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SCIENTIFIC INVESTIGATIONS

Efficacy and safety of intravenous iron in patients with restless legs syndrome with normal serum ferritin levels: a stratified subanalysis

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Study Objectives: Restless legs syndrome (RLS) has long been associated with iron deficiency. Current clinical guidelines recommend intravenous (IV) iron therapy for patients with serum ferritin levels ≤ 100 μg/L, but the effectiveness and safety of IV iron in patients with ferritin levels between 100 and 300 μg/L have not been well established. The aim of this study is to assess the efficacy and safety of IV iron in patients with RLS with serum ferritin levels both below and above the 100 μg/L threshold, hypothesizing no significant differences in therapeutic response between these groups.

Methods: We conducted a longitudinal retrospective analysis of 58 patients with RLS treated with 1,000 mg of ferric carboxymaltose, with baseline serum ferritin concentrations < 300 μg/L. Patients were divided into 2 groups: group A (serum ferritin < 100 μg/L) and group B (serum ferritin 100–300 μg/L). We compared changes in symptom severity (International Restless Legs Syndrome Severity Scale), substantia nigra iron deposits (substantia nigra echogenicity index), and systemic iron parameters.

Results: Both groups showed similar improvements in International Restless Legs Syndrome Severity Scale scores and substantia nigra echogenicity index. Serum ferritin increased significantly in group B posttreatment, while no major differences were observed in transferrin saturation or serum transferrin levels between the 2 groups. Regarding risk of iron overload, only 2 patients (group B) showed a transferrin saturation > 45%. No harm resulted to either patient, with no hepatic dysfunction observed.

Conclusions: IV iron therapy is effective in patients with RLS without hepatic iron overload with serum ferritin levels ranging from 100–300 μg/L. These findings challenge current guidelines and suggest that IV iron could be considered for a broader range of patients with RLS.

Keywords: restless legs syndrome, Willis Ekbom disease, iron replacement therapy, ferric carboxymaltose

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Intravenous iron therapy is an established treatment for patients with restless legs syndrome and serum ferritin < 100 μg/L. However, its effectiveness and safety in patients with serum ferritin between 100 and 300 μg/L remain unclear. This study evaluates whether intravenous iron is similarly beneficial in this population without resultant systemic iron overload.

Study Impact: This stratified subanalysis demonstrates that intravenous ferric carboxymaltose significantly improves restless legs syndrome symptoms and substantia nigra echogenicity in patients regardless of whether serum ferritin is below or above 100 μg/L (up to 300 μg/L). There was no evidence for hepatic iron overload. These findings suggest that current ferritin cutoffs may be overly restrictive and support broader use of intravenous iron in restless legs syndrome management.

INTRODUCTION

Since the clinical description of restless legs syndrome (RLS) in 1945, a relationship with iron deficiency has been recognized.[1] First reports of a therapeutic effect of intravenous (IV) iron dates back to 1953, and since then numerous studies have replicated these findings.[2,3] Furthermore, a number of investigations have suggested that brain iron deficiency plays a central role in the pathophysiology of RLS although the exact mechanisms have not been fully delineated. Despite an assumption of reduced brain iron stores, most patients with RLS have serum measures of peripheral iron stores within normal limits.[4–6] However, as there are no universally accepted methods for measuring central nervous system iron stores in patients with RLS in clinical practice, clinicians treating patients with RLS have utilized peripheral measurements of iron status to determine the need for iron supplementation. In particular, serum ferritin concentrations have been used together with percentage transferrin saturation (TSAT) to try predict efficacy and to avoid systemic iron overload.[7,8]

In 2018, the International Restless Legs Syndrome Study Group published clinical guidelines for the use of iron therapy in RLS based on expert consensus.[3] The guideline recommended that IV iron be considered if the TSAT was < 45% and serum ferritin ≤ 100 μg/L. This serum ferritin cutoff was based on 2 positive controlled trials of IV ferric carboxymaltose (FCM).[7,8] Although the inclusion criteria for both trials allowed for serum ferritin ≤ 300 μg/L, most participants had in practice much lower baseline ferritin levels. In the first trial, all participants who received FCM had baseline levels ≤ 91.1 μg/L.

