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Original Article

Clinical efficacy and safety of IV ferric carboxymaltose (FCM) treatment of RLS: A multi-centred, placebo-controlled preliminary clinical trial

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ABSTRACT

Objective: Intravenous (IV) iron has been used as a treatment to reduce Restless Legs Syndrome (RLS) symptoms, but two double-blinded trials of a frequently prescribed IV iron formulation, iron sucrose, failed to show lasting efficacy. This study evaluates efficacy and safety of a new IV iron formulation (ferric carboxymaltose, FCM) with molecular properties that may make iron more available for uptake to the brain than iron sucrose does.

Methods: In this 28-day, multi-centre, randomised, placebo-controlled trial 46 RLS patients were discontinued from all RLS treatment. Twenty-four received 500 mg FCM in two doses 5 days apart and 22 received a matching placebo. At day 28, those on placebo were given a single 1000 mg IV FCM and those not responding to initial treatment were given a third dose of 500 mg FCM. Patients were followed up for 24 weeks or until needing added RLS treatment.

Results: FCM significantly improved primary and secondary outcomes compared to placebo: International Restless Legs Syndrome study group severity scale (IRLS) average (SD) decrease of 8.9 (8.52) versus 4.0 (6.11), $p = 0.040$; Clinical Global Inventory of Change (CGI-1) very much or much improved 48.3% versus 14.3%, $p = 0.004$. Quality of life was also significantly improved. Of the 24 with initial iron treatment 45% responded and 29% remitted (IRLS $\leqslant$ 10) at day 28, and 25% continued free of other RLS medications at 24 weeks after treatment. The single 1000 mg dose on day 28 produced the same degree of treatment response as the divided dose, but the added 500 mg dose for those not responding to the initial treatment showed little benefit. There were no significant adverse events.

Conclusions: IV FCM provided a safe and effective treatment for RLS that lasted for at least 24 weeks for some patients. Larger studies are needed to confirm these results.

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1. Introduction

Ever since the appreciation of the close relationship between low iron status and Restless Legs Syndrome (RLS) [1] there has been interest in using IV iron treatments. This approach might not only reduce RLS symptoms, but also do so by addressing an underlying pathology in RLS. Nordlander pioneered this approach, reporting almost complete remission of RLS in most patients treated with repeated doses of IV iron dextran (total dose of about 1000 mg) [2]. Earley et al. [3] reported that a single dose of 1000-mg IV iron dextran produced complete symptom relief lasting 2 to more than 48 months for 6 out of the 10 patients treated. Neither of these studies used a placebo comparison. A placebo-controlled treatment trial of 1000-mg iron sucrose given as one infusion, however, failed to show any similar dramatic treatment responses [4]. By contrast, another placebo-controlled trial of IV iron sucrose given in repeated doses to RLS patients with low serum ferritin showed significant but very short-duration treatment benefits [5]. These studies raise three possibilities. First, the iron formulation may be important for producing treatment benefit. The longer-acting iron dextran with its slower release of iron may be more effective for improving brain iron status than the shorter-acting iron sucrose. Second, repeated small doses may be

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more effective than one large dose. Third, the prior treatment successes may have largely been placebo effect with the exception that IV iron offers some limited benefit to those with low serum ferritin ($\leqslant$45 mcg l^{-1}).

The iron dextran used in the prior studies had a significant risk of serious anaphylaxis/anaphylactoid reactions that have led to death [6]. The iron sucrose and iron gluconate formulations do not have a significant risk of anaphylaxis because they use carbohydrate moieties other than dextran. Both, however, are characterised by less stable binding of the iron to their respective carbohydrate moieties and, therefore, have to be given by slow infusion or in several small doses. This property complicates the administration of a dose as large as 1000 mg [7]. The newer iron formulation ferric caboxymaltose (FCM) has been approved for parental iron replacement for treatment of iron deficiency in Europe. Similar to iron dextran, it has the advantage of slower dissociation of iron from the complex than iron sucrose, but without any indication of problems with anaphylaxis. It has been shown to be well tolerated for treatment of iron deficiency [8,9] and provides an option of a potentially safer IV iron treatment for RLS.

This study was designed primarily to evaluate the safety and efficacy of IV FCM for RLS and persistence of treatment benefits over 24 weeks. The study design also explored two important considerations for IV iron treatment, that is, the benefits of repeated multiple doses versus a single dose and of increasing the dose for those who do not respond to the first fixed dose.

