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Longitudinal changes in LIC and other parameters in patients receiving different chelation regimens: Data from LICNET

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Abstract

Objectives: The liver remains the primary site of iron storage, with liver iron concentration (LIC) being a strong surrogate of total body iron. MRI-R2 can accurately measure LIC. The LICNET (Liver Iron Cutino Network) was established to diagnostics of liver iron overload by MRI-R2 subjects with hemochromatosis in hematological disorders. The aims of the study were to look at variation in LIC measurements during time across different chelation regimens.

Methods: This was a cross-sectional study of 130 patients attending 9 Italian centers participating in the LICNET. LIC comparisons over time (T_0 and T_1) were made using *t* test and/or Wilcoxon test.

Results: LIC significantly decreased from MRI1 to MRI2 although at high variance (median change −0.8 mg Fe/g dw, range: −29.0 to 33.0; $P = .011$) and 7.7% of patients shifted from LIC values of high risk (>15 mg Fe/g dw) to an intermediate-risk category (7-15 mg Fe/g dw). Median change in LIC and correlation with serum ferritin levels (SF), during different chelation regimens, is reported.

Conclusions: These findings suggest as longitudinal variation in the LIC is possible, across all chelation regimens. It confirms as SF levels not always can be used for estimating changes in LIC.

KEYWORDS

Iron chelation Therapy, Liver Iron Concentration, MRI, red cell disorders

1 | INTRODUCTION

Chronic iron overload is a serious complication of potentially lifesaving blood transfusions in different hematological diseases. Excess iron deposits in various tissues of the body, particularly the liver, heart, and endocrine glands.[1] Once the body's storage capacity is exceeded, free iron catalyzes the formation of highly reactive hydroxyl radicals, which leads to membrane damage and denaturation of proteins.

This process leads to tissue damage and ultimately to significant morbidity and mortality.[2] Indeed, organ failure due to chronic iron body iron burden may represent the major cause of death in patients with different hematological diseases who receive blood transfusions regularly without appropriate chelation therapy.[3-5]

Within 1 to 2 years of initiation of regular blood transfusions, evidence of iron overload is manifest as elevated liver iron concentration (LIC) values and elevated serum ferritin (SF) levels. An increased risk

of complications and iron-induced cardiac disease is observed in thalassemia patients with LIC values levels 7-15 mg Fe/g dry weight (dw) and above 15 mg Fe/g dw, respectively.[6] Therefore, the liver plays a central role in iron regulation and remains the primary site of iron storage, with LIC being a strong surrogate of total body iron burden.

However, few studies have investigated the relationships between changes in LIC and changes in SF during iron chelation therapy, especially in a setting of patients with low-moderate iron overloading.[7]

MRI to evaluate LIC may be particularly useful for differentiating true from apparent non-responding patients on the basis of SF trends alone. R2-MRI is a robust and validated technique (FerriScan Resonance Health Limited, Claremont, WA, Australia) approved by the FDA for the assessment of LIC.

The LICNET (Liver Iron Cutino Network) was established by Foundation Franco e Piera Cutino of Palermo (Italy), and it is addressed to diagnostics of liver iron overloading by R2-MRI in patients with hematological disorders. Recently, characteristics of baseline MRI values were published.[8]

In this current work, we extend our evaluation to determine longitudinal changes overtime in a large number of patients who had an additional MRI performed as part of LICNET, in a real-life setting using different chelation regimen.

2 | PATIENTS AND METHODS

This was a cross-sectional study of patients with hematological disorders attending 9 Italian centers participating in the LICNET. The LICNET protocol was approved on December 4, 2012, by our Ethical Committee. The underlying diagnoses were regularly transfused thalassemia major (TM), thalassemia intermedia (TI), sickle cell disease (SCD), myelodysplastic syndrome (MDS), and Diamond-Blackfan anemia (DBA). Transfused' status was defined as receipt of ≥7 mL/kg/mo of packed red blood cells. The inclusion criteria for the cross-sectional analysis were as follows: (i) underlying diagnosis above described; (ii) determination of two R2-MRI scans performed as part of the network, for those patients presenting between February 2013 and December 2016; (iii) transfusion dependence; (iv) same chelation treatment, as single agent, combined or alternating treatment[9] over time at first (MRI1) and second MRI (MRI2) determination. The used R2-MRI protocol at the centers follows that of St Pierre et al[10]

