AUB American University of Beirut
الجامعة الأميركية في بيروت

Study Proposal

RANDOMIZED TRIAL OF CAPTAFER® VS. ORAL IRON SULFATE IN THE TREATMENT OF IRON DEFICIENCY ANEMIA IN PATIENTS WITH ULCERATIVE COLITIS

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ABSTRACT

Ulcerative colitis (UC) is an inflammatory bowel disease (IBD) characterized by chronic inflammation limited to the mucosal layer of the colon. Anemia is a consistent clinical feature of IBD. It is encountered in one third of IBD patients [1], and is the most common extraintestinal complication of this disease [2]. Anemia has a significant impact on the quality of life of affected patients. Many patients with IBD frequently complain of chronic fatigue commonly caused by anemia and this may be as debilitating to patients as abdominal pain and diarrhea [3]. Anemia in IBD is multifactorial, but is most commonly the result of iron deficiency anemia (IDA) and rarely due to anemia of chronic disease (ACD) [4]. IDA is mainly due to chronic blood loss through ulcerations in the intestinal mucosa, reduced iron intake, and reduced absorption [5]. Meanwhile, ACD results mainly from the upregulation of hepcidin gene expression leading to a reduction in iron release from enterocytes and macrophages, but also, from the inhibition of proliferation and differentiation of erythroid progenitors as a result of proinflammatory cytokines secretion, which also blunts erythropoietin response [6]. New iron indices including zinc protoporphyrin, reticulocyte hemoglobin content, and the percentage of hypochromic red cells are used along with common biochemical parameters for assessment of iron status in anemia of IBD [7,8,9,10].

Oral iron supplementation has been used traditionally for the treatment of IDA but studies have shown that it may result in disease exacerbation by increasing oxygen free radicals within the lumen of the gut via the Fenton reaction [11]. Free radicals aggravate inflammation by causing lipid peroxidation in the colon, interfering with the function of macrophages and TH1 cells, and by increasing proinflammatory cytokines (IL-1, IL-6, GAMMA INF, TNF-A, IL-3, IL-4) which result in reduction of erythropoiesis. Further studies indicate that iron increases cancer risk by enhancing epithelial cell proliferation, nitrooxidative damage, and inflammation and that iron-enhanced oxidative stress may lead to increased mutagenesis and to cell death and ulceration [12]. Inhibition of inflammation-driven (and iron-enhanced) oxidative stress in UC patients (such as through the use of antioxidants) may be an important approach to suppressing inflammation and inhibiting

UC-associated carcinogenesis. Oral iron therapy is also associated with many side effects such as constipation, diarrhea, nausea, vomiting, abdominal pain and hyperchromia of feces.
A recent study done in University Hospitals Birmingham, United Kingdom, has shown that treatment with oral iron results in failure to control anemia in 2 out of 3 IBD patients, which is in part due to the side effects reported by over half of patients [13].

Because of the aforementioned complications and side effects of oral iron therapy, recent guidelines recommend the intravenous administration of iron [7]. However, and despite the recommendation of international expert guidelines and the availability of new intravenous iron preparations with a better safety profile, many gastroenterologists are still reluctant to administer iron intravenously for cost considerations, risk of iron overload, fear of hypersensitivity reactions, and side effects such as myalgia, tachycardia, dysgeusia and strong perspiration. [14]

Given the above, new therapies were sought, aiming at replenishing body iron stores by increasing its absorption. Heme iron contained in meat is absorbed better than non-heme iron, however meat promotes as well the absorption of non-heme iron contained in either meat and other foods. The factor that promotes the absorption of non-heme iron consists of certain carbohydrates present in the extra-cellular matrix of the muscular fibres of meat. Biochemical and molecular studies have shown that specific carbohydrates, which are oligosaccharides originating from glycosaminoglycans present in the extracellular matrix of muscle tissue, contribute to the enhancing effect of meat on iron uptake by the enterocyte. The fact that this increase in iron absorption relates predominantly to non-heme iron is of particular importance since non-heme iron is more difficult to absorb. Captafer is a new iron-free oral preparation that contains a special type of oligosaccharides from fish muscle tissue able to make the intestine absorb 3 to 5 times more iron in comparison to the "meat factor". Moreover, Captafer contains other vitamins and supplements that improve anemia, such as:

- Vitamin C, known for its property to facilitate iron absorption by reducing iron to the reduced ferrous state necessary for uptake;

- Vitamin E, an antioxidant, along with vitamin C it protects Fe^{++};
- Folic acid, necessary to prevent megaloblastic anemia and abnormalities in the fetal nervous system, vital during pregnancy;
- Zinc and Copper which act in different mitochondrial cytochromes-dependent systems and contribute to the use of iron by the biological systems.