2. Methods

2.1. Study design

This study was approved by the institutional review boards of each participating centre. This was a double-blinded, multi-centre, randomised, parallel-group, placebo-controlled study that compared the safety and efficacy of FCM to placebo in subjects with moderate-to-severe RLS (Fig. 1). The study had two efficacy observational periods and one follow-up period. Period 1 (day 0–day 28) was the primary efficacy observation period. Eligible subjects were randomised in a 1:1 ratio to group A or group B on day 0. Group A subjects received a 500-mg double blinded intravenous (IV) dose of FCM on day 0 and day 5. Group B subjects received a double-blinded IV solution of placebo on day 0 and day 5. All subjects were to return to the clinic on days 14 and 28 (2 weeks and 4 weeks after the initiation of study drug treatment on day 0) for efficacy and safety evaluations. Period 2 provided the two exploratory studies of the effects of: (1) a single FCM dose of 15 mg kg^{-1} or 1 000 mg, whichever was less for those on placebo in period 1 and (2) an added 500-mg dose of FCM for those who had an initial FCM treatment in phase 1 but at the end of that period met the criteria for an initial FCM dose, that is, International Restless Legs Syndrome study group severity scale (IRLS) $\geqslant$15 and serum ferritin $\leqslant$300 mcg l^{-1}. Period 2 started on day 28 after efficacy data were collected, group B subjects (those who received placebo in period 1) with a day 23 ferritin $\leqslant$300 ng ml^{-1} received a double-blinded dose of 15 mg kg^{-1} (maximum 1000 mg) of FCM. Group A subjects (those who received two doses of FCM, 500 mg in period 1) with a day 28 IRLS Rating Scale $\geqslant$15 and a day 23 ferritin $\leqslant$300 ng ml^{-1} received an additional (third) double-blinded dose of 500 mg of FCM. The remaining group A and B subjects received a double-blinded IV solution of placebo. Subjects were to return to the clinic on days 42 and 56 (2 weeks and 4 weeks after the study drug treatment on day 28) for efficacy and safety evaluations. Efficacy data collected on day 28 before treatment served as the baseline for this period. After day 56, subjects entered the follow-up (period 3), during which they returned to the clinic every 4 weeks for efficacy and safety evaluations until relapse (defined as requiring intervention for treatment of RLS due to lack of efficacy) or reaching day 168. During this follow-up period, all subjects were to have ferritin drawn every 4 weeks (not exceeding day 168) until the subject's ferritin returned to normal levels or within 30% of the subject's baseline value, if the baseline value exceeded the laboratory's maximum normal range value. Response duration to the treatment was defined as the period of time from the IV iron until the patient and/or investigator decided the RLS symptoms had returned with sufficient severity to require starting a medication.

This report focusses on the clinical response during the standard parallel group study in period 1. The results from periods 2 and 3 are presented as exploratory evaluations with some limited *post hoc* statistical analyses.

2.2. Outcome measures

This study used the clinical measures that have become accepted as the standards for large clinical trials of RLS treatment efficacy [10–13], that is, the IRLS and the Clinical Global Inventory of Change (CGI-1). Additional subjective outcome measures included the self-report patient global rating of change (PGI-1), the medical outcome study (MOS) sleep scale [14], and the RLS Quality of life scale (RLS-QoL) [15] which have also been used in most clinical trials of RLS. The patient completed Fatigue Severity Scale (FSS) was also used [16,17].

The actigraph (PAM-RL, Phillips-Respironics) was used to evaluate treatment effects on the motor sign of RLS, the periodic leg movements during the sleep period (PLMS) [18]. The PAM-RL detects the PLMS occurring while the patient is lying down during

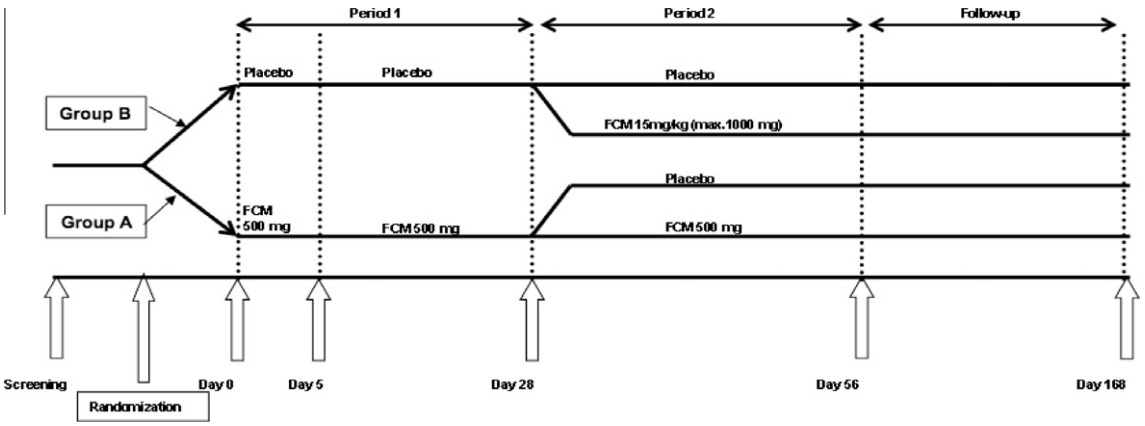

Fig. 1. Overall study design.

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