Aside from LIC (in mg Fe/g dry weight [dw]) at respective MRIs, data were collected for patient demographics (age and sex), median duration days (range) between MRI1 and MRI2, type of iron chelation regimen at the time of MRI assessments, and laboratory values at the time of MRI scans, including hemoglobin, SF levels, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and serum creatinine levels. Hepatitis C status was determined by ribonucleic acid polymerase chain reaction (RNA-PCR).

2.1 | Statistical analysis

Descriptive analysis was provided as medians (range) or percentages. Three classes of risk, on the basis of LIC values (low < 7; intermediate 7-15, high > 15 mg Fe/g dw) were considered in the analysis. Changes in parameters overtime between MRI1 and MRI2 were made using *t* test and/or Wilcoxon test.

Correlations between changes in LIC and SF levels were made using Spearman's correlation coefficient. All *P* -values are two-sided with the level of significance set at <.05.

3 | RESULTS

3.1 | Patients' characteristics

A total of 130 patients were evaluated in this analysis, with a median age of 35 years (range: 6 to 78) and including 60 (46.2%) men.

A total of 32 (24.6%) patients were on DFO monotherapy, 29 (22.3%) on DFP monotherapy, 52 (40.0%) on DFX monotherapy, 10 (7.7%) on DFO + DFP combination, and 7 (5.4%) on other combination.

The underlying diagnoses were TM (n = 86, 66.2%), TI (n = 33, 25.4%), SCD (n = 6, 4.6%), MDS (n = 3, 2.3%), and DBA (n = 2, 1.5%). Overall, 16 (12.3%) patients were positive for hepatitis C virus by PCR-RNA.

The median duration between MRI1 and MRI2 was 483 days (range: 184 to 1076). Patients' characteristics according to chelation regimens are summarized in Table 1.

3.2 | Blood requirement changes

Pretransfusion hemoglobin level was stable between MRI1 and MRI2 (median change for all patients 0.0 g/dL, range: −1.5 to −1.8; *P* = .5), and the blood requirement at the two scans was almost similar (median change 2.0 mL/kg/y, range: −636.8 to −124.9; *P* = .172).

Table 2 summarizes pretransfusion hemoglobin level and blood requirement changes between MRI1 and MRI2 according to chelation regimen.

3.3 | Changes in iron measures

3.3.1 | Liver iron concentration

When all patients were considered irrespective of chelation regimen, LIC significantly decreased from MRI1 to MRI2 although at high variance (median change −0.8 mg Fe/g dw, range: −29.0 to 33.0; *P* = .011).

Median changes in LIC for individual chelation regimens are summarized in Table 3, with all regimens showing a decrease over time (highest for DFO + DFP combination, median change −2.2 mg Fe/g dw) while only the DFO group demonstrated statistical significance.

When LIC thresholds of clinical significant were considered (Figure 1), 7.7% of patients shifted from LIC values of high risk (>15 mg Fe/g dw) to an intermediate-risk category (LIC 7-15 mg Fe/g dw) while the proportion of patients in the low-risk category (LIC < 7 mg Fe/g dw) remained the same.

All chelation regimens showed a similar trend of high- to intermediate-risk category transition while the other combination group mainly showed transition from intermediate-to-low risk (Figure 1).

