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Research Article

Novel Therapeutic Approach for the Treatment of Iron Anemia in Cardiovascular Diseases

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Abstract

The prevalence of iron deficiency reaches 30–50% in patients with stable chronic heart failure (HF) and is recognized as a major cause of anemia in this group, irrespective of sex, ethnicity, or left ventricular ejection fraction. Conventionally oral treatment based on classic iron salts are poor effective because of very high side effects and poor bioavailability reaching to no therapeutic response and very low patient compliance. The aim of the present study was to evaluate the efficacy and safety of Emoglofer® oral administration in patients with anemia deriving from heart failure or hypertensive heart disease considering a chronic administration regimen with two control time points (after three and six months of administration) monitoring the most important and standard iron metabolism parameters associated to iron anaemia (ferritin, sideremia, hemoglobin and hematocrit). All the parameters were already improved at T3 and, after six months of Emoglofer® administration, a further increase in serum levels of hemoglobin, ferritin and sideremia was observed as well as the hematocrit was found to be within the recommended values. The high therapeutic efficacy and the absence of typical gastro-intestinal side effects of Emoglofer® are due to the patented iron formulation (Phosphosome® iron) able to guarantee gastro-resistance and an optimum absorption profile in the intestine trough different mechanisms. The present study suggests that Emoglofer® oral administration is safe and is able to increase hemoglobin, ferritin, sideremia and hematocrit after three and six months from oral administration; more consistent controlled clinical trials should be conducted in order to deeply investigate the effect on anaemia correlated to cardiovascular diseases.

Keywords: Iron supplementation, Heart failure, Cardio-vascular diseases, Ferritin

Introduction

Iron Deficiency (ID) is defined as reduced iron availability resulting from depleted iron stores (e.g., during pregnancy), inadequate dietary intake (as in malnutrition or in vegetarian and vegan diets), impaired intestinal absorption (such as in chronic inflammation), or increased iron loss (e.g., menstrual blood loss in women of reproductive age). This condition exerts a marked negative influence on quality of life, affecting intrauterine development, diminishing both physical and cognitive performance, and increasing morbidity when concomitant with cardiovascular diseases such as Chronic Heart Failure (CHF), Acute Heart Failure (AHF), Atrial Fibrillation (AF) [1-5]. Other common medical conditions, such as diabetes, kidney failure, and malnutrition, are related to the development of iron deficiency [6,7].

The main clinical manifestations of iron deficiency include pallor and fatigue, resulting from hypochromic microcytic anemia, which is characterized by anisocytosis on blood smears and

increased red cell distribution width (RDW) on automated cell counts [8,9]. The prevalence of iron deficiency reaches 30–50% in patients with stable chronic heart failure (HF) and is recognized as a major cause of anemia in this group, irrespective of sex, ethnicity, or left ventricular ejection fraction [1-3]. Heart Failure (HF) is a complex and progressively increasing clinical syndrome, with an estimated prevalence ranging from 1.1% to 5.5%, corresponding to approximately 30–64 million people worldwide. Arterial hypertension remains one of the principals and most common risk factors contributing to the development of HF across the full spectrum of Left Ventricular Ejection Fraction (LVEF). [10-13]. As a chronic and debilitating condition, heart failure represents a leading cause of recurrent hospitalizations and substantial healthcare expenditure globally. Numerous comorbidities complicate the natural course of HF, exerting detrimental effects on disease progression.

These comorbidities simultaneously constitute potential therapeutic targets aimed at improving patient outcomes and quality of life. Within this framework, iron deficiency has gained increasing recognition in recent years as a crucial component of the comprehensive management of heart failure. Notably, ID appears to have a greater clinical impact on the course of HF than anemia itself, showing stronger associations with reduced exercise tolerance, impaired oxygen utilization, higher rates of hospitalization, and increased mortality among patients with HF [14-16]. Although mechanisms underlying the development of ID in HF have not been rigorously investigated, generally ID arises as a consequence of impaired iron absorption, augmented gastrointestinal loss, and reduced availability of utilizable iron from the reticuloendothelial system. In setting of HF, disease-specific pathophysiological consequences (intestinal oedema, insufficient dietary intake, drug interactions due polypharmacy, and polymorbidity) further perpetuate depletion of iron storages [17,18]. In addition, recent studies in chronic as well as acute HF showed that this dysregulation of hepcidin/ferroportin system causes a chronic state of inflammation that increases the amount of interleukin-6 (IL-6) and this alters the body's normal management of iron, affecting entry into cells, its transformation and its use, making it less available for physiological functions [19]. Also, the administration of some drugs used to treat heart conditions, such as cardioaspirin, can cause small, chronic blood loss, although not always visible. These losses, over time, lead to a reduction in iron reserves in the body [20-22]. Finally, in chronic heart failure, the reduction in cardiac output leads to a redistribution of blood flow toward vital organs such as the heart and brain, at the expense of splanchnic perfusion. This adaptive hemodynamic response results in chronic intestinal hypoperfusion, which causes subclinical ischemic injury to the mucosal layer. Chronic ischemia, in combination with venous congestion, induces microvascular and structural alterations within the intestinal wall, including villus atrophy, reduced functional capillary density, and increased epithelial permeability. These changes impair mucosal integrity and the absorptive function of enterocytes, thereby diminishing the capacity for intestinal iron uptake and transport [23]. Conventionally oral treatment based on classic iron salts are poor effective because of very high side effects and poor bioavailability reaching to no therapeutic response and very low patient compliance [24,25].

