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Evaluation of Oral Therapy Based on Ferric Sodium EDTA, in Combination With Vitamin C, Folic Acid, Copper Gluconate, Zinc Gluconate and Selenomethionine, in Iron-Deficiency Anemia: A Real-Life Study

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ABSTRACT

Iron deficiency (ID) and iron-deficiency anemia (IDA) are still frequent conditions in several patients' settings. Oral iron supplementation is one of available treatments of IDA, representing a convenient strategy since is cost-saving, effective and does not require intravenous (IV) access. However, often traditional oral iron therapies, mainly based on ferrous sulphate, are poorly tolerated, and with low iron absorption, causing gastrointestinal adverse events and limiting adherence to treatment and efficacy. The aim of this study is to evaluate the efficacy and safety of a new oral iron supplementation based on Ferric Sodium EDTA, in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel forte®) for IDA treatment in real-life clinical practice. Patients (N=103) were allocated to treatment with this new formulation at dosage of 1 tab/day, containing 30 mg of iron for 72 days. Patients were evaluated at basal conditions (T0), after 24 and 72 days of therapy (T1 and T2, respectively), collecting blood parameters of hemoglobin (Hb) and sideremia, evaluated as primary objective. The secondary outcomes were symptoms improvement (evaluated through a 4-points score) and safety profile of oral therapy. Treatment with Ferric Sodium EDTA in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel Forte®) showed improvements statistically significant ($P < 0.001$) of Hb and sideremia levels both at time T1 and T2. Symptoms evaluation showed an almost total resolution of symptomatology after only 72 days of therapy, and treatment was safe and well tolerated. In conclusion, this study confirmed the efficacy and the safety of the new oral iron formulation evaluated, for IDA patients in real-life clinical practice.

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Introduction

Iron deficiency (ID) and iron-deficiency anemia (IDA) are still frequent conditions in several patients' settings. The prevalence of anemia across all age groups and in both sexes is highest in Sub-Saharan Africa, South Asia, the Caribbean, and Oceania regions, according to latest reports in 2010. Furtherly, ID is considered one of the most important malnutrition syndromes continuing to be broadly widespread also in industrialized Countries [1-3]. Latest estimates confirm that ID affects more than 2 billion people worldwide and IDA remains the more frequent cause of anemia, representing approximately 50% of all anemia cases among non-pregnant and pregnant women, and 42% of cases in children under 5 years of age worldwide [1, 2]. Regarding adult men and postmenopausal women IDA occurs about in 2-5% of population [4]. Overall, almost one third of world's population (32.9%) was estimated to have anemia in 2010, with women of reproductive age and pregnant as category most at risk along with preschool age children and elderly [2, 3].

The World Health Organization (WHO) defines anemia as a hemoglobin (Hb) levels less than 13 g/dL in adult men and less than 12 g/dL in non-pregnant adult women [5]. The main anemia cause in premenopausal women is menstrual blood loss, while the most common cause of IDA in adult men and postmenopausal women is represented by blood loss from the GI tract. Other common causes of IDA are malabsorption, frequently related to other pathologies such as coeliac disease, or inflammatory bowel diseases, poor dietary intake, blood donation, gastrectomy and use of non-steroidal anti-inflammatory drugs (NSAIDs) that can

be responsible for micro-bleedings and occult bleedings [1,4].

Oral iron supplementation is one of available treatments of IDA, representing a convenient strategy since is cost-saving, effective and does not require intravenous (IV) access [1]. Oral iron therapy should be first line therapy according to European Medicines Agency (EMA) recommendations issued to limit the risk of allergic reactions correlated to IV iron administration [6]. Unfortunately, often traditional oral iron therapies, mainly based on ferrous sulphate, are poorly tolerated, and can have low iron absorption, causing gastrointestinal adverse events and limiting adherence to treatment and efficacy of oral therapy. For this reason, patients not complaint to oral iron therapy required IV iron treatment. However, IV iron therapy can expose patients to risk of adverse events on injection site, hypersensitivity reactions and to iron overload, that can induce oxidative damage to liver, heart, kidneys and increase the risk of infections, along with systemic inflammation and decrease antioxidant defenses of the body [7,8].

New iron sources have been available on the market with improved efficacy and tolerability, such as Ferric Sodium EDTA, consisting of a complex between ferric ion and ethylene diamine tetraacetate (EDTA) representing a highly bioavailable and stable source of iron. The complex between iron and EDTA (NaFeEDTA) is a stable chelate in acid pH conditions, preventing iron from binding to inhibitors of iron absorption from diet, such as phytic acid or phenolic compounds. Furtherly, the chelate is water soluble, allowing iron absorption in the duodenal tract, once Ferric Sodium EDTA crossed the stomach without modification and will be able to release ferric ion with change of pH [9,10].