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In the second trial, baseline levels were 53.5 ± 41.8 μg/L and communication with the authors revealed that only 6/32 participants had levels > 100 μg/L; 3 responded to IV iron and 3 did not.[8] Based on this data and the lack of experience with higher ferritin levels, the task force reached a consensus that initial treatment with IV iron should be limited to patients with serum ferritin levels ≤ 100 μg/L. However, they did endorse repeat administration of IV iron after 12 weeks for recurrence of symptoms if at that point serum ferritin was still ≤ 300 μg/L and TSAT < 45%.[3]

Several trials of IV iron have been published, summarized in **Table 1**. However, only one of these studies reported the number of participants with serum ferritin concentrations > 100 μg/L or provided subgroup analyses based on serum ferritin values. The study by Park et al[9] reported that 27/164 patients had serum ferritin concentrations in the 100–300 μg/L range. Of these patients, 55.6% were classified as responders (≥ 40% reduction in the IRLS from baseline to 4 weeks after FCM treatment) and 40.7% as remitters (posttreatment IRLS score ≤ 10),[10] compared to 65.9% and 46.9% in the overall group. Likely due to this limited data, recent guidelines for RLS management published by the American Academy of Sleep Medicine decided to maintain the recommendation that IV iron therapy be considered for patients with serum ferritin levels 75–100 μg/L.[11]

In 2020, we reported the outcomes of a series of 58 patients treated with IV FCM for patients with RLS with baseline serum ferritin concentrations < 300 μg/L, demonstrating safety and efficacy.[12] However, we did not perform a stratified analysis of the treatment outcome between those participants with serum ferritin below 100 μg/L and those with higher levels. We now report a stratified subanalysis of the data in our prior study, comparing outcomes of patients with lower and higher serum ferritin concentrations. Our hypothesis was that there would be no difference in efficacy of IV FCM in the 2 groups and that iron could be administered in both groups without systemic iron overload.

METHODS

Study design and patients

We performed a longitudinal retrospective study, in which 58 patients diagnosed with RLS, over the age of 18 years, and candidates for IV iron according to the International Restless Legs Syndrome Study Group guidelines (serum ferritin < 300 μg/L and TSAT < 45%) were included. Patients previously treated with IV iron, having received a blood transfusion or suffering known alteration in iron metabolism were excluded.

Baseline and follow-up visits included systemic iron parameters hemoglobin, serum ferritin, iron, transferrin, total iron-binding capacity and TSAT, severity of symptoms (IRLS scale) and substantia nigra echogenicity index (SNEI). SNEI, a value obtained by measuring substantia nigra area in the mesencephalon by means of transcranial sonography, serves as a marker of iron deposits in this location. Information regarding sex, age and presence of any inflammatory/chronic condition was also collected. After the baseline visit, the 58 patients received 1,000 mg of FCM (2 500-mg doses, 5 days apart). Other medications for RLS were modified during the follow-up depending on severity of symptoms.

In the new subanalysis, 2 subgroups were defined according to basal serum ferritin concentration: group A (basal serum ferritin < 100 μg/L) and group B (basal serum ferritin 100–300 μg/L).

Outcomes

The main outcomes were to evaluate differences in efficacy and safety of IV iron depending on basal serum ferritin (above or below 100 μg/L). The secondary outcome was to evaluate differences in the sample characteristics between the subgroups A and B (sex, age, RLS severity of symptoms, and presence of inflammatory/chronic condition).

Statistical analysis

A descriptive analysis was performed. For quantitative variables, the mean was used as a measure of central tendency and the standard deviation as a measure of dispersion (mean ± standard deviation). Baseline comparison between group A and group B regarding sex, age, baseline serum ferritin, presence of any chronic/inflammatory condition, baseline IRLS, and baseline SNEI was performed by mean of a paired-*t* test for quantitative variables or a Chi-square test for categorical variables. A paired-*t* test was used for comparison between group A and group B of IRLS and SNEI changes at follow-up.