Therefore, the scientific research is globally oriented to novel therapeutic approach in different fields with the aim to maximise the efficacy and patients' compliance reducing side effects [26-30]. Emoglofer® is an innovative nutraceutical specifically formulated with a new iron based patented technology called Phosphosome® iron. Particularly, Phosphosome® iron is a vehiculated formulation of iron pyrophosphate able to enhance the iron bioavailability and the therapeutic efficacy reducing side effects with a tested clinical effect in other therapeutic areas such as gynecology or gastroenterology [31,32]. The aim of the present study was to evaluate the efficacy and safety of Emoglofer® oral administration in patients with anemia deriving from heart failure or hypertensive heart disease considering a chronic administration regimen with two control time points (after three and six months of administration) monitoring the most important and standard iron metabolism parameters associated to iron anaemia (ferritin, sideremia, hemoglobin and hematocrit).

Materials and Methods

An Italian medical doctor with a specialization in cardiology, enrolled participants in the year 2022 evaluating their clinical manifestations during medical examination. In particular, the participants were selected according to defined inclusion criteria: patients with heart failure or hypertensive heart disease induced anemia with a present diagnosis of hypertension, dyslipidemia, diabetes mellitus. Considering these clinical conditions, a total of 37 patients were enrolled in the present survey; at the first medical examination, the doctor reported for each patient its age, gender, comorbidity and use of pharmacological treatments. Regarding pharmacological treatments, the main class used were antihypertensives, antiaggregant and anticoagulants. At the enrolling time (T0) serum values for ferritin, hemoglobin, sideremia and hematocrit were registered. Then, each participant administered Emoglofer® with a posology of one capsule/day and repeated the sub mentioned hematic parameters that were registered from the doctor after the follow-up visit at 3 months (T3) and at six months (T6).

Settings

The clinical survey has been conducted by an Italian medical doctor and is based on its clinical experience in patients taking Emoglofer®. The retrospective observational survey was conducted in accordance with the Standards of Good Clinical Practice of the European Union and the ethical principles expressed in the Declaration of Helsinki. Data were retrospectively collected in the year 2022 by the medical specialist. Ethical approval was not necessary according to National Code on Clinical Trials declaration because this data derives from a real-life retrospective study [33]. The aim of the present study was to evaluate the effect of Emoglofer® oral administration after three months (T3) and six months (T6) of treatment.

Results and Discussion

A significant problem in heart failure is reduced gastrointestinal absorption, mainly due to intestinal edema from venous congestion, diminished splanchnic blood flow, and altered mucosal function. These parameters diminish the efficacy of oral iron absorption in the duodenum and proximal jejunum that are the main areas for non-heme iron assimilation [34]. In addition, many HF patients take oral Proton Pump Inhibitors (PPIs), which elevate stomach pH and compromising absorption of oral iron salts [35,36]. Moreover, increased hepcidin levels in heart failure block ferroportin, the iron exporter on enterocytes, sequestering iron in intestinal cells and restricting its bioavailability.

In patients with consistent iron deficiency, the therapeutic effectiveness of oral iron is low because of poor therapeutic adherence. In fact, gastrointestinal side effects, including nausea, constipation, abdominal cramps, and a metallic taste, are commonly observed and may result in the cessation of medication [37]. In the present retrospective clinical survey, an innovative nutraceutical, Emoglofer®, was administered by patients with HF or hypertensive heart disease induced anemia with a present diagnosis of hypertension, dyslipidemia, diabetes mellitus (Figure 1).