Two studies have examined the safety and efficacy of Captafer [15][16], one in menstruating females and the other in a heterogeneous IBD patient group. Both studies confirmed safety and efficacy with 50-70% increase in serum iron and ferritin and improvement in hemoglobin with no adverse effects. [16][17]

The IBD study was an open-label single-arm pilot study. No formal randomized clinical trial (RCT) has ever been performed to demonstrate the safety and efficacy of Captafer in treating iron deficiency anemia in ulcerative colitis vs. standard oral iron therapy. The aim of this study is a head-to-head comparison of Captafer with standard oral iron therapy in a prospective, randomized, open label trial.

Fifty patients from the outpatient department at AUBMC will be enrolled in this randomized controlled trial. Patients with active left sided ulcerative colitis or active extensive disease with proven IDA will be enrolled. Study patients will receive the treatment following informed consent and will be followed up regularly by the study coordinator for side effects, compliance and adherence. A blood test for hemoglobin and hematocrit and other biomarkers of iron stores and repletion will be done on all patients at baseline and then after 4 weeks, 8 weeks, and 12 weeks of therapy.

Study Description:

A- Objective:

The objective of this study is to compare the efficacy and safety of Captafer which is an iron-free food supplement given twice daily, to oral iron therapy given at a dose of 195 mg twice daily for the same period of time in the treatment of iron deficiency anemia in ulcerative colitis patients.

Primary endpoint:

- Tolerability

- Response to iron repletion as using hemoglobin and hematocrit as surrogates
- Compliance and adherence (monthly pill count)

B- Patient population:

Fifty patients from the outpatient department and the endoscopy unit at AUBMC will be enrolled in this randomized controlled study. The primary gastroenterologist having a doctor-patient relationship with the ulcerative colitis patient will approach him and inquire about his willingness to participate in the aforementioned study. Given the primary approval of the patient the physician will then introduce the patient to the research fellow of the study. The research fellow will then approach patients in the endoscopy unit presenting with ulcerative colitis and iron deficiency anemia, inquiring about the inclusion and exclusion criteria. Patients who meet the inclusion criteria will receive a clear explanation of the purpose of the study. Those who agree to participate and sign an informed consent will be enrolled.

- Inclusion criteria
- Age above 18
- Confirmed diagnosis of ulcerative colitis
- Proven iron deficiency anemia (Hb<12, transferrin saturation <20%)
- Active left sided colitis or extensive disease (Mayo Score≥5 or Partial Mayo score ≥4)
- Exclusion criteria
- Age below 18
- Recently hospitalized for disease flare (within 3 months)
- Hemoglobinopathies (including thalassemia)
- Isolated proctitis
- Crohn's disease or indeterminate colitis

- Known Liver or kidney disease
- Known Celiac disease
- Small bowel resection
- Use of anticoagulants or aspirin
- Known intolerance to oral iron therapy
- Uninvestigated anemia
- Pregnant or lactating women
- Known hypersensitivity to iron sulfate
- Transfusion within the last 4 weeks
- Erythropoetin within the last 8 weeks
- Rhematoid Arthritis
- History of menometrorrhagia or frequent epistaxis
- Use of Stomach acid-reducing product (classical antacids, PPIs, H2-receptors Inhibitors)
- Gastritis