TABLE 1 Patients' characteristics

Parameter	All patients (n = 130)	DFO (n = 32)	DFP (n = 29)	DFX (n = 52)	DFO + DFP (n = 10)	Other combination (n = 7)
Median (range) age, (y)	35 (6-78)	37 (7-68)	37 (8-67)	34 (6-78)	34 (17-54)	33 (19-51)
Male, n (%)	60 (46.2)	19 (59.4)	14 (48.3)	17 (32.7)	5 (50.0)	5 (71.4)
Diagnosis, n (%)						
Thalassemia major	86 (66.2)	25 (78.1)	19 (65.5)	31 (59.6)	8 (80.0)	3 (42.9)
Thalassemia intermedia	33 (25.4)	5 (15.6)	7 (24.1)	17 (32.7)	2 (20.0)	2 (28.6)
Sickle cell disease	6 (4.6)	2 (6.3)	3 (10.3)	1 (1.9)	0 (0.0)	0 (0.0)
Myelodysplastic syndrome	3 (2.3)	0 (0.0)	0 (0.0)	3 (5.8)	0 (0.0)	0 (0.0)
Diamond-Blackfan anemia	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (28.6)
HCV PCR-RNA positive, n (%)	16 (12.3)	7 (21.9)	4 (13.8)	4 (7.7)	1 (10.0)	0 (0.0)
Median duration (range) between MRI1 and MRI2, (d)	483 (184-1076)	460 (251-807)	480 (184-809)	516 (238-981)	481 (352-1076)	522 (374-960)

DFO, deferoxamine; DFP, deferiprone; DFX, deferasirox; HCV, hepatitis C virus.

3.3.2 | Serum Ferritin level changes across underlying diseases

All chelation regimens except DFP monotherapy showed a decrease in SF level between MRI1 and MRI2 although at high variance (median change for all patients −63.5 ng/mL, range: −3524.0 to 4026.0, $P = .566$), while only DFO monotherapy showed a statistically significant decrease which was also of highest magnitude (median change −237.2 ng/mL, $P = .003$) (Table 3).

3.4 | Changes in laboratory measures

The median change in serum creatinine, ALT, and AST levels across all chelation regimens between MRI1 and MRI2 is summarized in Table 4.

Serum creatinine levels remained essentially unchanged, while liver enzyme levels remained the same or mildly decreased with none of the changes being statistically significant for any of the chelation regimens.

3.5 | Correlation between serum ferritin level and LIC

The change in SF levels and LIC between MRI1 and MRI2 correlated well when all patients were considered ($r = .409$, $P < .001$), but was mainly significant for monotherapies (Table 5).

4 | DISCUSSION

Our previous LICNET study demonstrated that around one-third of patients with hemoglobinopathy across a large network in Italy continue to have high LIC thresholds >7 mg Fe/g dw with around 15%-20% of patients having very high levels >15 mg Fe/g dw.[8] Interestingly, even a considerable proportion of patients with TI showed LIC thresholds >7 mg Fe/g dw both in transfused (37.3%) and in non-transfused (19.5%) cohort.[8] Transfused SCD patients showed LIC thresholds >7 mg Fe/g dw and >15 mg Fe/g dw in 20.6% and 17.6%, respectively.[8] Finally, although large trial on MDS, using deferasirox, and a single case-control study on determination of LIC in 31 patients with DBA have been published by means of noninvasive magnetic liver susceptometry with a superconductive quantum interference device (SQUID), no previous reports on LIC changes, determined as R2-MRI, during the real-life experience have been reported.[11,12]

This current work extends our previous evaluation to determine longitudinal changes overtime in a large number of patients who had an additional MRI performed as part of LICNET, in a real-life setting using different chelation regimen.

Overall patients, across all chelation regimens, showed a statistically significant difference in variation in LIC between MRI1 and MRI2 ($P = .011$, Table 3). Overall variation in LIC, during a period of 483 (184-1076) days, was −0.8 (−29.0-33.0) mg Fe/g dw. Instead, there was not statistically significant difference in pretransfusion Hb ($P = .5$) and in blood requirement (0.172) at MRI1 and MRI2 timing. Overall 7.7% of patients, across different chelation regimens and during a period of 483 (184-1076) days, moved from high-risk group (LIC > 15 mg Fe/g dw) to intermediate-risk group (LIC 7-15 mg Fe/g dw) with stabilization of iron overloading in patients in low-risk group at baseline (Figure 1). All chelation regimens were able to move LIC from high-risk group (LIC > 15 mg Fe/g dw) to intermediate-risk group (LIC 7-15 mg Fe/g dw) (Figure 1). In the other combination group, the patients moved from the intermediate-risk group (LIC 7-15 mg Fe/g dw) to the low-risk group (LIC < 7 mg Fe/g dw). However, the overall variation in SF level was not statistically significant ($P = .566$) (Table 3).