As reported in Figure 1.1, hemoglobin levels in patients with IDA correlated with cardiological diseases were on average low at T0 with a mean value of about 11.3 g/dL. After three months of Emoglofer® oral administration, the medium value raised up to 12.6 g/dl with a successive further increase of about 17% with respect to T0 reaching a mean value of about 13.2 g/dL (T6). In addition, also for ferritin very interesting results were obtained after Emoglofer® administration. In fact, at T3 a conspicuous increase of hematic levels of about 41% was detected and, extending therapy up to 6 months, the mean value of ferritin was about 58 ng/mL with an overall increase of about 137% with respect to the T0 (Figure 1.2). Ferritin, as reported from the European Society of Cardiology (ESC) is one of the main blood parameters considered in the evaluation of iron deficiency in patients with cardiovascular diseases and the capability of oral therapies of restore its value represents a challenge for the scientific community because often oral therapies resulted ineffective and is forced to resort to intravenous therapy [37]. In order to have a most consistent panel of iron metabolism parameters, also hematocrit and sideremia were monitored in the present clinical survey (Figure 2).

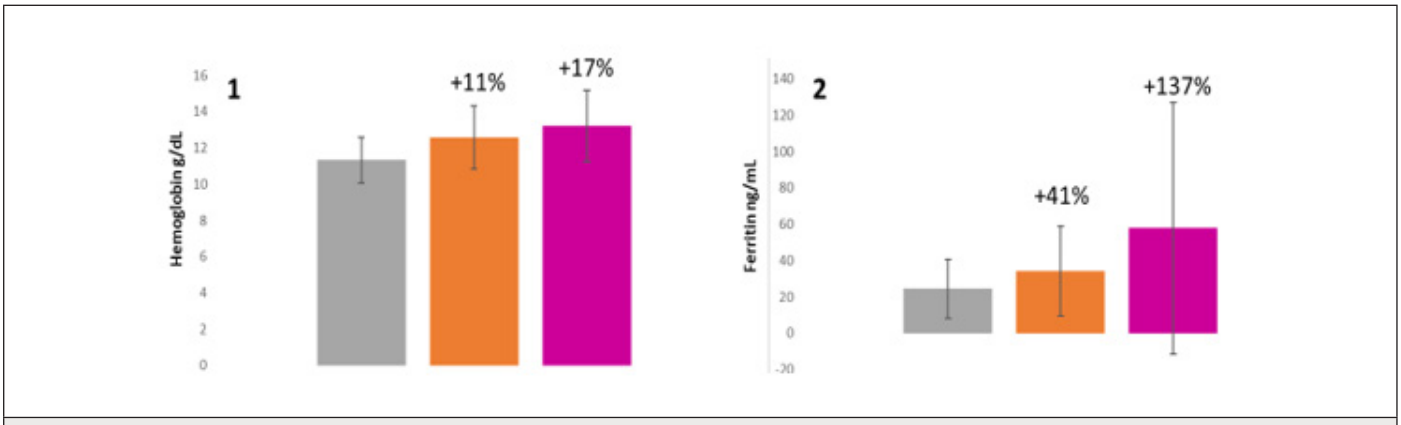

Figure 1: Hemoglobin levels at T0 (grey), after 3 months (orange) and 6 months (purple) of treatment with Emoglofer® (1); Ferritin levels at T0 (grey), after 3 months (orange) and 6 months (purple) of treatment with Emoglofer® (2). Data are expressed as mean ± standard deviation.