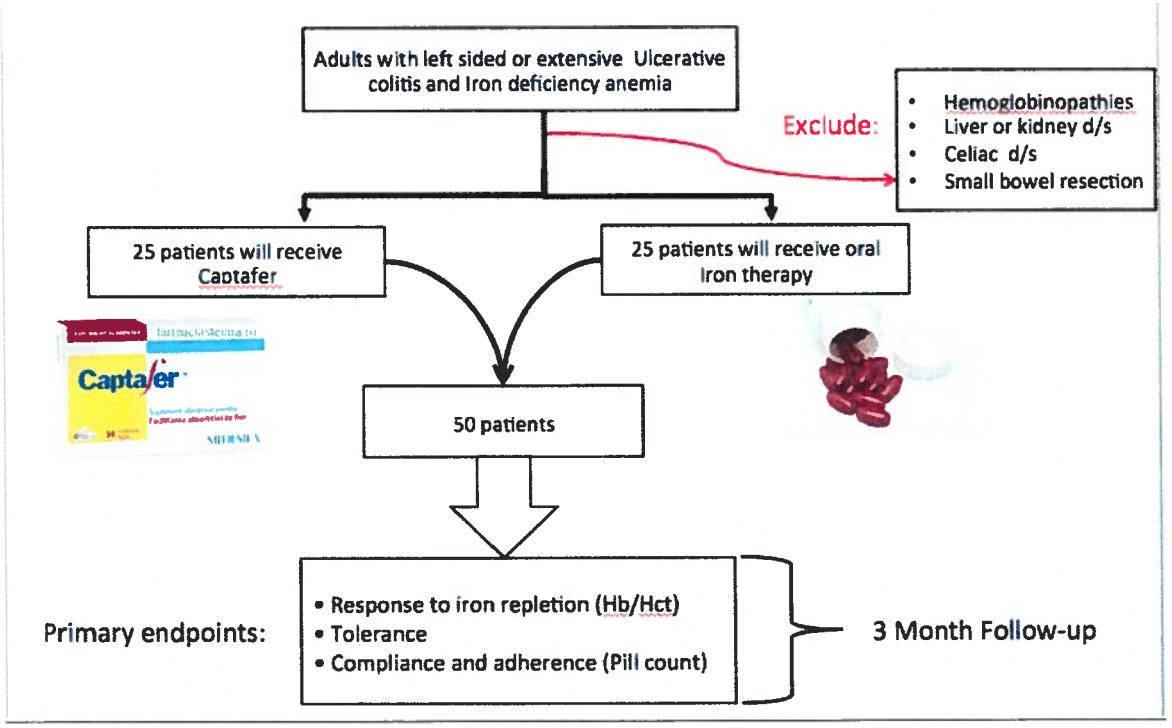
C- Design and methods:

This is an open-label, prospective, randomized controlled study. After documentation of iron deficiency anemia (Hb<12, transferrin saturation <20%), the patients will receive a clear explanation of the purpose of the study. Those who agree to participate and sign an informed consent will be enrolled. Patients will then be randomized to one of the two arms of the study based on a computer-based randomization system. Twenty-five patients will be started on Captafer and the other 25 patients will receive iron supplementation. The patients will be assessed for tolerance, compliance and adherence regularly after the onset of their treatment regimen through phone calls and at regular scheduled office visits. The Inflammatory Bowel Disease Questionnaire (IBDQ) for QoL will be completed at baseline and at 3months of therapy.

Anemia response to treatments will be assessed via biochemical and blood parameters including: hemoglobin/hematocrit, reticulocyte count, ferritin level, and transferrin saturation. These tests will be performed at baseline and then at week 4, week 8, and week

12 of therapy in both groups. The Captafer and oral iron therapy tablets will be provided monthly to patients at no costs.

Patients treated with Captafer will be taking 2 tablets daily for 3 months. Patient treated with oral iron supplement will be taking 2 capsules of oral iron sulfate 195 mg daily. Compliance and side effects will be evaluated by phone calls during the treatment period. Given the fact that intestinal absorption of nonheme iron is improved by food rich in iron absorption enhancers (Vitamin C, Beef, Poultry, Salmon, Pork, Citric acid) and decreased by food rich in iron absorption inhibitors (phytic acid, egg protein, certain minerals that compete with iron for absorption, tannic acid (in tea), coffee, cocoa, fiber); participants enrolled in this study will be asked to fill a dietary assessment questionnaire to estimate their oral iron intake and their overall nutritional status.



D- Statistical Interpretation:

Response to therapy will be evaluated using the change in blood parameters (Hb/Hct, ferritin, transferrin, and reticulocyte count). Success of therapy will be evaluated according to modified intent-to treat and per-protocol analyses.

The study sample size was calculated based on the primary end points of tolerability with a significance level (α) of 0.05, a Power ($1-\beta$) of 0.9 with an expected 90% tolerability and adherence for Captafer vs. 60% for oral iron. At these parameters, and taking a non-inferiority limit of 5% the sample size was calculated to be 48.

Quality of life will be assessed using the Inflammatory Bowel Disease Questionnaire (IBDQ). Compliance and adherence will be assessed through reported pill count. Tolerance will be measured using the rate of discontinuation and incidence of adverse events that preclude the continuation of treatment.

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