis found that variation in body iron stores, as assessed by magnetic determinations of hepatic iron, accounted for only ~57% of the variation in plasma ferritin, suggesting that the remainder was the result of other factors, such as hemolysis, ineffective erythropoiesis, ascorbate deficiency, inflammation, and liver disease. **The 95% prediction intervals for hepatic iron concentration, given the plasma ferritin, were so broad as to make a single determination of plasma ferritin an unreliable predictor of body iron stores. Variability resulting from factors other than iron status limits the clinical usefulness of the plasma ferritin concentration as a predictor of body iron stores.**

(Brown et al. 2011)

A retrospective audit was conducted on clinical data from 40 consecutive subjects with haemolytic anaemias or ineffective hematopoiesis who had been monitored non-invasively for LIC over a period of at least one year. LIC was measured with spin density projection assisted R2-magnetic resonance imaging (R2-MRI).

At initial R2-MRI measurement, 4 of the 14 subjects who had LICs in the range associated with greatly increased risk of cardiac disease and early death (> 15 mg Fe/g dry tissue) had serum ferritin concentrations below 1000 µg/L. Furthermore, 3 of the 20 subjects at initial R2-MRI measurement who had LICs in the optimal range (< 7 mg Fe/g dry tissue) had serum ferritin concentrations greater than 2500 µg/L

Link 10: Identification of high LIC leads to clinical decisions to increase chelator dose and increased patient counselling to improve adherence to chelation therapy resulting in reduced body iron burden.

The Evidence

(Pakbaz et al. 2005)

Adherence to deferoxamine (DFO) is vital for the long-term survival of patients with thalassemia; however, currently no measure exists to quantify adherence directly. In this study, 90 patients with thalassemia major underwent liver iron concentration (LIC) assessment by SQUID biosusceptometer, were asked to rate their adherence to DFO using a Numerical Likert Scale (NLS), and were educated about complications of iron overload. Of 38% (n = 28) of patients who rated themselves as very compliant, 19 had elevated LIC related to inadequate dosing of DFO and nine reported nonadherence in the past. Adherence improved after counseling and LIC decreased by 25% (7–60%) in eight previously noncompliant patients who returned for subsequent LIC over 15 months. In conclusion, the NLS seems to be a simple but reliable tool to assess patients' adherence to DFO. **Education and frequent noninvasive LIC assessments can improve adherence and iron burden.** Elevated LIC does not necessarily reflect concurrent noncompliance; however, it can be an indi- cation of nonadherence in the past.

(Brown et al. 2011)

Aim: To determine whether total body iron stores in patients with haemolytic anaemias or ineffective haematopoiesis improved after the introduction of non-invasive monitoring of liver iron concentrations (LIC).

Method: A retrospective audit was conducted on clinical data from 40 consecutive subjects with haemolytic anaemias or ineffective hematopoiesis who had been monitored non-invasively for LIC over a period of at least one year. LIC was measured with spin density projection assisted R2-magnetic resonance imaging (R2-MRI).

Results: The geometric mean LIC for the cohort dropped significantly ($p = 0.008$) from 6.8 mg Fe/g dry tissue at initial measurement to 4.8 mg Fe/g dry tissue at final measurement. The proportion of subjects with LIC in the range associated with greatly increased risk of cardiac disease and death (>15 mg Fe/g dry tissue) dropped significantly ($p = 0.01$) from 14 of 40 subjects at initial measurement to 5 of 40 subjects at final measurement. A total of 19 clinical decisions based of LIC results were documented in the case notes. Decisions comprised initiation of chelation therapy, increasing chelator dose, decreasing chelator dose, and change of mode of delivery of deferioxamine from subcutaneous to intravenous.

Conclusions: **The data support the hypothesis that introduction of non-invasive monitoring of LIC can lead to a decreased body iron burden through improved clinical decision making and improved feedback to patients and hence improved adherence to chelation therapy.**

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