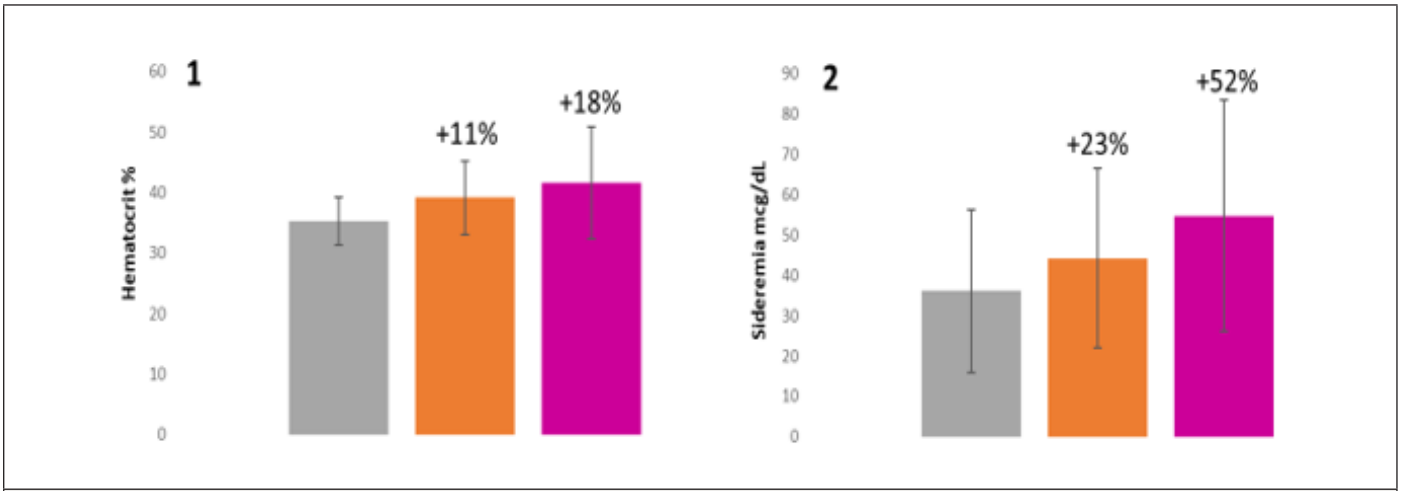

Figure 2: Hematocrit percentage at T0 (grey) and after 3 months (orange) and 6 months (purple) of treatment with Emoglofer® (1); sideremia levels at T0 (grey) and after 3 months (orange) and 6 months (purple) of treatment with Emoglofer® (2). Data are expressed as mean ± standard deviation.

After three months of treatment with Emoglofer®, both hematocrit and sideremia were increased of 11% and 23% respectively and, continuing the therapy up to T6 the mean values were further enhanced of 18% and 52%. No side effects were detected in the present clinical survey confirming the safe profile of Emoglofer® as well as its efficacy to ameliorate different parameters associated with iron deficiency. These results are consistent in terms of efficacy and patients' compliance with other clinical survey obtained with products containing the patented technology Phosphosome® iron in other therapeutic areas like gastro-intestinal and gynecology [31,32]. These interesting results are strictly correlated to the patented technology, Phosphosome® iron in the formulation of Emoglofer®. In fact, as reported in previous bibliographic data, Phosphosome® iron showed an improved resistance to gastric digestion and higher intestinal absorption than conventional ferric pyrophosphate. In the follicle-associated intestinal epithelium model (FAE), Phosphosome® iron induced larger iron absorption than in the Caco-2 monolayer, most likely due to the transcytosis ability of M cells. The larger iron absorption in the Phosphosome® iron treated FAE model corresponds to higher ferritin level, proving physiological iron handling that was once delivered by the patented formulation. Finally, the formulation did not induce any alterations in viability and barrier integrity. The in vitro study concluded that, Phosphosome® iron enhanced iron absorption and ferritin expression, while preserving any adverse effects [38]. The present retrospective clinical survey, could be considered as a starting point for the validation of Emoglofer® as therapeutic tool in the treatment of anaemia in patients with heart failure or other cardiovascular conditions; more specific clinical trials including more specific hematic parameters such as transferrin saturation and hepcidin are needed to confirm the potentially clinical application.

Conclusion

A total of 37 patients with diagnosed anemia correlated to heart failure, hypertensive heart disease with a present diagnosis of hypertension, dyslipidemia, diabetes mellitus was enrolled in the present retrospective clinical survey and were orally treated with Emoglofer® monitoring the main parameters of iron metabolism: hemoglobin, sideremia, ferritin and hematocrit after three and six months from the administration miming a chronic dosage regimen. All the parameters were already improved at T3 and after six months of Emoglofer® administration a further increase in serum levels of hemoglobin, ferritin and sideremia were observed as well as the hematocrit was found to be within the recommended values. The high therapeutic efficacy and the absence of typical gastro-intestinal side effects of Emoglofer® are due to the patented iron formulation (Phosphosome® iron) able to guarantee gastro-resistance and an optimum absorption profile in the intestine trough different mechanisms. The present study suggests that Emoglofer® oral administration is safe and is able to increase hematocrit, ferritin, sideremia and hematocrit after three and six months from oral administration; more consistent controlled clinical trials should be conducted in order to deeply investigate the effect on anemia correlated to cardiovascular diseases.

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Authors' contributions

All authors contributed equally to the manuscript and read and approved the final version of the manuscript.

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None.

Conflicts of Interest

We declare that Umberto Di Maio is a Shedir Pharma Group S.p.A. member and Antonino Bagnulo is a Neilos S.rl

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