Several studies confirmed efficacy of Ferric Sodium EDTA in treating IDA and ID patients, including women of reproductive age, pregnant women, preschool age children, and adolescents [11-21]. A new food supplement based on the association of Ferric Sodium EDTA with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine, named Ferachel Forte®, showed efficacy in improvements IDA in several studies performed with different patients' type, for example elderly, frailty, and chronic kidney disease (CKD) anemic patients [22-28]. This new formulation was designed to improve iron absorption and erythropoiesis, since active ingredients like vitamin C, copper and zinc are broadly recognized for having a role in increasing iron absorption and transportation in the blood stream and into the cells, in addition, selenium and folic acid are important factors in hemoglobin and DNA synthesis and in several enzymatic processes needful for cellular lifecycle [29-31].

The aim of this study is to evaluate the efficacy and safety of Ferric Sodium EDTA, in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel forte®) treatment in IDA patients in real-life clinical practice.

Materials and Methods

This is a prospective, real-life study conducted on 103 consecutive outpatients (45 men and 58 women), mean age 49.84 (±17.92) years, with recent IDA diagnosis, according to WHO definition and with Hb concentration < 13 g/dL in males and < 12 g/dL in females.

Patients were allocated to treatment with Ferric Sodium EDTA in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel Forte®, AQMA Italia S.p.A, Milan, Italy) 1 tab/day, containing 30 mg of iron for 72 days. Subjects were informed of the study procedures and provided written informed consent. Local ethic boards approved the protocol. The study was conducted in accordance with the Declaration of Helsinki guidelines regarding ethical principles for medical research involving human subjects.

Patients were evaluated for this study at basal conditions (T0), after 24 day of therapy (T1) and after 72 days of therapy (T2), collecting laboratory tests including Hb and iron blood (sideremia) levels. Blood samples were collected in the morning after an overnight rest, by antecubital venous puncture. Plasma and serum samples were obtained by centrifugation and frozen at -70°C until further laboratory analysis. All blood parameters were measured using standard automated laboratory methods on Cobas 6000 (Roche, Rotkreuz, Switzerland), by using the relative kits, according to the manufacturer's instructions.

All patients filled in an assessment questionnaire at each time point, for evaluation of symptoms of tiredness, fatigue, weakness, tachycardia, and pallor, by assigning a score according to the severity of the symptom, as follows: intense: 3 points, moderate: 2 points, mild: 1 point, absent: 0 points. Information regarding adverse events eventually reported were added as evaluation of safety. The questionnaire also provided a question about the benefit obtained from the treatment at day 72 (T2) and its entity, explained by following parameters: a) no benefit; b) real benefit; and c) great benefit.

The primary objective was to assess the improvement of Hb and sideremia levels at T1 and T2. The secondary outcome was to obtain information on the improvement of symptoms along with safety profile of the oral therapy.

Statistical analysis was performed using Paired T-test with Microsoft excel analysis program for Windows 11 Pro, by comparing all blood parameters and symptoms scores included in the study collected at T0, T1 and T2. The differences were considered significant when $P<0.05$.

Results

A total of 103 patients were included in the study. Enrolled patients reflected the real-life clinical practice as were consecutively included in the study once the IDA was diagnosed through blood parameters of Hb and sideremia evaluation after routinely outpatient screening. Patients were enrolled also in case of comorbidity and the most frequent concomitant pathologies were hypertension, dyslipidemia, type 2 diabetes mellitus, and arthrosis. Less frequently patients had Chronic Obstructive Pulmonary Disease (COPD), depression syndromes, and fibromyalgia. Baseline characteristics of patients are shown in Table 1.

Table 1: Baseline characteristics of patients enrolled in the study

Variable	Patients (N=103)
Male/female, N	45/58
Age (years), mean (± SD)	49.84 (17.92)
Comorbidities, N (%)	62 (60.2)
Hb (g/dL), mean (± SD)	9.32 (0.74)
Sideremia (µg/dL), mean (± SD)	14.21 (6.93)

Blood parameters evaluated as primary endpoint in patients treated with Ferric Sodium EDTA in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel Forte®) showed an improvement statistically significant ($P < 0.001$) of Hb and sideremia levels, as reported in Table 2. Also of note, from T0 to T2 Hb level increased of 2.75 g/dL and sideremia level has been more than tripled.

Table 2: Blood parameters of patients (N=103) treated with Ferric Sodium EDTA in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel Forte®)

Blood parameters, mean (±SD)	T0 (baseline)	T1 (24 days)	T2 (72 days)	P value (T1 vs T0)	P value (T2 vs V1)
Hb (g/dL)	9.32 (0.74)	10.40 (0.65)	12.07 (0.64)	< 0.001	< 0.001
Sideremia (µg/dL)	14.21 (6.93)	26.73 (8.84)	43.32 (6.78)	< 0.001	< 0.001

Regarding the secondary outcome consisting of symptoms evaluation, data are reported in Table 3, showing an almost total resolution of symptomatology after only 72 days of therapy, while patients reported an important improvement already after 24 days of treatment with Ferric Sodium EDTA association.