Ethics

All individuals read, understood, and signed informed consent to participate in the original study and allowed their data to be used for our study. The subanalyses reported in his paper did not require acquisition of any new additional data.

RESULTS

Population characteristics (Table 2)

Of the 58 individuals, 36 had basal serum ferritin < 100 μg/L (group A) and 22 had serum ferritin 100–300 μg/L (group B). No significant differences between the 2 groups existed regarding sex, age, baseline IRLS, or baseline SNEI. The mean values of baseline serum ferritin was 53.44 ± 4.66 μg/L in group A and 172.38 ± 12.54 μg/L in group B ($P < .001$). The presence of any chronic/inflammatory condition was 8.34% in group A and 22.7% in group B ($P = .123$).

Changes in IRLS and SNEI following treatment (Table 3)

Among the total sample (n = 58), mean IRLS scores improved with treatment (mean of 6.5 points at first visit and 9.1 points at second visit, performed 88 ± 42 and 199 ± 120 days after receiving the treatment. Group A and group B obtained similar results, with comparable results in baseline and follow-up IRLS score, and no significant differences observed between the 2 groups. Regarding SNEI, both groups had a mean value below the defined cut-off point to define hypoechogenicity of substantia nigra (< 0.21 cm^2)[13] (**Table 3**). Group A showed lower baseline

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Table 1—Summary of the main investigations conducted using FCM vs placebo.

Study	Arms of Treatment	Serum Ferritin Levels at Baseline (Inclusion Criteria)	Treatment Receiving	Mean Basal Serum Ferritin (μg/L) in Treated with FCM	Information Regarding-Treated Patients with Basal Serum Ferritin > 100 μg/L	Primary Endpoint	Result (Change in IRLS)	*P*
Trenkwalder et al (2017)[17]	59 FCM/51 placebo	Serum ferritin < 75 μg/L, or TSAT < 20% + serum ferritin < 300 μg/L	1,000 mg IV FCM vs placebo	41.93 ± 34.55	N/A	Change in IRLS (week 4)	FCM group: −9.6 ± 1.4 vs placebo group: −5.0 ± 1.5	.021
Allen et al (2011)[7]	24 FCM/19 placebo	Serum ferritin ≤ 300 μg/L or TSAT < 45% and hemoglobin within normal range	Total dose of 1,000 mg of FCM (500 mg + 500 mg 5 days apart)	28.1 ± 22.9 in females and 70.0 ± 22.8 in males	N/A	Change in IRLS and CGI-I (day 28)	FCM group 8.9 ± 8.52 vs placebo group 4.0 ± 6.11	.040
Cho et al (2016)[14]	32 FCM/32 placebo	Serum ferritin ≤ 300 μg/L, TSAT < 45% and hemoglobin > 12 μg/dL	1,000 mg IV FCM vs placebo	53.5 ± 41.8	N/A	Change in IRLS and VAS (week 6)	FCM group −11.9 ± 8.04 vs placebo group −7.88 ± 5.89	.03
Cho et al (2018)[18]	32 FCM/32 placebo	Serum ferritin < 300 μg/L, TSAT < 45% and hemoglobin > 12 μg/dL	500 mg IV FCM vs placebo	50.7 ± 40.8	N/A	Change in IRLS and VAS (week 6)	FCM group −8.3 ± 7.5 vs placebo group −4.8 ± 8.7	.100
Earley et al (2024)[19]	107 FCM/101 placebo	Serum ferritin ≤ 300 μg/L or TSAT < 45% and hemoglobin within normal range	Different FCM doses (750 mg [1]/1,125 mg [1]/1,500 mg [93]/2,250 [1]/3,000 [11]) vs placebo	64.8 ± 51.2	N/A	Change in IRLS (day 42)	FCM group −8.0 (CI 95%: −9.5, −6.4) vs placebo group −4.8 (CI 95%: −6.4, −3.1)	.2987
Cho et al (2013)[8]	25 LMW IV iron dextran	Serum ferritin < 300 μg/L	1 g LMW IV iron dextran	39.6 ± 36.0	N/A	Change in ferritin CSF levels (week 3)	N/A	N/A
Park et al (2020)[9]	164 FCM	Serum ferritin ≤ 300 μg/L or TSAT ≤ 45%	1 g IV FCM	60.6 ± 48.5	27/164 had serum ferritin 100–300 μg/L	Change in IRLS	N/A	N/A