In the DFO group (32 patients), we observed a median change in LIC of 1.4 mg Fe/g dw (−14.8-8.1) (median LIC at MRI1, 4.1 mg Fe/g dw (0.5-43.0), at MRI2 2.6 mg Fe/g dw (0.6-43.0)) and a median

TABLE 2 Blood requirement changes

Parameter	All patients (n = 130)	DFO (n = 32)	DFP (n = 29)	DFX (n = 52)	DFO + DFP (n = 10)	Other combination (n = 7)
Median pretransfusion Hb (range) at MRI1, g/dL	9.3 (7.8-10.3)	9.6 (7.8-10.3)	9.2 (8.6-9.9)	9.3 (7.9-10.0)	9.2 (8.5-9.6)	8.9 (8.4-9.2)
Median pretransfusion Hb (range) at MRI2, g/dL	9.3 (7.8-10.8)	9.7 (8.0-10.5)	9.3 (8.0-10.8)	9.1 (7.8-10.0)	9.2 (8.5-9.6)	9.2 (8.8-9.5)
Median change in pretransfusion Hb (range), g/dL	0.0 (−1.5-1.8)	0.0 (−1.2-1.1)	0.1 (−0.5-1.8)	−0.1 (−1.5-1.0)	0.0 (−0.3-0.1)	0.3 (0.0-0.4)
P -value for change (Wilcoxon)	.500	.802	.028	.456	.705	.102
Median blood requirement (range) at MRI1, mL/kg/y	142.6 (15.4-774.9)	121.6 (50.0-774.0)	163.0 (58.0-341.9)	134.7 (15.4-678.1)	198.6 (67.0-758.8)	156.0 (86.0-249.0)
Median blood requirement (range) at MRI2, mL/kg/y	140.4 (11.0-337.7)	120.0 (11.0-298.0)	154.0 (37.0-255.0)	146.0 (24.0-337.7)	217.0 (71.0-288.4)	154.0 (119.0-249.4)
Median change in blood requirement (range), mL/kg/y	2.0 (−636.8-124.9)	−0.7 (−179.2-68.8)	3.0 (−304.9-40.0)	1.5 (−578.1-124.9)	5.3 (−636.8-44.0)	9.0 (−36.0-60.0)
P -value for change (Wilcoxon)	.172	.422	.668	.187	.110	.249

DFO, deferoxamine; DFP, deferiprone; DFX, deferasirox; Hb, hemoglobin.

TABLE 3 Changes in iron measures

Parameter	All patients (n = 130)	DFO (n = 32)	DFP (n = 29)	DFX (n = 52)	DFO + DFP (n = 10)	Other combination (n = 7)
Median LIC (range) at MRI1, mg Fe/g dw	5.2 (0.4-43.0)	4.1 (0.5-43.0)	10.7 (0.5-43.0)	4.0 (0.4-43.0)	7.4 (0.4-20.5)	9.7 (0.8-16.9)
Median LIC (range) at MRI2, mg Fe/g dw	5.0 (0.50-43.1)	2.6 (0.6-43.0)	10.1 (1.0-43.1)	4.2 (0.5-43.0)	7.4 (0.7-15.8)	9.6 (3.0-43.0)
Median change in LIC (range), mg Fe/g dw	−0.8 (−29.0-33.0)	−1.4 (−14.8-8.1)	−1.9 (−18.5-20.2)	−0.5 (−29.0-13.2)	−2.2 (−4.7-1.0)	−1.3 (−4.5-33.3)
P -value for change (Wilcoxon)	**.011**	**.002**	.545	.515	.074	1.000
Median SF (range) at MRI1, ng/mL	961.5 (121.0-9468.0)	815.0 (228.0-9468.0)	1200.0 (206.0-5774.0)	907.0 (121.0-5616.0)	958.0 (249.6-2500.0)	1258.0 (496.0-2417.0)
Median SF (range) at MRI2, ng/mL	926.0 (89.8-9800.0)	647.1 (143.0-5993.0)	1500.0 (100.0-9800.0)	920.0 (89.8-7000.0)	1181.0 (156.0-2663.0)	924.0 (434.0-4547.0)
Median change in SF (range), ng/mL	−63.5 (−3524.0-4026.0)	−237.2 (−3524.0-1224.0)	281.0 (−846.0-4026.0)	−36.0 (−278.0-3800.0)	−63.7 (−187.6-805.0)	−124.0 (−723.0-2130.0)
P -value for change (Wilcoxon)	.566	**.003**	.068	.721	.333	.237