Table 3: Symptoms scores of patients (N=103) treated with Ferric Sodium EDTA in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel Forte®)

Symptom*	T0 (baseline)	T1 (24 days)	T2 (72 days)
Tiredness	2.24 (0.53)	1.37 (0.79)	0.32 (0.47)
Fatigue	2.03 (0.73)	1.07 (0.75)	0.19 (0.40)
Weakness	2.17 (0.58)	1.10 (0.70)	0.19 (0.40)
Tachycardia	1.62 (0.68)	0.79 (0.65)	0.13 (0.33)
Pallor	0.48 (1.00)	0.31 (0.68)	0.03 (0.17)

* Scores were assigned according to the severity of the symptom, as follows: Intense= 3 points, moderate= 2 points, mild= 1 point, absent= 0 points. Scores are expressed as mean (±SD).

Overall, about safety outcome the treatment with Ferric Sodium EDTA in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel Forte®) was safe and well tolerated, since only 2 patients (1.94%) reported mild adverse events (AEs). One patient reported constipation, resolved by increasing the intake of fluids and fiber in the diet, the other one patient reported nausea, resolved by assuming treatment after meal. No patient has discontinued therapy.

Furtherly, almost all patients reported to having benefit from the treatment, in particular, 50.5% of patients (N=52) reported a real benefit and 46.6% (N=48) reported a great benefit from treatment.

Discussion

This is a real-life study conducted on 103 consecutive outpatients with recent IDA diagnosis, treated with Ferric Sodium EDTA in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel Forte®) 1 tab/day, containing 30 mg of iron for 72 days.

IDA is a disease still to frequent in the normal clinical practice and in general medicine and for general practitioners it is important to have new tools to act in time with oral therapies in order to avoid the need for IV iron therapy, which is essential in patients with severe IDA when levels of Hb are too low and treatment with oral therapies is not effective. Unfortunately, oral therapies with poor tolerability, as traditional iron sulphate therapies, are still too used, with frequent occurrence of AEs, mainly of gastrointestinal type, approximately in a third of treated patients [32]. This high frequency of AEs can negatively affect treatment compliance and consequently lead patients to discontinue therapy, leaving untreated IDA, which can get worse and becoming treatable only with IV iron or in the worst case with transfusions. However, IV iron treatment can expose patients to several AEs, as injection site reactions, phlebitis, thrombophlebitis, hypersensitivity reactions and to risk of iron overload, that can in turn cause damage to other organs like liver, heart, kidneys and increase the risk of infections and systemic inflammation [7,8].

Ferric Sodium EDTA is a new iron source, broadly used for foods fortification strategies put in place to stem the problem of ID and recognized as iron source with elevated bioavailability and good safety profile [9,10]. This new iron source has been largely studied alone and in combination with other active ingredients like vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine, showing important results in anemia improvement in several patient types [11-28].

The new formulation based on Ferric Sodium EDTA in association of with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel Forte®), has been designed to improve iron absorption and to exploit synergic effect of active ingredients used. Latest studies published regarding this product showed its efficacy and safety as oral treatment in non-dialysis-dependent CKD elderly patients with secondary anemia not responders to a previous treatment period based on ferrous sulphate. [24] Another study demonstrated the possibility of replacing intravenous iron administration with this product for treat CKD patients in conservative therapy, with good efficacy, tolerability and significant economic savings [23]. More recently another study conducted on patients with CKD treated with this new formulation showed not only a significant improvement of iron blood parameters and tolerability, but also the possibility of reducing the systemic inflammatory status in this kind of patients where the inflammation contributes to the IDA worsening [22].

Since these previous studies involved specific patients types, we have considered useful for scientific community to study in deep the use of Ferric Sodium EDTA in association of with vitamin C,

folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel Forte®) in general medicine and in real-life settings, including in this analysis also patients with comorbidities and with different basal conditions, including young adults, elderly, men and women in reproductive age and in post-menopausal age.

Results showed a statistically significant improvement of iron blood parameters and of symptoms scores, with good tolerability and great benefit for patients. However, this study has limitations including the lack of a comparison therapy and the lack of the evaluation of eventual bias or confounding factors derived from the other therapies assumed by patients. Furtherly, the sample size is not too large, but it can be representative of a part of patients who normally go to the doctor in daily clinical practice. Further studies will be useful for deepen the lacking aspects of this preliminary evaluation.

In conclusion, this study confirmed the efficacy and the safety of treatment with Ferric Sodium EDTA, in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel Forte®) in IDA patients in real-life clinical practice.

Conflicts of Interest: The authors declare no conflict of interest.

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