CI = confidence interval, FCM = ferric carboxymaltose, IRLS = International Restless Legs Syndrome Severity Scale, IV = intravenous, LMW = lower molecular weight, N/A = nonavailable, VAS = visual analog of severity, TSAT = transferrin saturation.

Table 2—Population characteristics.

	Total Sample (n = 58)	"A" Group Baseline Serum Ferritin < 100 μg/L (n = 36)	"B" Group Baseline Serum Ferritin 100–300 μg/L (n = 22)	*P*
Baseline serum ferritin mean ± SD (μg/L)	98.55 ± 71.09	53.44 ± 4.66	172.38 ± 12.54	.0001
Sex (F:M)	28:30	20:16	8:14	.343
Age (years)	56.24 ± 15.4	55.94 ± 16.31	56.73 ± 14.14	.8529
Chronic inflammatory condition	8.62%	3/36 (8.34%)	5/22 (22.7%)	.123
Baseline IRLS	27.63 ± 7.67	27.35 ± 8.99	28.3 ± 4.16	.75
Baseline SNEI (cm^2)	0.193 ± 0.059	0.185 ± 0.041	0.206 ± 0.079	.2418

F = female, IRLS = International Restless Legs Syndrome Severity Scale, M = male, SD = standard deviation, SNEI = substantia nigral echogenicity index.

SNEI and had a statistically significant increase at follow up (baseline 0.184 ± 0.037, first visit 0.21 ± 0.049 cm^2 (P = .0072); second visit 0.197 ± 0.031 cm^2 (P = .0142). while there were no significant increase in group B. However, differences between the groups were not statistically significant at any time point. **Figure 1** summarizes the changes in IRLS and SNEI by group mean during the follow-up period.

Changes of systemic iron parameters

Data regarding serum ferritin, TSAT, and serum transferrin at baseline and in the follow-up visits are included in **Table 4**. Serum ferritin was significantly higher in group B compared to group A during the follow-up period. In contrast, no statistically significant differences between group A and group B were observed on serum TSAT. Baseline differences between both groups' mean serum transferrin values narrowed after iron administration.

Risk of iron overload

Two out of the 58 patients showed a persistent TSAT value > 45% on 2 consecutive measurements and were considered to be at a potentially higher risk for iron overload. These 2 individuals had a basal serum ferritin between 100 and 300 μg/L (group B). Hence, the potential risk of iron overload in group A was 0/36 (0%) vs 2/22 (9.09%) in group B (P = .07).

Further follow-up 15 months following infusion revealed that the TSAT in the first patient normalized to 38%. In the second patient, the TSAT was still raised > 45% 8.8 months after infusion and the patient was shown to be heterozygous for the H63D mutation. In both cases transaminase levels always remained within normal limits.

DISCUSSION

The present investigation aimed to explore differences in efficacy and safety of IV iron in RLS depending on baseline serum ferritin. Baseline sample characteristics were similar between group A and group B for most clinical and laboratory data, except for baseline serum ferritin and serum transferrin. As expected, the presence of chronic or inflammatory conditions were more frequent among group B patients. Serum ferritin is a nonspecific marker of inflammation and therefore its levels may be elevated without indicating higher systemic iron. For this reason, it is always mandatory to assess other systemic iron parameters unaffected by inflammation, such as TSAT, to

Table 3—Evolution of severity of symptoms (IRLS) and SNEI.