DFO, deferoxamine; DFP, deferiprone; DFX, deferasirox; LIC, liver iron concentration; dw, dry weight; SF, serum ferritin.

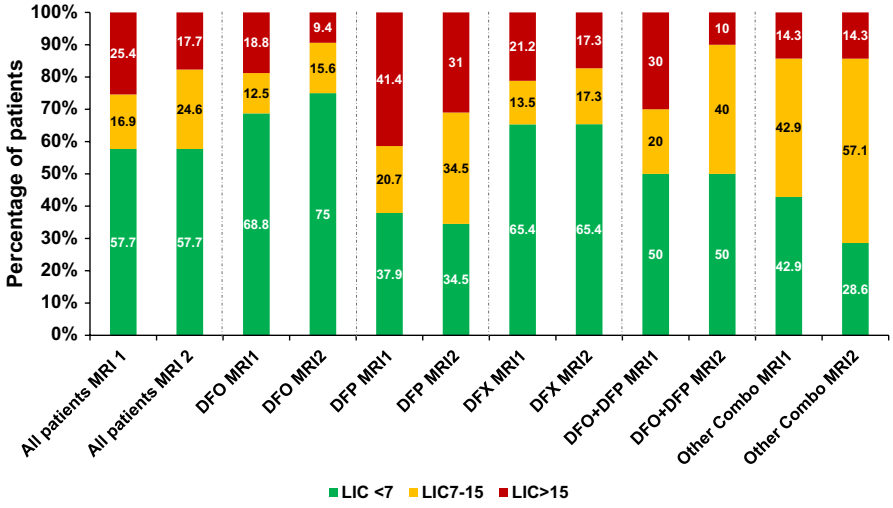

FIGURE 1 Change in LIC (liver iron concentration in mg Fe/g dry weight) categories between MRI1 and MRI2. DFO, deferoxamine; DFP, deferiprone; DFX, deferasirox