	Total Sample (n = 58)	"A" Group Baseline Serum Ferritin < 100 μg/L (n = 36)	"B" Group Baseline Serum Ferritin 100–300 μg/L (n = 22)	*P*
IRLS				
Baseline IRLS	27.64 ± 7.8	27.32 ± 9.21	28.27 ± 3.95	.7459
First evaluation IRLS	21.1 ± 8.3	21.39 ± 9.59	20.59 ± 5.79	.7564
Second evaluation IRLS	18.58 ± 7.42	18.4 ± 7.53	18.85 ± 7.42	.8691
SNEI				
Baseline SNEI	0.193 ± 0.058	0.184 ± 0.037	0.206 ± 0.079	.2418
First evaluation SNEI	0.206 ± 0.472	0.21 ± 0.049	0.202 ± 0.044	.6908
Second evaluation SNEI	0.200 ± 0.0294	0.197 ± 0.031	0.204 ± 0.029	.6126

IRLS = International Restless Legs Syndrome Severity Scale, SNEI = substantia nigral echogenicity index.

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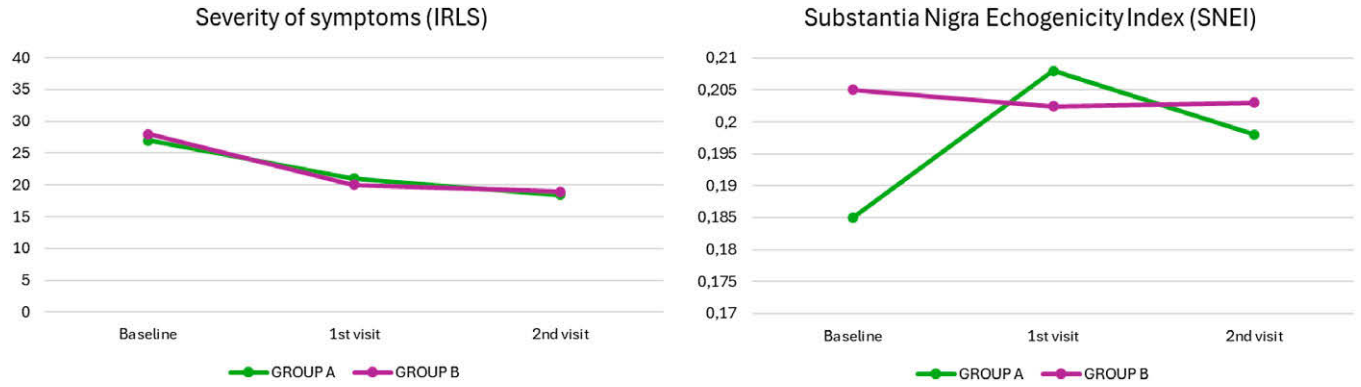
Figure 1—Evolution of the means of IRLS and SNEI.



IRLS = International Restless Legs Syndrome Severity Scale, SNEI = substantia nigral echogenicity index.

determine whether systemic iron stores are high. Although serum ferritin remained higher in group B throughout the follow-up period, the evolution of all other systemic iron markers remained almost identical in both groups, indicating that serum ferritin values alone do not accurately reflect peripheral iron status in RLS. Furthermore, serum transferrin rapidly decreased after IV iron administration in both groups A and B, reaching similar values in the first and second visit (see **Figure 2**). The primary function of serum transferrin is to bind iron in the bloodstream and transport it to various tissues. Physiologically, when iron levels decrease, serum transferrin increases to enhance iron uptake. Conversely, when iron levels rise, serum transferrin decreases. The observed decrease in serum transferrin after IV iron provides evidence that RLS is not associated with disturbances in systemic iron metabolism.

Regarding the clinical effectiveness of IV iron in RLS, patients with basal serum ferritin > 100 µg/L showed equal improvement in IRLS compared to those with serum ferritin ≤ 100 µg/L. As previously demonstrated, patients with RLS without evidence for systemic iron deficiency benefit from iron replacement therapy,[14] and clinical benefit does not seem to depend on baseline or short-term follow-up serum ferritin values. Therefore, based on efficacy, it would seem reasonable to consider intravenous iron therapy for all patients with moderate to severe RLS with serum ferritin concentration less than 300 µg/L. Interestingly, hypoechogenicity of the substantia nigra, quantified by the SNEI, was observed in both groups. An increase in SNEI was only observed in group A individuals, despite clinical improvement in both groups. Further investigations are needed to clarify the conditions under which this

Table 4—Evolution of systemic iron parameters.

	Total Sample (n = 58)	"A" Group Baseline Serum Ferritin < 100 µg/L (n = 36)	"B" Group Baseline Serum Ferritin 100–300 µg/L (n = 22)	*P*
Serum ferritin				
Baseline	98.55 ± 71.72	51.96 ± 23.49	174.79 ± 56.83	.0001
First evaluation	339.68 ± 148.26	271.71 ± 104.45	450.91 ± 143.53	.0001
Second evaluation	296.61 ± 120.74	240.58 ± 102.91	385.60 ± 90.87	.0001
TSAT				
Baseline	27.17 ± 8.17	26.63 ± 8.5	28.1 ± 7.68	.5275
First evaluation	36.38 ± 9.87	37.34 ± 9.76	34.8 ± 10.1	.3691
Second evaluation	34.06 ± 14.26	33.75 ± 10.48	34.56 ± 10.47	.86
Serum transferrin				
Baseline	258.66 ± 5.64	267.32 ± 42.56	244.07 ± 32.08	.0451
First evaluation	229.16 ± 40.38	229.49 ± 43.64	228.53 ± 34.56	.9361
Second evaluation	231.81 ± 36.43	235.15 ± 34.03	225.79 ± 40.93	.4320

TSAT = transferrin saturation.

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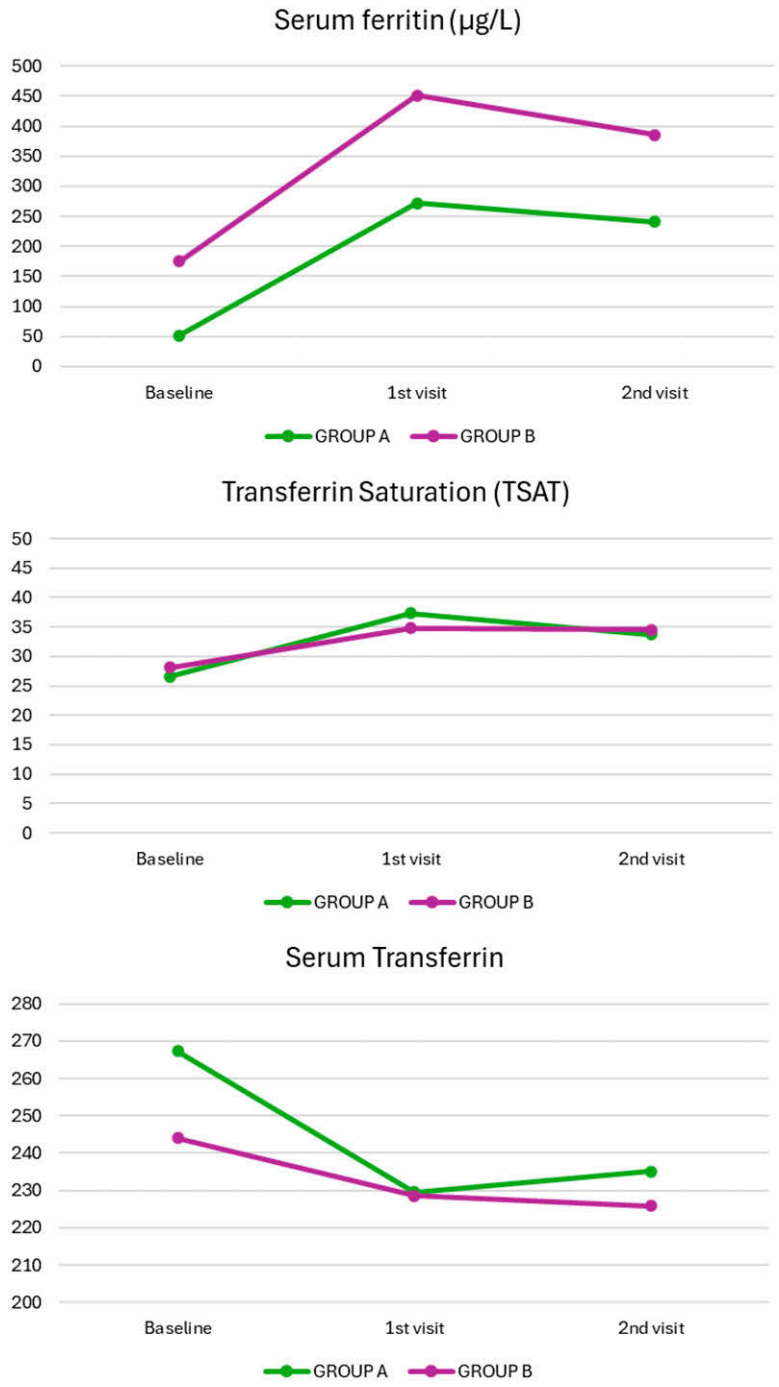
Figure 2—Evolution of systemic iron parameters.