TABLE 4 Changes in laboratory measures

Parameter	All patients (n = 130)	DFO (n = 32)	DFP (n = 29)	DFX (n = 52)	DFO + DFP (n = 10)	Other combination (n = 7)
Median SCr (range) at MRI1, mg/dL	0.6 (0.1-1.1)	0.6 (0.2-1.0)	0.6 (0.3-1.1)	0.5 (0.1-1.1)	0.6 (0.4-1.0)	0.6 (0.4-0.8)
Median SCr (range) at MRI2, mg/dL	0.6 (0.2-1.3)	0.6 (0.2-1.1)	0.6 (0.3-1.1)	0.6 (0.2-1.3)	0.6 (0.5-0.9)	0.6 (0.3-0.8)
Median change in SCr (range), mg/dL	0.0 (−0.4-0.6)	0.0 (−0.4-0.4)	0.0 (−0.2-0.2)	0.0 (−0.3-0.6)	0.0 (−0.1-0.2)	0.1 (−0.1-0.3)
P -value for change (Wilcoxon)	.068	.331	.585	.153	.194	.480
Median ALT (range) at MRI1, IU/L	29.0 (8.0-185.0)	29.0 (13.0-149.0)	26.0 (13.0-79.0)	29.0 (8.0-185.0)	29.0 (13.0-95.0)	37.0 (18.0-185.0)
Median ALT (range) at MRI2, IU/L	24.0 (8.0-147.0)	21.0 (12.0-101.0)	24.0 (9.0-147.0)	25.5 (9.0-144.0)	25.5 (8.0-95.0)	44.0 (12.0-134.0)
Median change in ALT (range), IU/L	−2.0 (−156.0-116.0)	−3.0 (−115.0-22.0)	−4.0 (−41.0-87.0)	−2.0 (−156.0-99.0)	0.0 (−13.0-21.0)	−1.0 (−111.0-116.0)
P -value for change (Wilcoxon)	**.023**	.061	.658	.130	.726	.917
Median AST (range) at MRI1, IU/L	28.0 (11.0-115.0)	32.0 (13.0-115.0)	28.5 (14.0-59.0)	25.0 (11.0-79.0)	24.0 (18.0-84.0)	30.0 (24.0-52.0)
Median AST (range) at MRI2, IU/L	25.0 (12.0-105.0)	23.5 (15.0-105.0)	26.0 (14.0-72.0)	23.5 (12.0-96.0)	24.0 (13.0-87.0)	30.0 (19.0-52.0)
Median change in AST (range), IU/L	0.0 (−65.0-42.0)	−2.0 (−65.0-21.0)	1.0 (−30.0-38.0)	0.0 (−60.0-42.0)	0.0 (−0.9-6.0)	0.1 (−19.0-22.0)
P -value for change (Wilcoxon)	.890	.224	.432	.632	.623	.750

DFO, deferoxamine; DFP, deferiprone; DFX, deferasirox; SCr, serum creatinine; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

change in SF levels of 237.2 ng/mL (−3524.0-1224.0) (median SF at MRI 815.0 ng/mL (228.0-9468.0), at MRI2 647.1 ng/mL (143.0-5993.0)). In 2002, Maggio et al during randomized clinical trial on 144 TM assigned to deferiprone (75 mg/kg/d) (n = 71) or deferoxamine (50 mg/kg/d) (n = 73) for 1 year, showed a mean reduction in LIC, determined by liver biopsy of 0.350 ± 0.524 mg Fe/g dw and of SF levels of 232 ± 619 ng/mL.[13] Galanello et al[14] in 30 patients treated with DFO compared with 29 patients treated with DFO + DFP obtained a decrease in LIC of −0.239 ± 0.474 mg Fe/g dw determined by SQUID and in SF levels of 349 ± 573 ng/mL.

In the DFP group (29 patients), we observed a median change in LIC of 1.9 mg Fe/g dw (−18.5-20.2) (median LIC at MRI1 10.7 mg Fe/g dw (0.5-43.0), at MRI2 10.1 mg Fe/g dw (1.0-43.1)) and a slight increase in median change in SF of 281.0 ng/mL (−846.0-4026.0) (median SF at MRI1 1200 ng/mL (206.0-5774.0), at MRI2 1500 ng/mL (100.0-9800.0)). These data confirmed previous results about the

TABLE 5 Correlation between serum ferritin and liver iron concentration change between MRI1 and MRI2

Parameter	All patients (n = 130)	DFO (n = 32)	DFP (n = 29)	DFX (n = 52)	DFO + DFP (n = 10)	Other combination (n = 7)
Spearman's coefficient (rs)	0.409	0.405	0.471	0.407	0.370	0.286
P –value	<.001	.022	.023	.003	.293	.535

DFO, deferoxamine; DFP, deferiprone; DFX, deferasirox; LIC, liver iron concentration.

effect of DFP on the LIC in patients with TM. Indeed, Maggio et al[13] in 71 patients treated with DFP, obtained a mean reduction in LIC of 1.02 ± 3.5 mg Fe/g dw. The greater decreasing in LIC, in this DFP-treated group, could be due to the higher values of LIC, in this cohort of patients, at baseline. However, the SF response, in DFP group, was not associated with that of LIC.

The lack of association between SF response vs LIC was well addressed by Porter et al[15] In a post hoc analysis of the EPIC study, comparing SF levels vs LIC in 317 patients with transfusion-dependent thalassemia (TDT), they showed that SF response predicted LIC response in 80% of patients with TDT treated with DFX for 1 year. Thus, only 20% of patients with SF response did not respond in terms of LIC. By contrast, in patients without SF response 52% showed an LIC response and 48% did not. This has important implications for the management of patients, suggesting as a SF response is more likely to indicate a downward trend in LIC, whereas a lack of SF response is equally likely to indicate LIC decrease as no LIC decrease. Previously, Puliyel M et al[16] in a retrospective cohort study of 134 patients with transfusion-dependent anemia, followed over a period of up to 9 years, found similar data with an agreement between SF trends and LIC changes in only 74% of cases and with opposite direction change in SF level to that of LIC in 26% of cases.

In the DFX group (52 patients), the median change in LIC was 0.5 mg Fe/g dw (−29.0-13.2) (median LIC at MRI1 4 mg Fe/g dw (0.4-43.0), at MRI2 4.2 mg Fe/g dw (0.5-43.0)) and the median change in SF was 36 ng/mL (−278.0-3800.0) (median SF at MRI1 907 ng/mL (121.0-5616.0), at MRI2 920 ng/mL (89.8-7000.0)). The ESCALATOR study showed, in 233/237 enrolled patients who completed 1-year treatment, as DFX treatment gave a mean reduction in LIC of 3.4 mg Fe/g dw (Mean baseline LIC of 18.0 ± 9.1 mg Fe/g dw).[17] Even Cassinerio et al[18] showed, during 5-year study, a significant reduction in LIC (5.36 ± 3.58 mg/g dw at baseline vs 3.35 ± 2.68 mg/g dw at final evaluation, $P = .004$). In a retrospective analysis on 264 patients receiving doses of >30 mg/kg/d with a median exposure of 36 weeks, Taher et al[19] showed statistically significant median decrease in SF levels of 440 ng/mL ($P < .0001$) (with a median SF levels at predose escalation in pediatric and adult patients of 3843 and 3930 μg/L, respectively. Chang et al[20] showed, during 7 years of treatment with DFX, as the mean of SF levels decreased significantly by 2566 ng/mL ($P < .001$). The data of literature showed decrease in LIC and SF that are bigger than the ones reported in our study. However, the slight decrease in LIC and SF levels, in this DFX-treated group, could be due to the lower values of LIC and SF at baseline in comparison with those reported on literature. Instead, it is well known that significant decreases in SF and LIC are most common in patients with baseline values above 2500 μg/L and higher values of LIC.[1,21,22]

In the DFO + DFP group (10 patients), we observed a median change in LIC of 2.2 mg Fe/g dw (−4.7-1.0) (median LIC at MRI1, 7.4 mg Fe/g dw (0.4-20.5), at MRI2 7.4 mg Fe/g dw (0.7-15.8)) and a median change in SF levels of 63.7 ng/mL (−187.6-805.0) (median SF at MRI1 958 ng/mL (249.6-2500.0), at MRI2 1181 ng/mL (156.0-2663.0)). Galanello et al[14] on the 29 patients treated with DFO + DFO obtained a decrease in and LIC 0.065 ± 0.615 mg Fe/g liver and in SF levels of 248 ± 791 ng/mL. In 2009, Maggio et al showed the results of 5 years of alternating DFO + DFP treatment over 275 patients with a significant linear reduction over time of SF of 115. 3 ng/mL.[23]

The limit of this study is that it does not allow any comparisons among different chelation regimens. Indeed, being a cross-sectional study with different sample size and baseline LIC values among different cohorts of chelation regimens during real life, this does not lead to reach effectiveness conclusions about single chelation regimens.

In conclusion, these findings suggest as longitudinal variation in the LIC is possible, during the real life, across all chelation regimens Moreover, it confirms as SF levels not always can be used for estimating changes in LIC. However, because the increased risk of complications is related to LIC values, direct determination of LIC in this setting of patients should be pursued.[6]

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