TSAT = transferrin saturation.

biomarker may serve as a predictor of clinical response to IV iron in RLS, as has been observed in a previous study.[15]

To date, no formulation of IV iron has been approved by regulatory bodies for RLS. Safety is still the most common reason for caution with the use of iron replacement therapy in RLS, with risk of producing systemic iron overload being the major concern. However, patients with RLS have apparently unaltered peripheral iron metabolism, with signs of a physiological response to IV iron, as can be observed by the reduction in serum transferrin after treatment and this homeostatic response probably serves to prevent iron overload. Our study demonstrates that the risk is low, being only slightly higher when serum ferritin is between 100 and 300 µg/L (group B). Even in the few patients with TSAT greater than 45% at follow-up, the clinical course was favorable, without evidence for hepatic dysfunction. If RLS recurs after a successful response to the first infusion, it is obligatory to recheck TSAT to be certain it has not increased > 45%. If this occurs, a genetic test for

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hemochromatosis should be offered and further iron infusions deferred. Iron overload is the key feature of hemochromatosis. However, several cases of RLS and hemochromatosis have been published, indicating that both conditions may coexist.[16] But even if patients heterozygous for the hemochromatosis mutation are undetected, the risk of harm from single infusions of intravenous iron seems to be low.

The main limitation of our investigation is that it is an observational real-world experience, hence follow-up visits were not homogeneous. Also, patients remained on medications for RLS with doses being reduced whenever intravenous iron therapy was successful in improving symptoms.

CONCLUSIONS

The role of iron therapy in RLS has been changing over time with growing evidence about the pivotal role of brain iron in RLS pathophysiology. With increasing awareness about serious side effects with the use of certain RLS therapies, such as augmentation with dopamine agonists, iron therapy should be considered a first line treatment for RLS. Extending a recent practice guideline,[11] our study suggests that intravenous iron therapy can be effectively used without systemic iron overload in patients with moderate or severe RLS with serum ferritin in the range of 100–300 μg/L and TSAT < 45%. It is also important to remember that the purpose of iron treatment in RLS is to increase central nervous system iron. Therefore, better understanding of the mechanisms involved, including further investigations of the role of SNEI and other neuroimaging techniques that can be used in clinical practice to measure basal ganglia iron, is an important future priority.

ABBREVIATIONS

FCM, ferric carboxymaltose
IV, intravenous
RLS, restless legs syndrome
SNEI, substantia nigra echogenicity index
TSAT, transferrin saturation

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DISCLOSURE STATEMENT

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